

## Original Article

## The application of intraoperative near-infrared indocyanine green videoangiography and analysis of fluorescence intensity in cerebrovascular surgery

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### Abstract

**Objective:** To evaluate the usefulness and limitations of the intraoperative near-infrared (NIR) indocyanine green videoangiography (ICG-VA) and analysis of fluorescence intensity in cerebrovascular surgery.**Methods:** Forty-eight patients received ICG-VA during various surgical procedures from May 2010 to August 2010. Included among them were 45 cases of cerebral aneurysms and 3 cases of cerebral arteriovenous malformations (AVMs). The infrared fluorescence module integrated into the surgical microscope was used to visualize fluorescent areas in the surgical field. An integrated analytical visualization tool constantly analyzed the fluorescence video sequence and generated it in the form of an intensity diagram for objective interpretation.**Results:** Overall, the procedure of ICG VA was done 158 times in 48 patients. There was no adverse effect of ICG dye. In cerebral aneurysm cases, the images obtained were of high resolution. In 4 cases, incomplete clipping was detected by ICG-VA and allowed suitable adjustment to completely obliterate the aneurysm. In 3 aneurysm cases, the intensity diagram of ICG VA provided valuable information. ICG-VA identified the feeding arteries, the draining veins, and nidus in all 3 AVM cases, which was confirmed by an immediate analysis of fluorescence intensity.**Conclusions:** ICG-VA provides high resolution images allowing real-time assessment of the blood flow in surgical field. The intensity analysis function, in addition, is a useful adjunct to improve the accuracy of the clipping and decrease the complication rates in cerebral aneurysm cases. In cerebral AVM cases, with the help of color map and intensity diagram function, the superficial feeders, drainers, and nidus can be identified easily.**Key Words:** Cerebral aneurysm, cerebral arteriovenous malformation, indocyanine green videoangiography**Access this article online****Website:**  
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## INTRODUCTION

Fluorescence angiography was first used in neurosurgical procedures by Feindel to evaluate cerebral microcirculation by using the fluorescent dye “fluorescein.”<sup>[4]</sup> With the use of indocyanine green (ICG) as a novel fluorescent dye, and the initial report by Raabe *et al.* in 2003,<sup>[16]</sup> several authors have recommended ICG videoangiography (ICG-VA) as a useful adjunct in cases of extracranial–intracranial bypass, cerebral aneurysms, and cerebral arteriovenous malformations (AVMs).<sup>[1,3,7,11-14]</sup> During the intraoperative ICG-VA, the neurosurgeons rely on direct inspection of fluorescent vessels in the surgical field to confirm their blood flow. In May 2010, a new system with analytical visualization tool (FLOW 800, Carl Zeiss, Oberkochen, Germany) became available at our center. The intensity color map and graphic analytical functions of this new system are visualization tools for rapid interpretation of fluorescence video sequences generated using ICG VA. The color map employs colors to instantly identify the direction and sequence of blood flow. In the intensity graphic diagram, the surgeon can freely define the regions to be evaluated and the peak fluorescence values of arteries and veins appear at two different times. These functions are useful for identifying the feeding arteries and arterialized veins in cerebral AVMs and also, have a definitive role in aneurysm surgery. The utility of microscope-integrated visual analysis of blood flow dynamics for the rapid interpretation of fluorescence video sequences has never been evaluated. This study presents our preliminary experience with the application of intraoperative near-infrared (NIR) ICG-VA and objective analysis of blood flow dynamics in cerebrovascular surgery in the form of fluorescence intensity.

## MATERIALS AND METHODS

### Patient population

Data regarding 45 cases of cerebral aneurysms and 3 cases of cerebral AVMs who were subjected to microsurgical treatment at our center from May 2010 to August 2010 were collected and evaluated retrospectively. Of these 48 cases, 15 were male and 33 were female. The mean age was 59.2 years (range 11–78 years). Among the 45 cases of cerebral aneurysms, there were 38 patients with unruptured aneurysms and 7 patients with ruptured ones. Those with ruptured aneurysms, the Hunt and Hess grade was grade II in 1 patient, grade III in 3 patients, and grade IV in another 3. Among the 3 cases of cerebral AVMs, there were 2 Spetzler Martin grade II AVMs and one was Spetzler Martin grade IV. Two patients underwent preoperative embolization.

A written informed consent for the use of intravenous ICG injection was obtained preoperatively from the

patient or his/her relatives depending on the patient’s condition. The surgical procedures to occlude the aneurysms or resect the AVM nidus were performed as usual. Intraoperative ICG-VA was performed according to the surgeon’s decision, before or/and after the clip application in aneurysm cases and similarly once before, 2–4 times during the resection, and once after the resection of the AVM.

Following clipping of the aneurysm, micro-Doppler examination was routinely performed in all patients to assess blood flow in parent artery and other branching vessels. In most cases we also used endoscopy to directly visualize the adequate application of the clip. A three-dimensional computed tomography angiography (3D-CTA) examination was done in all cases before and 2–3 days following the surgery.

All 3 AVM cases underwent Digital Subtraction Angiography (DSA) 6–9 days postoperatively. The results of resection shown by ICG-VA and DSA were compared.

### Intraoperative ICG videoangiography

Intraoperative ICG-VA was performed in all cases during the surgery. The NIR fluorescence module integrated into the surgical microscope (Carl Zeiss Surgical GmbH, Flow 800, 73447 Oberkochen, Germany) was used to visualize fluorescent areas in the surgical field and permitted the recording of a video of the emitted fluorescent light. The recommended dose of ICG-VA is 0.2–0.5 mg/kg and the daily dose should not exceed 5 mg/kg. In this series, all patients received a standard dose of 12.5 mg per injection dissolved in 2.5 mL of water. The recording was started and a calculated bolus of ICG was administered to the patient by the anesthesiologist on the surgeon’s command. Real-time video images of arterial, capillary, and venous phases of angiogram were observed on the video screen. The recorded video signal was simultaneously analyzed by an analytical visualization tool (FLOW 800, Carl Zeiss, Oberkochen, Germany) integrated into the surgical microscope and interpreted as an intensity diagram and a color map, which helped to study the findings objectively.

## RESULTS

Altogether, 45 cerebral aneurysms and 3 AVMs were treated in this series. Overall, the procedure of ICG VA was done 158 times in 48 patients. None of the cases had any adverse effect related to the ICG dye. In all these cases, the images obtained were of high resolution and allowed real-time assessment of the blood flow in the surgical field. The results were analyzed as follows:

1. In the 3 AVM patients, ICG-VA was performed before and after the resection. Two of these 3 patients had the injection twice and 1 patient had it 4 times during the resection. The video recorded before or during resection was simultaneously analyzed by the

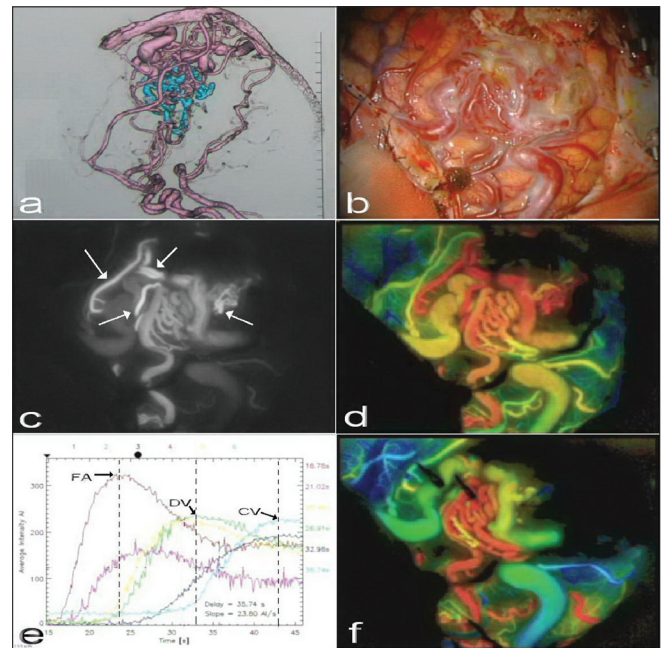
analytical visualization tool. The feeding arteries, draining veins, and nidus in all 3 AVM cases were identified and this was confirmed by the immediate analysis of the fluorescence intensity by way of a graph and a color map. The postoperative DSA disclosed that the nidus was totally resected in all the cases and the results corresponded to the intraoperative ICG-VA findings.

- In all 45 cases of cerebral aneurysms, the ICG VA detected incomplete clipping in 4 cases (4/45, 8.9%), including one case of delayed filling of ICG, which was confirmed by the intensity diagram. All these 4 residual aneurysms were completely occluded after clip adjustment and repeat ICG VA demonstrated the complete obliteration later. In addition, the ICG VA identified the perforating arteries arising close to or from the neck of the aneurysm in the surgical field of 12 aneurysms and allowed real-time assessment of the blood flow. In 2 of these 12 cases, clip was readjusted after the occlusion of a perforating artery was detected following an initial clip application. There was no major branch occlusion or residual aneurysm on the postoperative 3D-CTA.

In all the following illustrative cases, the intensity diagram of ICG VA provided valuable information. Although, these are only representative cases and further studies are required to validate the final efficacy, the information generated by the fluorescence intensity graph in all these cases (1 AVM and 2 aneurysms) was found extremely useful.

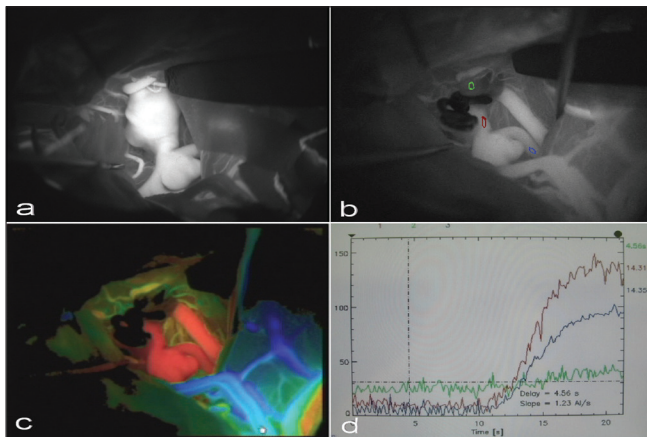
### Illustrative cases

**Case 1:** This 56-year-old patient had a Spetzler–Martin Grade IV right parietal arteriovenous malformation (AVM), which was incidentally detected during a routine brain screening medical program. DSA revealed that the nidus was fed by the right anterior, middle, and posterior cerebral arteries, and was draining into superior sagittal sinus. This patient underwent 3 procedures of embolization and presented to us with a sudden-onset hemiparesis due to an intracerebral hemorrhage after the last embolization. The hematoma was evacuated and decompression surgery was also performed. Seven months after this surgery, this patient was re-admitted in our hospital for definitive resection of the nidus. Intraoperative ICG-VA clearly demonstrated feeding arteries from anterior and middle cerebral arteries. The subsequent intensity diagram and color map facilitated the distinction of AVM vessels, namely, feeding arteries, draining veins, arterialized veins from other normal vessels, such as arteries *en passage* [Figure 1]. After temporary clipping of the feeders, the nidus was completely resected. This patient had ICG injection 4 times during resection of the AVM. ICG revealed no residual fistula or AVM nidus on the surface of the resection cavity. Complete resection of the AVM was confirmed by postoperative DSA.



**Figure 1:** (a) Preoperative 3D-CT angiogram demonstrating a grade IV right parietal arteriovenous malformation (AVM), which had been partially embolized before surgery. The AVM was fed by right anterior, middle, and posterior cerebral arteries. (b) Intraoperative view showing the nidus and dilated draining veins. (c) Corresponding indocyanine green videoangiography showing the feeder arteries (arrow) and early venous filling during the late arterial phase. (d) The color map employs colors to instantly identify the direction and sequence of blood flow. Red represents the initial blood inflow, followed by a gradient color scale for subsequent blood flow sequences. (e) Intensity diagram showing the peak fluorescence values of feeding arteries (FA), draining veins (DV), and cortical veins (CV) appear in 3 different periods. (f) After clipping the superficial feeding arteries, the color of the draining veins changed from orange to green

**Case 2:** A 53-year-old woman presented with recurrent severe headache. She was found to have 2 aneurysms located in the right middle cerebral artery [Figure 2a]. Following complete microsurgical dissection of the aneurysms, parent vessels and their branches, intraoperative ICG-VA was performed. The blood flow in the aneurysms and the MCA branches was clearly observed before clip application. After clipping of the proximal aneurysm, ICG-VA was repeated to confirm the exclusion of the aneurysm and to detect any residual blood flow in the clipped aneurysm. However, due to the repeated injections of ICG within a short interval, the originally injected volume was still detectable in the aneurysm [Figure 2b]. Hence it was difficult to confirm the occlusion of aneurysm on the basis of simple ICG-VA. To clear this dilemma, the intensity diagram function integrated into the surgical microscope was used to check the variation in the blood flow of clipped aneurysm over time. The curve of the aneurysm had no obvious upslope, which implied complete obliteration on the color map [Figure 2c and 2d]. Therefore, no readjustment was



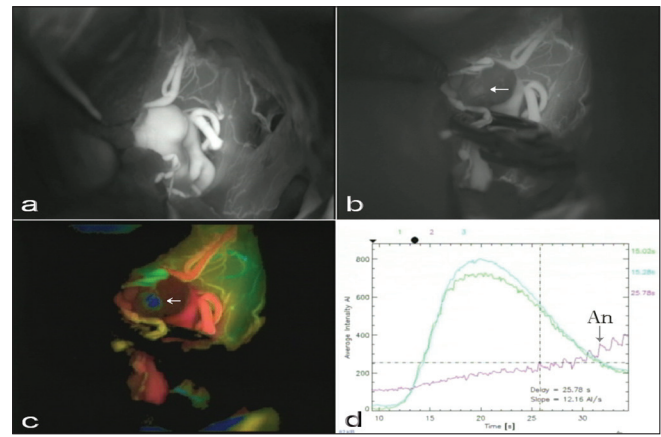
**Figure 2:** (a) Intraoperative indocyanine green videoangiography (ICG-VA) image showing 2 aneurysms located on the right middle cerebral artery. (b) Repeat ICG-VA after clipping of the proximal aneurysm showing the originally injected volume still detectable in the aneurysm (green mark). (c) Corresponding color map showing the aneurysm region was devoid of any flow. (d) The intensity diagram demonstrating that the curve of aneurysm (green color) had no obvious upslope, which implied complete obliteration

warranted and we left the clips in place based on this finding. Later, the complete obliteration of the aneurysm was re-confirmed by postoperative 3D-CTA examination obtained 2 days after surgery.

**Case 3:** A 62-year-old woman presented with progressive headache and vertigo and was diagnosed as having 2 aneurysms arising from right A2-anterior communicating artery junction, one projecting anteroinferiorly and the other projecting medially [Figure 3a]. After clipping of the first aneurysm, micro-Doppler examination detected no flow in the aneurysm. The arterial phase in the ICG-VA also showed lack of flow into the aneurysm and normal flow in the nearby perforating artery. However, the venous phase showed a glimmer of fluorescence visible in the aneurysm sac [Figure 3b], suggestive of residual filling of the aneurysm. The corresponding color map showed a portion of the aneurysm with blue color and a delayed ascending curve (purple color) was detected in the intensity [Figure 3c and d], thus confirming a residual aneurysm. The clip was then readjusted and ICG-VA was repeated. This time it showed complete absence of flow within the aneurysm. A postoperative 3D-CTA demonstrated complete obliteration of the aneurysm.

## DISCUSSION

ICG is a NIR fluorescent dye that was approved by the Food and Drug Administration in 1956 for cardiocirculatory and liver function diagnostic uses. After an intravenous injection, the ICG binds tightly to plasma proteins and remains restricted within the intravascular compartment. After a half-life of 3–4 min, it is eliminated from circulation exclusively by the hepatic metabolism



**Figure 3:** (a) Intraoperative indocyanine green videoangiography (ICG-VA) after complete dissection of the first aneurysm showing the filling in the aneurysm. The anterior communicating artery and both A2 segments are clearly observed prior to clip application. (b) The post clipping ICG-VA during the venous phase demonstrating a glimmer of fluorescence in the aneurysmal sac (arrow), suggestive of residual filling into the aneurysm. (c) Corresponding color map showing a portion of the aneurysm with a blue color (arrow). (d) The intensity diagram showing the fluorescence intensity curve of the aneurysm (purple curve) as a continuously ascending curve with a slope value of 12.16 AI/S (average intensity/second)

into the bile juice. It is used for evaluating the cardiac output, the hepatic functions, and also to assess the blood flow across the vascular anastomosis. It is used widely in ophthalmology for assessing the retinal microcirculation.<sup>[10]</sup> In 2003, Raabe *et al.*<sup>[16]</sup> reported their initial clinical experience with ICG angiography in neurovascular cases. In their cases, the postoperative angiographic results corresponded to the intraoperative ICG-VA findings. Subsequently, several authors have been recommending ICG-VA as a useful adjunct to the intraoperative or postoperative DSA.<sup>[2,5-7,10,12]</sup> Microscope-integrated ICG-VA technology focuses on obtaining high-resolution and high-contrast NIR images after an intravenous injection of ICG dye, making it possible to assess the blood flow in the cerebral vasculature within the surgical field. At our center, the surgical microscope integrated with infrared fluorescence module is used as an adjunct during the clipping of the intracranial aneurysms since 2007.<sup>[9]</sup> Traditionally, during the intraoperative ICG-VA, the neurosurgeons rely on direct inspection of fluorescent blood flow to confirm the complete obliteration of an aneurysm. In May 2010, a new system with analytical visualization tool became available. This is a review of our preliminary experience with this technique in patients with cerebral aneurysms or AVMs to analyze the clinical value of this modification.

ICG-VA is a noninvasive and safe method of real-time blood-flow assessment that can be used in patients with intracranial aneurysms, AVMs, and other vascular lesions. As compared with DSA, ICG VA directly gives a reliable display of the blood flow in the smallest

perforator visible in the surgical field. The simplicity, speed, excellent image quality, and resolution provided by the microscope integrated ICG-VA allows a surgeon to readjust the clip before an irreversible damage can occur. The information provided by ICG VA can be used either as complementary to DSA for visualization of small arteries or as an alternative to DSA in noncomplex aneurysms.<sup>[16]</sup> Furthermore, ICG-VA is also a useful tool for identification of AVM feeding arteries and draining veins, helping the surgeon to formulate and modify an operative strategy for selectively obliterating the feeding arteries while preserving the draining veins.<sup>[12]</sup>

The major limitation of ICG-VA is the restricted view offered in accordance to the concerned surgical approach.<sup>[1,7,8,12,13]</sup> Only vessels directly visible in the operative field can be assessed with ICG-VA. Vessels that are covered by blood clots, aneurysm, or brain tissue are not visible to the surgeon and also cannot be observed with this technique. Consequently, ICG is frequently of limited use for deep-seated AVMs and multiple injections need to be given throughout the surgery to identify and guide the nidus resection.<sup>[12]</sup> So, in our series, the surgeon usually cleared the surgical field by evacuation of the blood clots or removing the cottonoid covering the vessels before injection of ICG. During the ICG-VA process, the surgeon occasionally may need to retract the brain tissue and vessels gently or adjust the angle of microscope to get the optimal view of different vessels.

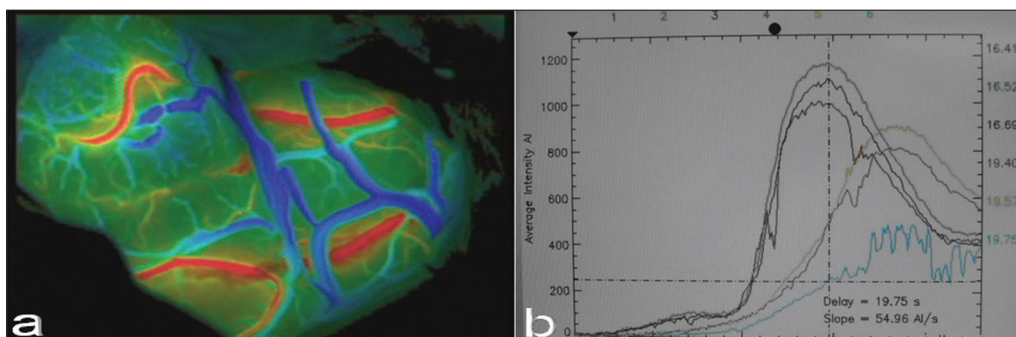
Another limitation of ICG VA is that the calcification, atherosclerotic plaque or thick wall of the aneurysm may attenuate the fluorescent signals and affect the ICG angiographic results.<sup>[15-17]</sup> In such cases, it may be difficult for a surgeon to identify any residual filling. Also, in cases of incomplete aneurysmal occlusion with small residual neck hidden behind the dome or clips, it may be difficult to confirm, by direct inspection alone, the slow filling of fluorescent blood in the aneurysm sac.

The intensity color map and graph functions are analytical visualization tools for rapid interpretation of fluorescence

video sequences generated using ICG VA. The infrared fluorescence module has been designed for excitation in the wavelength ranging from 700 to 850 nm and for fluorescence visualization in the wavelength ranging from 780 to 950 nm. The image, which cannot be observed through the surgical microscope, is visualized using a special camera on the touch-screen monitor assembled with the microscope. After adjusting the focus, the field of interest is set at the center with the recommended working distance of less than approximately 300 mm. A configured button on the handgrip activates the fluorescence function. The surgical field is illuminated by a light source (NIR-light) with a wavelength covering the ICG absorption band. Video recording is also started immediately when the fluorescence function has been activated. The video signal is constantly analyzed for fluorescence flow.

The color map employs colors to instantly identify the direction and sequence of blood flow. Red represents the initial blood inflow (arteries), followed by a gradient color scale for subsequent blood flow sequences with veins demonstrating blue color [Figure 4a]. All the information from video sequences is compiled into these visual maps, which are analyzed at a glance. In case 1, as multiple feeding arteries got filled simultaneously during the early arterial phase, the surgeon had to repeat the video several times to confirm all the feeding arteries in the superficial surgical field. The visual color map featured an overview of blood flow dynamics and facilitated identifying the feeding arteries at a single glance. In our experience, the intensity color map was more helpful in AVM cases than in aneurysm cases.

In the intensity graphic diagram, the surgeon can freely define the regions to be evaluated. The peak fluorescence values of arteries and veins appear at 2 different times [Figure 4b]. This function is useful for identifying the feeding arteries and arterialized veins more precisely in cerebral AVMs. And, before the application of clip in the aneurysm cases, the fluorescence intensity curve of aneurysm has a peak fluorescence value similar to



**Figure 4: (a) The color map of a sylvian fissure employing different colors to instantly identify the direction and sequence of blood flow. Red represents the initial blood inflow, followed by a gradient color scale for subsequent blood flow sequences. (b) In the intensity diagram, the peak fluorescence values of arteries and veins appear at 2 different times**

the curve of parent artery. After clipping, the peak fluorescence value of aneurysm disappears, and the curve is almost horizontal, indicating a complete obliteration of the aneurysm and no residual filling of the blood in it. In case of incomplete obliteration of the aneurysm, there is a residual blood flow in the aneurysm and the peak fluorescence value of aneurysm will decrease but will not disappear.

The ICG dye has a plasma half-life of 3–4 min.<sup>[3,16]</sup> ICG procedure should preferably be repeated after 15 min. However, after clipping of the aneurysm, to reduce the risk of irreversible damage to perforators, sometimes the surgeon may need to repeat the ICG procedure after 5 or 10 min. In such situations, the originally injected volume may still remain detectable in the aneurysmal sac, which may give false-positive results. In case 2, the intensity diagram function integrated into the surgical microscope was used to check the variation in the blood flow of aneurysm over time and as a result the curve of the aneurysm had no obvious upslope, although there was fluorescent signal detected in the region. We left the clips in place based on this finding and the postoperative 3D-CTA examination confirmed the complete obliteration of the aneurysm. In our illustrative case 3, the view of arterial phase indicated complete obliteration, but there was a suspicious signal in the venous phase. A continuously ascending curve in the intensity diagram implied slow contrast filling of the aneurysm sac implying an incomplete obliteration of the aneurysm.

The surgeon could retract the brain tissue or adjust the angle of microscope to get the optimal view during ICG-VA. However, if the intensity color map and diagram functions were to be performed, the interested vessels needed to be kept in the same location during the whole ICG VA process.

As mentioned above, the study still has certain limitations. Due to small number of cases, especially the AVM ones, larger-scale systematic studies and clinical research enrolling more patients are required to further assess the value of the analytical fluorescence intensity function.

## CONCLUSION

ICG-VA allows a real-time assessment of the blood flow during procedures involving the cerebral aneurysms and AVMs. The intensity diagram function is a very useful adjunct to ICG-VA for objectively documenting the blood flow in the aneurysmal sac and in the vessels involved in an AVM. The color map demonstrates an overview of the blood flow dynamics at a single glance and facilitates

distinction between feeding arteries, draining veins, and nearby arteries *en passage*. Thus, it may minimize the complications and lead to improved outcomes in cerebrovascular surgery.

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