



Application of Intraoperative FLOW 800 Indocyanine Green Videoangiography Color-Coded Maps for Microsurgical Clipping of Intracranial Aneurysms

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■ **OBJECTIVE:** Indocyanine green (ICG) videoangiography (VAG) is an established method for assessment of cerebral blood flow during microsurgical clipping of intracranial aneurysms. FLOW 800 is a surgical microscope-integrated software program that shows the cerebral blood flow in color-coded maps, thus providing semi-quantitative and real-time analysis of ICG data. We aimed to establish reference values for FLOW 800 parameters before and after microsurgical clipping of intracranial aneurysms and to evaluate the potential of FLOW 800 to guide intraoperative decisions.

■ **METHODS:** We retrospectively reviewed 54 patients (mean age, 53.6 ± 11.6 years) who underwent microsurgical clipping for 60 aneurysms and intraoperative evaluation of ICG fluorescence dynamics using FLOW 800 color-coded maps. FLOW 800 data were correlated with patient characteristics, clinical outcomes, and intraoperative decision making.

■ **RESULTS:** There were no significant differences in FLOW 800 data between ruptured and unruptured aneurysms ($P > 0.05$). Likewise, the hemodynamic parameters were not significantly different before and after definite clip placement ($P > 0.05$). However, in 2 cases, analysis of transit times by FLOW 800 analysis showed a hemodynamically significant clip stenosis that might have been missed by

conventional ICG-VAG and resulted in adjustment of the clip position. Overall, there was 1 cerebral infarction, which was not related to clip placement.

■ **CONCLUSIONS:** FLOW 800 is a useful adjunct to ICG-VAG for intraoperative assessment of cerebral perfusion and may help to identify hemodynamically relevant clip stenosis. The beneficial impact of FLOW 800 on clinical outcome after microsurgical clipping needs to be confirmed by comparative studies.

INTRODUCTION

Since its introduction in 2003, indocyanine green (ICG) videoangiography (VAG) has become a widely accepted technique for intraoperative assessment of aneurysm occlusion and parent artery patency during microsurgical clipping of intracranial aneurysms.¹ The feasibility and efficacy of this technique have been confirmed by several studies.²⁻⁷ Potential drawbacks of conventional ICG-VAG are that it can assess only the vasculature directly within the field of view and lacks any quantitative interpretation of the imaging data.⁸ Hence, a reliable assessment of cerebral blood flow can sometimes be difficult.

FLOW 800 is a surgical microscope-integrated software program that allows semi-quantitative analysis of ICG data via

Key words

- Aneurysm
- Cerebral infarction
- Clipping
- FLOW 800
- ICG

Abbreviations and Acronyms

- acTT:** Arteriocortical transit time
avTT: Arteriovenous transit time
CT: Computed tomography
DSA: Digital subtraction angiography
Fmax: Maximum fluorescence intensity
ICG: Indocyanine green
RIA: Ruptured intracranial aneurysm
ROI: Region of interest
SAH: Subarachnoid hemorrhage
TTP: Time-to-peak

UIA: Unruptured intracranial aneurysm

VAG: Videoangiography

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Table 1. Baseline Patient Characteristics

Characteristics	
Age (years)	
Mean \pm standard deviation	53.6 \pm 11.6
Range	25–76
Gender, n (%)	
Female	39 (72.2)
Male	15 (27.8)
Subarachnoid hemorrhage	
	43 (79.6)
World Federation of Neurosurgical Societies grade, n (%)	
1	15 (34.9)
2	10 (23.3)
3	8 (18.6)
4	3 (7.0)
5	7 (16.3)
Fisher grade, n (%)	
1	2 (4.7)
2	0 (0)
3	23 (53.5)
4	18 (41.9)

fluorescence dynamics.⁹ The software creates a color-coded map, which visualizes the direction and sequence of blood flow in the brain vessels based on the temporal fluorescence appearance after ICG injection. The analysis of fluorescence profiles allows a comparative assessment of the flow rate at specific regions of interest (ROIs) within the field of view.⁹ Although the use of FLOW 800 software for the microsurgical treatment of arteriovenous malformations has been reported in several studies,^{9–11} larger series on its use for intracranial aneurysms are

rare. Moreover, in the available literature, there is a lack of reference values of FLOW 800 parameters that describe the cerebral blood flow during aneurysm surgery.

The objective of this study was to report our single-center experience in using FLOW 800 software for in-depth analysis of cerebral blood flow during microsurgical clipping of 60 intracranial aneurysms. We calculated reference values for distinct parameters obtained by FLOW 800 software before and after clip placement. Moreover, we aimed to evaluate the cerebral infarction rate and the potential of FLOW 800 color-coded maps to guide intraoperative decisions.

METHODS

This is a retrospective single-center review of consecutive patients who underwent microsurgical clipping of ruptured (RIA) or unruptured (UIA) intracranial aneurysms and intraoperative evaluation of ICG fluorescence dynamics using FLOW 800 color-coded maps. According to the institutional guidelines, no ethics committee approval was required for this retrospective study.

Procedural Details

The patients underwent a routine digital subtraction angiography (DSA) scan before surgery to confirm aneurysm location, size, and morphology. The decision for surgical aneurysm treatment was made on a case-by-case basis after interdisciplinary discussion and consensus among vascular neurosurgeons and neurointerventionalists. A pterional craniotomy was the standard approach for aneurysms of the middle cerebral artery, posterior communicating artery, and internal carotid artery. Anterior communicating artery aneurysms were accessed via a pterional or a midline approach via frontal craniotomy. In cases of the pterional approach, the sylvian fissure was split according to the exposure needed. The pericallosal artery aneurysms were accessed via an interhemispheric approach after frontal craniotomy. The posterior inferior cerebellar artery aneurysm was clipped via a suboccipital approach. The posterior cerebral artery aneurysm was clipped after subtemporal craniotomy. Proximal control of the main arteries was achieved by carefully dissecting the arachnoid membrane around the arteries until a temporary clip could be placed. If necessary, after complete dissection of the aneurysm neck and dome was performed, the intraoperative findings were correlated with three-dimensional angiography to contemplate a clipping strategy and to select the appropriate aneurysm clips. For intraoperative assessment of aneurysm occlusion and parent artery patency, microDoppler ultrasonography and ICG-VAG were performed. After surgery, the patients were admitted to an intensive care unit. A cranial computed tomography (CT) scan was performed on the first postoperative day to exclude rebleeding and cerebral infarction. In patients with subarachnoid hemorrhage (SAH), transcranial Doppler ultrasonography was performed on a daily basis to determine the blood flow velocity in the brain vessels. A mean cerebral blood flow velocity ≥ 120 cm/second and/or an increase by ≥ 50 cm/second within 24 hours was considered as indicative for cerebral vasospasm.¹² In case of new neurologic deficits or suspicion of vasospasm, a cranial CT scan with angiography and perfusion was additionally performed.

Table 2. Baseline Aneurysm Characteristics

Variable	Value (n = 60)
Aneurysm location	
Anterior communicating artery	20 (33.3)
Pericallosal artery	3 (5.0)
Middle cerebral artery	19 (31.7)
Internal carotid artery	5 (8.3)
Posterior communicating artery	11 (18.3)
Posterior inferior cerebellar artery	1 (1.7)
Posterior cerebral artery	1 (1.7)
Aneurysm size (mm)	5.7 \pm 2.8
Neck width (mm)	3.9 \pm 1.7
Values are number (%) except where indicated otherwise.	

Table 3. Mean Values for Delay, Time-To-Peak, Maximum Fluorescence Intensity, Arterioarterial Transit Time, Arteriocortical Transit Time, and Arteriovenous Transit Time Before and After Clip Placement

Variable	Before Clip Placement (n = 23)	After Clip Placement (n = 56)	P Value
Arterial delay (seconds)	18.8 ± 8.0 (8.3–38.9)	18.2 ± 11.0 (4.2–73.5)	0.8
Cortical delay (seconds)	20.7 ± 8.1 (9.6–40.3)	19.7 ± 11.4 (1.9 ± 75.1)	0.7
Venous delay (seconds)	24.0 ± 7.3 (12.0–41.6)	23.5 ± 11.4 (5.3 ± 77.5)	1.0
Arterial TTP (seconds)	21.9 ± 8.9 (10.7 ± 43.2)	21.6 ± 12.2 (6.3 ± 75.7)	0.9
Venous TTP (seconds)	32.2 ± 8.0 (23.5 ± 41.5)	31.6 ± 14.7 (13.9–80.3)	0.9
Arterial Fmax (AI)	906 ± 346 (298–1639)	742 ± 328 (230–1685)	0.1
Venous Fmax (AI)	634 ± 234 (180–931)	530 ± 291 (151–1600)	0.3
Arterioarterial transit time (seconds)	0.1 ± 0.2 (0.0–0.4)	0.13 ± 0.5 (0.0–0.7)	0.8
Arteriocortical transit time (seconds)	1.9 ± 0.9 (0.6–3.8)	2.0 ± 0.8 (0.6–4.9)	0.7
Arteriovenous transit time (seconds)	5.2 ± 2.3 (1.3–9.0)	5.6 ± 2.4 (1.3–14.3)	0.4

TTP, time-to-peak; Fmax, maximum fluorescence intensity; AI, average intensity.

FLOW 800 Analysis

For intraoperative analysis of cerebral blood flow, we used an OPMI Pentero surgical microscope with integrated ICG technology (Carl Zeiss GmbH, Oberkochen, Germany). The use of ICG for aneurysm surgery represents an established technique and has been described in detail previously.⁴ After intravenous administration of 10 mg ICG, fluorescence is induced with a microscope-integrated light source (wavelength, 700–800 nm) and recorded by a nonintensified camera, allowing for a real-time evaluation of arterial, cortical, and venous blood flow. The number of intraoperative ICG runs was left at the discretion of the neurosurgeon. Generally, intraoperative ICG-VAG was performed at baseline and after permanent clip placement. In case of clip repositioning, the ICG-VAG was repeated.

The surgical microscope was equipped with the FLOW 800 software module (Release 2.21 [Carl Zeiss GmbH, Oberkochen, Germany]), which enables semi-quantitative and real-time analysis of the ICG data. After injection of ICG, the software continuously records the fluorescence intensity as arbitrary intensity units at all image points within the field of view and automatically compiles the video data obtained by the nonintensified camera into a color-coded map. These maps visualize the sequence of fluorescence appearance for each image point using an intuitive color scale, highlighting regions with early appearance of fluorescence (e.g., arteries) in red and regions with late appearance in blue (e.g., veins). For in-depth evaluation of blood flow in specific areas within the field of view, the fluorescence intensity profile can be determined and compared in up to 8 freely definable ROIs.

In the current study, we analyzed the following parameters based on the fluorescence intensity curves:

- 1) The maximum fluorescence intensity at a specific ROI after application of ICG is denoted as maximum fluorescence intensity (Fmax).
- 2) The time-to-peak (TTP) is the interval between baseline and Fmax.

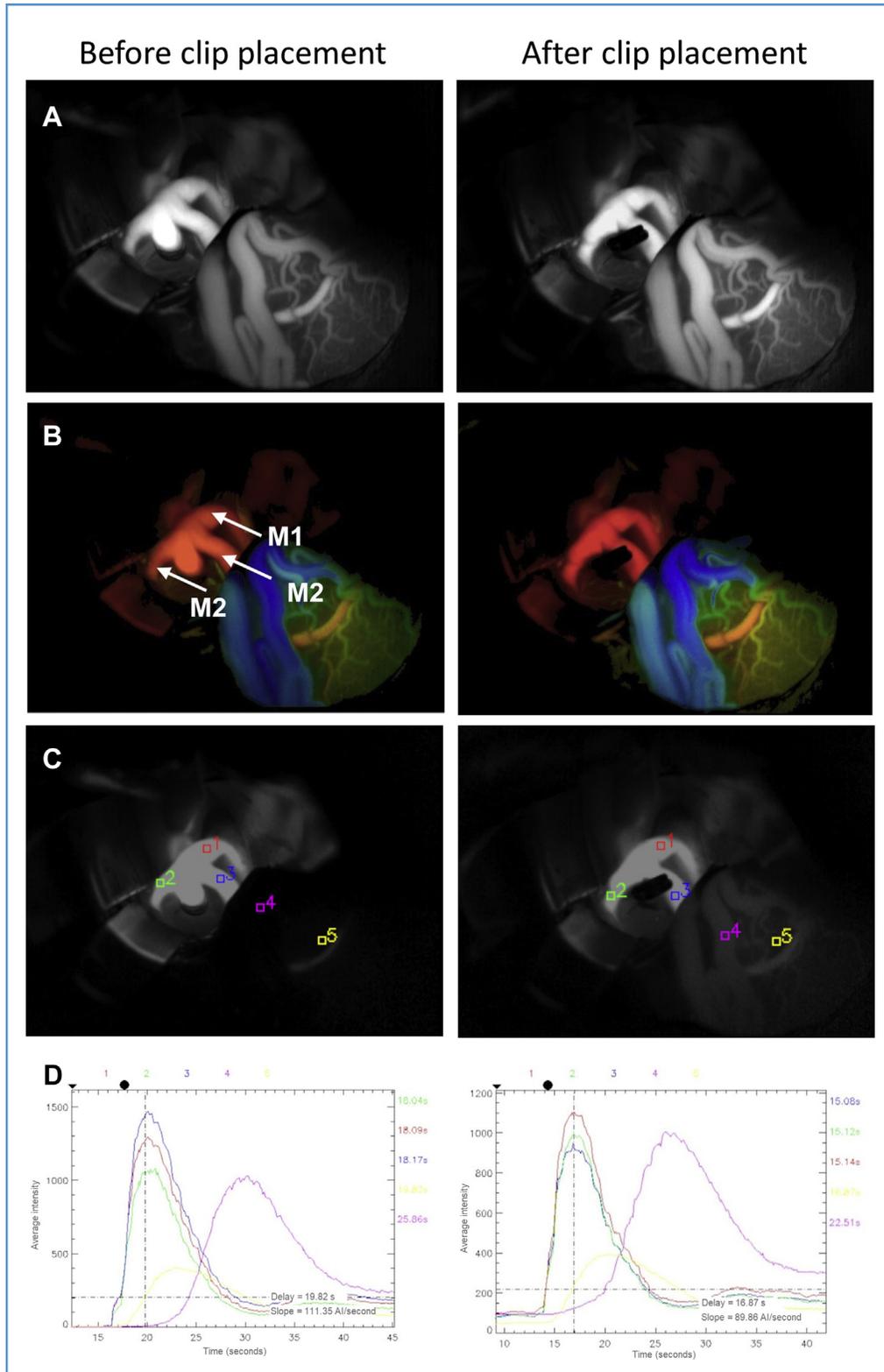
- 3) The delay is defined as the time interval (in seconds) between baseline and half-Fmax at any specific ROI within the surgical site.
- 4) The time interval between the delay in afferent arteries and efferent arteries was denominated as arterioarterial transit time (aaTT), that between arteries and cortical capillaries as arteriocortical transit time (acTT), and that between arteries and veins as arteriovenous transit time (avTT), respectively.

Data Collection

The following variables were collected retrospectively from the medical charts and operation records: patient age, gender, initial neurologic status, aneurysm rupture status, World Federation of Neurological Societies grading scale score, Fisher score, temporary parent artery clipping, clip repositioning, procedure-related cerebral infarction, number of ICG runs, and FLOW 800 results. Procedure-related cerebral infarction was defined as any new ischemic lesion on postoperative CT or magnetic resonance imaging within 48 hours after surgery that could be clearly related temporally and spatially to the clipping procedure and the parent artery of the treated aneurysm. The CT and magnetic resonance imaging scans were thoroughly reviewed to evaluate if vasospasm was present, which might have been the cause for cerebral infarction.

Statistical Analysis

For statistical analysis, the collected data from the FLOW 800 module were exported in an MS Excel file. Categorical variables were presented as numbers and percentages and compared using the χ^2 and Fisher exact tests, when appropriate. Continuous variables were presented as means ± standard deviation and tested for normality using the Shapiro-Wilk test. Groups were compared using the 2-sided unpaired Student t test (for normally distributed data) and the Mann-Whitney U test (for nonnormally distributed data). All calculations were performed using SPSS software



(version 25 [IBM Corp., Armonk, New York, USA]). A P value < 0.05 was considered as statistically significant.

RESULTS

Patient and Aneurysm Characteristics

The study population consisted of 54 patients who underwent 56 procedures for microsurgical clipping of 60 aneurysms. Of these patients, 11 (13 procedures, 15 aneurysms) were treated for unruptured aneurysms on an elective basis and 43 (43 procedures, 45 aneurysms) with SAH were treated for a ruptured aneurysm. The mean patient age was 53.6 ± 11.6 years (range, 25–76 years) and 39 patients (72.2%) were female. Among the 43 patients with SAH, 10 (23.3%) had an initial World Federation of Neurosurgical Societies score of 4 or 5 and 18 patients (41.9%) presented with Fisher grade 4 bleeding. Baseline patient characteristics are summarized in [Table 1](#).

Of 60 aneurysms, 20 (33.3%) were located at the anterior communicating artery, 19 (31.7%) at the middle cerebral artery, 11 (18.3%) at the posterior communicating artery, 5 (8.3%) at the internal carotid artery, 3 (5.0%) at the pericallosal artery and 2 (3.3%) at the posterior circulation.

The mean aneurysm size was 5.7 ± 2.8 mm and the mean neck width was 3.9 ± 1.7 mm. Baseline aneurysm characteristics are listed in [Table 2](#).

FLOW 800 Analysis

A total of 81 ICG-VAGs were performed, representing an average of 1.4 ICG investigations per procedure. ICG investigation and subsequent FLOW 800 analysis were feasible and conclusive in all cases. The mean values for delay, TTP, Fmax, and transit times at baseline are listed in [Table 3](#). Before clip placement, the mean arterial delay was 18.8 ± 8.0 seconds (range, 8.3–38.9 seconds). The mean cortical delay was 20.7 ± 8.1 seconds (range, 9.6–40.3 seconds) and the mean venous delay was 24.0 ± 7.3 seconds (range, 12.0–41.6 seconds). The mean aaTT at baseline was 0.1 ± 0.2 seconds (range, 0.0–0.4 seconds), the acTT was 1.9 ± 0.9 seconds (range, 0.6–3.8 seconds) and the avTT was 5.2 ± 2.3 seconds (range, 1.3–9.0 seconds). There were no significant differences in any of the analyzed parameters between the UIA group and the RIA group ($P > 0.05$, respectively).

Mean values for delay, TTP, Fmax, and transit times after clip placement are listed in [Table 3](#). After permanent clip placement, the mean arterial delay was 18.2 ± 11.0 seconds and ranged from 4.2 to 73.5 seconds. The mean cortical delay was 19.7 ± 11.4 seconds (range, 1.9–75.1 seconds) and the mean venous

delay was 23.5 ± 11.4 seconds (range, 5.3–77.5 seconds). After clip placement, the mean aaTT was 0.13 ± 0.5 seconds (range, 0.0–0.7 seconds), the mean acTT 2.0 ± 0.8 seconds (range, 0.6–4.9 seconds), and the mean avTT was 5.6 ± 2.4 seconds (range, 1.3–14.3 seconds). There were no significant differences in any of the analyzed parameters between the UIA group and the RIA group ($P > 0.05$, respectively). Furthermore, there was no significant difference in the analyzed parameters before and after permanent clip placement ($P > 0.05$, respectively; [Table 3](#)).

There was a strong correlation between arterial and cortical delay ($R = 0.997$; $P < 0.001$) and between arterial and venous delay ($R = 0.972$; $P < 0.007$), respectively. Moreover, acTT correlated significantly with avTT ($R = 0.698$; $P < 0.001$).

An illustrative case of FLOW 800 analysis before and after clip placement is shown in [Figure 1](#).

Clip Repositioning and Infarction Rate

Overall, repositioning of the aneurysm clip was performed in 10 cases (17.9%). Of these cases, clip repositioning was performed in 2 cases after FLOW 800 analysis. The absolute values for aaTT, acTT, and avTT in both patients before and after clip placements are listed in [Table 4](#). In both patients, after initial clip placement, ICG-VAG did not show a clear stenosis of the parent artery. However, in the first patient the results of the FLOW 800 analysis showed an increased acTT (3.7 seconds), and a slightly prolonged avTT (5.9 seconds) compared with the average values as shown in [Table 3](#). After clip repositioning, both parameters were within normal ranges (acTT, 2.6 seconds; avTT, 5.2 seconds). A baseline ICG run was not performed in this patient; however, a relatively high acTT after initial clip placement indicated parent vessel stenosis. In the second patient, aaTT (3.92 seconds), acTT (2.7 seconds), and in particular avTT (8.6 seconds) were markedly increased compared with baseline (aaTT, 0.31 seconds; acTT, 2.1 seconds; avTT, 3.4 seconds). After replacement of the aneurysm clips, the TTs were back to normal (aaTT, 0.30 seconds; acTT, 1.5 seconds; avTT, 3.3 seconds). Both patients were free of symptoms after surgery and cerebral infarction was excluded by postoperative CT.

The rates for overall and symptomatic cerebral infarction were 1.8% (1/56), respectively. The only patient with postoperative infarction was clipped for a recurrent previously ruptured anterior communicating artery aneurysm. The infarction was caused by accidental perforator injury after pterional craniotomy and was not related to parent artery stenosis. The patient had a motor aphasia postoperatively and was transferred to a rehabilitation center with mild disability (modified Rankin Scale score 1).

Figure 1. A 55-year-old woman underwent microsurgical clipping for an unruptured aneurysm at the right middle cerebral artery bifurcation. (A) Indocyanine green (ICG) videoangiography (10 mg ICG intravenously) as seen through the operating microscope before and after clip placement. (B) FLOW 800 software analyzes the fluorescence intensity as function of time and provides a color-coded map that shows the brain vessels in contrasting colors depending on the fluorescence appearance after ICG injection (arteries, red; cortical capillaries, yellow/green; veins, blue). (C) Furthermore, FLOW 800 software enables a detailed analysis of the fluorescence profile at specific regions of interests (e.g., parent artery [1, M1 segment, 2 and 3, M2 segments]), cortical capillaries (5) and cortical veins (4). (D) The fluorescence intensity shown as arbitrary intensity units as function of time within the regions of interests. Based on these curves, maximum fluorescence intensity, delay, and transit times can be readily calculated. After clip placement, the fluorescence curves show a similar profile to that before clip placement, in particular in the cortical capillaries and the veins, which is indicative for an undisturbed blood flow in the branching vessels. AI, average intensity.

Table 4. Values for Arterioarterial Transit Time, Arteriocortical Transit Time and Arteriovenous Transit Time for 2 Patients, in Which the Clip Was Repositioned After FLOW 800 Analysis

Case Number	Aneurysm Location	Arterioarterial Transit Time (seconds)			Arteriocortical Transit Time (seconds)			Arteriovenous Transit Time (seconds)		
		Baseline	Clip1	Clip2	Baseline	Clip1	Clip2	Baseline	Clip1	Clip2
1	MCA (ruptured)	N/D	0.15	0.11	N/D	3.7	2.6	N/D	5.9	5.2
2	MCA (unruptured)	0.31	3.92	0.30	2.1	2.7	1.5	3.4	8.6	3.3

MCA, middle cerebral artery; N/D, not done.

An illustrative case for clip replacement after FLOW 800 analysis caused by parent artery stenosis is shown in [Figure 2](#).

DISCUSSION

The current study investigated the feasibility and efficacy of FLOW 800 software as adjunct to conventional ICG-VAG, which allows semi-quantitative and real-time evaluation of cerebral blood flow during microsurgical clipping of intracranial aneurysms. In 2 cases, the results of the imaging study provided additional information and altered the surgical strategy. The rate of cerebral infarction related to clip position was 0%. To the best of our knowledge, our series represents the largest study on the use of intraoperative FLOW 800 software for microsurgical treatment of intracranial aneurysms.

Microsurgical clipping of intracranial aneurysms can be difficult and is associated with a low but not negligible risk of cerebral infarction, which is a major cause of disability related to aneurysm surgery.¹³ The overall incidence of symptomatic and asymptomatic cerebral infarction after microsurgical clipping of UIAs was 10.9% (208/1917) in the International Study of Unruptured Intracranial Aneurysms (ISUIA),¹⁴ 12.1% (44/363) in the study by Kunz et al.,¹³ and 12.6% (43/338) in the study by Li et al.¹⁵ Among ruptured aneurysms, cerebral infarction was reported in 21.0% (33/157) by Goertz et al.¹⁶ and in 45.3% (163/360) by Yao et al.¹⁷

Intraoperative DSA represents the gold standard for intraoperative assessment of vessel patency and aneurysm occlusion.⁸ The use of this technique has been recommended by several investigators and might alter the surgical strategy in 7%–34% of cases.⁴ However, it can be difficult to predict the need for intraoperative DSA on a selective basis.¹⁸ Moreover, because intraoperative DSA is elaborate and time-consuming, it has not been established as a standard diagnostic tool for intraoperative assessment of cerebral blood flow in many neurovascular centers.⁴

Compared with intraoperative DSA, surgical microscope-integrated ICG-VAG represents a simple and time-efficient method for intraoperative analysis of parent artery patency and aneurysm occlusion. In the prospective study by Raabe et al.,⁴ adjustment of the aneurysm clip was performed in 9% based on the information provided by ICG-VAG and there was no incidence of clinically relevant parent artery stenosis. Likewise, Jing et al.⁵ reported a clip repositioning rate of 11.9% after ICG-VAG

and a strong correlation between ICG-VAG and postoperative angiography. Hardesty et al.¹⁹ compared ICG-VAG and intraoperative DSA and reported similar rates of ischemic stroke and clip repositioning in both groups.

Although these results seem promising, some concerns are raised regarding the accuracy and the lack of measurable quantitative values of ICG-VAG. For instance, Washington et al.⁸ compared ICG-VAG and intraoperative DSA in 49 patients and calculated an agreement rate of only 75.5% between the 2 techniques. Furthermore, these investigators reported that ICG-VAG missed 3 aneurysm remnants and 4 vessel occlusions (14.3%) that required clip adjustment after performance of intraoperative DSA. The investigators attributed these adjustments to obscuration of the clipped aneurysm or the parent artery from the field of view and the presence of fluorescence dye within the affected vessel via collateral blood flow.⁸

Although conventional ICG-VAG allows only a subjective assessment of cerebral blood flow in aneurysms and arteries, FLOW 800 software provides additional semi-quantitative information of the fluorescence profile in brain vessels in real time.⁹ This method required the same technical setup as for conventional ICG-VAG, with the exception of the additional FLOW 800 software module. FLOW 800 provides a color-coded map that highlights the brain vessels in different colors for optimized assessment of the vascular anatomy. The software does not measure the absolute blood flow in brain vessels but allows a comparative assessment of blood flow in the vasculature within the field of view based on the recorded fluorescence intensity profile.

In the current study, we reported the average values for several parameters obtained by FLOW 800 analysis both before and after clip placement. The baseline values obtained in our series are within the range of similar studies. For instance, Kamp et al.²⁰ reported a mean acTT of 1.5 seconds, which is comparable to our results (1.9 ± 0.9 seconds). In the study by Schubert et al.,²¹ the mean avTT was 4.3–4.5 seconds and thus in the range of our findings (5.2 ± 2.3).

There were no statistically significant differences of baseline values between patients who had SAH and those who did not have SAH. This finding might be related to the fact that most patients underwent microsurgical clipping before the onset of vasospasm. It might be speculated that the transit times are altered in patients with severe vasospasm because of narrowing of the brain vessels.^{22,23}

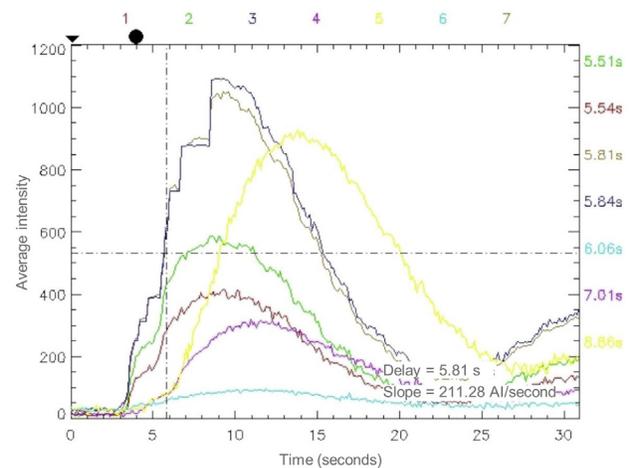
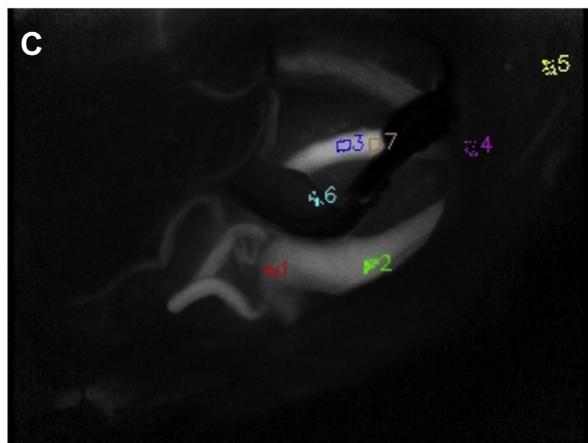
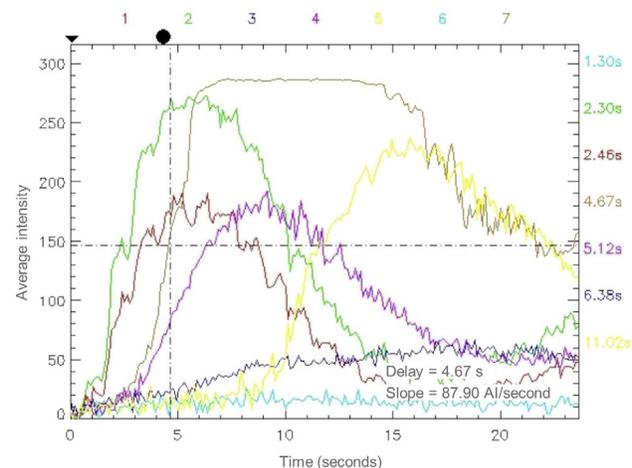
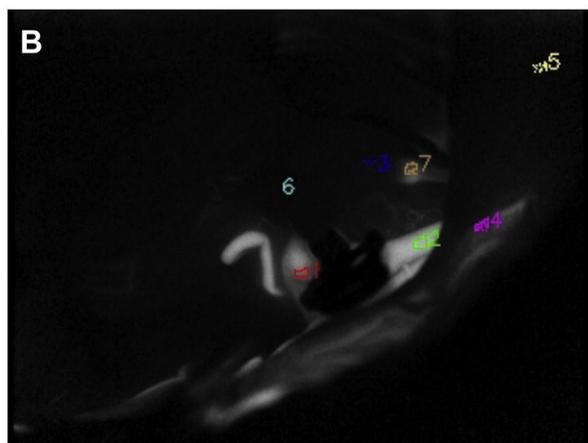
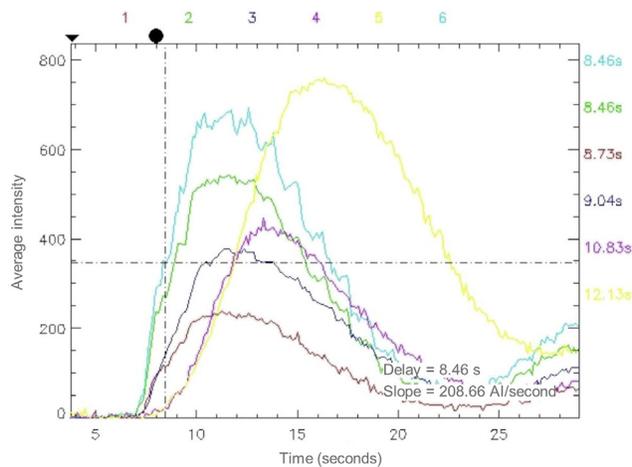
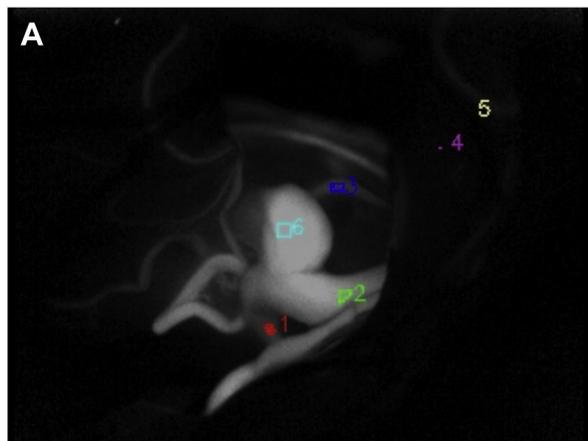


Figure 2. A 43-year-old female patient underwent microsurgical clipping for an unruptured aneurysm at the left middle cerebral artery bifurcation. **(A)** The baseline fluorescence profile in arteries (1, 2, 3), the cortical capillaries (4), veins (5), and the aneurysm (6) before clip placement. **(B)** After initial clip placement the fluorescence intensity in the aneurysm (6) is markedly reduced, indicating sufficient occlusion of the aneurysm. However, FLOW 800 analysis shows delayed filling of the temporal M2 segment (3), the cortical capillaries (4), and veins (5), representing a stenosis of the M2 segment by the clip branches. A detailed analysis of the intensity curves by FLOW 800 software showed a marked increase

of the arterioarterial transit time (TT) in the M1 and M2 segments (before clipping, 0.31 seconds; after clipping, 3.92 seconds). Moreover, there was an increase in the arteriovenous TT (before clipping, 3.4 seconds; after clipping, 8.56 seconds) and the arteriocortical TT (before clipping, 2.1 seconds; after clipping, 2.66 seconds). **(C)** After clip replacement, the values normalized (arterioarterial TT: 0.3 seconds; arteriovenous TT, 3.3 seconds; arteriocortical TT, 1.47 seconds). Postoperative computed tomography excluded cerebral infarction (not shown) and the patient was free of symptoms. AI, average intensity.

The analyzed FLOW 800 parameters were not significantly different at baseline and after definite clip placement, which could be expected, because vessel patency and blood flow should not be impaired by proper clip positioning.

The parameters in our study were associated with a relatively large standard deviation, in particular the parameters delay, TTP, and Fmax, which represent absolute numbers. Although we aimed to standardize the ICG procedures including administration of a constant ICG bolus, maintaining constant circulation parameters between the ICG runs and optimized time management (interval from bolus application to manual start of the program), these parameters showed a great variability between the individuals. Moreover, the parameters even showed a pronounced intra-individual variability in patients with multiple ICG runs. One reason for the great variability of data might be that synchronization of ICG administration of the anesthesiologist and start of data acquisition by the neurosurgeon can be challenging in a real-world surgical setting. Furthermore, we attribute this large range to differences in the heart rate, blood flow velocity, volume status, blood pressure, patient size, changing the surgical field, and number of previous ICG runs, which may increase the background fluorescence. Because we report our real-world experience with FLOW 800, we did not systematically analyze the intraindividual and interindividual variability of FLOW 800 data. Hence, determination of cutoff values for delay, TTP, and Fmax that indicate pathologic blood flow seems to be difficult.

For this reason, we advocate performing a baseline analysis first, which can be compared with the fluorescence profile after clip placement. Furthermore, we believe that comparative assessment of transit times (i.e., aaTT, acTT, and avTT) before and after clip placement is the most useful approach to identifying hemodynamically relevant clip stenosis, because these parameters represent relative numbers and are thus more robust against influencing factors compared with absolute numbers (e.g., delay, TTP, and Fmax). Moreover, intraoperative assessment of the transit time is simple, because it requires only determination of blood flow in the afferent parent artery and the efferent arteries (i.e., aaTT), cortical vessels (i.e., acTT), and veins (i.e., avTT). The transit times had a smaller range and standard deviation and showed a higher consistency among repeated measurements in a single patient compared with the delay. As also shown in [Figure 2](#), an increase of transit times between parent and branching arteries or between parent arteries and cortical capillaries may be indicative of reduced blood flow, even if the conventional ICG-VAG may appear normal or the parent artery is obscured from the field of view by the aneurysm clip or by surrounding structures.

Using this approach, we were able to detect hemodynamically relevant stenosis in 2 patients (3.3%), which would have been missed by ICG-VAG alone. In both patients, the information obtained from the analysis altered the surgical strategy and resulted in repositioning of the aneurysm clips. Afterward, the cerebral blood flow profile normalized and cerebral infarction was excluded by postoperative CT in both patients.

A lesson learnt from the 2 cases with parent artery stenosis after initial clip placement is that calculation of all transit times

(aaTT, acT, and avTT) is necessary to evaluate cerebral blood flow accurately. For instance, although acTT was markedly increased in the first case, aaTT and avTT showed the strongest increase in the second case. The definition of cutoff values for transit times remains challenging, especially because of the limited number of cases with disturbed perfusion in our series. From our clinical experience and because of a certain interindividual variability, we recommend performing FLOW 800 measurements before and after clipping. Any prolongation in transit time should be indicative for careful further surgical inspection and may require clip repositioning.

The overall rate of procedural infarction was 1.8% in a mixed population of ruptured and unruptured aneurysms, which is considerably lower than in the studies cited earlier. In the only patient with cerebral infarction, brain damage was caused by perforator injury and not attributable to clip placement.

In the 2 patients with clip repositioning after FLOW 800 analysis, it remains speculative whether the parent artery stenosis after initial clip placement would have resulted in clinically relevant cerebral infarction. Because we did not perform a comparative study, the beneficial impact of FLOW 800 analysis on clinical outcome after microsurgical clipping remains unanswered and should be addressed by further studies.

Limitations

The limitations of this study are mainly related to its retrospective design. FLOW 800 analysis was used at the discretion of the neurosurgeon and not in a standardized fashion, which complicates the interpretation of the results. Baseline ICG-VAG was missing in several cases. Moreover, we did not include a control group, which makes comparison with other intraoperative techniques difficult. Because we conducted a single-center study, the number of included patients was only moderate. A further limitation was that the differentiation between procedure-related infarction and vasospastic ischemia is difficult in patients with SAH, which in turn can lead to a bias of the interpretation of the imaging results. Being aware of these limitations, we showed that FLOW 800 analysis can provide additional information to ICG-VAG to detect hemodynamically relevant artery stenosis intraoperatively, which might further increase the safety of microsurgical clipping. Larger and comparative studies are necessary to provide a definite conclusion on this method.

CONCLUSIONS

FLOW 800 software provides semi-quantitative and real-time analysis of ICG data, which allows comparative analysis of cerebral blood flow during clipping of intracranial aneurysms. In our study, FLOW 800 analysis showed 2 hemodynamically significant clip stenoses that would have been missed by conventional ICG-VAG and resulted in adjustment of the clip position. The beneficial impact of FLOW 800 on clinical outcome after microsurgical clipping needs to be confirmed in further studies.

REFERENCES

1. Raabe A, Beck J, Gerlach R, Zimmermann M, Seifert V. Near-infrared indocyanine green video angiography: a new method for intraoperative assessment of vascular flow. *Neurosurgery*. 2003;52:132-139.
2. Roessler K, Krawagna M, Dörfler A, Buchfelder M, Ganslandt O. Essentials in intraoperative indocyanine green videoangiography assessment for intracranial aneurysm surgery: conclusions from 295 consecutively clipped aneurysms and review of the literature. *Neurosurg Focus*. 2014;36:E7.
3. de Oliveira JG, Beck J, Seifert V, Teixeira MJ, Raabe A. Assessment of flow in perforating arteries during intracranial aneurysm surgery using intraoperative near-infrared indocyanine green videoangiography. *Neurosurgery*. 2007;61(3 suppl):63-72 [discussion: 72-73].
4. Raabe A, Beck J, Seifert V. Technique and image quality of intraoperative indocyanine green angiography during aneurysm surgery using surgical microscope integrated near-infrared video technology. *Zentralbl Neurochir*. 2005;66:1-6.
5. Jing Z, Ou S, Ban Y, Tong Z, Wang Y. Intraoperative assessment of anterior circulation aneurysms using the indocyanine green video angiography technique. *J Clin Neurosci*. 2010;17:26-28.
6. Ferroli P, Nakaji P, Acerbi F, Albanese E, Broggi G. Indocyanine green (ICG) temporary clipping test to assess collateral circulation before venous sacrifice. *World Neurosurg*. 2011;75:122-125.
7. Imizu S, Kato Y, Sangli A, Oguri D, Sano H. Assessment of incomplete clipping of aneurysms intraoperatively by a near-infrared indocyanine green-video angiography (Niicg-Va) integrated microscope. *Minim Invasive Neurosurg*. 2008;51:199-203.
8. Washington CW, Zipfel GJ, Chicoine MR, et al. Comparing indocyanine green videoangiography to the gold standard of intraoperative digital subtraction angiography used in aneurysm surgery. *J Neurosurg*. 2013;118:420-427.
9. Shah KJ, Cohen-Gadol AA. The application of FLOW 800 ICG videoangiography color maps for neurovascular surgery and intraoperative decision making. *World Neurosurg*. 2019;122:e186-e197.
10. Fukuda K, Kataoka H, Nakajima N, Masuoka J, Satow T, Iihara K. Efficacy of FLOW 800 with indocyanine green videoangiography for the quantitative assessment of flow dynamics in cerebral arteriovenous malformation surgery. *World Neurosurg*. 2015;83:203-210.
11. Kalyvas J, Spetzler RF. Does FLOW 800 technology improve the utility of indocyanine green videoangiography in cerebral arteriovenous malformation surgery? *World Neurosurg*. 2015;83:147-148.
12. Viski S, Olah L. Use of transcranial Doppler in intensive care unit. *J Crit Care Med*. 2017;3:99-104.
13. Kunz M, Bakhshai Y, Zausinger S, et al. Interdisciplinary treatment of unruptured intracranial aneurysms: impact of intraprocedural rupture and ischemia in 563 aneurysms. *J Neurol*. 2013;260:1304-1313.
14. Wiebers DO, Whisnant JP, Huston J 3rd, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362:103-110.
15. Li M, Wu J, Chen X, et al. Symptomatic and silent cerebral infarction following surgical clipping of unruptured intracranial aneurysms: incidence, risk factors, and clinical outcome. *Neurosurg Rev*. 2018;41:675-682.
16. Goertz L, Kabbasch C, Borggreffe J, et al. Preoperative three-dimensional angiography may reduce ischemic complications during clipping of ruptured intracranial aneurysms. *World Neurosurg*. 2018;120:e1163-e1170.
17. Yao P-S, Chen G-R, Zheng S-F, Kang D-Z. Predictors of postoperative cerebral ischemia in patients with ruptured anterior communicating artery aneurysms. *World Neurosurg*. 2017;103:241-247.
18. Klopfenstein JD, Spetzler RF, Kim LJ, et al. Comparison of routine and selective use of intraoperative angiography during aneurysm surgery: a prospective assessment. *J Neurosurg*. 2004;100:230-235.
19. Hardesty DA, Thind H, Zabramski JM, Spetzler RF, Nakaji P. Safety, efficacy, and cost of intraoperative indocyanine green angiography compared to intraoperative catheter angiography in cerebral aneurysm surgery. *J Clin Neurosci*. 2014;21:1377-1382.
20. Kamp MA, Slotty P, Turowski B, et al. Microscope-integrated quantitative analysis of intraoperative indocyanine green fluorescence angiography for blood flow assessment: first experience in 30 patients. *Neurosurgery*. 2012;70:65-73 [discussion: 73-74].
21. Schubert GA, Seiz-Rosenhagen M, Ortler M, Czabanka M, Scheufler KM, Thome C. Cortical indocyanine green videography for quantification of acute hypoperfusion after subarachnoid hemorrhage: a feasibility study. *Neurosurgery*. 2012;71:ons260-ons267 [discussion: ons267-ons268].
22. Ohkuma H, Manabe H, Tanaka M, Suzuki S. Impact of cerebral microcirculatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2000;31:1621-1627.
23. Grosset D, Straiton J, Du Trevou M, Bullock R. Prediction of symptomatic vasospasm after subarachnoid hemorrhage by rapidly increasing transcranial Doppler velocity and cerebral blood flow changes. *Stroke*. 1992;23:674-679.

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