Ex Vivo and In Vivo Imaging Study of Ultrasound Capsule Endoscopy

John H. Lee
Division of Gastroenterology,
Massachusetts Institute of Technology,
77 Massachusetts Avenue,
Cambridge, MA 02139
e-mail: jhl33@mit.edu

Giovanni Traverso
Division of Gastroenterology,
Massachusetts Institute of Technology,
77 Massachusetts Avenue,
Cambridge, MA 02139;
Brigham and Women's Hospital,
75 Francis Street,
Boston, MA 02115
e-mail: cgt20@mit.edu

David Ibarra-Zarate
Tecnologico de Monterrey,
Escuela de Ingenieria y Ciencias,
Eugenio Garza Sada 2501 sur col.
Tecnológico c.p,
Monterrey, Nuevo León 64849, México
e-mail: david.ibarra@tec.mx

Duane S. Boning
Division of Gastroenterology,
Massachusetts Institute of Technology,
77 Massachusetts Avenue,
Cambridge, MA 02139
e-mail: boning@mtl.mit.edu

Brian W. Anthony
Division of Gastroenterology,
Massachusetts Institute of Technology,
77 Massachusetts Avenue,
Cambridge, MA 02139
e-mail: banthony@mit.edu

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Wireless capsule endoscopy (WCE) has revolutionized the capacity for evaluation of the gastrointestinal (GI) tract, but its evaluation is limited to the mucosal surface. To overcome this, ultrasound capsule endoscopy (UCE) that can evaluate the deeper structures beyond the mucosal surface has been proposed and several studies focusing on technology development have demonstrated promising results. However, investigations of the potential for clinical utility of this technology are lacking. This work had two main goals: perform ex vivo and in vivo imaging studies in a swine model to (1) evaluate if acoustic coupling between a capsule with a specific size and GI tract can be achieved only through peristalsis autonomously without any human control and (2) identify key issues and challenges to help guide further research. The images acquired in these studies were able to visualize the wall of the GI tract as well as the structures within demonstrating that achieving adequate acoustic coupling through peristalsis is possible. Critical challenges were identified including level of visualization and area of coverage; these require further in-depth investigation before potential clinical utility of UCE technology can be concluded. [DOI: 10.1115/1.4046352]

Introduction

Imaging of the gastrointestinal (GI) tract is essential for diagnosis and monitoring of various diseases such as occult GI bleeding, inflammatory bowel disease, and cancer. Various imaging modalities are currently part of the standard of care including endoscopy, computed tomography (CT), magnetic resonance imaging, transabdominal ultrasound (TUS), and wireless capsule endoscopy (WCE). WCE was initially developed by Iddan et al. [1] and was commercialized by Given Imaging, Ltd., (now Medtronic, Dublin, Ireland), receiving Food and Drug Administration (FDA) approval in 2001 as a diagnostic tool for the evaluation of the small intestine [2]. Since then a number of other WCE devices have become commercially available [3–5]. WCE has demonstrated significant utility in diagnosing pathology, which previously would have required more invasive procedures: for example, the identification of sources of occult GI bleeding, evaluation of treatment response in Crohn's disease, and diagnosis of celiac disease [6–8]. However, WCE is limited to optical evaluation of the surface of the GI mucosa due to utilizing optical camera(s). Though modalities such as double-balloon enteroscopy are capable of evaluating the mucosal wall for further delineation of masses and possible sites of inflammation, they are significantly more invasive and require deep sedation [2]. Alternative modalities using CT or magnetic resonance imaging necessitate various contrast agents, significant capital expenses, and exposure to ionizing radiation in the case of CT. Prior studies utilizing TUS have demonstrated some promise for evaluating the small intestine, which is the most difficult part of the GI tract to examine due to its length and tortuous course [9–11]. However, visualization can be significantly limited if pockets of gas are present or if there is an abundance of abdominal subcutaneous fat.

To overcome the limitations of WCE, the concept of a wireless ultrasound capsule endoscopy (UCE) has been proposed by multiple groups in the past [12–15]. Such a device could take advantage of the benefits of WCE with the added capabilities of ultrasound imaging. The envisioned usage of such a device is almost identical to the currently available WCE. The patient receives the capsule at the doctor's office and swallows it. As the capsule travels along the GI tract via peristalsis, it acquires ultrasound images, processes the data, and wirelessly transmits the data to a base station worn on the patient. After imaging is completed, the data stored on the base station are uploaded onto a computer where it is further processed and viewed by the doctor. Unlike TUS, UCE could benefit from improved visualization since the imaging is performed from the inside and therefore is not limited by factors such as patient's abdominal girth. Gas pockets in the lumen will limit visualization; however, unlike in TUS, it will be limited only to that segment of the bowel. Also, since the required penetration

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depth is much less, a higher frequency transducer can be used, providing higher resolution.

The main components of wireless UCE are shown in Fig. 1, which are an ultrasound transducer, ultrasound imaging electronics, a controller, a radio, power management electronics, and a power source. The ultrasound transducer block represents a generic form of a transducer, which may be a single element or an array transducer. The ultrasound imaging electronics will take the form that corresponds to the selected transducer design. The controller may be implemented as a field-programmable gate array (FPGA), a microcontroller, or an application-specific integrated circuit that is standalone or integrated into another component such as the imaging electronics or the radio. The radio can be either a transmitter or a transceiver depending on whether any data or commands need to be sent to the device from the base station. The power management block generates all required power supplies from the power source including the high voltage necessary for the pulser. The power source can be either batteries or coils for receiving wireless power from outside of the body.

One of the most important design criteria is the size of the capsule. Studies on WCE have shown that the capsule size has to be limited to around 1 cm in diameter and 3 cm in length in order to minimize the risk of obstruction, and this requirement also applies to UCE. The reported retention rate for WCE varies widely from 0 to 13% with increasing size increasing the chance of obstruction [16–19].

While there are many commonalities between UCE and WCE, an important issue unique to UCE is that acoustic coupling between the capsule and the tissue is required for imaging to be possible. One way to accomplish this is to have an acoustic medium, such as a water-based liquid, between the capsule and the tissue by having the patient drink the liquid before swallowing the device. However, to ensure that the capsule is always surrounded by the liquid, the liquid would have to be viscous to retard its transit through the GI tract and the patient may be required to drink a large volume. Since an important goal of this device is to enable the patient to continue normal activity during imaging, requiring the bowel to be distended is not the most optimal or convenient approach.

Previous studies on UCE have suggested that peristalsis may provide enough contractile force around the capsule to provide adequate acoustic coupling. Intestinal peristalsis provides a natural means of contact between the capsule and the tissue. The fluid produced by the mucosal glands could provide additional coupling during contraction. If adequate acoustic coupling can be provided via peristalsis, little or no external coupling medium may be needed for imaging and the patient can essentially continue their normal activity.

Relying on peristalsis to generate acoustic coupling also has implications on the size of the capsule. For adequate coupling to occur during the contractile cycle of the peristalsis, the capsule must be tightly squeezed by the intestine, which means having a larger diameter will likely enable better contact with the tissue and thus better coupling. While there have been several studies with ex vivo experiments using swine intestine tissue that showed good imaging results, there have not been sufficient in vivo experiments to demonstrate whether the typical diameter of around 1 cm is large enough to produce sufficient contact between the capsule and the tissue.

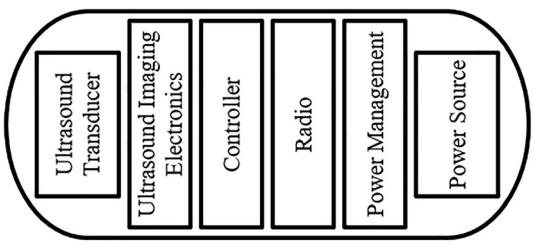

Fig. 1 Main components of UCE including an ultrasound transducer, ultrasound imaging electronics, a controller, a radio, power management electronics, and a power source

Since the proposal of UCE, a number of studies have been published, mostly focusing on the technology development [20–23]. Lay et al. [24] performed an in vivo imaging study using a swine model investigating achievable image quality and maximum tolerable power consumption. While the study demonstrated that acquiring high quality ultrasound images is possible, the scope of the study was limited due to the prototype lacking radial scanning ability.

In this work, ex vivo and in vivo imaging studies were performed in a swine model with two main objectives. First was to evaluate if acoustic coupling between a capsule with a specific size and GI tract can be achieved only through peristalsis autonomously without any human control. Second was to identify key issues through the imaging study to help guide further research in UCE technology. In order to accomplish these goals, a prototype based on mechanical scanning transducer design previously described by Lee et al. [15] was developed and ex vivo and in vivo imaging studies were performed in a swine model.

Methods

Prototype Development. It is important to note that the purpose of this prototype was solely to conduct this imaging study rather than to demonstrate or achieve the best possible transducer design. The developed prototype is shown in Figs. 2(*a*) and 2(*b*). The size of the capsule is 1 cm in diameter and 4 cm in length. It consists of a 10 MHz, 2 mm diameter unfocused disc transducer (UTX, Inc., Holmes, NY), a microstepper motor with 16:1 gear (Micromo, Clearwater, FL), a capsule body and cover, and a 4 m long tether. The diameter of the transducer was chosen to have the near-field to far-field transition occur within the desired imaging depth. An unfocused transducer was used because its beam width changes more gradually as a function of the image depth, providing a more consistent image quality along the axial direction. The tether is made of a 3.3 mm (outer diameter) polytetrafluoroethylene (PTFE) sleeving, and it houses a mini coaxial cable for the transducer and four wires for the stepper motor. The body of the capsule was 3D-printed with Objet500 Connex 3D Printer (Stratasy, Eden Prairie, MN) with a proprietary acrylonitrile butadiene styrene-like material. The capsule cover was machined from TPX® (polymethylpentene) rod (Goodfellow, Coraopolis, PA) with 0.8 mm wall thickness. TPX is a material often used in ultrasound applications because of its tissue-like acoustic impedance. The chamber inside the capsule cover was filled with distilled water.

The single-channel imaging system designed to be used with the prototype is shown in Fig. 2(*c*). MAX14811 high voltage pulser (Maxim Integrated, San Jose, CA) was used for bipolar pulsing, and the received chain consisted of MAX4937A T/R switch (Maxim Integrated) and AFE5801 analog front end (Texas Instruments, Dallas, TX) with 12-bit analog-to-digital converter operating at 40 mega samples per second. Basic signal processing functions and communication with the computer were done using Spartan-3 FPGA (Xilinx, San Jose, CA). The stepper motor was driven with DRV8836 (Texas Instruments), a simple H-bridge IC, in full step mode. Each frame consisted of 320 scan lines (angular resolution of 1.125 deg) with a frame rate of 2 fps.

While the goal of the prototype was to model the envisioned UCE technologies, some design compromises had to be made in order to make the development practical and timely. First, the device was not wireless but tethered because the custom electronics necessary for ultrasound imaging and wireless communication were not available. However, given that the tether is flexible, it was expected to have minimal impact on the ability of the capsule to make contact with the tissue. In order to prevent the coaxial cable from tangling, the direction of rotation was reversed every

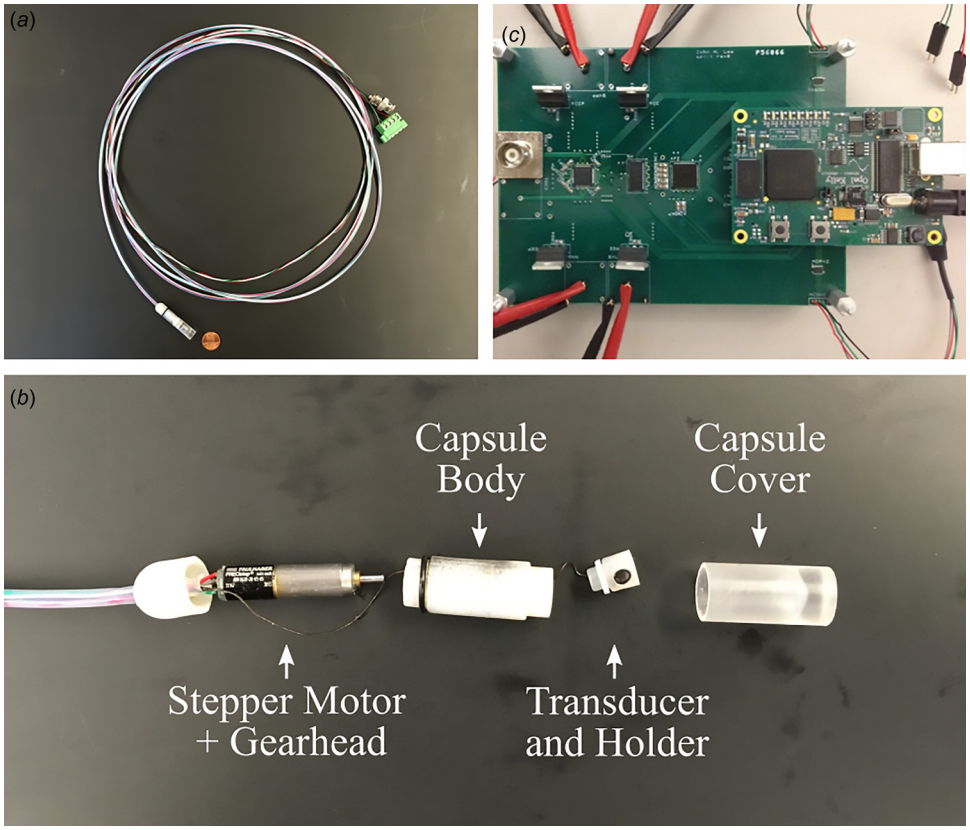

Fig. 2 Mechanical scanning-based tethered prototype for feasibility study. (*a*) Capsule and 4 m long tether encasing the coaxial cable for the transducer and four wires for the motor. (*b*) Exploded view of the capsule showing the motor, capsule body, transducer, and capsule cover. (*c*) Ultrasound imaging electronics designed for single-channel imaging.

other turn, which was a simple and effective solution for the purpose of this prototype. Wang et al. [23] have also demonstrated a mechanical scanning-based prototype with inverting direction of rotation using a rotary solenoid-coil motor and an internal spur gear. Second, while the capsule diameter was designed for 10 mm, adhering to the size of WCEs, the prototype length is longer at 40 mm to accommodate the stepper motor and the gearhead. While the capsule is longer than the desired length for clinical use, the length of the capsule should have far less significant impact on acoustic coupling and resulting images compared to its diameter.

Prototype Evaluation. In order to evaluate the performance of the prototype, a phantom with 0.3 mm diameter nylon monofilament fishing line (Trilene XT, Berkley, Columbia, SC) was created. Fishing line was chosen over wire because of its similar acoustic impedance to tissue. The phantom consists of two rings of 15 fishing lines with diameters of 14 mm and 20 mm at 2 mm and 5 mm away from the capsule wall, respectively.

Ex Vivo Imaging. Ex vivo imaging was performed with pig esophagus and small intestine tissues shown in Fig. 3(*a*) to explore potential challenges in imaging and to evaluate the performance of the prototype. The tissues were immersed in a beaker of distilled water with the capsule placed inside the organ as shown in Fig. 3(*b*).

In Vivo Imaging. All in vivo procedures were conducted in accordance with protocols approved by the Massachusetts Institute of Technology Committee on Animal Care. A Yorkshire pig of approximately 50 kg was placed on a liquid diet consisting of Ensure® (Abbott, Abbott Park, IL) and apple juice to achieve an empty stomach prior to ultrasound imaging. Prior to the procedure, the animal was fasted overnight. On the day of the procedure, the animal was sedated using an intramuscular injection of Telazol (tiletamine/zolazepam) 5 mg/kg, xylazine 2 mg/kg and atropine 0.04 mg/kg. The pig was intubated and maintained on isoflurane (1–3% inhaled). The tether of the prototype capsule was threaded into an endoscope and was introduced into the pig esophagus and small intestine. Once the device was introduced into the region, imaging was performed in a fixed position in order to observe the peristaltic wave as it propagates around the capsule.

Results

Prototype Evaluation. Figure 4 shows the B-mode image of the fishing line phantom acquired with the developed prototype.

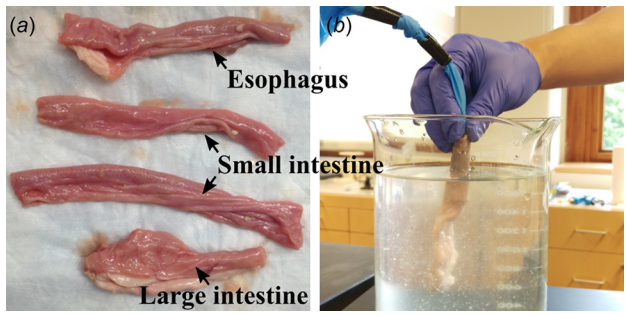

Fig. 3 (*a*) Tissues used in ex vivo imaging study. (*b*) Imaging setup showing the capsule inserted into a segment of esophagus and immersed in a beaker of distilled water.

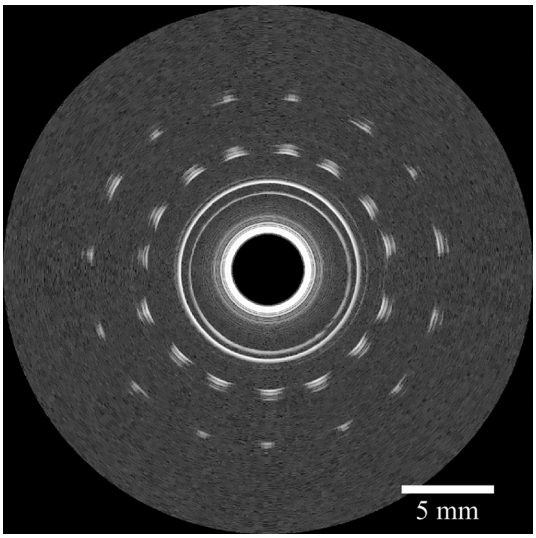

Fig. 4 B-mode image of monofilament fishing line phantom. The phantom consists of two rings of 15 fishing lines with diameters of 14 mm and 20 mm corresponding to 2 mm and 5 mm away from the capsule wall, respectively. The dynamic range of the image is 60 dB.

The dynamic range of the image is 60 dB. Due to the dimension of the fishing line, it is difficult to exactly quantify the axial and lateral resolutions, although they can be deduced from the image. The fact that the anterior and posterior walls of the wire can be distinguished in the image implies that the axial resolution is at least higher than 300 μm. The lateral resolution can be estimated from the image by measuring the 6 dB echo width, which is around 680 μm. Accounting for the diameter of the line, which is 300 μm, the lateral resolution can be estimated to be around 380 μm. While these values are estimates, they agree with the estimation based on the transducer dimension. The overall attenuation due to the round-trip path through the cover was measured by imaging a flat reflector positioned 1.5 mm away from the outer wall of the cover as shown in Fig. 5. Total attenuation of 3.35 dB was observed in the envelope detected signal.

Ex Vivo Imaging. Figures 6(*a*) and 6(*b*) show resulting B-mode images of esophagus and small intestine, respectively. The two rings in Fig. 6(*a*) are from the echoes due to the inner and outer walls of the capsule cover. The mucosa, submucosa, and inner and outer muscularis layers can be visualized as shown in Fig. 6(*b*). Ex vivo imaging is a useful way to assess the imaging performance of the prototype with real tissue. Also, it provides an opportunity to evaluate different imaging scenarios to see how the resulting images are affected. One important finding is the effect of the position of the capsule with respect to the tissue on the resulting image quality, which is shown Fig. 6(*b*). On the right side of the image, the structure of the intestinal wall is clearly visualized because the capsule is making a direct contact with the tissue providing adequate acoustic coupling. The visualization is less clear on the left side of the image because the tissue is not making a direct contact with the capsule and the angle of the tissue relative to the acoustic beam is oblique.

In Vivo Imaging. Figures 7(*a*) and 7(*b*) show the B-mode images of the esophagus. As is in ex vivo imaging, different layers of the esophagus wall can be identified. There was a good circumferential visualization around the capsule, which implies that adequate contact was achieved likely due to the small lumen of the esophagus. Also, unlike the ex vivo setting where the tissue is completely relaxed, the GI tract inside the body is mostly in a contracted state, making the effective lumen diameter smaller, which also contributes to increased acoustic coupling and improved visualization.

Figures 7(*c*) and 7(*d*) show the images of the small intestine. Figure 7(*c*) shows the case where the peristaltic wave in the small intestine causes circumferential contact between the capsule and the tissue. Different layers of the small intestine can be visualized. The group of arrows in Fig. 7(*c*) shows the visualizations of other loops of intestine abutting the section from which the capsule is imaging. However, due to the attenuation of the ultrasound energy, the layers within the abutting intestinal wall could not be visualized. The section noted in Fig. 7(*d*) is an example of air or gas pockets in the intestine. The repeating arcs visible in the left lower section of the image are due to the reverberation from the capsule cover caused by total reflection of the ultrasound.

Discussion

It is important to note that the goal of this work was not to provide a final assessment on the feasibility of UCE. While several works have been reported focused on preliminary technology options, it is the view of the authors that there has not been

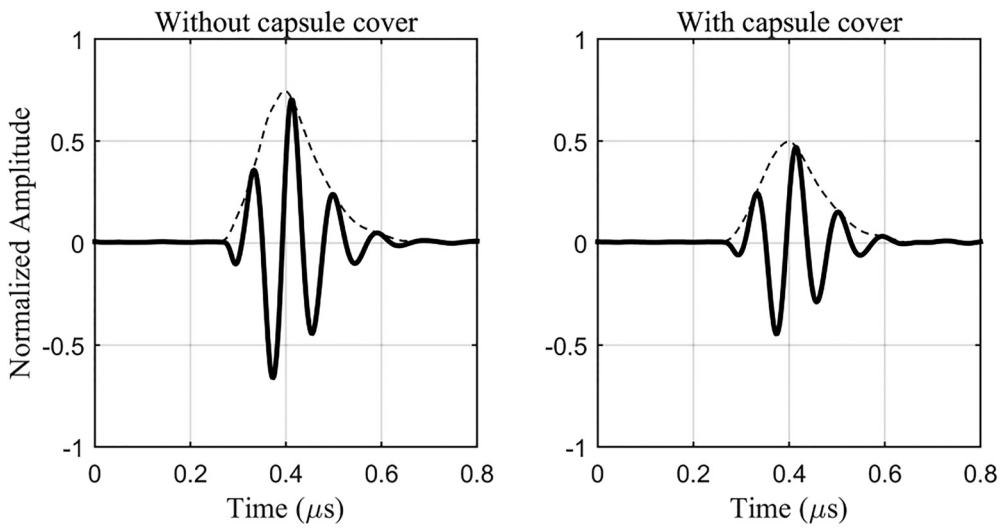

Fig. 5 Capsule cover attenuation measurement made with a flat reflector. A-lines measured without and with the cap are shown on the left and right, respectively. The radio frequency signals are shown as solid lines and the envelope-detected signals as dashed lines. Attenuation of 3.35 dB was observed in the envelope detected signal.

sufficient amount of investigation and evidence to say whether UCE technology has enough potential for clinical utility even when the technological challenges are solved. Therefore, the broad goal of this work was to perform imaging studies to determine whether and where further, more in-depth studies are warranted. With that, the specific goals of this study were to perform imaging studies to (1) evaluate if acoustic coupling between a capsule with a specific size and GI tract can be achieved only through peristalsis autonomously without any human control and (2) identify key issues to help guide further research in UCE technology.

To begin, the fishing line phantom imaging and the ex vivo imaging demonstrated that the imaging performance of the prototype was sufficient for the purpose of the in vivo imaging study. Certainly, a higher resolution can be achieved with a higher frequency transducer as demonstrated by Wang et al. [23]; however, in the context of overall system design, it is important to also consider other aspects of the system such as power consumption and cost.

One limitation of the prototype is the presence of a tether that houses the transducer coaxial cable and the wires for the motor. Although the material for the tether was chosen to make it as flexible as possible, it still resulted in restricting the capsule's mobility. Therefore, when the capsule was left in the intestine during imaging, it was not truly free to move. While this limitation made it challenging to study the transit behavior of the capsule via peristalsis, it was still possible to evaluate the effect of peristalsis on acoustic coupling by fixing the position of the capsule as the peristaltic wave propagates around it. In order to accurately evaluate the real-world clinical scenario, the development of a wireless device that can freely travel through the GI tract is necessary. However, this requires a significant investment and effort, including developing an application-specific integrated circuit. With a wireless device, an in vivo experiment can be conducted with the animal model awake and carrying out normal daily activities, providing a much more accurate model of the actual intended use case.

The ex vivo imaging study demonstrated that the prototype device was able to identify different layers of the intestinal wall and achieve near circumferential visualization when the relative position between the capsule and tissue was adequate. The in vivo imaging demonstrated that it is possible to achieve acoustic coupling with peristalsis without having to distend the organ with external coupling agent. While the initial results from the in vivo imaging study were promising, it also sheds some light on important hurdles faced by the UCE technology.

First, both ex vivo and in vivo imaging studies demonstrated the importance of the relative position between the capsule and the tissue on the resulting image. While the study in this work showed that peristalsis of the intestine can provide adequate coupling, it also showed that during relaxation parts of the peristaltic cycle, acoustic coupling is minimal and the level of visualization can be low. In addition, prior findings from WCE technology showed that the capsule can tumble when the lumen is large or if there is gas pocket, in which case the capsule will make contact with only a small area of the intestine, resulting in significantly limited visualization. Ultrasound imaging in general, compared to other imaging modalities, is known for its difficulty in getting high quality images because it is strongly affected by factors such as patient characteristics and, especially, the level of operator's experience. Given that it is difficult to acquire high quality images necessary for clinical use even with an experienced sonographer who has a complete control of the probe, whether acceptable image quality can be achieved by an autonomous device with no control of its position or pressure against the tissue is uncertain. The imaging study performed here was not able to fully explore this question. This is a critical issue that must be more fully investigated in order to move UCE technology forward.

Another important question remains around the achievable area of coverage of the GI tract, since this is intimately linked to the sensitivity of this technology as a clinical tool. WCE, which has a front-facing (and/or a rear-facing) camera, can achieve a large surface area per image because optical cameras can have large depth of focus, provided adequate lighting and lensing. This allows the three-dimensional surface area within the lumen to be captured. Also, with the low transit speed and relatively high frame rate, there is significant overlap between successive images that makes it possible to reconstruct the GI luminal surface by combining multiple successive images. In comparison, the coverage per image for UCE is much lower due to the different imaging principle of ultrasound. Unlike WCE that can only capture the surface, UCE acquires an additional dimension along the direction into the wall of the intestine (radial or axial direction), but at the cost of the dimension along the length of the intestine (slice thickness), which is significantly diminished to around the beam width of a transducer. This means that to get an acceptable coverage to warrant clinical utility, a high frame rate that allows acquiring finely spaced images along the length of the GI tract, enough to be able to reconstruct a three-dimensional ultrasound image of the GI

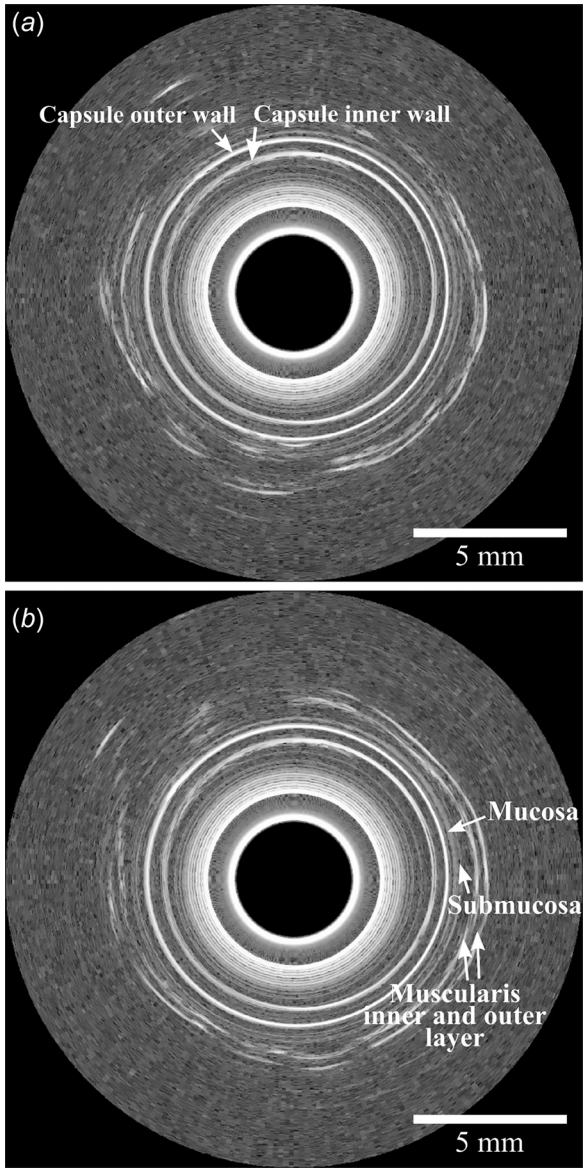

Fig. 6 B-mode images of pig (*a*) esophagus and (*b*) small intestine tissues with 60 dB of dynamic range. The two rings in the images noted (*a*) are from the echoes due to the inner and outer walls of the capsule cover Different layers of the esophageal and intestinal wall were visualized.

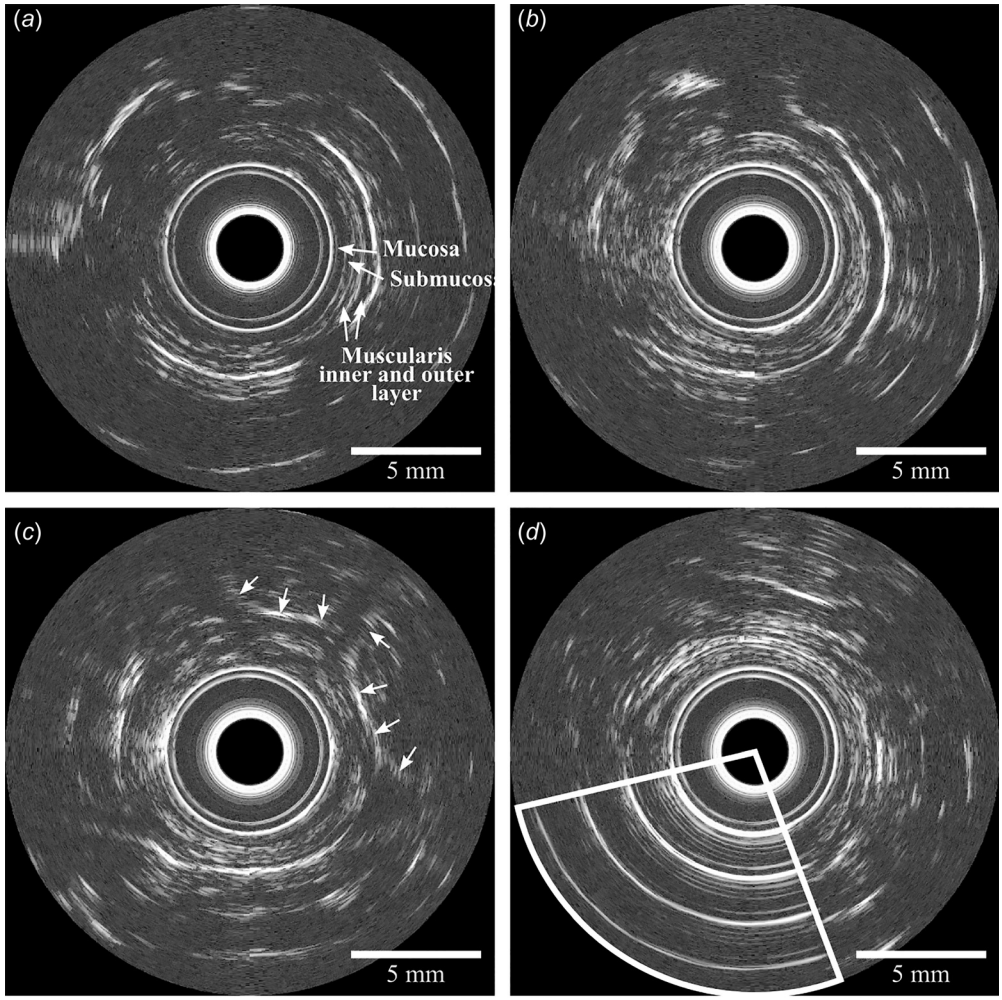

Fig. 7 B-mode images of in vivo (*a*) and (*b*) esophagus and (*c*) and (*d*) small intestine with 60 dB dynamic range. (*a*) and (*b*) show good circumferential visualization around the capsule identifying different layers of the esophageal wall. Layers of intestinal wall can be visualized in (*c*) and (*d*) as well. (*c*) shows visualization of other loops of intestine marked by the black arrows. (*d*) shows an example of air or gas pockets in the intestine that causes reverberation from the capsule cover as marked by the white arc.

tract, is necessary. This is, of course, assuming that the capsule travels only longitudinally through the GI tract, which is not necessarily a valid assumption, given that the capsule travels uncontrolled via peristalsis and that it is known from WCE that the capsule can also tumble. While the effect of peristalsis on acoustic coupling was studied in this work, its effect on the capsule movement and the coverage could not be studied here. While it is critical to study the effect of peristalsis on capsule movement and the resulting images and coverage, important hurdles such as the tether need to be resolved.

The ability of UCE to examine the deeper structure within the intestinal wall provides important additional information to WCE. Combining optical imaging of WCE and ultrasound imaging of UCE can help tackle some of the challenges discussed in this work. Having optical images to help localize the acquired ultrasound images will help aid reconstruction. However, incorporating both imaging modalities increases system complexity as well as power and space requirements.

Ultrasound capsule endoscopy is an exciting technology, but there are significant yet interesting challenges both in terms of technology and clinical utility. On the technology front, one of the most important tasks is developing components such as transducer, electronics, antenna, and battery that can fit inside a small capsule whose maximum size is essentially fixed by human anatomy and physiology. Also, it is critical to keep the cost of the device low enough to make the device disposable. While these are challenging problems, lessons learned from WCE as well as other capsule devices could help tackle these challenges for UCE. However, even when the technological issues are completely resolved, it is still unclear whether the issues associated with visualization and coverage can be overcome to allow UCE to be a useful clinical tool. We believe that the promising results from the imaging studies performed in this work warrant further studies to assess these issues in depth and work toward innovative solutions to tackle them.

Conclusions

In this paper, we developed a prototype for UCE and performed ex vivo and in vivo imaging studies in a large animal model. Imaging done in pig esophagus and small intestine demonstrated that adequate acoustic coupling can be achieved through peristalsis of the GI tract. The study also highlighted important challenges faced by the UCE technology, including significant variation in the level of visualization depending on the relative position of the capsule and the tissue as well as limited area of coverage due to the nature of B-mode ultrasound imaging.

While the concept of UCE is not new and some initial work on technology development has shown promising results, there have been limited studies of challenges outside of technology

development. The novelty of this work is that this was the first in vivo imaging study to our knowledge that utilized a realistic imaging device allowing the evaluation and identification of some of the key issues and challenges faced by UCE technology. The experiments performed in this work not only showed promise, but also identified several important challenges and questions that could not be answered as of yet, mainly due to the technological challenges. As the technology continues to develop and mature, the questions raised in this work need to be further investigated in depth in order to be able to draw a definitive conclusion about the feasibility and potential clinical utility of UCE technology.

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