Original Article

Intraoperative Anatomical and Hemodynamic Analysis of Intracerebral Arteriovenous Malformations by Semi-quantitative Color-coded Indocyanine Green Videoangiography

Abstract

Objective and Background: To evaluate possible roles for indocyanine green (ICG)-based FLOW 800 software in surgical treatment of cerebral arteriovenous malformations (AVMs). **Methods:** We perform ICG videoangiography several times for each step of AVM resection to elucidate feeders, drainers, and cerebral perfusion. **Results:** Since 2010, 22 AVM surgeries in our department have been conducted using FLOW 800 intraoperatively. We demonstrated ICG angiograms, color-coded images, and semi-quantitative curves for AVMs. By reviewing all these modalities, we would define vascular structure of the AVM, proceed with resection, and finally recheck for any remnant. **Conclusions:** ICG FLOW 800 software helps the surgeon to recognize feeding and draining vessels of an AVM intraoperatively. Further studies to evaluate semi-quantitative acquired data regarding blood flow and tissue perfusion are warranted.

Keywords: *Cerebral arteriovenous malformation, cerebral blood flow, drainer, feeder, indocyanine green videoangiography*

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Introduction

Arteriovenous malformations (AVMs) are vascular lesions which can be treated in a variety of ways depending on their angiographic grade. Surgery of AVM can be hazardous even in Spetzler–Martin (S-M) Grade 1 or 2, and it is very important for the surgeon to identify the feeding vessels and the draining veins properly. Surgery can be performed without significant risk in S-M Grade 1–2 AVMs where radiosurgery and embolization can be used either as the primary treatment or in combination with surgery.[1,2] Some of the most critical steps in AVM surgery are to distinguish arteries from veins, to follow hemodynamic changes of the AVM and the surrounding brain tissue during the operation, and to detect any residual AVM at the conclusion of the surgery. For these goals, a variety of intraoperative adjuncts is usually implemented such as conventional angiography, Doppler ultrasound, or indocyanine green (ICG) videoangiography (VA).

Compared with conventional angiography, ICG-VA has been accepted as a less-invasive, simple, real-time, and repeatable technique. However, its findings are demonstrated qualitatively in a gray-scale map, and it is difficult, if not impossible, to evaluate decreased vascular blood flow or angiographic circulation time quantitatively or to differ arteries from veins intraoperatively.[3] In 2003, Raabe *et al.* first reported their initial clinical experience with ICG-VA for the assessment of flow in neurovascular cases.[4] Before the advent of a recently popularized system named FLOW 800, only anatomical data could be acquired from ICG angiography making its application of limited value for cerebral AVMs. FLOW 800 software compiles the information from conventional ICG-VA into a continuous color scale map to identify the direction and sequence of vascular blood flow.[5] FLOW 800 helps differentiate arteries and veins and also check for the remaining AVM, gradual nidus occlusion, blood flow arrival time, and blood flow of the peripheral brain.[6]

In this paper, we present our experience with FLOW 800 in treating cerebral AVMs since its introduction to our center with more emphasis on its technical application and then discuss our findings and the

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current literature regarding its pros and cons in surgery of cerebral AVM and other vascular lesions.

Methods

All patients diagnosed with AVM S-M Grade 1 or 2 will be candidate for microsurgery in our department. Furthermore, some Grade 3 AVMs will be offered surgery, either alone or as an adjunct to other therapies including radiosurgery and embolization. We use OPMI PENTERO microscope with INFRARED 800 camera equipped with FLOW 800 software (Carl Zeiss, Oberkochen, Germany) which was introduced to our institute in May 2010. Since its introduction, all vascular procedures including AVMs are performed using ICG-VA and analysis by this software. After surgically exposing the AVM, a primary ICG-VA is performed after intravenous injection of ICG (25 mg dissolved in 10 cc sterile water) to obtain primary anatomical and physiological information of the vessels. Color-coded image from FLOW 800 is used to differentiate cortical feeding artery and vein at a glance which guides the surgeon to adopt the appropriate strategy toward the lesion. Any region of interest (ROI) can be defined for the software to provide semi-quantitative information of its hemodynamic properties. Some parameters are calculated directly by the software including average intensity (showed in arbitrary intensity units), delay time (i.e., the time interval from 0% to 50% of maximum fluorescence intensity [MFI]), and the slope of the curve. On the other hand, there are some other indices presented in the literature known to be correlated with perfusion characteristics of tissues which simply can be computed with ImageJ software (version 1.46, National Institute of Health, USA) after delivering the data from the microscope station.[6,7] Transit time is the time interval between MFI in the artery and parenchyma, and rise time is defined as the time during which fluorescence intensity rises from 10% to 90% of its peak. Other variables that can be measured manually include MFI, time to peak (i.e., from the appearance of fluorescence to MFI), and cerebral blood flow index (CBFI) which is defined as the ratio of MFI to rise time.[6] These parameters can be calculated for each vessel, and their changes should be tracked throughout the procedure. We still doubt the validity and reliability of these semi-quantitative data for clinical judgment, and their application is under further investigations in our institute.

While maintaining the gliotic plane around the AVM and exposing the deeper aspects of the lesion, further images would be obtained at the request of the surgeon. New semi-quantitative data regarding the surrounding brain parenchyma should be constantly compared with the previous information. As the resection progresses, color changes in blood vessels may help the surgeon to take the next step. For example, abnormal blood flow in a draining vein at the end of the procedure usually indicates a hidden arterial feeder and necessitates a search for it. More detailed

technical nuances to remove AVM have been described in detail elsewhere.[8] All the data in the text are described as mean ± standard deviation (minimum – maximum).

Results

During the time of the study, 22 patients with AVM were operated in our center with the average age of 37.22 ± 17.46 (11–72) years and male:female ratio of 1:1 [Table 1]. The location of the AVM was consistent with the volume of the brain parenchyma with the frontal lobe being the most common site followed by temporal, occipital, and parietal lobes. There were two cerebellar AVMs in our series. In this series, 68.2% of cases were S-M Grade I or II, and 13.6% were Grade IV without anyone categorized under Grade V. On average, 1.18 ± 0.85 embolization sessions were performed for each case where four cases did not undergo preoperative embolization at all. Eighteen patients (81.8%) showed good recovery on follow-up and only one case (4.5%) suffered severe disability. Two illustrative cases are presented to clarify the application of FLOW 800 software during AVM surgeries. None of the patients showed remnant of AVM requiring reintervention in their follow-up computed tomography-angiography or digital subtract angiography.

Case 1

A 55-year-old man presented with intracerebral hemorrhage and his angiographic evaluation revealed a S-M Grade 4 AVM in his right parietal area [Figure 1a] and was selected for microsurgery. As demonstrated in Figure 1c-f, ICG studies are helpful in different stages of the surgery. After opening the dura, the AVM is observed [Figure 1b], and ICG-VA shows the precise anatomy of the vessels [Figure 1c]. To distinguish arteries from veins, this image was further reinforced by the color-coded FLOW 800 [Figure 1d] where one can observe the feeding artery in red and the draining vein in blue. This visual color map featured an overview of blood flow dynamics and facilitated identifying the feeding arteries at a single glance. As the operation goes on, changes of blood flow in AVM can be tracked by further color-coded images [Figure 1e]. When the resection was completed, a final ICG-VA depicted total AVM removal with no residual nidus [Figure 1f].

Case 2

Figure 2a-f shows a 62-year-old man diagnosed with a cerebellar AVM with feeders from left superior and posterior inferior cerebellar arteries. After exposing the lesion, ICG-VA demonstrates AVM vessels [Figure 2a]. Figure 2b illustrates the same view after being rendered by the FLOW 800. Early appearing blood flow is showed in red and late appearing flow in blue. After selecting ROIs for the software, semi-quantitative characteristics of the blood flow in desired vessels were analyzed and demonstrated in curves by the FLOW 800 [Figure 2c]. After microsurgical resection of the AVM was complete, ICG-VA showed no

Table 1: Summary of twenty-two patients operated for arteriovenous malformations. Age, gender, location and side of arteriovenous malformations, Spetzler-Martin grade, size, and number of preoperative embolization are presented in the table. The outcome of the patient is categorized from severe disability to good recovery

| *n*	Age	Sex	Location	Side	Grade	Size	Embolization sessions	Outcome
1	28.00	Male	Frontal	Left	2.00	Small	3.00	Good recovery
2	37.00	Male	Frontal	Right	1.00	Small	0	Good recovery
3	14.00	Female	Frontal	Left	1.00	Large	0	Good recovery
4	51.00	Female	Temporal	Right	4.00	Large	3.00	Good recovery
5	19.00	Female	Frontal	Right	2.00	Small	1.00	Good recovery
6	28.00	Female	Frontal	Left	3.00	Small	2.00	Good recovery
7	23.00	Female	Temporal	Left	1.00	Small	1.00	Mild disability
8	72.00	Male	Frontal	Left	2.00	Small	1.00	Good recovery
9	52.00	Male	Temporal	Left	1.00	Small	1.00	Good recovery
10	32.00	Male	Occipital	Right	2.00	Small	1.00	Good recovery
11	30.00	Female	Occipital	Right	4.00	Small	2.00	Mild disability
12	28.00	Male	Frontal	Left	3.00	Medium	1.00	Mild disability
13	55.00	Male	Parietal	Right	4.00	Large	1.00	Severe disability
14	19.00	Male	Temporal	Left	3.00	Medium	1.00	Good recovery
15	11.00	Male	Frontal	Right	2.00	Medium	1.00	Good recovery
16	48.00	Female	Frontal	Left	2.00	Medium	1.00	Good recovery
17	13.00	Female	Frontal	Left	2.00	Medium	2.00	Good recovery
18	62.00	Male	Cerebellar	-	1.00	Medium	1.00	Good recovery
19	55.00	Male	Cerebellar	Right	3.00	Medium	1.00	Good recovery
20	52.00	Female	Occipital	Left	1.00	Small	0	Good recovery
21	39.00	Female	Frontal	Right	1.00	Small	0	Good recovery
22	51.00	Female	Temporal	Right	2.00	Medium	2.00	Good recovery
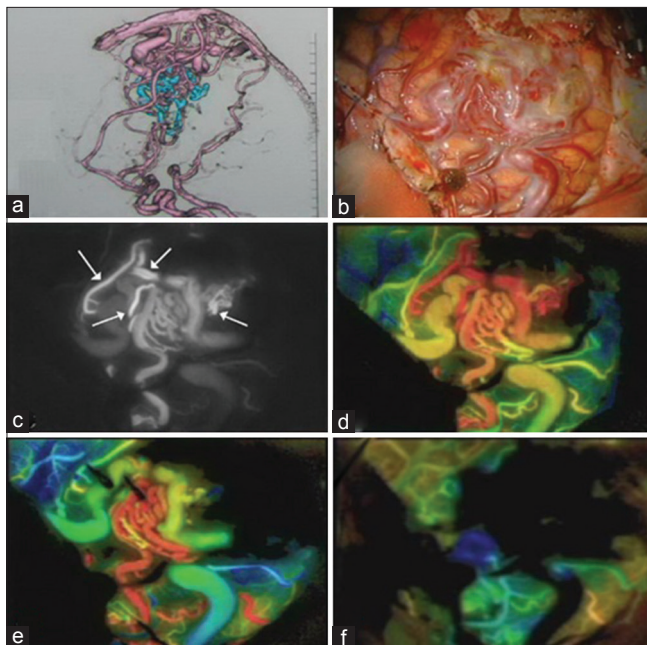
Figure 1: Right parietal arteriovenous malformation in a 55-year-old man. (a) Reconstructed computed tomography angiogram shows the location, feeding artery, and draining vein of the arteriovenous malformation. (b) After opening the dura, the lesion appears on the brain cortex. (c) Videoangiography after indocyanine green injection immediately after dural opening. (d) Color-coded image after analysis of Figure 1c with FLOW 800. (e) Color-coded imaging after ablation of some feeding arteries. Note the color changes in the vessels indicating hemodynamic changes of the arteriovenous malformation. (f) Color-coded imaging after complete resection of the arteriovenous malformation confirming no remnant of the lesion

remnant of the AVM [Figure 2d]. Visual color map showed hemodynamic changes after AVM resection [Figure 2e] in contrast with preresection status [Figure 2b]. Furthermore, analytical graphs show changes in flow parameters immediately after AVM resection [Figure 2c and f]. To make it easy to understand, we removed all curves of Figure 2c except for one to demonstrate image analysis performed with ImageJ software [Figure 3]. Time to peak, rise time, and MFI are all showed on the curve. Although CBFI is also calculated, we should notice that this curve is derived from a venous blood flow not brain parenchyma and this index is demonstrated as an example to explain its calculation.

Discussion

FLOW 800 applications in cerebral arteriovenous malformation surgery

ICG is a near-infrared fluorescent dye used widely in ophthalmology for assessing the retinal microcirculation.[9,10] It binds tightly to plasma proteins and remains restricted within the intravascular compartment. Its half-life is 3–4 min and it is eliminated by hepatic metabolism, so it can be injected repeatedly during the operation.[11] FLOW 800 is an analytical visualization tool for the rapid and reliable interpretation of fluorescence video sequences of INFRARED 800. There are three categories of images obtained using ICG and FLOW 800: ICG-VA which allows a real-time assessment of the blood flow during AVM
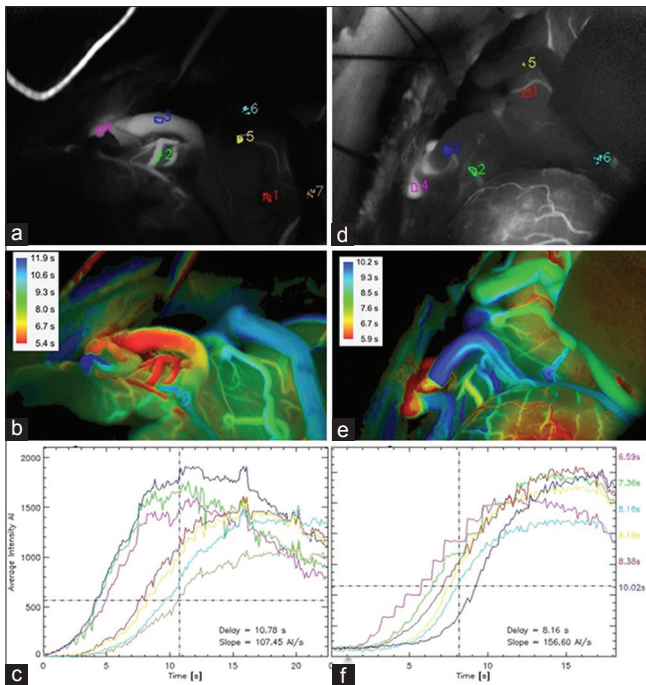
Figure 2: A cerebellar arteriovenous malformation in a 62-year-old man. (a) Indocyanine green videoangiography after exposing the lesion. Different vessels have been marked for the software to compute their hemodynamic properties. (b) Color-coded image of the same view in Figure 2a produced with FLOW 800 software. The blood flow is depicted in range of color from red to blue depending on the arrival time. (c) Analysis of the markers in Figure 2a is demonstrated in curves. Arterial flow reaches its peak earlier than venous blood flow. (d-f) The same images as Figure 2a-c after resection for comparison. Compare the color of the vasculature before [Figure b] and after (e) resection of the arteriovenous malformation. (f) Curves indicate hemodynamic changes in vessels after arteriovenous malformation resection
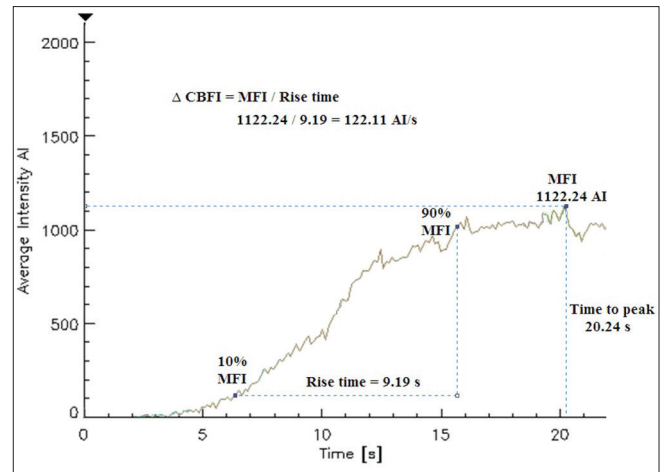

Figure 3: Hemodynamic properties of blood flow in a vessel after image analysis by ImageJ. Maximum fluorescence intensity is defined as the highest intensity of fluorescence for a defined area, and time to peak is the time interval from the appearance of fluorescence until its peak. Rise time is the time interval when fluorescence intensity rises from 10% to 90% of maximum fluorescence intensity. Cerebral blood flow index is calculated as the ratio of maximum fluorescence intensity to real time

surgery, the colorful visual map which demonstrates an overview of the blood flow dynamics at a single glance and facilitates distinction between feeding arteries, draining veins, and nearby normal arteries, and finally the intensity diagram whose function is a useful adjunct to ICG-VA for objectively documenting the blood flow in the vessels involved in an AVM.

FLOW 800 supports an in-depth interpretation of fluorescence videos by creating an objective colorful evaluation of the results. By compiling all the information from the fluorescence video sequences into one image, the visual maps feature an overview of blood flow dynamics, right down to the smallest blood vessels. Peak fluorescence values are displayed in the form of different shades of gray, whereas temporal fluorescence maps employ colors to instantly identify the direction and sequence of the blood flow. The color coding is based on the flow velocity so that one can actually place a temporary clip and observe the changes in the blood flow dynamics. This map employs colors to instantly identify the direction and sequence of blood flow. This function is beneficial for visualizing feeding arteries and draining veins when treating AVMs. To enable an accurate identification of vessel blood flow,

a continuous color scale is used. Red color represents the initial blood inflow, followed by a gradient color scale for subsequent blood flow sequences.

The comparative function of FLOW 800 enables direct comparison of fluorescence imaging sequences intraoperatively to visualized blood flow changes. Blood flow before and after clipping can be contrasted easily using this system. Curves show variations in blood flow over time in a certain region. By knowing the features of a curve typical for an artery, a draining vein, or a normal vein, the surgeon may differentiate the vessels after being analyzed by the software. Furthermore, comparative analysis of the curves before and after the resection may help the surgeon to learn completeness of the resection. However, we should be aware of the limitations of the infrared-based systems as they do not demonstrate deeply located lesions which may result in some residual AVM only to find in a postoperative angiography.[12]

Intraoperative ICG-VA cannot differentiate arterial feeders from draining veins precisely, and some efforts to modify the technique have been made in recent years. Kono *et al*. reported a patient for whom they performed intra-arterial injections of ICG through preoperatively introduced transfemoral catheters placed in the carotid and vertebral arteries.[3] They could recognize feeders from draining vessels based on their appearance in chronological order which happened after intra-arterial but not intravenous injection of ICG. Before the introduction of FLOW 800 to our department, we also relied on the timing of fluorescence to distinguish arteries from veins during AVM surgery.[13] Compared with this technique, using FLOW 800 is less invasive and provides the surgeon with one shot of all the feeders and draining veins differing in their colors. Furthermore, the latter depicts hemodynamic characteristics

of the AVM in each step of the procedure which can be judged by the surgeon to proceed with the operation accordingly.[14]

Limitations of FLOW 800

FLOW 800 system bears the common limitations of ICG-VA. Although its role is limited in deep-seated lesions, in our experience with properly dissected and exposed AVMs, it can provide easily interpretable and reproducible information throughout the surgery.

We should be very careful when interpreting the semi-quantitative data produced by the software. One should always keep it in the back of his mind that these data are produced by postprocedure analysis, and their quantities are not meant to be solely relied on. Furthermore, data calculated with image analysis software (e.g., ImageJ) are not truly measured. Although some efforts have been made to make a correlation between the raw values and other clinical or paraclinical standardized data,[6,15,16] currently, these are too far from being applied into practice. For example, we are not sure whether a claimed ischemic area by the software, really is. The cerebral blood flow ratio of a ROI to normal brain tissue has been used to define ischemia,[17] and some reports attempted to validate CBFI obtained with FLOW 800 accordingly.[6] However, we should know that such a study requires an external validation, and relying on the surgeon's judgment to define an ischemic or normal zone is not enough. So far, such a study has not been performed for FLOW 800 system. One major obstacle to externally validate these values is defining a gold standard tool to measure hemodynamic parameters intraoperatively with which our new data can be compared. Hence, we believe that information produced by the software in form of curves should only contrast pre- with post-resection hemodynamic state of the vessels or tissues until further reports validate the software. Furthermore, current data are not conclusive about the reliability and reproducibility of this information, and we do not know whether factors such as changes in blood pressure during the operation, ICG dosage or the rate of injection, or the site of ROI will affect the final results.

Even if we accept validity and reliability of the achieved data, it is still not clear how they will affect the outcome. When several prognostic factors are important in treating a disease, defining a role for a new modality will be very difficult if not impossible and requires a very well-designed trial with well-matched patients included in this study. Optimistically, we should expect some impact analysis reports to show the efficacy of this technology on the outcome of AVM patients.[6] Realistically speaking, we do not recommend such a study. Several large case series have clarified prognostic factors for AVM surgeries with which we select our patients in accordance.[18] This patient selection has resulted in good surgical outcome of AVM

case series published recently[19,20] and to detect therapeutic value of adding a new tool to our current armamentarium may not be an easy task. This is true, especially when these lesions are usually treated at the hands of skillful neurosurgeons all over the world whose experience may overshadow any new therapeutic adjunct in clinical terms. Notwithstanding previous facts, we still believe with further reports on this new modality; it can be helpful to relax surgeon's minds, even the most experienced, at some points during AVM operations.

FLOW 800 applications in neurovascular surgery

Previously, we introduced our preliminary experience with the application of FLOW 800 in cerebral AVM surgeries.[5,21] Since then, more reports on its cerebral applications have emerged which we have discussed in great detail elsewhere,[22] and here, we just mention them in brief. Holling *et al*. reported five cases of pial or dural arteriovenous fistula treated microsurgically using FLOW 800.[15] They used this method to detect small fistulae and also quantitatively assessed flow parameters of the fistula and the tissue perfusion. Ueba *et al*. reported their experience with the utility of FLOW 800 in resection of a spinal cord hemangioblastoma in a 19-month-old child.[23] Furthermore, Benedetto *et al*. resected a spinal cord hemangioblastoma using FLOW 800 intraoperatively.[24] They could depict the vascular pattern of the lesion and also dynamic changes of flow in the tumor throughout the procedure. In another study, FLOW 800 was used with great success during carotid endarterectomy to depict plaque characteristics and to receive semi-quantitative hemodynamic information before and after the plaque removal.[25] Our experience with aneurysm surgery proved this system to be useful in demonstrating the anatomy of the vessels and their blood flow before and after clipping.[22] In another article, Kamp *et al*. reviewed their first thirty patients with different cerebral vascular pathologies operated with the help of FLOW 800.[6] They compared hemodynamic characteristics of suspected ischemic brain tissue with normal tissue to judge the degree of brain ischemia in or around the lesions.

As reviewed above, various cervical, spinal, and cerebral vascular pathologies are addressed increasingly with the use of intraoperative FLOW 800, and more reports should be expected in the future to define its value and limitations for each pathology.

Conclusion

Advancements in medical facilities are to help physicians treat their patients in a more convenient yet efficient way. FLOW 800 helps surgeons with different aspects of AVM surgery including judging feeder and drainer, monitoring a gradual nidus occlusion during the operation, and finally checking for any AVM remnant after the resection. According to the current literature, we are not certain whether FLOW 800 is able to measure dynamic properties

of the pathological and normal brain tissues. However, we believe that this system is one of the tools to make surgeons feel more confident while performing AVM surgery by identifying arteries and veins. More data on the ground from different centers are required to define a definite role for its usage in AVM surgery and also to externally validate semi-quantitative data calculated by the software.

Conflicts of interest

There are no conflicts of interest.

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