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Intraoperative Indocyanine Green Imaging Technique in Cardiovascular Surgery

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1. Introduction

The number of patients with arteriosclerotic disease requiring revascularization surgery such as coronary arterial bypass grafting (CABG) is increasing [1]. In CABG, off-pump CABG (OPCAB) has reduced incidence of operative mortality, which was reported to be as low as 0.6% in the Japanese database of 2009 cases and has enabled surgical treatment for those patients who could not tolerate conventional CABG under cardiac arrest [1]. However, off-pump technique can adversely deteriorate the quality of coronary anastomosis due to technical difficulties, potentially leading to a higher rate of graft occlusion or stenosis [2]. In addition, surgery for peripheral arterial disease (PAD) has become more complicated due to an increasing number of patients with longer period of chronic renal failure [3]. They often necessitate revascularization surgery to the paramalleolar arteries.

In both groups, quality of anastomosis affects the prognosis: an inadequate graft perfusion in CABG deteriorates cardiac function while that in PAD patient may lead to an amputation of ischemic limb. Graft patency and quality of anastomosis has been evaluated postoperatively by means of fluoroscopic angiography or computed tomography angiography (CTA). However, a redo surgery for restoring an adequate perfusion based on these assessment has a higher risk compared to the primary surgery, and thus intraoperative assessment of graft is desirable. Since intraoperative coronary angiography (CAG) is not necessarily feasible unless hybrid operating room is equipped, transit time flowmeter (TTF) has been employed [4, 5]. However, it does not provide morphological information and some alternative to fluoroscopic CAG is anticipated. Indocyanine green (ICG) angiography could be an alternative.

Intestinal ischemia remains a devastating complication in vascular surgery, especially in surgical repair of abdominal aortic aneurysms (AAA) [6, 7]. The incidence of intestinal ischemia in elective surgery for AAA and emergency surgery for ruptured AAA is reported to be 6% and 42%, respectively [6, 7]. In cases of suspected intestinal ischemia, however, it is not easy to make a treatment strategy of either revascularization or intestinal resection based on the inspection and digital palpation. ICG imaging system may provide another useful clue for decision-making [8].

In this chapter, basic principles to the clinical applications of ICG imaging in cardiovascular surgery are described [9].

2. Property of ICG

Indocyanine green is a hydrophilic tricarbocyanine dye that rapidly binds to plasma proteins in the body and is mostly incorporated to the liver and excreted in the bile [10]. As ICG in the blood is exposed to near infrared ray of 760- 780 nm wave length, it generates fluorescence of 800 - 850 nm wave length (Figure 1A, B) [10, 11]. Our preliminary study showed that the peak spectral absorption of ICG diluted in the human blood was at 760 - 780 nm (Figure 2) [12]. The amplitude of ICG fluorescent luminescence is not proportional to its concentration but is highest at the ICG concentration of 2.5×10^{-3} mg/mL.

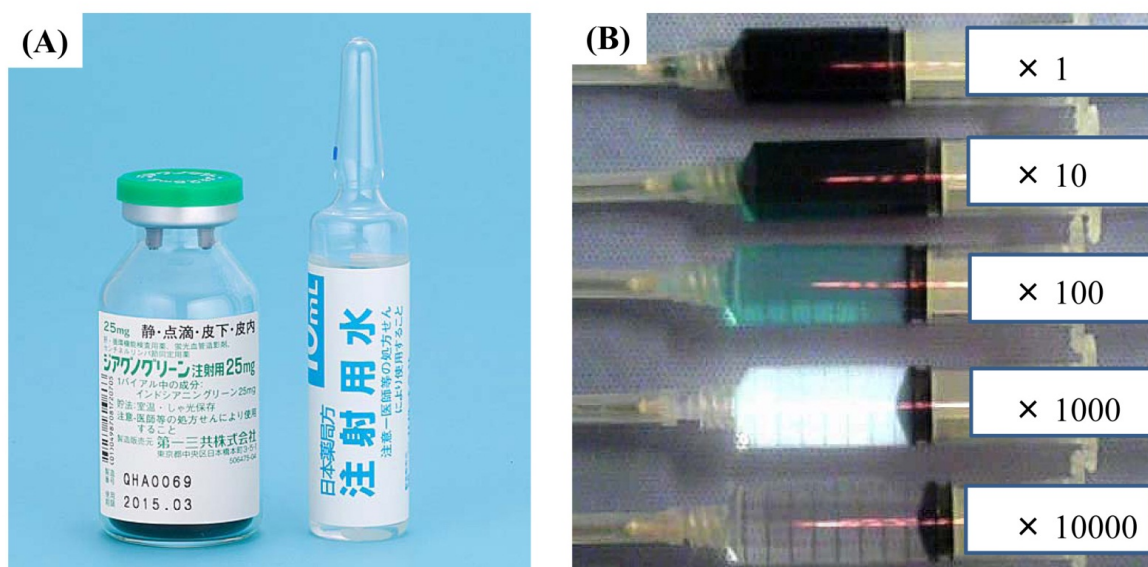


Figure 1. ICG and fluorescent luminescence in various dilution. A: drug product of ICG (Diagnogreen™; DaiichiSankyo Co., Tokyo, Japan). B: Fluorescent luminescence is not proportional to its concentration. The luminescence was highest at a concentration of 2.5×10^{-3} mg/mL.

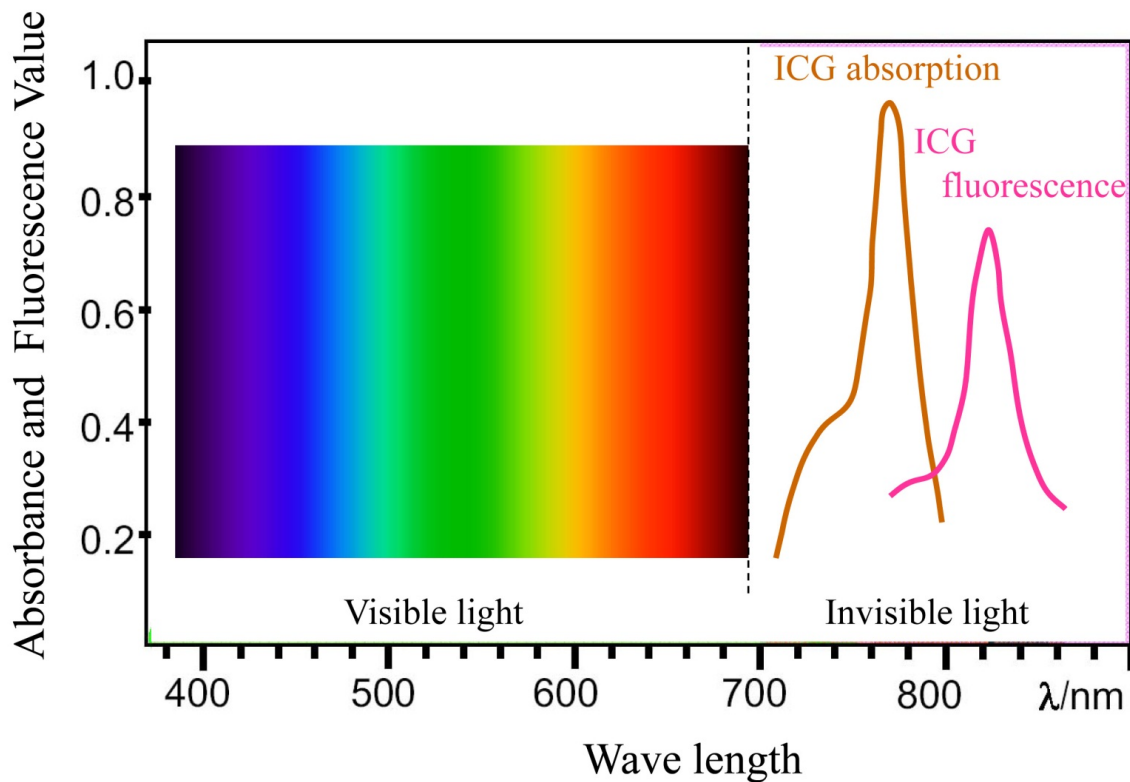


Figure 2. Absorbance and fluorescence value of ICG. ICG emits a flash of light with a wavelength of 806nm. The peak spectral absorption of ICG diluted in human blood is 760 - 780 nm.

3. ICG angiography

Fluorescence property of ICG has been used not only in ophthalmology as fluorescein fundus angiography to visualize retinal and choroidal circulation but for breast cancer surgery (sentinel node mapping), gastroenterological surgery, and cardiovascular surgery [8, 13, 14]. Following intravenous injection of ICG, fluorescence generated in the blood by near infrared light is captured by a camera and the vessels are visualized, although fluorescence is partially absorbed by the water and hemoglobin. This principle was applied to the commercially available intraoperative imaging system, SPY™ (Novadaq Technologies Inc., Toronto, Canada) and Photodynamic Eye (PDE; Hamamatsu Photonics K.K., Shizuoka, Japan) [15, 16]. The PDE enable to image with a hand-held camera in the surgical

field. These devices visualize the blood flow clearly in monochrome imaging under irradiation of excitation light after ICG injection. The former emits a low-intensity laser (2.7 watts) and demonstrates angiographic image at a frame rate of 30 per second. They allow irradiation and recording time for up to 34 seconds but demonstrate the vessels in monochrome image. These systems have been applied to coronary and graft angiography [17] and peripheral arterial surgery [18].

4. Characteristics of ICG angiography

ICG angiography has several advantages. First, it can visualize arterial blood flow by intravenous injection of ICG without catheter manipulation or contrast agent. Second, stenotic portion can be visualized like fluoroscopic angiograms. Third, it takes only ten minutes from preparation to imaging.

However, ICG angiography systems mentioned above have several drawbacks. First, they use laser light source, and the time duration for irradiation is limited to 35 seconds because of the danger of thermal injury. Second, the angiograms are shown in monochrome, making it difficult to recognize the color of tissue. Third, penetration of fluorescence is poor and vessels in the deep layer is hardly visualized.

We have developed a new ICG imaging system, HyperEye Medical System (HEMS, Mizuho Co., Tokyo, Japan) to solve these problems (Figure 3) [9, 12]. It is composed of an imaging unit, a control unit and a monitor. The imaging unit consists of multiple light-emitting diodes (LEDs) which is allocated around an ultra-sensitive color charged-coupled device (CCD) imaging camera with non-Bayer color filter arrays (HyperEye Technology; SANYO Co., Ltd, Tokyo, Japan). This camera detects near infrared rays (380-1200 nm) and visible light at 30 frames per seconds. The control unit is composed of a personal computer and a controller for recording and adjusting the focus, iris and range of imaging.

HEMS can demonstrate the fluorescent images on the background of natural color (Figure 4), which facilitates surgeons to recognize the vessels in the surgical field [12]. Unlimited recording is another advantage of this system because it uses LEDs as the light source. The imaging head is draped by a sterile cover and is placed at 30 to 50 cm above the targets (Figure 5A). The illumination area is approximately 78.5cm² (5 × 5 × 3.14cm) on the surgical field. A 5mg of ICG (Diagnogreen™, DaiichiSankyo Co., Tokyo, Japan) dissolved in 2 mL of distilled water is injected via a central venous catheter and is flushed by 10 mL of saline per each imaging sequence (Figure 5B) [19]. The right atrium immediately glows white, then right ventricle and pulmonary artery, followed by ascending aorta and the coronary grafts as well as native coronary arteries. Cardiac output affects the time lag of opacification. The images are recorded using a digital image-processing system such as audio video interweave (AVI) or Smart Draw (SDR) format.

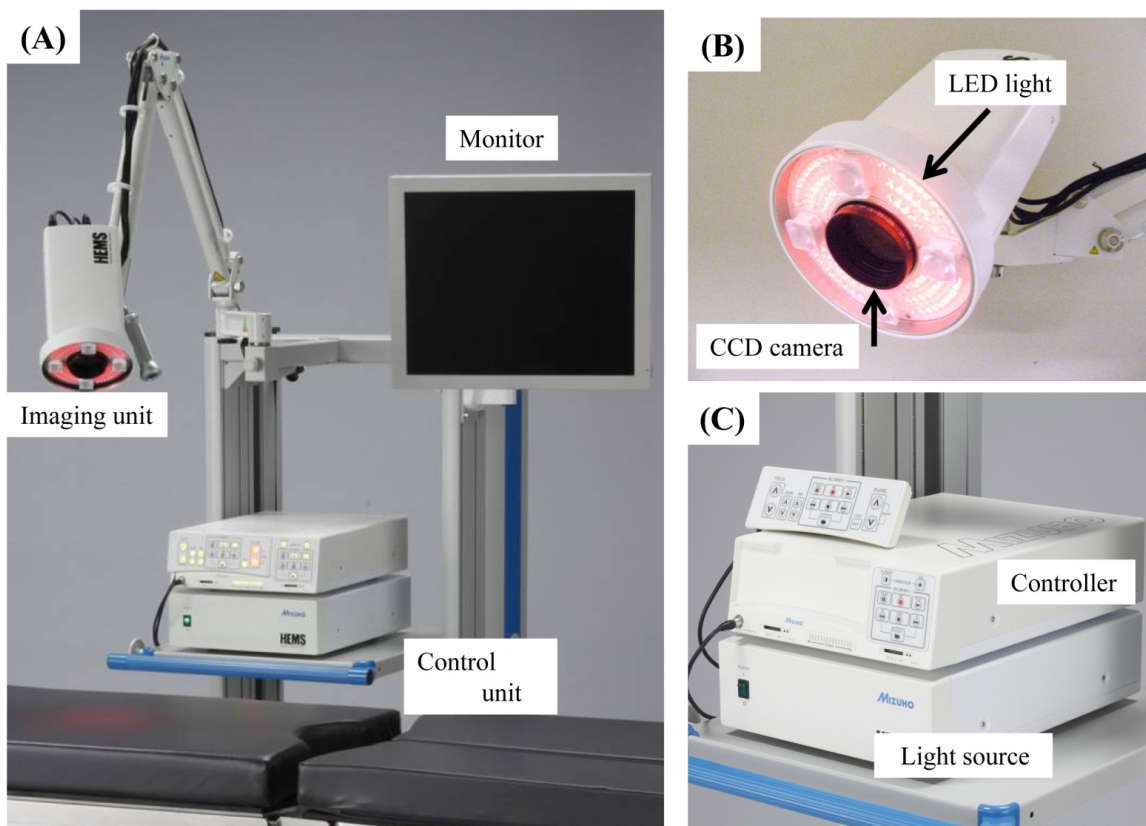


Figure 3. HyperEye Medical System (HEMS) A: Full view of HEMS, composed of imaging unit, control unit, and monitor. B: The imaging head consists of multiple light-emitting diodes (LED) and an ultrasensitive color charge-coupled device (CCD) camera. C: Control unit consists of controller and analyzing system.

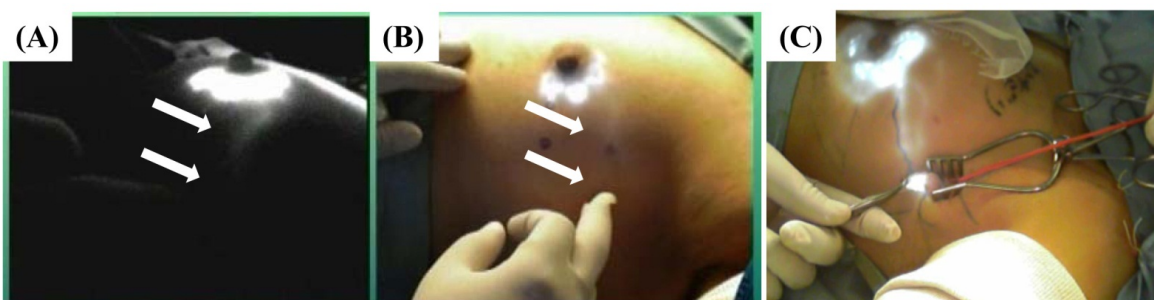


Figure 4. Sentinel node mapping in breast cancer surgery. The ICG stream in lymphatic duct is observed from subareolar to the axillar lymph nodes after ICG injection to subcutaneous of areolar. A: Fluorescence emitted from ICG injected in the breast. The lymphatic duct is identified as fluorescence line (arrow). B: The ICG stream in lymphatic duct. C: ICG in the axillar lymph nodes. The sentinel lymph node is identified as strong fluorescence leading out of lymphatic duct.

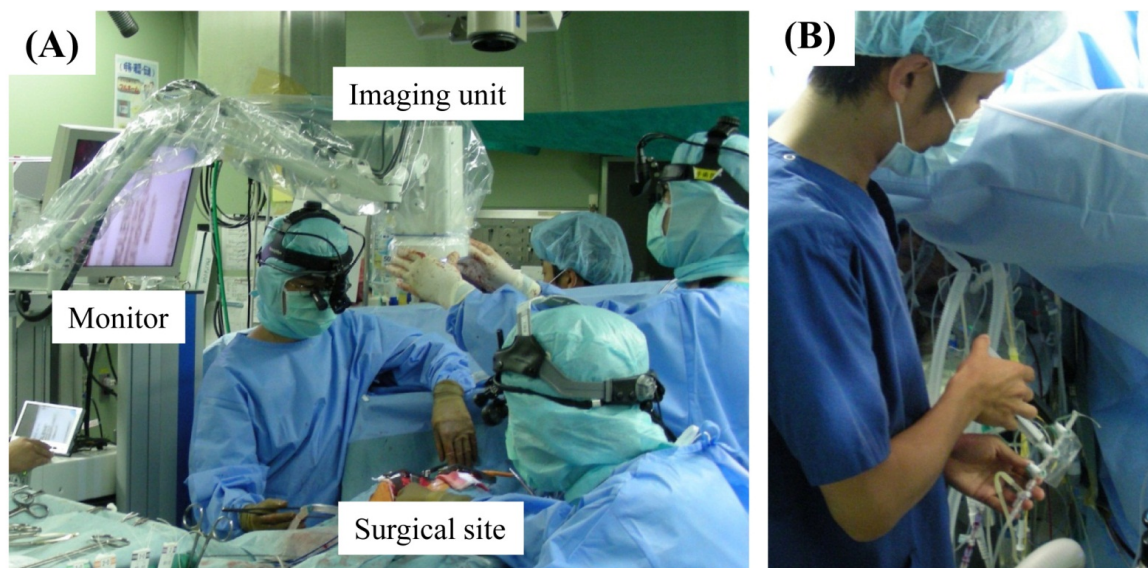


Figure 5. HEMS in use during cardiac surgery. A: The imaging head is draped by a sterile cover and placed at 30 to 50 cm above the targets. B: ICG solution is injected via a central venous catheter.

5. Application of ICG angiography in CABG

Since the first report of intraoperative ICG coronary angiography by Rubens et al. and Detter et al. in 2002, usefulness of this modality have been reported by several investigators (Table 1) [5, 12, 16, 17, 20-22]. Reuthebuch and Taggart showed the clinical utility of the SPY system for assessment of the quality of bypass grafts of usage from experience [20, 21]. Takahashi et.al. described the verification of ICG angiography with using the SPY imaging system [16].

TTF (MediStim AS, Oslo, Norway) has been used as well in CABG for intraoperative assessment of coronary graft [23]. The time for ultrasound beam to travel from one crystal across a vessel to another crystal is called as transit time. In TTF, the graft flow is assessed by three parameters: mean graft flow, pulsatility index, and diastolic filling percentage. Desai et al. researched the utility of two intraoperative assessments of graft, TTF and ICG graft angiography [24]. A total of 139 grafts were reviewed and the sensitivity and specificity of ICG angiography to detect greater than 50% stenosis or occlusion were 83.3% and 100%, respectively. When TTF shows an unusual data, however, imaging modality may be helpful for making treatment strategy.

Investigators	Year	Patients	Graft No	Sensitivity	Specificity
Rubens	2002	20	-	-	-
Reuthebuch	2003	38	124	-	-
Taggart	2003	84	213	-	-
Balacumaraswami	2004	200	533	-	-
Takahashi	2004	72	290	-	-
Desai	2006	46	139	83.3	100
Handa	2009	39	116	100	100
Handa	2010	51	129	85.7	100

- : not shown, ICG: indocyanine green, CABG: coronary artery bypass grafting

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Table 1. Reported clinical studies on the indocyanine green imaging system in coronary artery bypass grafting

We have assessed coronary grafts by means of HEMS since 2007 and have classified the flow pattern as follows [12].

1. Normal flow: smooth opacification of the graft and then coronary artery (Fig 6A).
2. Abnormal flow:

Delay: delayed graft enhancement compared to other grafts (Fig 6B)

Occlusion: no enhancement of the graft (Fig 6C)

The results of HEMS assessment were compared with fluoroscopic CAG one year after CABG and have found that the former accurately predicted the outcomes of grafts (Figure.6D-F). [12]. Thus, visualization of graft flow is helpful for surgeons to make decisions of revision in the operating room.

Visualization of myocardial perfusion is another feature of HEMS. Figure 6C shows an obstructed anastomosis in the left internal thoracic arterial graft, causing perfusion defect in the anterior wall around the anastomosis, whereas myocardium in the diagonal region is well opacified. Detter et. al. reported that myocardial perfusion can be quantitatively assessed by ICG angiography with digital image processing system [25].

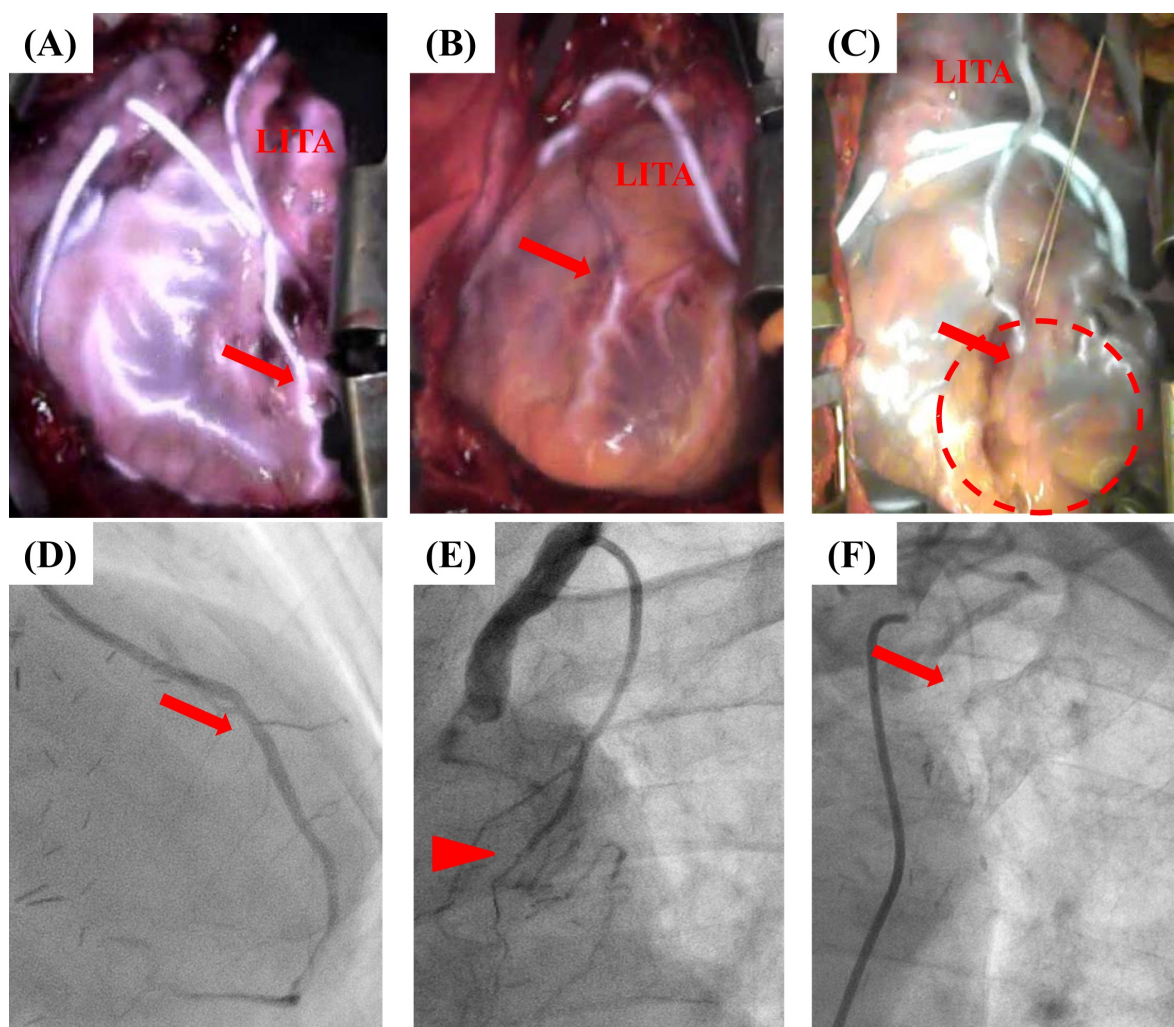


Figure 6. HEMS assessment of coronary arterial grafts. Coronary arterial bypass grafts images created by HEMS (A-C) and fluoroscopic angiography (D-F). Arrows indicate coronary anastomoses, arrow heads indicate occluded point of graft. A: Smooth opacification of graft and distal coronary artery. B: Delayed graft flow. C: Absence of fluorescence in the left anterior descending artery (LAD) despite of opacification of left internal thoracic artery (LITA) graft. There was perfusion defect in the anterior myocardial wall (circled dot line), while myocardial perfusion in the diagonal region is apparent. D-F: Fluoroscopic coronary angiography corresponding to A to C, respectively.

6. Application to peripheral arterial surgery

HEMS has been also applied to peripheral arterial surgery for assessing the blood flow in the saphenous vein graft anastomosed to the paramalleolar artery [19]. Blood flow in vascular prosthesis such as Dacron or Polytrafluoroethylene (PTFE) graft cannot be assessed due to poor penetration of fluorescence (Figure 7). Although there are varying time delay from ICG injection to opacification of graft, assessment of arterial graft via intravenous ICG injection is an advantage of HEMS. Since the target (graft) is immobile unlike coronary angiography, the image is clear despite a long distance from the injection site [18, 19].

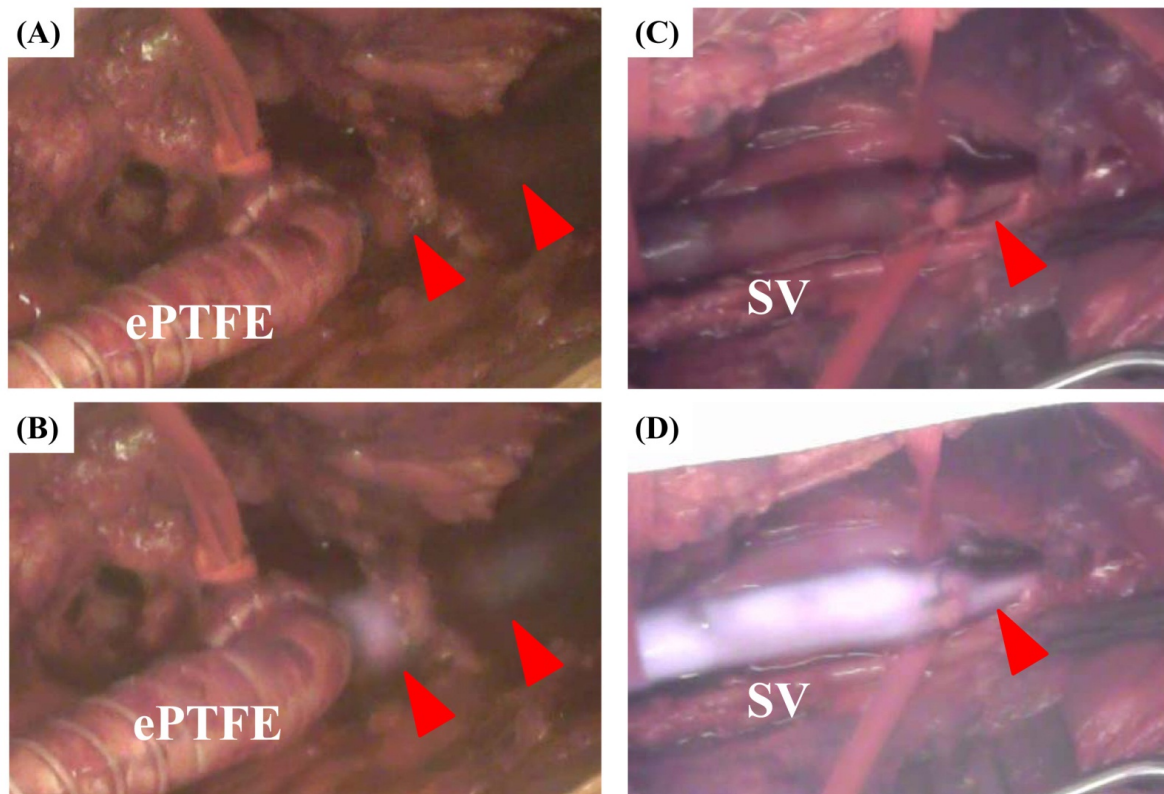


Figure 7. HEMS assessment of graft in peripheral arterial surgery. Visual image and ICG angiogram in ePTFE graft (A,B) and saphenous vein graft (C, D). Opacification is poor in PTFE graft. PTFE: polytetrafluoroethylene. SV: saphenous vein. Arrow heads show native peripheral arteries.

Figure 8 compares the intraoperative HEMS image and postoperative CT angiogram in a case of arterial revascularization. The blood flow through the anastomosis was smooth (Figure 8A) and there was no stenosis at the anastomosis by CTA (Figure 8B). Figure 9 demonstrates the data of a case who underwent bypass grafting to the posterior peroneal artery (PTA) with a saphenous vein graft [19]. HEMS revealed an inadequate blood flow in the PTA distal to the anastomosis (Figure 9A), although TTF showed fairly acceptable graft flow (7 mL/min of mean flow: Figure 9B). Based on the HEMS findings, an additional bypass to the PTA was placed with a saphenous vein graft. HEMS following additional grafting showed smooth flow in the graft as well as in the PTA distal to the anastomosis (Figure 9C). The TTF assessment showed doubled graft flow (15 mL/min, Figure 9D). Since the TTF data can be largely affected by hemodynamic condition as well as peripheral perfusion area, it is not easy to make reliable TTF criteria. HEMS may be helpful for making a decision in such instances.

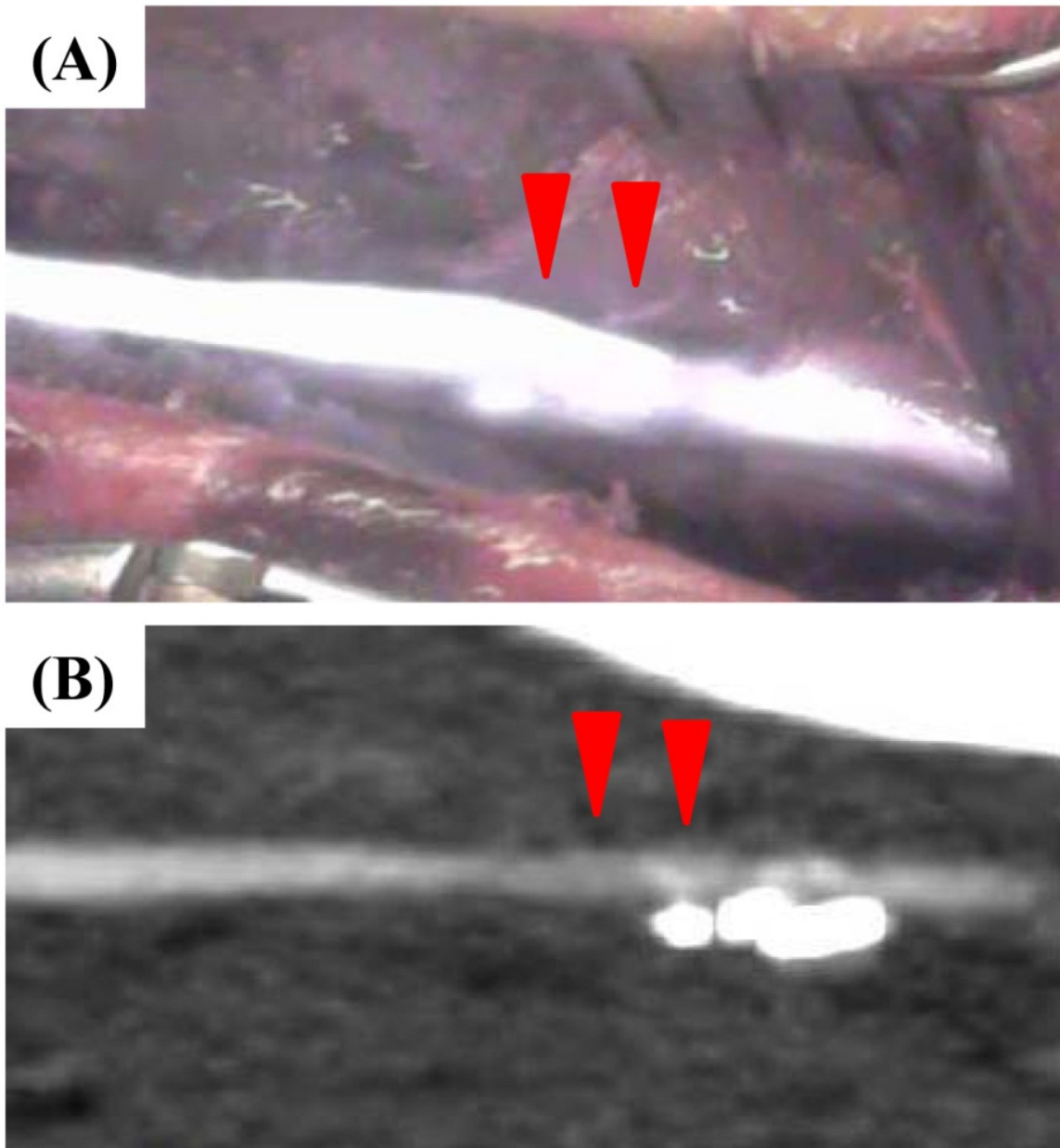


Figure 8. Intraoperative ICG angiogram compared with postoperative CT angiogram. The patient underwent femoro-tibial arterial bypass with saphenous vein graft. A: ICG angiogram of femoro-tibial arterial bypass with saphenous vein graft. Blood flow through the anastomosis is smooth. B: The CTA showed there was no anastomotic stenosis.

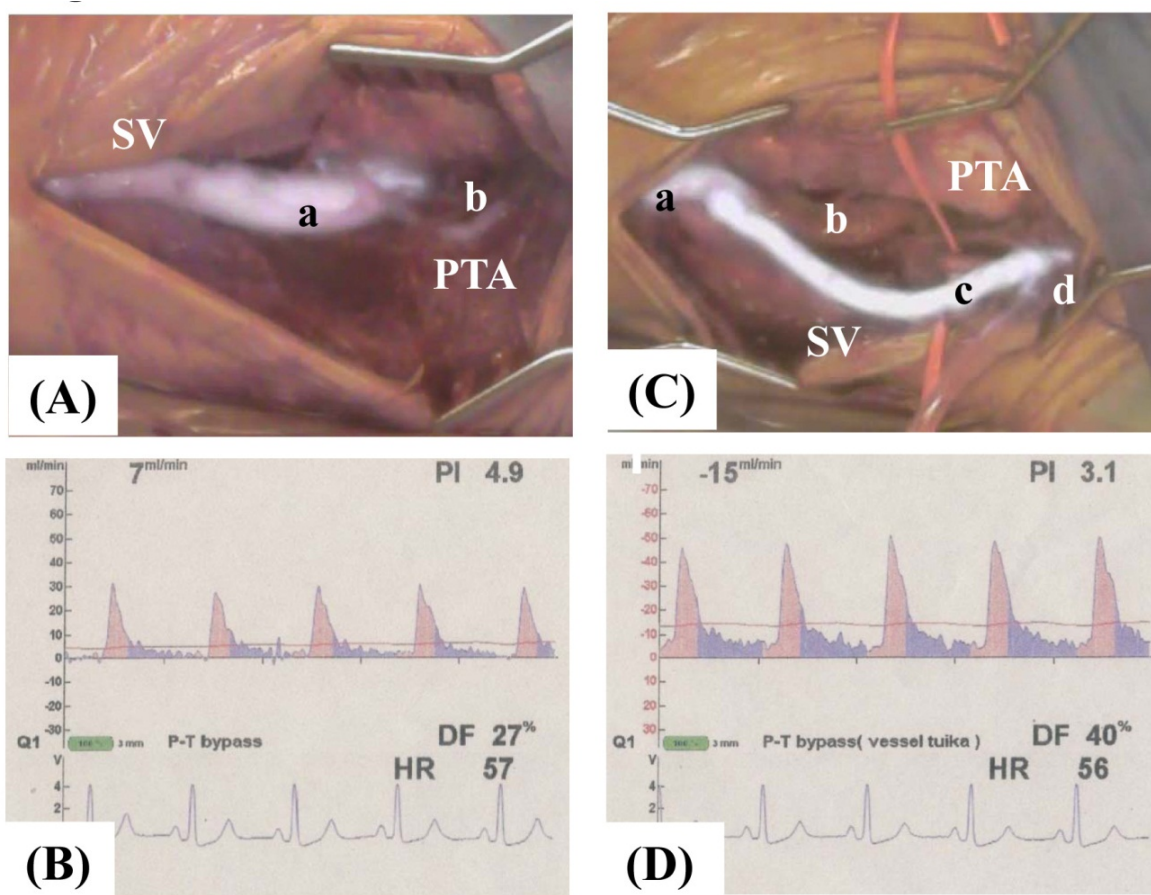


Figure 9. HEMS assessment and transit time flowmetry (TTF) data in peripheral arterial surgery. A: HEMS image of saphenous vein (SV) graft which was anastomosed to the posterior tibial artery (PTA). Fluorescence is poorly detected in the PTA (b). B: TTF data showing graft flow in the initial bypass (a). C: An improved flow in HEMS assessment in additional SV (c) as well as in the PTA (d). D: TTF data showing doubled graft flow after revised bypass (c). (Reprinted from Eur J Vasc Endovasc Surg 2012; 43:426- 432)

7. Application to AAA surgery

Intestinal ischemia is one of undesirable complications in AAA surgery. It can be well demarcated caused by embolism of mesenteric artery or poorly demarcated in diffuse malperfusion. HEMS is capable of visualizing the blood flow in the mesenteric artery as well as tissue perfusion in the intestinal wall (Figure 10) [9, 19]. The mesenteric artery is opacified first, then marginal artery, and illuminescence sequentially spreads to the entire intestines and colon, but slightly delayed in the sigmoid colon, probably because inferior mesenteric artery arises at the most distal portion of the aorta.

Bowel necrosis can develop under markedly reduced perfusion despite the presence of detectable blood flow in the mesenteric artery [19, 26]. Assessment of tissue perfusion such as intestinal wall appears to be a unique and advantageous feature of HEMS which allows a longer duration for imaging.

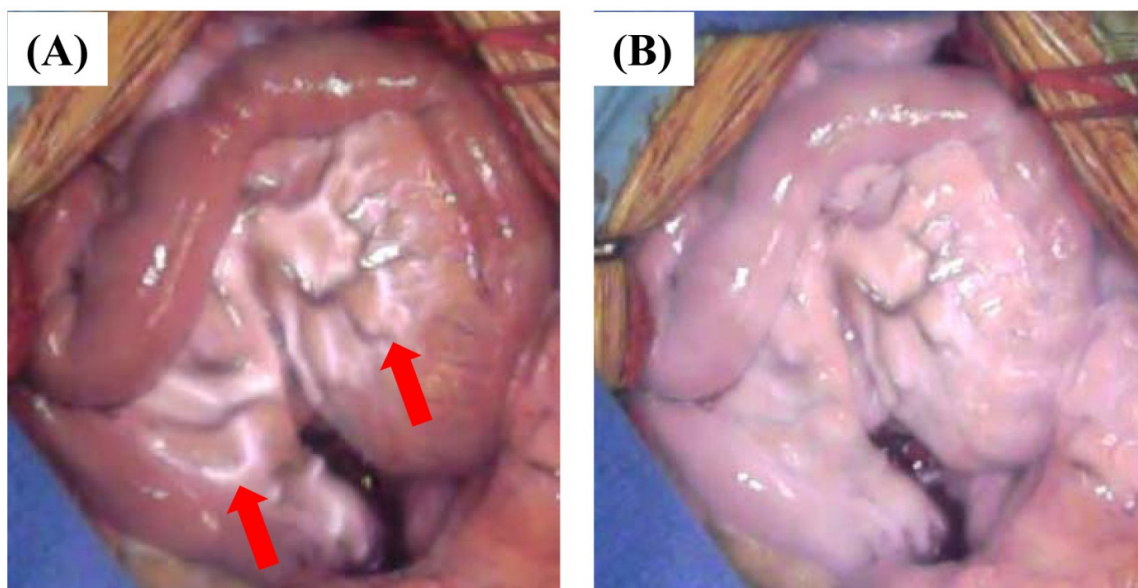


Figure 10. HEMS images showing sequential mesenteric perfusion. A: Fluorescence appears first in the mesenteric arteries (arrow). B: The entire mesenterium and intestinal wall is opacified. (Reprinted from *Eur J Vasc Endovasc Surg* 2012; 43:426- 432)

Champagne et al. reported the incidence of ischemic colitis following surgery for ruptured AAA as 42% [27]. Shock status in the preoperative period is the most important predictor of ischemic colitis [28]. Although resection of necrotic intestine and colon is necessary to rescue the patients, it is not easy to determine the extent of resection by visual inspection. Figure 11 shows the corresponding images of inspection and HEMS images in two cases. Figure 11A shows the appearance of intestine in an 85 year-old woman who underwent emergent surgery for ruptured AAA. HEMS revealed malperfusion in the sigmoid colon (Figure 11B). Figure 11C is the visual finding of an 80 year-old woman after transient hypotension during AAA surgery. The intestine appeared to be diffusely malperfused in spotty fashion (Figure 11C). HEMS showed spotty malperfusion of intestinal wall (Figure 11D). ICG opacification in addition to the color image of surgical field facilitates to precisely locate the ischemic region [19].

8. Limitation of ICG angiography

Despite the advantages of HEMS, quick and less invasive assessment without contrast agent as well as assessment of tissue perfusion superimposed on the color views [9, 19, 29], it also has several limitations to be noted.

First, penetration of fluorescence is less than 2 to 3 mm and visualization of blood flow is limited to the superficial portion of the vessel and tissue [25]. The coronary artery covered with adipose tissue or hemostatic stuff cannot be visualized clearly.

HEMS does not provide the projectional image as in fluoroscopic angiography but the en-face view of superficial layer. Therefore, densitometric analysis for assessing the severity of stenosis is not feasible.

The intensity of brightness is not absolute but rather relative. Furthermore, HEMS assessment can be affected by hemodynamic status such as blood pressure or cardiac output. Therefore, the results cannot be simply compared among individuals.

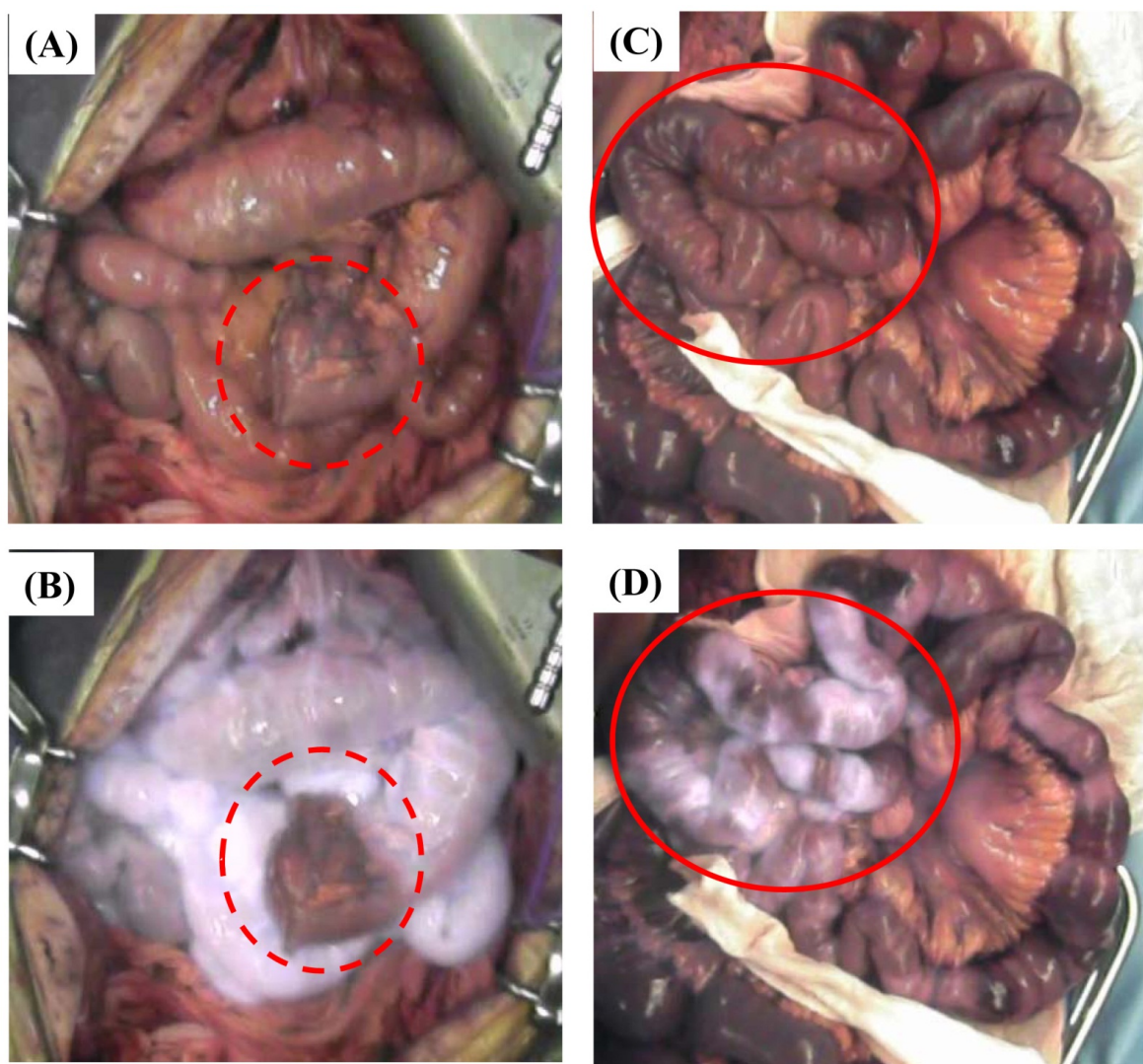


Figure 11. HEMS images showing intestinal ischemia. A,B: Segmental ischemia in the sigmoid colon in an 85 year-old female patient who underwent emergent surgery for ruptured abdominal aortic aneurysm (AAA). The sigmoid colon appears slightly ischemic in visual inspection (A) but is apparent in ICG angiograms (B). C,D: Diffuse and spotty ischemia in an 80 year-old female patient after transient hypotension during AAA surgery. (Reprinted from *Eur J Vasc Endovasc Surg* 2012; 43:426- 432)

9. Future prospects of HEMS

Despite the qualitative nature of HEMS assessment, we have ambitiously attempted more quantitative analysis of data obtained in peripheral arterial surgery and AAA surgery [19]. The transitional changes of intensity appear to indicate the smoothness of graft flow or tissue perfusion, although further investigation is necessary.

TTF is likely to reflect another aspect of graft function which is different from that obtained in HEMS. The combination assessment may be useful for assessing the graft with higher sensitivity and specificity compared to each single assessment.

10. Conclusion

HEMS is a simple, safe, and reliable imaging tool for intraoperative assessment of blood flow. It enables intraoperative assessment in surgical treatment for ischemic heart disease, peripheral arterial disease, or abdominal aortic aneurysm and may facilitate to optimize the surgical outcomes by detecting unexpected trouble and alerting additional revision or intervention.

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