# Cerebral Angiography (Cerebral Aneurysm)

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**Summary**

- Intraoperative ICG videoangiography (ICGVAG) is useful to confirm the occlusion of cerebral aneurysms and patency of bypass vessels.
- Semi-quantitative analysis based on the brightness of the region of interest (ROI) and its time trend remains a problem to solve.
- Surgeons should understand the characteristics of each microscope instrument and the limitations of ICGVAG.

## 1 Introduction

In this chapter, we first describe how indocyanine green videoangiography (ICGVAG) came to be used in neurosurgery. Intraoperative indocyanine green (ICG) imaging for cerebrovascular surgery, which was covered by insurance in 2016, has become an essential intraoperative examination for neurosurgeons throughout Japan, and we have accumulated more than 700 cases. We introduce here the improvement of the accuracy of the anatomical understanding and the quantitative evaluation of blood flow in the observation by various methods, based on the previous reports.

## 2 Development History of Indocyanine Green Videoangiography

Indocyanine green was a fluorophore approved for clinical use by the U.S. Food and Drug Administration (FDA) in 1956. Among a variety of applications, ICG was first used for the assessment of blood flow in ophthalmology (fundus and retinal angiography) at the outpatient level since the 1970s and in vascular surgery since around 2002. Since the initial experience of ICG videoangiography in the field of neurosurgery in 2003 [1], this technique has widely been used with the term "ICG videoangiography," because fluorescence images are usually recorded and assessed quantitatively with a microscopic imaging system [2–4]. The use of ICG videoangiography in cerebrovascular surgery is similar to fundus/retinal angiography in that blood flow in the target vessels can be visualized in real time within 1–2 minutes after intravenous injection of ICG.

In the first report of ICGVAG in the field of neurosurgery, a quite primitive imaging system in which an infrared light filter was attached to the lens of a consumer video camera was used [1]. However, the simplicity of their imaging techniques as well as the principle of on-site angiography greatly appealed to neurosurgeons so that the ICGVAG system was quickly installed in various surgical microscopes around the world. I myself witnessed the world's first clinical study of a microscope in which this system was installed while studying in the USA in 2005 and remember being shocked by the simplicity and minimally invasive nature of ICGVAG. I also had the opportunity to use the Carl Zeiss PENTERO® 900 microscope equipped with ICGVAG for the first time in Japan and to make an initial report. Since then, almost all surgical microscopes, endoscopes, and exoscopes used in the field of neurosurgery have been equipped with the ICGVAG system [5].

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/978-981-19-7372-7_9.

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T. Ishizawa (ed.), *Fluorescence-Guided Surgery*, https://doi.org/10.1007/978-981-19-7372-7_9

## 3 Advantages of Indocyanine Green Videoangiography in Cerebral Aneurysm Surgery

Conventional radiographic cerebral angiography (digital subtraction angiography, DSA), which is usually performed by the Seldinger method from the femoral or the radial artery, is considered to be the golden standard for confirming anastomotic patency and complete closure of cerebral aneurysm. However, DSA has not been used routinely for intraoperative assessment because it is invasive to patients and technically demanding, especially in neurosurgery, where the head is fixed with metallic fixation devices and the patient may be placed in the lateral or prone position. ICGVAG, on the other hand, is administered by peripheral vein and is the same method as intravenous digital subtraction angiography (IVDSA), making it extremely simple. In addition, since the cerebral blood vessels to be observed exist in the subarachnoid space and are not buried in the brain parenchyma, direct and clear observation is possible. This would be the main cause of the spread of ICGVAG in the field of neurosurgery. In addition, the high number of cerebral aneurysm surgery and severity of postoperative complications, the affinity between microscopic surgery and fluorescence imaging, and assurance for the safety of ICG would promote the use of ICGVAG.

## 4 Case Presentations

### 4.1 Basic Technique of Indocyanine Green Videoangiography Imaging (Fig. 9.1)

Once the target cerebral aneurysm, its parent vessel, and peripheral vessels are exposed and captured in the field of view, the microscope used is changed to "ICG mode" or "near-infrared light mode." ICG (2.5 mg/mL, usually at a dose of 0.10–0.25 mg/kg) is injected intravenously via a peripheral vein with a bolus. Surgical lighting in the OR should be turned off. The time from intravenous injection of ICG to visualization of blood flows depends on the heart rate, blood pressure, and other factors, but it usually takes a few seconds to 30 seconds for ICG to reach the intracranial area. Fluorescence images can be visualized clearly for the first 30 minutes, although this technique can be used repeatedly after waiting for the washout of ICG from background structures. ICGVAG images are automatically recorded and can be reviewed in the OR when needed. In the imaging mode for ICGVAG, fluorescent blood vessels are contrasted in white, yellow, blue, etc., according to the microscopic system to be used.

### 4.2 Confirmation of Complete Occlusion Following Aneurysm Clipping

In the clipping technique, which is the golden standard for the treatment of cerebral aneurysms, the aneurysm neck is occluded with a clip to block blood flow into the aneurysm and prevent rupture. Before the development of the ICGVAG, intraoperative radiographic angiography (DAA) and/or the Doppler method were used for this purpose. In the use of ICGVAG for confirmation of aneurysm occlusion, it is necessary to observe the presence or absence of reentry of blood flow for about 1 minute and the retention of the contrast medium injected before clip occlusion (Fig. 9.1d). It is not clear whether additional clip placement is necessary when minute blood flow in the aneurysm neck is detected by ICGVAG, and whether the aneurysm will thrombose if left untreated, but we do perform additional clips.

### 4.3 Confirmation of Anastomotic Patency in the Treatment of Cerebral Aneurysms (Movies 9.1, 9.2, 9.3, and 9.4)

Although clipping is the standard surgical treatment for cerebral aneurysms, sometimes aneurysms are treated by closing the aneurysm together with the parent vessel and reconstructing the peripheral vessel (anastomosis). ICGVAG can also be used to confirm the patency of the reconstructed vessel in aneurysm surgery as well as in the treatment for cerebral ischemia. Although most of the recipients are 1–2 mm in diameter, they are depicted with blood flow from the donor because the peripheral side flows only from the donor. ICGVAG may visualize retrograde blood flow in recipient arteries through intracranial peripheral blood vessels even if the forward blood flow from the donor is poor. In such a case, ICGVAG should be performed again after the recipient is temporarily closed. Sometimes, the direction of blood flow is unclear in ICGVAG (Movie 9.5) due to a variety of technical factors. Since the direction of inflow is important information for detecting central stenosis of the donor, some microscopic imaging systems are equipped with a function to delineate the direction of blood flow by indicating the increase of fluorescence intensities with color codes and by measuring the timing of fluorescent increase in each region of interest (ROI) set on the vessels.

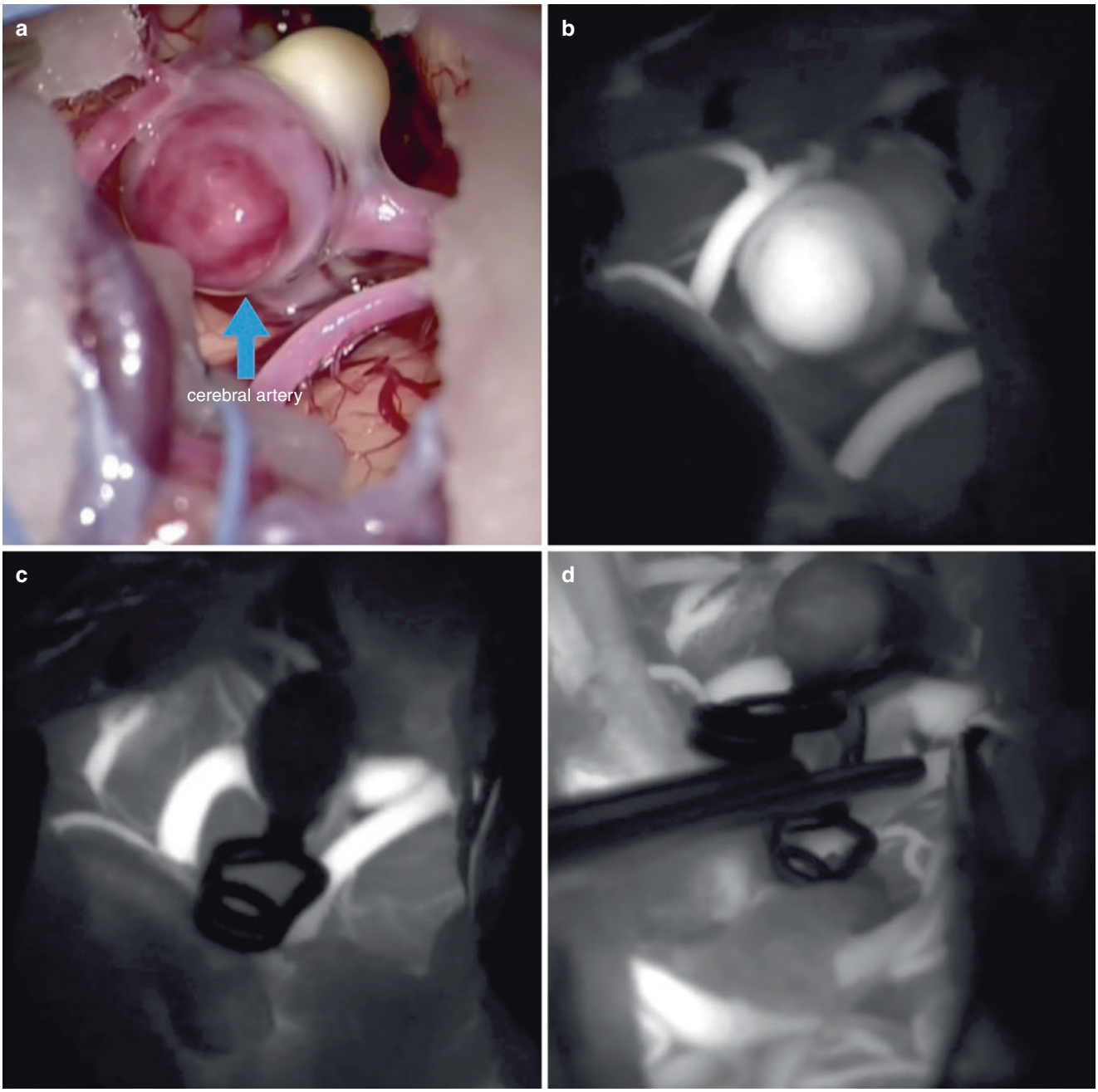


**Fig. 9.1** Indocyanine green videoangiography imaging of clipping for middle cerebral artery. (**a**) After opening the Sylvian fissure, the middle cerebral artery is exposed just before clipping. There is a thickened area in the aneurysm wall. (**b**) Pre-clipping ICGVAG findings. The thick wall of the aneurysm is less stained by the contrast medium. (**c**) ICGVAG findings immediately after clipping. There is no contrast within the aneurysm. (**d**) ICGVAG findings after the addition of the second clip. Contrast material remains in the aneurysm, suggesting complete occlusion

**Point**

- Indocyanine green videoangiography has clear advantages over conventional radiographic angiography (DSA) in terms of simplicity and safety.
- Fluorescence images should be observed for 1 minute after intravenous injection of ICG and visualization of the target vessel/aneurysm.
- Efficacy and limitations of ICGVAG for confirmation of aneurysm occlusion and graft patency have been reported.
- Understanding the characteristics of ICG and imaging systems is essential for obtaining clear and accurate information.

## 5 Clarification of Indocyanine Green Fluorescence Images by Advanced Image Processing

Since the beginning of the application of ICG fluorescence imaging for intracranial diseases, limitations in image definition due to anatomical situations have been pointed out. In other words, ICGVAG is limited in its ability to delineate small vessels (0.1–0.3 mm) in narrow and deep areas. In the intracranial space, there are many vessels with a diameter of around 0.2 mm that can cause serious complications when occluded (the anterior choroidal artery, the lateral lenticulostriate artery, etc.). These vessels are in contact with the preferred site of cerebral aneurysms and may be occluded as a result of aneurysm closure. Another difficult situation is the treatment for the bifurcations of the anterior and posterior communicating arteries. They are often located on the back of the aneurysm, narrowing at greater depths, and the clips are often placed in front of the observation field, which makes it difficult to illuminate target regions from an appropriate orientation [1]. Aneurysms developing in these regions should be clipped completely because of the higher risk of postoperative rupture. In addition, ICG fluorescence images are usually demonstrated in a separate field of view rather than in the microscopic field of view in the eyepiece (Movie 9.2), which makes it difficult for surgeons to differentiate the target vessel and evaluate its patency.

Advances in image processing technology may overcome these problems in ICGVAG. A possible solution is to superimpose translucent fluorescence images on full-color images within the field of view of the eyepiece (Fig. 9.2). Another method is to brighten the entire surgical field to enhance the identifiability of anatomical structures (Movie 9.2). The former approach still has limitations in a discrepancy in the pixel position and framerate between fluorescence images and white-light color images. Brightening fluorescence images makes simultaneous observation of the surgical field by white light imaging difficult. Further development of image processing technology is supposed to solve the remaining problems of ICGVAG for the use of complicated surgical procedures.

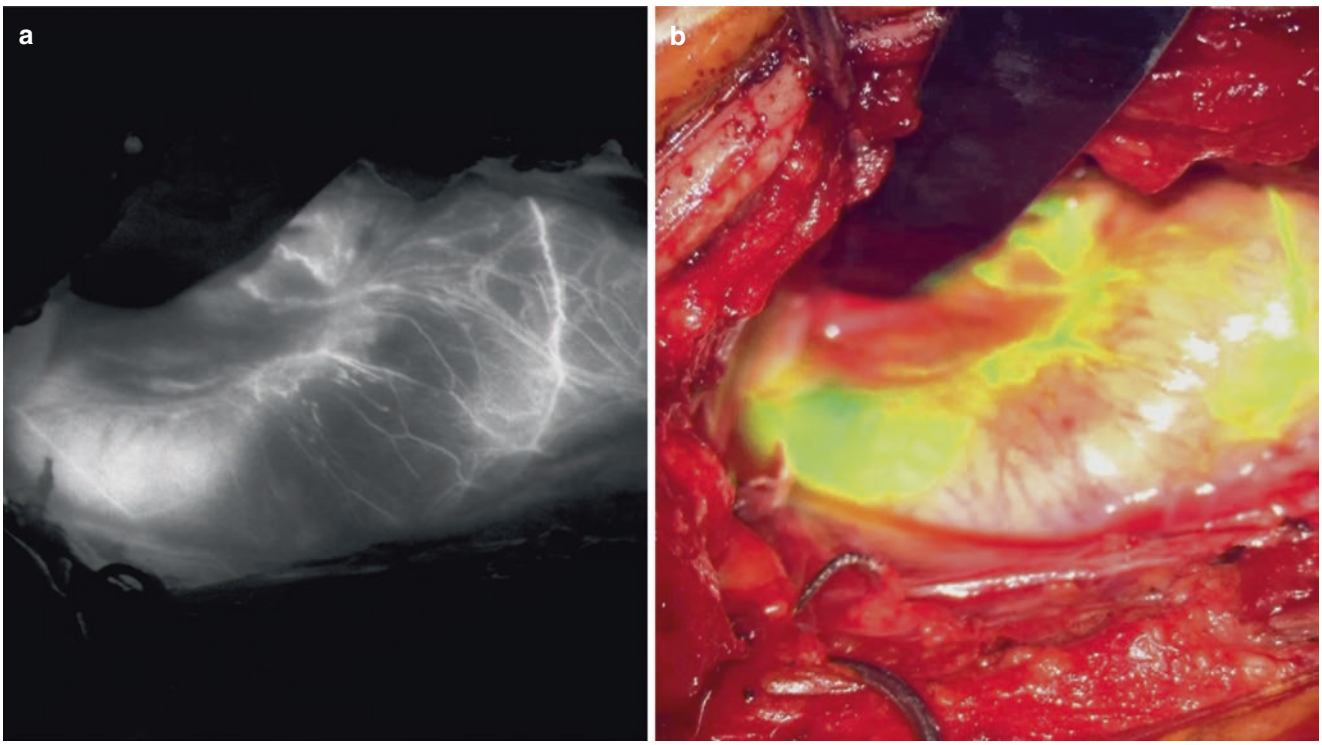


**Fig. 9.2** Indocyanine green videoangiography superimposed image during carotid endarterectomy. (**a**) Grayscale fluorescence images. (**b**) Superimposed image of ICGVAG using the KINEVO 900 (Carl Zeiss) during left carotid endarterectomy. In this model, the ICGVAG image is drawn in yellow tone and superimposed in the mirror field of the eyepiece to prevent the surgeon from shifting his field of view

## 6 Difference Between Indocyanine Green and Fluorescein as a Fluorophore

Fluorescein is another fluorescent contrast agent for cerebral blood flow analysis [4], although it is not covered by insurance in Japan except for its use in ocular angiography. In the field of cerebrovascular surgery, a shorter half-life of ICG is suitable for repeated use during surgery, but on the other hand, ICG is contraindicated in patients with a history of iodine hypersensitivity. Characteristics of ICG and fluorescein are summarized in Table 9.1. As shown in Fig. 9.3 and Movie 9.3, our conclusion from the comparative study is that ICG and fluorescein are useful for the visualization of thick vessels and thin vessels, respectively.

**Table 9.1** Comparison of indocyanine green and fluorescein (FC)

| | Half-life | Visualization of microscopic blood vessels | Repeated inspection | Iodine | Insurance coverage | Wavelength of maximum fluorescence | Wavelength of maximum absorption |
|---|---|---|---|---|---|---|---|
| ICG | Short: 3 ~ 4 min | Bad | 15 min | Include | Available | 835 nm | 805 nm |
| FC | Long | Good | Over 30 min | Not include | N/A | 525 nm | 480 nm |

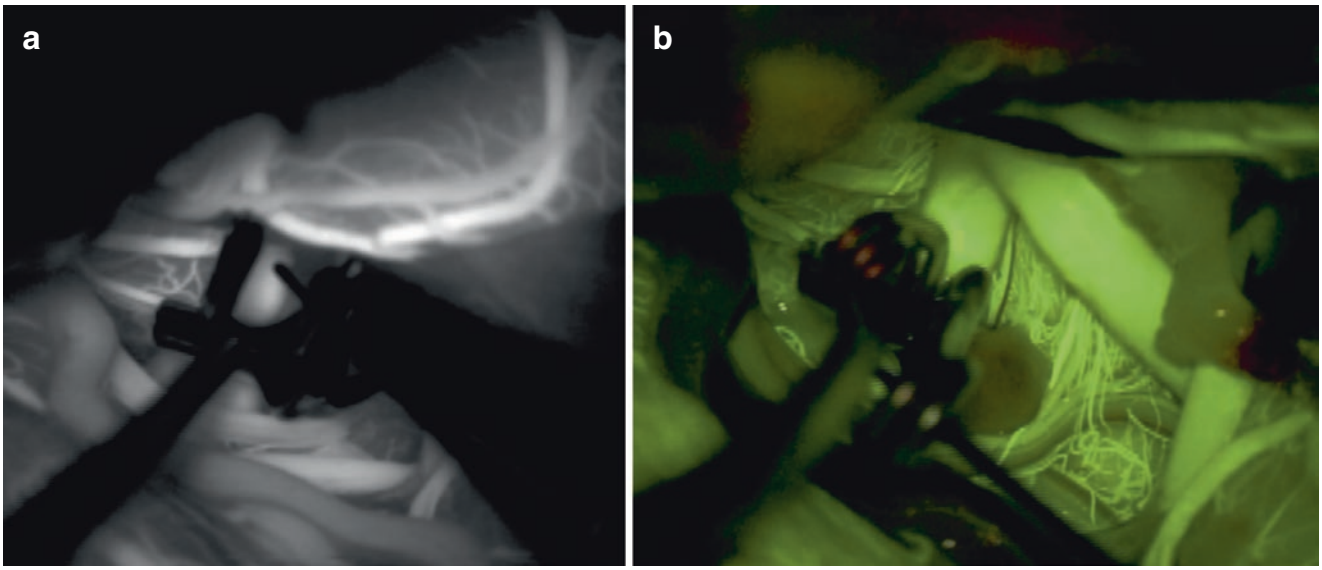


**Fig. 9.3** Indocyanine green and fluorescein imaging findings in the same field of view (the Sylvian fissure). (**a**) ICG. (**b**) Fluorescein

## 7 Applications of Quantitative Evaluation of Fluorescence Signals

There are two methods of quantitative evaluation of cerebral blood flow: one is to measure the transit time in perfusion images, that is, the timing of drawing the target tissue, and the other is to measure the maximum fluorescence intensity of the target tissue or the fluorescent increase per unit time (Figs. 9.4, 9.5, 9.6, and Movie 9.6). Each of these measurement methods has its own problems to be solved [3–6], and at the present stage, it is often only possible to observe relative changes in the same operation.

Assessment of tissue perfusion by ICG fluorescence imaging involves several problems. The infusion rate of ICG, blood pressure, heart rate, and cardiac output may affect the inflow of ICG into intracranial space. The influence of light scattering, such as indirect illumination from surrounding tissues, may also affect the degree of intracranial flow. For example, even non-perfused regions can show fluorescence signals when surrounded with highly perfused tissues [6] (Fig. 9.6). In addition, since the evaluation of fluorescence intensity is based on the average values of the target areas, shifting the target areas will affect the calculations (Fig. 9.5). In the current software for quantitative assessment of blood flows during neuro-

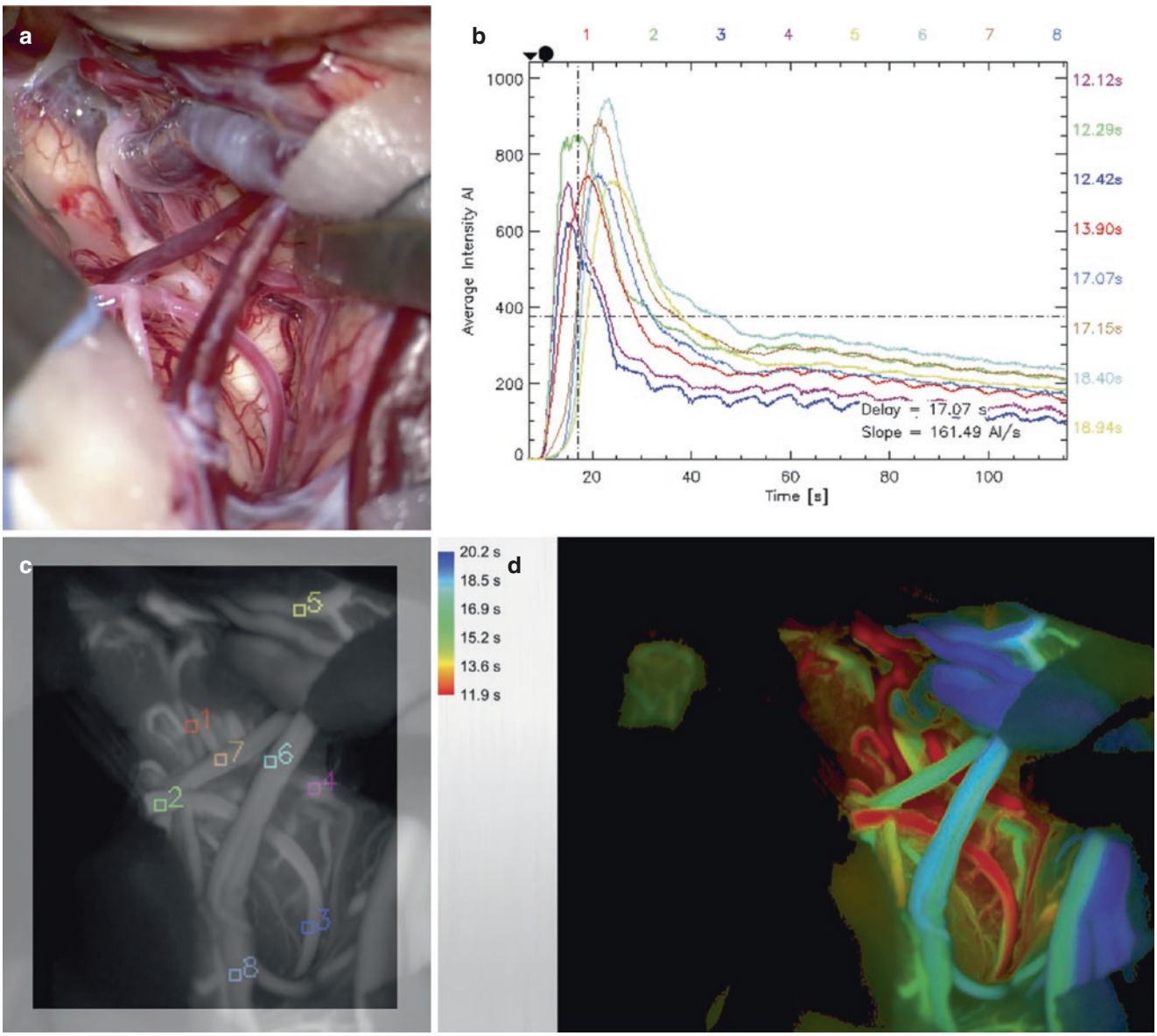


**Fig. 9.4** Indocyanine green videoangiography and Color Code Map installed in PENTERO® 900 (Carl Zeiss). (**a**) After the opening of the Sylvian fissure. Middle cerebral artery, Sylvian vein, frontal lobe, temporal lobe. (**b**) Trends of fluorescence intensities in each ROI. Differences between arteries and veins are observed in the time to maximum intensity and the maximum fluorescence intensity. (**c**) ICGVAG image and ROI setting site. (**d**) Color Code Map image. Early-phase areas are depicted in red tone and late-phase areas are depicted in blue tone

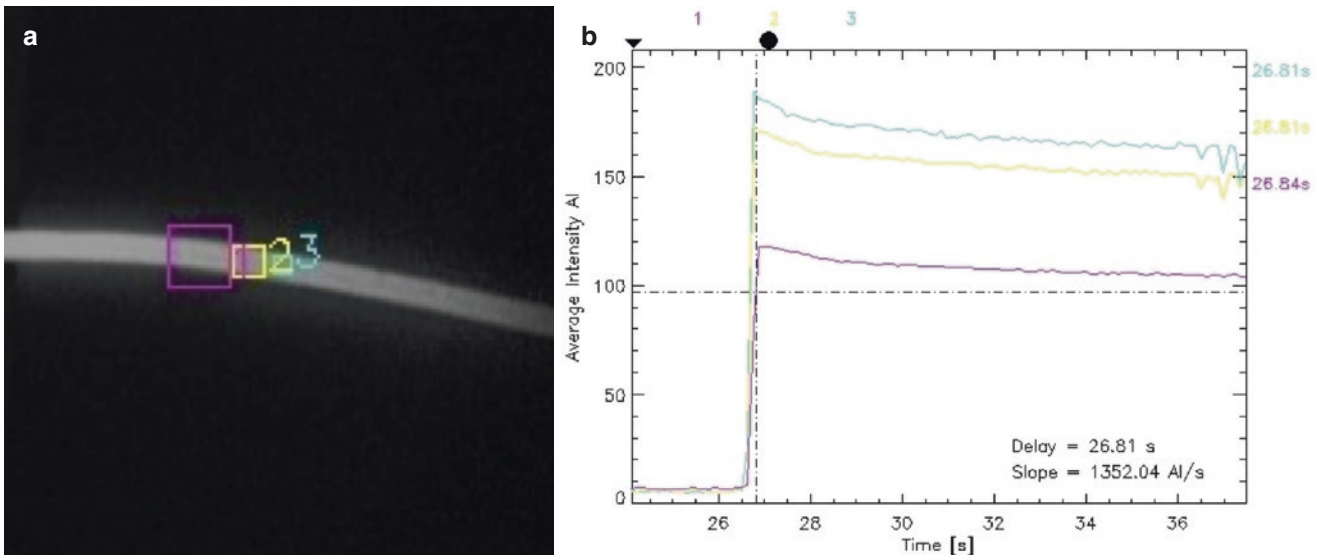


**Fig. 9.5** Size and location of the ROI and the outcome of quantitative assessment. (**a**) After injecting ICG into the artificial blood vessel of the phantom, a square ROI was set with three different sizes. (**b**) The red number 1, in which the ROI extends outside the simulated artery, has the lowest luminance, and the light blue number 3, in which the ROI is limited within the simulated artery, has the highest luminance evaluation. This indicates that the fluorescence intensity is measured based on the average signal intensity of the ROI

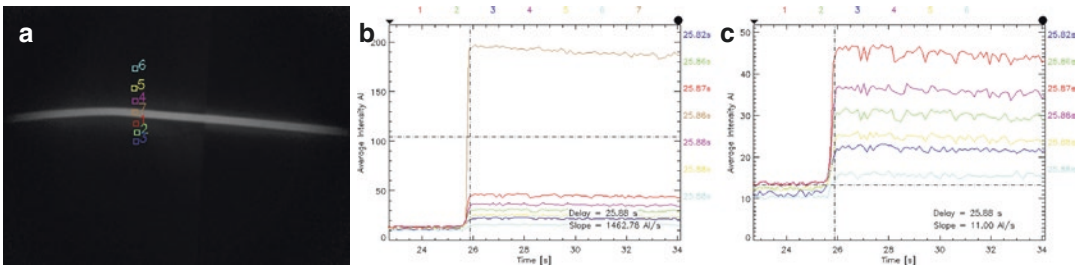


**Fig. 9.6** Relationships between distance from the ROI and values of fluorescence intensity. (**a**) After injection of ICG into the simulated artery, a square ROI of the same size was set on the simulated artery and at a distance of 2 mm from it. (**b**) The ROI on the simulated artery in brown No. 7 has the highest intensity, but there is also an increase in intensity in other areas where ICG was not injected at all. (**c**) Expanded image of the middle graph, excluding brown number 7. The ROI close to the simulated artery has high evaluated luminance, and as the distance increases, the fluorescence intensity decreases to 4, 5, and 6 due to diffusion of fluorescence signal in the areas free from ICG

surgery, fluorescence signals are calculated based on the mean fluorescence intensities of the ROI set on the target region [2–4, 6]. For this reason, when ICG fluorescence imaging is used for quantitative evaluation, the position, focus, shooting range, and visual axis (orientation) of the microscope cannot be moved at all. Even if the same surgical field is captured, quantitative measurement of fluorescence signals can differ according to the size of the ROI. Therefore, in the quantitative assessment of cerebral blood flow by fluorescence imaging, surgeons should consider possible bias associated with the dose and speed of ICG injection, cardiac output, serum albumin levels, and the size of the ROI [7].

## 8 Evaluation of the Patency by Temporary Occlusion of the Supplying Vessel

Indocyanine green fluorescence angiography can be used to confirm vascular patency by temporary occlusion or the target vessel prior to intravenous injection of ICG and reopening during the observation [2, 3]. For example, ICG fluorescence imaging during temporary occlusion of the proximal side of a vessel buried in the sulcus can be used to evaluate the patency of blood flow to the distal side and the development status of collateral arteries. Alternatively, a

delayed reopening of the vessel after intravenous ICG infusion can also be used to confirm the presence or absence of blood flow in the target regions.

## 9 Effect of Pharmacological Properties of Indocyanine Green on Fluorescence Imaging

Indocyanine green videoangiography imaging can be repeated in about 15 minutes after a single intravenous injection because of its half-life [1, 2, 7]. On the other hand, when the aneurysm neck is closed immediately after the first imaging, ICG is retained in the aneurysm and shows fluorescence signals after about 20 minutes, which can be used for confirmation of complete closure of the aneurysm neck. ICG is a water-soluble tricarbocyanine dye that binds to plasma proteins (mainly β-lipoprotein) after intravenous administration and fluoresces. Therefore, in a patient with low LDL-cholesterol or blood dilution by intraoperative fluid infusion, the sensitivity of ICGVAG can decrease.

## 10 Conclusions

Indocyanine green videoangiography is useful to confirm the occlusion of cerebral aneurysms and patency of bypass vessels. The clinical impact of intraoperative fluorescence imaging on surgical outcomes has also been reported recently, although we still need large prospective studies for the standardization of imaging techniques and patient selection. Further development of image processing technology will enable clearer visualization of minute vessels in 3D.

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