Quantitative Blood Flow Assessment by Multiparameter Analysis of Indocyanine Green Video Angiography

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BACKGROUND: **Measurements of quantitative blood flow are crucial during brain vascular surgery. Indocyanine green video angiography (ICG-VAG) is an accepted method of blood flow visualization; however, quantitative techniques have not yet been established. Thus, the aim of this study was to further develop ICG analysis for visualizing intraoperative flow changes.**

METHODS: **We conducted basic experiments and clinical investigations to establish a relationship between ICG-VAG and measured blood flow. We evaluated several parameters and identified optimal indicators that precisely reflect blood (or fluid) flow. Both in vitro and in vivo studies were performed to calculate the interval between baseline and the intensity peak (Grad) and to measure actual flow rate.**

RESULTS: **Grad and actual flow rate showed good exponential correlation, with R^2 values of 0.90 in vitro and 0.82 in vivo. In a representative patient (case 3), we performed intraoperative flow analysis using FlowInsight, which identified a marked elevation in Grad on the brain surface. Because this observation is predictive of brain hyperperfusion, we used these data to carefully manage blood pressure postoperatively.**

CONCLUSIONS: **Grad is the optimum parameter for estimating flow conditions. Although ICG-VAG provides only visual profiles of blood circulation in the brain, this procedure has the potential to be widely used in clinical situations. ICG-based flow measurement can be used to identify normal and abnormal blood flow conditions, such as graft flow and vascular pathology. The novelty of this technique is that the fluorescence intensity of Grad enables surgeons to quantitatively measure real blood flow.**

INTRODUCTION

The fluorescent dye indocyanine green (ICG) has been used clinically to evaluate cardiac output[1] and hepatic function and in ophthalmic angiography for more than 3 decades. It shows peak spectral absorption at approximately 830 nm with an excitation wavelength of 800 nm. ICG binds tightly to plasma proteins and lipids and emits fluorescence signals in vascular structures, making it possible to observe blood flow conditions in both arterial and venous structures during vascular neurosurgery under a microscope. ICG has a half-life of 150–180 seconds and is removed from the circulation exclusively by the liver. This brief half-life permits repeat ICG injections and comparisons of blood flow status before and after neurosurgical procedures.

The first clinical application of ICG, termed ICG video angiography (ICG-VAG), was described in 2003 by Raabe et al.[2] ICG-VAG reveals gray-scale intensity changes in florescence signals over time

Key words
- Flow assessment
- FlowInsight
- Indocyanine green
- Quantitative
- Video angiography

Abbreviations and Acronyms
AT: Arrival time
BV: Blood volume
CEA: Carotid endarterectomy
ECA: External carotid artery
FBS: Fetal bovine serum
Grad: gradient
ICA: Internal carotid artery
ICG: Indocyanine green
IMP SPECT: 123I-N-isopropyl-p-iodoamphetamine single-photon emission computed tomography
MFV: Mean flow velocity
ROI: Region of interest
SPECT: Single-photon emission computed tomography
TTFM: Transit time ultrasound flowmeter

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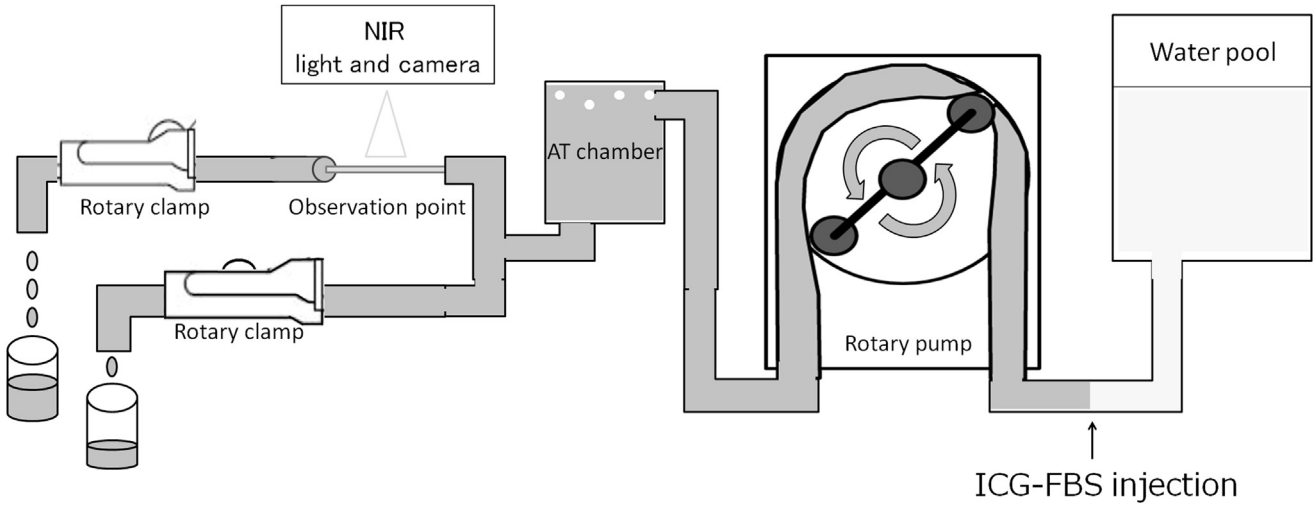

Figure 1. Indocyanine green (ICG) flow phantom model and video angiography system. A rotary pump provides constant pulsatile flow at 150 mL/min. The air trap chamber is useful for trapping small air bubbles and diluting the ICG dye. Flow rates at observation points were varied using 2 rotary clamps. NIR, near-infrared; FBS, fetal bovine serum.

and is used to confirm complete clipping of aneurysms, apart from patency of branch arteries and bypass grafts. Although currently ICG-VAG provides only qualitative or semiquantitative evaluation, we strongly believe that it is essential to establish quantitative evaluation by analyzing changes in ICG intensity over time. Previously published reports, including those from our laboratory, have suggested possible correlations between some of the parameters related to ICG-VAG analysis and actual blood flow measured with a transit-time flowmeter.[3,4]

Based on the foregoing factors, we believe that quantitative ICG-VAG measurement will have a significant clinical impact in vascular brain surgery. Thus, we designed a 2-step study that consisted of basic experiments and clinical investigations of ICG-VAG to determine optimal parameters for quantitative measurement of blood flow.

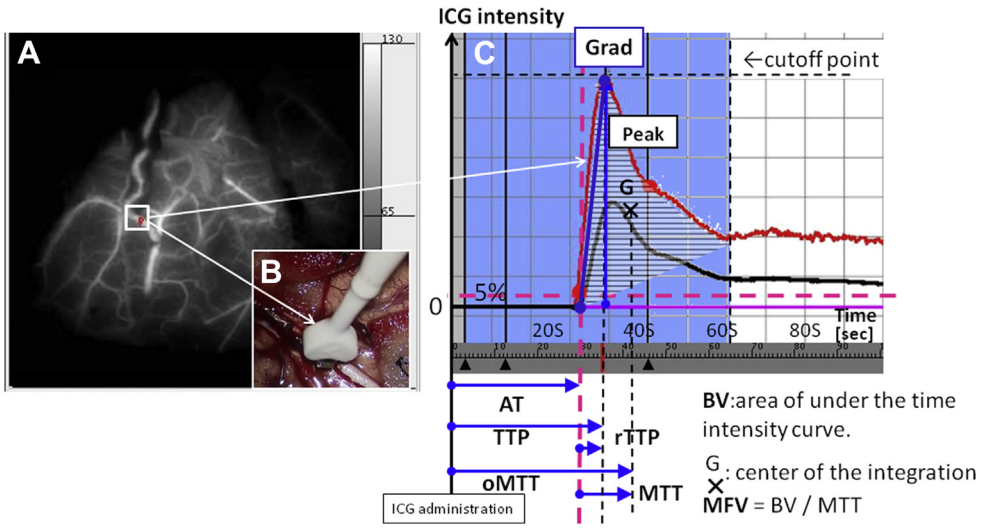

Figure 2. (**A**) Indocyanine green (ICG) video angiography of superficial temporal artery—middle cerebral artery bypass surgery (case 7). (**B**) The blood flow was measured with a transit-time flowmeter. (**C**) The time—intensity curve was analyzed with FlowInsight. The *red line* represents the time—intensity curve of the region of interest, and the *black curve* indicates the average of all pixels. Mean flow velocity (MFV) is one of parameters used for predicting blood flow: MFV = blood volume (BV)/mean transit time (MTT). Grad, gradient; AT, arrival time; TTP, time to peak; rTTP, relative time to peak; oMTT, objective mean transit time.

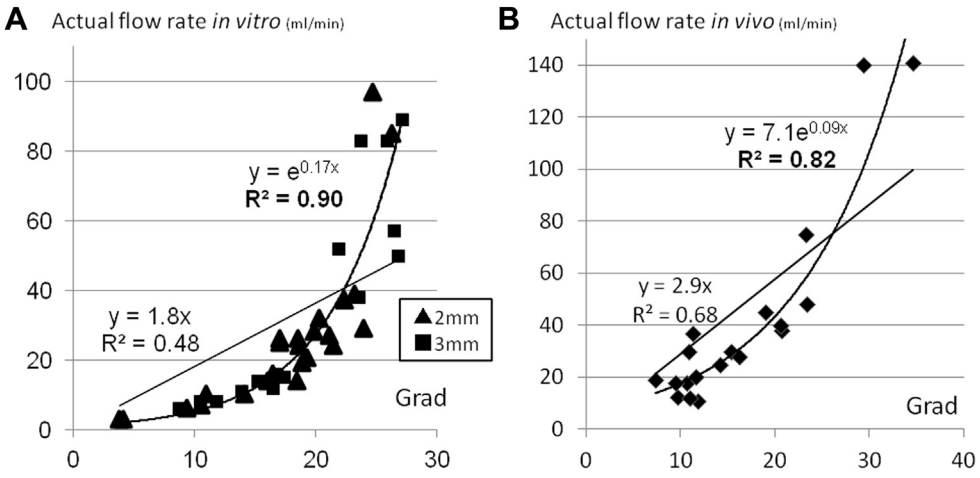

Figure 3. (**A**) Relationship between gradient (Grad) and actual flow rate in phantom cases, showing exponential correlation, with an R^2 value of 0.90. (**B**) Relationship between Grad and actual flow rate in patients also showing an exponential correlation, with an R^2 value of 0.82.

METHODS

ICG-VAG Phantom Model

For our basic experiments, we used a blood flow model consisting of a rotary pump from a hemodialysis unit (MF-01; JMS, Hiroshima, Japan), silicon tubes of various diameters, 3-way stopcocks, connectors, and a water pool. We used a similar model with flow phantoms, which have reported perfusion rates of 0–400 mL/min.[5,6]

Table 1. Baseline Characteristics of 19 Measurement Points and Measured Results

Case	Age (years)/Sex	Diagnosis	Measurement Point	Vessel Diameter (mm)	Actual Flow (mL/minute)	Gradient	MFV
1	39/Male	Moyamoya disease	STA-MCA bypass	2.3	11	11.8	5630
2	38/Male	Moyamoya disease	STA-MCA bypass	1.2	19	7.4	3802
3	40/Male	Moyamoya disease	STA-MCA bypass	1.7	25	14.2	5052
4	40/Female	Moyamoya disease	STA-MCA bypass	1.6	12.5	9.7	5327
5	56/Male	ICA occlusion	STA-MCA bypass	1.4	37	11.3	5678
6	40/Female	Moyamoya disease	STA-MCA bypass	1.4	38	20.7	8564
7	38/Male	Moyamoya disease	STA-MCA bypass	2.1	12	10.9	6927
8	52/Male	ICA occlusion	STA-MCA bypass	1.3	30	10.8	4299
9	12/Female	Moyamoya disease	STA-MCA bypass	2.5	18	10.7	5654
10	35/Female	Moyamoya disease	STA-MCA bypass	2.0	20	11.6	4880
11	71/Female	Unruptured aneurysm	MCA	3.2	40	20.6	8641
12	73/Female	Unruptured aneurysm	MCA	1.5	18	9.5	5509
13	45/Male	Unruptured aneurysm	MCA	1.9	30	15.4	7778
14	75/Female	Unruptured aneurysm	MCA	3.5	48	23.3	9942
15	75/Female	Unruptured aneurysm	MCA	3.1	28	16.2	6875
16	82/Male	ICA stenosis	Internal shunt	2.7	45	19.0	10,764
17	76/Male	ICA stenosis	Internal shunt	3.0	141	34.6	14,077
18	68/Male	ICA stenosis	Internal shunt	2.7	140	29.4	7818
19	82/Male	ICA stenosis	Internal shunt	3.0	75	23.3	6903

MFV, mean flow velocity; STA, superficial temporal artery; MCA, middle cerebral artery; ICA, internal carotid artery.

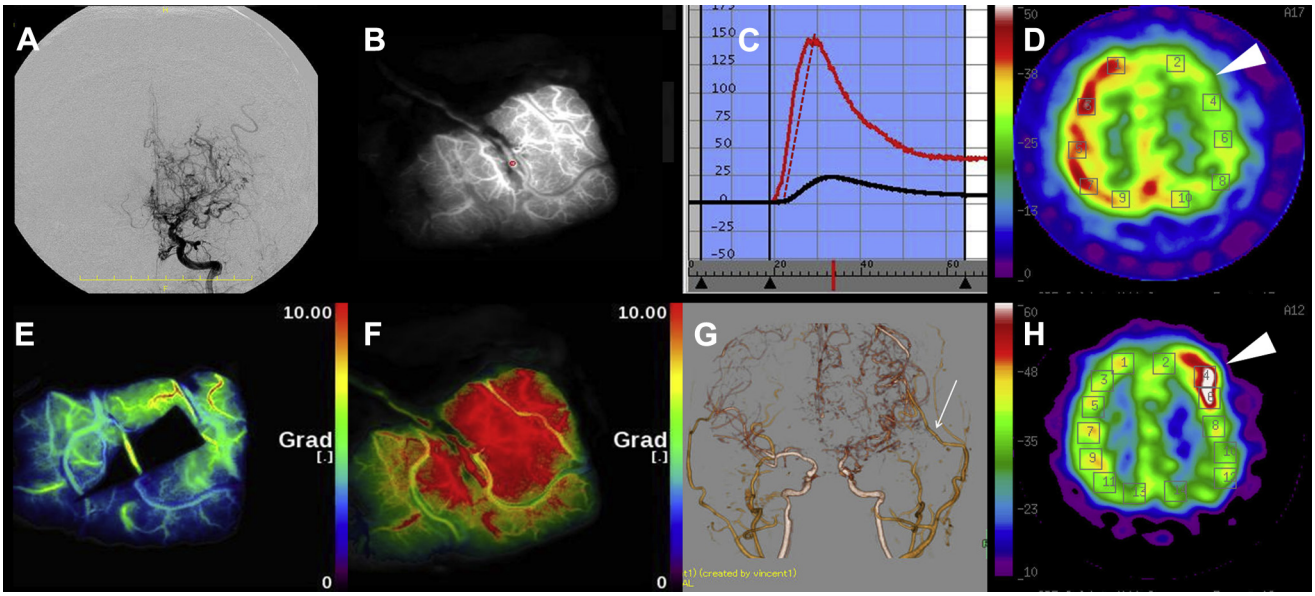

Figure 4. Illustrative case 3, a 40-year-old male with moyamoya disease, with a left transit-time ultrasound flowmeter probe flow rate of 25.0 mL/minute. (**A**) Preoperative left internal carotid artery angiography. (**B**) Postoperative indocyanine green (ICG)-video angiography at 18 seconds after ICG bolus injection. (**C**) Region of interest and time–intensity curve generated automatically by FlowInsight. (**D**) Preoperative resting-state 123I-N-isopropyl-p-iodoamphetamine single-photon emission computed tomography (IMP SPECT). (**E** and **F**) Preoperative (**E**) and postoperative (**F**) same-scale color map fusion images of gradient (Grad) and peak. The postoperative image shows high vascular Grad in a wide area. (**G**) Postoperative 3-dimensional computed tomography angiography showing an external carotid–internal carotid bypass graft (*white arrow*). (**H**) Postoperative IMP SPECT showing hyperperfusion of the frontal lobe (*white arrowhead*).

As shown in Figure 1, a 4-mm silicone tube was connected to the water pool and pump to create controlled flow. At the proximal side of the phantom system, a mixing buffer chamber was connected to dilute the ICG dye and the fluid. The flow rate was between 0 and 150 mL/min, close to values seen during vascular neurosurgery. The main pump provided stationary flow to the chamber and a 4-mm tube with 3-way stopcocks, which was divided into 2 branches (Figure 1).[7] The total volume of pooled water was 2000 mL. We used ICG (Diagnogreen; Daiichi Sankyo, Tokyo, Japan) at a concentration of 2.5 mg/mL mixed in water in accordance with the manufacturer's instructions. We verified that ICG alone did not fluoresce even when excited with near-infrared light (800 nm). Each measurement used 0.5 mL of ICG–fetal bovine serum (FBS) solution, mixed at a 1:3 ratio of ICG to FBS (Biowest, Nuaillé, France). The injected ICG-FBS passed through a small chamber and flowed into the branches. The flow rate of the main pump was fixed at 150 mL/minute, and flow was divided into 2 tubes with diameters of 2 mm and 3 mm. In addition, the flow rate in each tube was changed using rotary tube clumps (Figure 1). We administered repeated 0.5-mL bolus injections of ICG-FBS solution. After each bolus injection, we also injected 1 mL of water to achieve rapid, uniform mixing of the bolus ICG-FBS solution with minimum dilution within the phantom system. Because the additional water remained within the main tube, we could obtain pure time–intensity curves for the ICG-FBS solution.

Flow Measurements in Phantom Experiments

Regions of interest (ROIs) were placed on silicone tubes with diameters of 2.0 mm and 3.0 mm under a microscope (OH4; Leica Microsystems, Heerbrugg, Switzerland) with software appropriate for ICG signal analysis. Each ICG-VAG clip was recorded at 60 frames per second (high quality) on the hard disk of the microscope. The working distance was fixed at 206 mm, magnification was 2×, and light power was 100% from a 300W xenon lamp. The software automatically and selectively copied clips longer than 20 seconds, analyzed time–intensity changes in florescence in each pixel, and calculated parameters to evaluate fluid flow.

Flow Measurements in Human Subjects

For quantitative analysis of ICG-VAG, we administered a bolus of ICG and analyzed changes in fluorescence intensity over time. The fixed working distance, magnification, and light power were identical to the values in the phantom experiments. Flow was measured in the external carotid artery (ECA)–internal carotid artery (ICA) bypass grafts, branches from cerebral aneurysms, and internal shunt tubes after carotid endarterectomy (CEA). During the procedure, blood flow was measured at all the aforementioned targets using transit-time ultrasound flowmeter (TTFM) probes (VeriQ; Medistim, Oslo, Norway), with probe sizes of 1.5–5 mm.

For the blood flow investigations, we used settings identical to the basic experiments. After the measurement settings were fixed, a 0.04 mL/kg ICG solution (25 mg of ICG dissolved in 10 mL of water) was injected, and one target area was illuminated at the ICG excitation wavelength. The recorded ICG-VAG video clip was automatically transferred via a closed local area network to the intensity analysis program to calculate different parameters. This program, FlowInsight, was originally developed at our institute and Infocom Ltd.

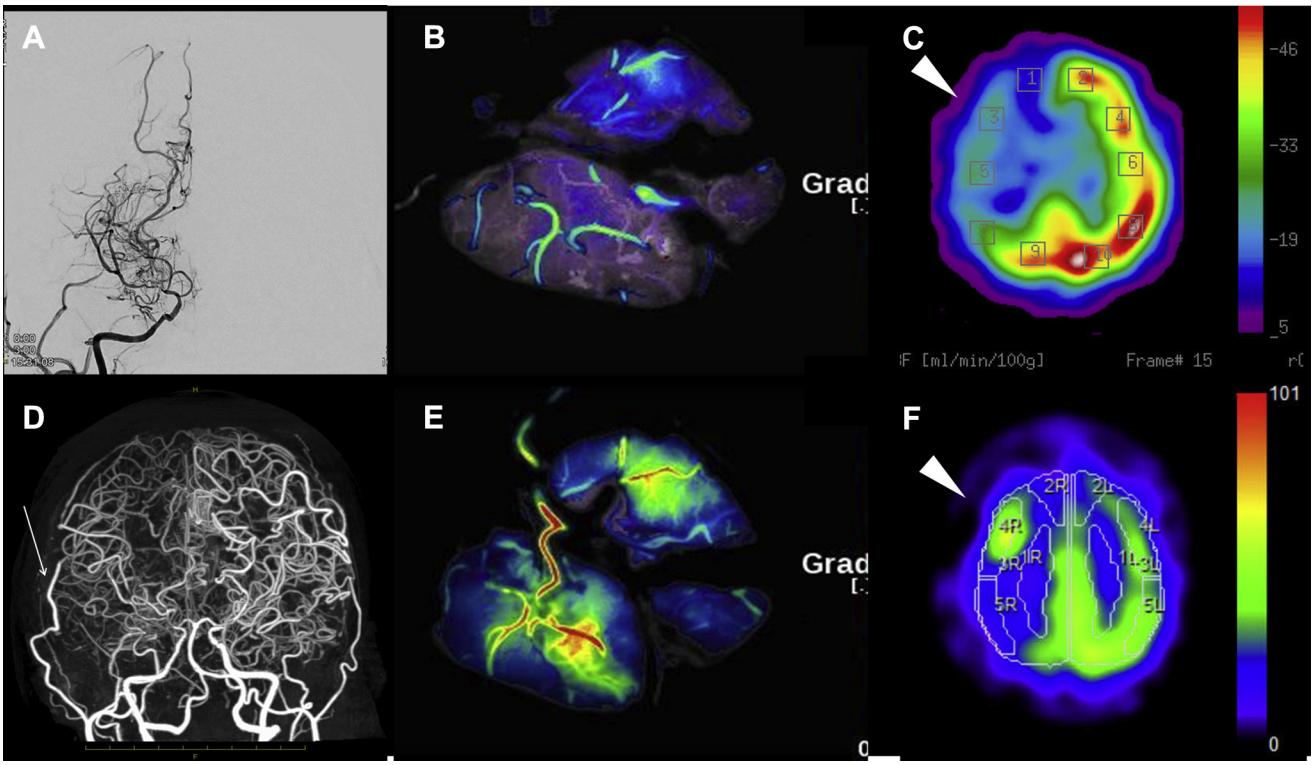

Figure 5. Illustrative case 10, a 35-year-old female with moyamoya disease, with a left transit-time ultrasound flowmeter probe flow rate of 20.0 mL/minute. (**A**) Preoperative right internal carotid artery angiography. (**B**) Preoperative same-scale color map fusion images, showing gradient (Grad) and peak. (**C**) Preoperative resting-state 123I-N-isopropyl-p-iodoamphetamine single-photon emission computed tomography (IMP SPECT). (**D**) Postoperative 3-dimensional computed tomography angiography showing an external carotid–internal carotid bypass graft (*white arrow*). (**E**) Postoperative color map fusion images showed successful revascularization. Calculated value was 20.8 mL/min. (**F**) Postoperative IMP SPECT showing normalized perfusion of the right frontal lobe (*white arrowhead*).

(Tokyo, Japan). This study was approved by the Asahikawa Medical University's Research Ethics Committee (no. 148).

Postacquisition Data Processing for Quantitative ICG-VAG

Real-time ICG analysis was done using the FlowInsight software running in Linux on a 13-inch MacBook Pro (Apple, Cupertino, California, USA). Because ICG intensity changes over time, we applied perfusion-based data processing for real-time ICG data analysis.[8] When the ROI was placed on the target(s), the software automatically generated the time–intensity curves for the ROIs. FlowInsight also automatically detected initial intensity peaks and determined baseline values (Figure 2). The analysis of ICG dynamics yielded 8 parametric maps, as follows.

Arrival time (AT) was defined as the duration between ICG injection and the time at which intensity reached 5% of the maximum peak. Gradient (Grad) was defined as the intensity gradient between AT and the maximum peak. Time to peak was defined as the interval between ICG injection and the maximum peak, and blood volume (BV) was defined as the intensity integration between AT and the endpoint of the initial peak. Mean transit time was defined as the interval between 5% of the maximum peak and the mean time point of BV. Mean flow velocity (MFV) was obtained by dividing BV by mean transit time (Figure 2).

We superimposed each ICG-VAG video clip with parameter maps to emphasize the time domain information. Consequently, each pixel was associated with multiple parameters depending on ICG intensity dynamics and VAG-generated color-coded video clips. All parametric data on ROIs were calculated within 3 minutes of data acquisition. Clinical analyses were done predominantly in real time and intraoperatively.

Statistical Analyses

We used Excel 2007 (Microsoft, Redmond, Washington, USA) and R version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses. All data are expressed as mean ± standard error. Nonlinear regression was used to analyze the relationships between actual flow rate and Grad, MFV, and other parameters. Coefficients were considered statistically significant if the R^2 value exceeded 0.50 and P value was <0.05.

RESULTS

Flow Measurements in the Phantom

A clear, exponentially correlated relationship ($R^2 = 0.90$; $P < 0.001$) among the fluorescence parameter, Grad, and actual flow rate on the graduated cylinder was observed in the 2.0- to 3.0-mm tubes (Figure 3A). We found that Grad could precisely reflect

actual flow rates of 5–150 mL/minute despite a variation in tube diameters. MFV also demonstrated a similar exponential correlation with fluid flow in these tubes ($R^2 = 0.65$; $P < 0.001$). Because AT and time to peak were affected by the timing of the injection by each investigator, these parameters did not reflect flow conditions. Higher flow speeds on ICG-VAG led to lower fluorescence intensities and broad peak intensity widths, resulting in greater BV and lower MFV. In our basic experiments, we found that Grad could estimate actual flow rate, and based on these results, we confirmed that the fluid flow in tubes can be estimated by ICG-VAG. These basic experiments also provide proof that this technique can be applied to measure fluid flow in clinical scenarios.

Flow Measurements in Patients

Based on the results from our basic experiments, we measured blood flow in 17 surgical cases, comprising 15 arteries and 4 internal shunt tubes (Pruitt–Inahara shunt tube; LeMaitre Vascular, Burlington, Massachusetts, USA) during CEA (Table 1). Ten patients underwent ECA–ICA bypass. During clipping of the middle cerebral artery (MCA) aneurysms, blood flow in 5 branch arteries was measured as well.

Actual flow rate, measured using TTFM probes on bypass grafts, was recorded as 11–40 mL/minute (average, 22.3 ± 3.2 mL/min). Measured blood flow was 18–48 mL/minute (mean, 32.8 ± 5.1 mL/minute) in the MCA branches and 45–141 mL/minute (mean, 100.3 ± 24.0 mL/minute) in the internal shunts. The relationship between the actual flow rate and Grad was exponentially proportional, with a R^2 value of 0.82 and $P < 0.001$ (Figure 3B). In addition, a positive correlation was found between MFV and actual flow rate. The MFV may be an additional indicator of blood flow ($R^2 = 0.36$; $P = 0.04$). Based on these results, we identified Grad as the best indicator in clinical practice, with MFV as another option.

Illustrative Cases

Case 3. This 40-year-old male with moyamoya disease was admitted to our hospital with intermittent right-hand weakness. Angiography demonstrated left MCA occlusion and basal collateral vessels. Surgery consisted of a combination of direct arterial microanastomosis and indirect synangiosis. Intraoperative actual flow rate in the ECA–ICA bypass graft, measured by TTFM, was 25.0 mL/min. During surgery, real-time analysis was performed, and Grad and peak fusion images were acquired. Because these images suggested a marked increase in blood flow on the brain surface, we maintained the patient's blood pressure during the postoperative period to avoid postoperative hyperperfusion. 123I-N-isopropyl-*p*-iodoamphetamine single-photon emission computed tomography (IMP-SPECT) revealed a hyperperfused region where the graft had been placed on the left frontal lobe (Figure 4 and Video 1). Intraoperative ICG analysis accurately predicted postoperative hyperperfusion.

Case 10. This 35-year-old female with moyamoya disease was admitted to our institution for transient left hemiparesis. Angiography showed right MCA occlusion, posterior cerebral artery stenosis, and basal collateral vessels. Intraoperative flow rate measured by TTFM was 20.0 mL/min, and that calculated using intraoperative Grad and an approximate expression was 20.8 mL/min. Grad adequately reflected actual flow, and patient's blood pressure was maintained within the normal range. Postoperative IMP-SPECT demonstrated normalized perfusion in the right frontal lobe (Figure 5).

Video available at WORLDNEUROSURGERY.org

DISCUSSION

Our findings show that Grad is the best indicator for precisely reflecting blood (fluid) flow. Furthermore, during the surgical procedures, we identified Grad as the best parameter and MFV as the second-best parameter indicating flow conditions. We believe that such blood flow measurements can contribute to the identification of normal and abnormal circulatory conditions, such as graft flow and vascular pathology. FlowInsight-based analysis of ICG-VAG provides quantitative results before and after the surgical procedures, which are particularly relevant in superficial temporal artery (STA)–MCA bypass surgery, which carries a risk of altered blood flow and direction, graft stenosis, or hyperperfusion syndrome. The information on blood flow conditions can contribute to effective clinical decision making. This technique emphasizes the clinical impact of vascular pathology, and should be made widely available.

A previous study that measured cerebral blood flow in swine by radio microspheres demonstrated a linear correlation between blood flow index (corresponding to Grad in the present study), which implies luminance changes in transcranial near-infrared spectroscopy after ICG administration.[9] Another recent clinical report suggested that Grad reflects blood flow, and that it should be a predictive factor for hyperperfusion syndrome.[10,11] To the best of our knowledge, there is no established technique for flow quantification using ICG-VAG, and not even in experimental phantoms. We confirmed clear peaks in each pixel by using a single path of ICG circulation in the phantom system. Florescence peaks with one path in the basic experiment were similar to those observed in vivo. Because differences in the diameter of the time–intensity curves are affected by flow speed, we concluded that BV and MFV, although related to peak width, would not show a positive correlation with blood (liquid) flow. The results from our basic and clinical experiments clearly demonstrate that Grad and MFV are better indicators of blood flow, which also encouraged us to establish a noninvasive technique to measure blood flow. We encountered hyperperfusion in our clinical cases. Figure 4 shows a representative case with hyperperfusion that was predicted by intraoperative ICG-VAG analysis. We maintained the patient's low blood pressure for 3 days after the operation to counter this hyperperfusion.

Various factors that affect ICG-VAG include injected ICG dose, pump flow rate, power of the light source, working distance, magnification, and camera sensitivity.[12,13] Despite these factors, and because the measurement conditions were fixed, we identified Grad and MFV as critical indicators correlated with actual flow rate. For example, Grad values of 10 and 20 corresponded to flow rates of 20 and 40 mL/min, respectively. We measured high flow rates in the internal shunt tubes of CEA shunts located between the common carotid

artery and the ICA. It was ideal to obtain measurements not only in the blood vessels, but also in the internal shunt tubes as the flow range varied between 5 and 150 mL/minutes. We believe that our technique can be widely adapted to various flow conditions in basic and clinical scenarios.

Yamamoto et al.[14] reported that a coronary artery bypass graft will remain patent if the mean flow rate is maintained at >5 mL/min.[14] Thus, there is a high probability of obstruction in the low Grad group, suggesting a relationship with low bypass flow rate. Nakagawa et al.[15] reported that the patency of anastomotic vessels can be evaluated as a quantitative measure of rendering time rather than as a change in fluorescence intensity. Our findings also characterize the exponential correlation between Grad and actual flow rate.

In this study using ICG-VAG for quantitative evaluation, our results show that blood flow correlates well with Grad and MFV. To our knowledge, this is the first basic and clinical study to quantitative assess blood flow in various blood vessels by measuring ICG fluorescence. The positive correlation observed between Grad and MFV suggests the useful of these parameters as future indicators.

CONCLUSIONS

ICG-VAG has great potential as a tool for quantitating blood flow and guiding intraoperative decision making. Our findings await further validation, which could open the door to monitor brain circulation and function. The novelty of this technique is that the fluorescence intensity parameter of Grad enables surgeons to quantitatively measure actual blood flow.

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