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Simultaneous white light and laser speckle contrast imaging for *in-vivo* blood flow imaging during laparoscopic surgery: An alternative to fluorescence-based endoscopy

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ABSTRACT

Real-time intraoperative blood perfusion monitoring is an important aid for avoiding the anastomotic leaks (AL) in laparoscopic ('keyhole') surgery which in turn reduces patients' length of hospitalization and healthcare cost. The occurrence of AL at the rate of 11% to 15% (in rectal surgery, AL also varies with the surgical site) is a burden to patients and the healthcare system. Visualization of intraoperative surgical regions of interest is conducted by intravenous injection of the fluorescent contrast agent - indocyanine green (ICG). However, intravenously ICG administration is limited by non-linear fluorescence intensity with concentration, risk of an allergic reaction, and aggregation in aqueous solution. The fluorescence persists limits the frequency of repeated imaging and real-time assessments. Therefore, an alternative approach allowing label-free visualization would be advantageous. To this end, laser speckle contrast imaging (LSCI) is a potential alternative technique for real-time, label-free, and full-field blood flow monitoring techniques. We have developed a prototype medical device using a commercial rigid endoscope that allowed simultaneous white light imaging as well as blood perfusion monitoring using LSCI. The prototype was assessed for simultaneous white-light endoscopy and flow-monitoring of objects, such as; colored cardboard, a motility standard, occluded fingers, and oral mucosa of the human mouth - all positioned at various distances (e.g., 50mm, 70mm, and 100mm) from endoscope tip. We envision that this bimodal, label-free prototype allowing simultaneous blood flow measurement and white light imaging capability will prove a valuable tool for laparoscopic surgeries.

Keywords: ICG, Blood perfusion, Anastomotic leak, Laser speckle contrast imaging (LSCI), Laparoscopic surgery, Medical device.

1. INTRODUCTION

Laparoscopic surgical intervention are preferred choices by clinicians wherever feasible because of minimal incision and shorter post-surgery hospitalization compared to open surgery. Postoperative outcomes depend on several factors: good surgical technique, duration of surgery, open or laparoscopic surgery, blood transfusion and patient health.[1] A major adverse event following gastrointestinal surgery is anastomotic leakage (AL); tissue ischemia at the anastomosis site is an important contributing factor. The greater the tissue microcirculation at the surgical site, the faster the healing process[2]. Anastomotic leakage (AL) is a major problem with reported occurrence rate ranging from 11%-15% in rectal surgery that will vary depending on the type of surgery and the site of anastomosis[3-5]. These high rates lead to prolonged hospitalization of patients and fatality in some case[4]. The choice of an optimal site for the anastomosis is based on subjective clinical indicators such as the bleeding of the edges of resected margins and palpable pulsations of mesenteric arteries. Currently, the only perfusion assessment technique in frequent use in laparoscopic surgical procedures is indocyanine green (ICG) fluorescence imaging [3-5].

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There are several ICG based commercial laparoscopic systems available on the market with advanced features for simultaneous white light imaging and perfusion assessment. For example, PINPOINT endoscope NIR fluorescence imaging system from Styker,[6] which was used for a prospective, multicenter, randomized, controlled, and parallel clinical study for intraoperative perfusion assessment outcomes in left-sided/low anterior resection (PILLAR)[3,4]. From PILLAR III clinical study[4], conducted on 347 patients who underwent resection defined as anastomosis within 10 cm of the anal verge at 25 centers, it was concluded that there was no evidence of additional clinical benefits of routine indocyanine green fluoroscopy for tissue perfusion evaluation in comparison to the standard practice being followed by experienced surgeons.

There are many commercially available ICG based fluorescence-guided laparoscopic surgical (FGS) systems reviewed by DSouza *et. al.*[7] ICG is the United States Food and Drug Administration (FDA) approved contrast agent for human use. The sterile, water-soluble, tricarbocyanine compound is administered intravenously or intra arterially. It absorbs NIR light at 800 nm, and fluoresces at 830 nm. ICG exhibits rapid bonding with lipoprotein in blood plasma and is thus confined to the intravascular compartment with minimal leakage into the interstitium and is excreted by the liver into bile. However, it has limitations such as – nonlinear fluorescence quantum yield vs. concentration, allergy due to presence of sodium iodide in ICG injection and aggregation in aqueous solutions. For example, the estimation of the blood circulation using ICG is determined by its concentration present in the blood plasma; i.e., larger diameter blood vessels will give more intense fluorescence signal than small diameter vessels.

Unquestionably, ICG based laparoscopic medical devices are important developments assisting clinicians with knowledge of tissue blood flow to make intraoperative decisions and procedures more successful. On other hands, LSCI is a non-contact and wide-field qualitative characterization technique that has been extensively used as an imaging tool for blood flow measurements in clinical applications.[8-13] A few noticeable developments on laparoscopic implementation of LSCI for simultaneous color imaging and blood flow imaging were reported. For example, Zheng *et. al.* developed dual-display laparoscopic vision system integrating LSCI with a commercially available 10mm rigid laparoscope but made it relatively bulky by using two separate camera for color imaging and laser speckle imaging, and demonstrated its clinical usability on rat bowel ischemia and pig bowel perfusion study[14]. Meanwhile, Bray *et al*. developed LSCI based laparoscopic system for tissue perfusion of the knee patients requiring arthroscopic knee surgery but was not designed to visualize flows in individual vasculature[15]. To this end, we have developed an alternative bimodal laparoscopic imaging modality that allowed simultaneous real-time white light imaging and label-free perfusion monitoring using laser speckle contrast imaging (LSCI).

2. METHODOLOGY

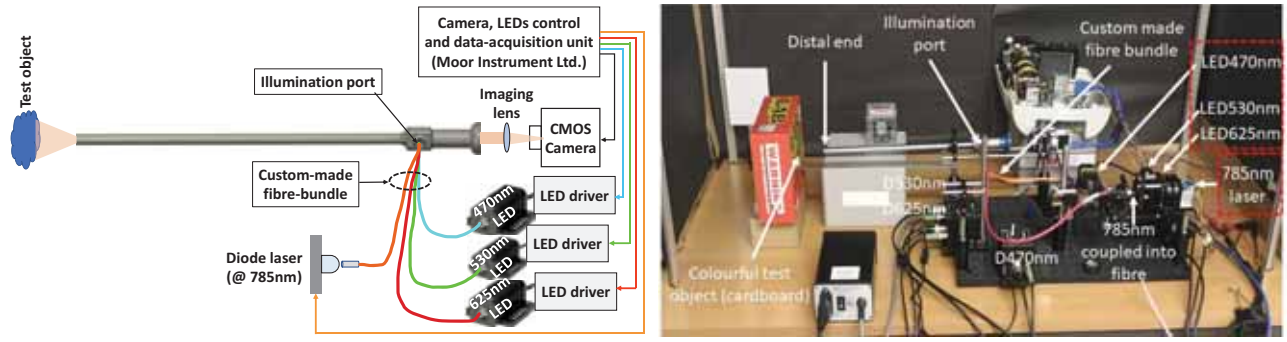
2.1 Background

The fundamental theoretical background behind the laser speckle contrast imaging (LSCI) for flow measurement has its roots linked to Goodman's work[16], followed by first biological application in retinal vasculature imaging by Fercher and Briers[17,18]. Briefly, when a laser light illuminates a scattering object, speckle pattern is generated due to the random interference. The speckle contrast is expressed as the ratio of standard deviation to the mean speckle intensity in a window of pixels (usually 5x5 or 7×7 pixel grids). Within a given integration time, the speckle pattern gets blurred due to movements of the scattering objects, thus decreasing the speckle contrast which gives information about the (relative) motion of objects. The speckle contrast values lies between 0 and 1, where 0 represents the fastest motion and 1 represents no motion (stationary). Camera exposure time and sample dynamics, both affect the speckle contrast and are inversely proportional to the speed of scattering objects.[19,20]

2.2 Experimental set up

Figure 1(a) shows the schematic diagram and Fig. 1(b) is the laboratory view of experimental set up for the bimodal imaging allowing simultaneous real-time white light imaging and contrast-agent-free perfusion monitoring based on Laser Speckle Contrast Imaging (LSCI) principle. The system was developed using 0-degree 10mm diameter rigid endoscope (ERPA, Netherlands), NIR diode laser (785nm, 90mW), customized fibre lightguide, fibre-coupled RGB

LEDs source (M470F3, M530F2, M625F2 from Thorlabs), USB 3.0 CMOS camera and a commercial software (Moor Instrument Ltd.) for controlling the sequential illumination, image acquisition and data processing. Briefly, 785nm diode laser was coupled into multi-mode fibre (Thorlabs) via coupling optics. A custom made lightguide was prepared using four multi-mode fibre which were securely mounted into a 3D printed fibre insert in such a way that RGB light carrying fibers were arranged on the vertices of a triangle and laser carrying fibre was central. The distal end of custom made fibre bundle (light guide) was connected to the illumination port of the endoscope via custom made 3D printed adaptor. The proximal ends of RGB light carrying fibers were connected with respective LEDs sources via SMA connector. The scattered light from sample was imaged into the CMOS sensor via imaging lens (AB coated, Thorlabs). An enclosure was designed using CAD (Fusion 360, Autodesk, USA) and the 3D printed unit allowed to couple the endoscope with camera followed by lens tube in prototype (not shown here). The sequential illumination of RGB LEDs, NIR laser light and their exposure-time was controlled by the commercial software (Moor Instrument Ltd.) and the acquired data was processed for white light and speckle contrast imaging.

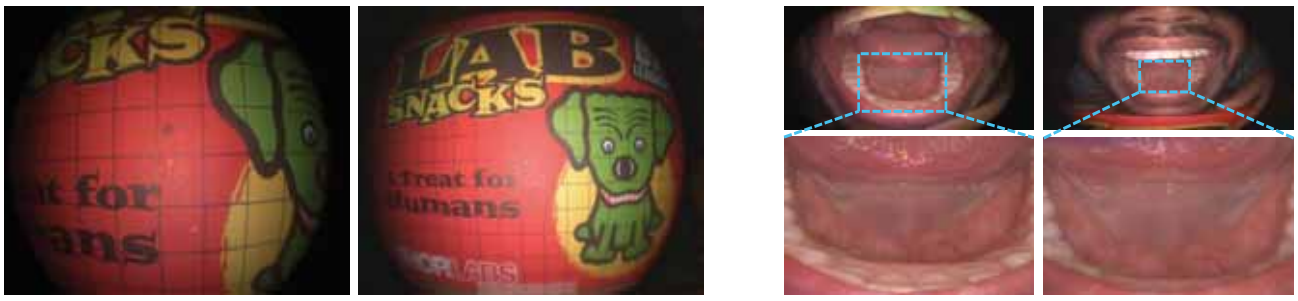


(a) (b)

Figure 1. (a) Schematic diagram, and (b) Laboratory view of the experimental set up of bimodal imaging modality for simultaneous real-time white light imaging and label-free perfusion monitoring based on laser speckle contrast imaging (LSCI) principle.

3. RESULTS AND DISCUSSION

All experimental recordings were carried out within a closed-box/dark-room to prevent ambient light artifacts. The prototype was tested first for white light (color) imaging of colorful region on cardboard (including red, green, blue, yellow, white and black colors) placed at varying distances (i.e., 50mm and 100mm) from endoscope tip as shown in Fig. 2 (a), (b). Then oral mucosa of human mouth, closely mimicking the intra-operative microvasculature, was also imaged as shown in Fig. 2 (c), (d) with zoomed ROIs (dashed-rectangle) below each figure. The driver current of each LEDs source was set in a way to achieve 'cool whitelight' corresponding to 5500K color temperature of chromaticity diagram[21]



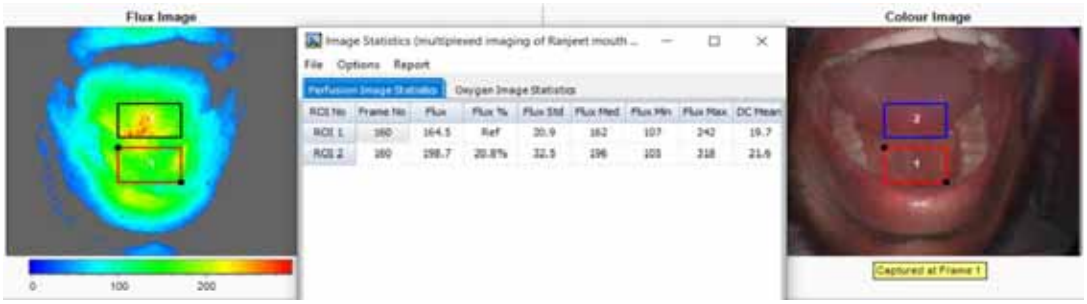
(a) **(b)** **(c)** **(d)**

Figure 2. White light imaging ('cool white light' corresponding to the 5500K CCT) of test objects positioned at two different distance away from the endoscope tip (distal end). Colorful ROI of carboard position at (a) 50mm and (b) 100mm. Human oral mucosa positioned approximately at (c) 50mm and (d) 100mm (with zoomed dashed-rectangle ROI below each figure).

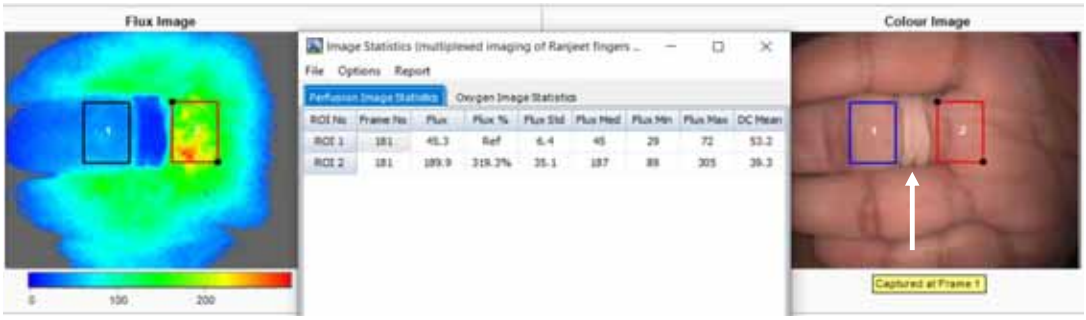
Then prototype was tested for simultaneous speckle imaging (blood perfusion) and white light (color) imaging using different types of test objects. For example; motility standard, human oral mucosa, occluded human finger (dorsal side) as shown in Fig. 3 (a-c), respectively. Before testing with live human specimens for speckle imaging using near infrared diode laser (785nm), it was ensured that the laser power exiting from the distal end should be within the biological safe limit and was measured to 5mW which was further reduced under cross-polarization (wire-grid polarizer, Edmund Optics) arrangement implemented to reduce the glare/back-reflections arising from wet surfaces. In laparoscopic surgeries, generally 50 mm working distance from the distal end is assumed to be fairly sufficient but there is no set standard. The working distance can be further adjusted by retracting laparoscope in-and-out within trocar. Thus, for initial evaluation of prototype, all aforesaid test samples were imaged by placing them slightly more than 50mm away (approx. 70mm). The imaging capability of prototype for other working distances will be investigated in future.

Calibration unit, as a reference object, was shaken well to disperse any sedimentation and then allowed to settle before experimenting with it. Each Figure contains *three* panels. *Left panel* shows the laser speckle contrast image (henceforth known as 'Flux Image', also perfusion image), *middle panel* shows the perfusion image statistics estimated for two ROIs for a particular frame and *right panel* shows the white light image (henceforth known known as 'Colour Image'). The control unit triggered individual LEDs and laser source sequentially, and recorded number of image frames (here 612 frames in case of motility standard). One frame was randomly selected (164^{th}) for the quantification of flux values (in perfusion unit [pu]). The mean flux values from two rectangular (Blue and Red color, inscribed by number '1' and '2', respectively) region of interest (ROI) as shown in the *left panel* of Fig. 3(a) was estimated to 154.0pu and 0.5pu. The details are evident from the statistics in the *middle panel* of Fig. 3(a). The 256 color palette below to each Flux Image in the *left panel* represents the flux values (Blue represents 0pu, and Red represents 300pu). Obviously, the static reflector of calibration unit exhibits flux value 0.5pu which is close the zero as ideally it should be. The very similar procedure was followed for multiplex imaging of human oral mucosa, occluded human fingers (dorsal side) and the results were shown in Fig. 3(b) and (c), respectively. A total 416 frames were recorded for multiplex imaging of human oral mucosa and a particular frame (160^{th}) was used for the estimation of mean flux values from two ROIs (marked by red and blue rectangles with inscribed number '1' and '2', respectively as shown in the *left panel* of Fig. 3(b)) which were found to 164.5pu and 198.7pu, respectively. Finally human fingers (dorsal side) occlusion test was carried out which is shown in Fig. 3 (c). A rubber band was wrapped around finger (marked by arrow) to create temporary occlusion as visible in the right panel of Fig. 3(c). A total 614 frames were recorded and one frame (181^{st}) was used for the estimation of mean flux values. Two ROIs (marked by blue and red rectangles) were selected across the rubber band on occluded finger and the mean flux values were estimated to 45.3pu and 189.9pu, respectively. A very significant difference in blood flow is evident from the perfusion imaging (flux values) of two regions of same finger occluded by rubber band.

(a)



(b)



(c)

Figure 3. Simultaneous blood-flow/perfusion imaging (Flux image, *left panel* of each images) and white light imaging (Colour image, *right panel* of each images) using laparoscopic implementation of LSCI, along with perfusion image statistics (*middle panel*) estimated for two ROIs for a particular frame when different test objects (a) calibration unit, (b) human oral mucosa, (c) fingers with occlusion (dorsal view, occluded finger marked by arrow) were positioned at 70mm away from the distal end.

4. CONCLUSIONS

We have developed a prototype and demonstrated it for simultaneous white light and blood perfusion endoscopy using commercial rigid endoscope and software. A major advantage over current contrast-agent based fluoroscopy techniques is that blood flow can be achieved in real-time in a non-invasive manner, without the requirement to remove white light source from the site of investigation. This modality doesn't require any exogenous contrast agent. Further modifications are ongoing to enhance the imaging capability and for testing it in pre-clinical studies. We anticipate that this bimodal, label-free LSCI prototype enabling *in-vivo* white light and blood flow imaging in real-time will prove a valuable tool for laparoscopic surgeries.

5. ACKNOWLEDGEMENTS

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DECLARATION

Dr. Rodney Gush and industry partner (Moor Instrument Ltd.) have commercial interest in this medical device.

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