Microsurgical Clipping of Intracranial Aneurysms Assisted by Neurophysiological Monitoring, Microvascular Flow Probe, and ICG-VA: Outcomes and Intraoperative Data on a Multimodal Strategy

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■ OBJECTIVE: **The aim of this study is to report data on a multimodal monitoring strategy based on the intraoperative use of neurophysiological monitoring, flowmetry by microflow probe, and intraoperative indocyanine green video angiography (ICG-VA) during microsurgical clipping of intracranial aneurysms.**

■ METHODS: **This retrospective analysis was performed on 85 consecutive patients undergoing clipping of 96 intracranial aneurysms with the present monitoring strategy. Patient outcomes were evaluated by assessing rate of aneurysm exclusion and postoperative occurrence of ischemic injury. Intraoperative data for the strategy in addition to changes in each monitoring technique depending on aneurysm features were reported.**

■ RESULTS: **Complete aneurysm exclusion was achieved in 98.9% of cases. Postoperative symptomatic ischemic injury was recorded in 2.08% aneurysms. Clip repositioning occurred in 40.6% of cases: because of motor evoked potential (MEP) decrease in 9.3%, flowmetry in 22.91%, and ICG-VA in 8.3% of treated aneurysms (1.05% after ICG injection, 7.4% after the squeezing maneuver). The role of each technique differed according to aneurysm features; flowmetry alterations occurred more frequently in distal than in proximal aneurysms ($P = 0.0001$) and in atherosclerotic aneurysms ($P = 0.0001$). MEP impairment occurred more often in proximal aneurysms ($P < 0.05$). ICG-VA disclosed remnant aneurysms mainly in atherosclerotic aneurysms ($P < 0.05$); only one false negative remnant neck was recorded with a negative predictive value of 98.8%.**

■ CONCLUSIONS: **Microsurgical clipping assisted by a multimodal monitoring strategy achieved a high rate of aneurysm exclusion with low morbidity in our series. Our data show that the 3 techniques used in our strategy were complementary and that a monitoring strategy can be tailored to aneurysm features.**

INTRODUCTION

Surgery represents an effective treatment for intracranial aneurysms. The aim of surgery is to exclude the aneurysm saving the patency of parent and perforating arteries to avoid ischemic brain injuries. Although advanced preoperative and intraoperative imaging techniques are available,[1-3] minimizing

Key words
- Flowmetry
- ICG-VA
- Intracranial aneurysm
- Microsurgical clipping
- Neurophysiological monitoring

Abbreviations and Acronyms
ACoA: Anterior communicating artery
CR: Clip repositioning
CRS: Clip-related stroke
CT: Computed tomography
CTA: Computed tomography angiography
DSA: Subtraction angiography
H&H: Hunt and Hess
ICA: Internal carotid artery
ICG: Indocyanine green
ICG-VA: Indocyanine green video angiography
IONM: Intra operative neuro monitoring
I.S.: International System
MCA: Middle cerebral artery
MEP: Motor evoked potential
MRI: Magnetic resonance imaging
NM: Neurophysiological monitoring
P-comm: Posterior communicating artery
SAH: Subarachnoid hemorrhage
SSEP: Somatosensory evoked potentials

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ischemic injury during microsurgical clipping of an intracranial aneurysm remains a major challenge of cerebrovascular surgery. Currently, the reported mortality rate of unruptured aneurysms ranges between 0.4% and 1.5%,[4] and the mortality rate of ruptured aneurysms is up to 50%.[5] Morbidity rates of microsurgery for unruptured intracranial aneurysms are reportedly 2.2%–21.0%,[6] and morbidity owing to ischemic complications is reported up to 7.6%.[7] In this scenario, intraoperative techniques are crucial during clip positioning for real time assessment of complete aneurysm exclusion and the detection of any arterial branch injury, thereby allowing prompt clip repositioning (CR) and theoretically avoiding an ischemic brain injury. Intraoperative monitoring to avoid a clip-related ischemic event can be done by checking flow drop during clip positioning (Doppler, flowmetry), by evaluating the consequence of flow drop on brain function (neurophysiological monitoring), or by direct visualization of vessel involvement with indocyanine green–video angiography (ICG-VA) that can simultaneously provide data on aneurysm exclusion. However, there are still no definite guidelines and few data are available on multimodal monitoring strategies in aneurysm surgery.[8] The current study retrospectively analyzed data for 96 intracranial aneurysms that underwent microsurgical clipping assisted by a multimodal monitoring strategy based on neurophysiological monitoring (NM) with transcranial monitoring of motor evoked potentials (MEPs), and somatosensory evoked potentials (SSEPs), flowmetry with perivascular probe (Charbel Micro-flowprobe; Transonic System, Ithaca, New York, USA) and ICG-VA. The aim of the study was to establish the effects of these combined techniques on patient outcomes (rate of aneurysm exclusion and occurrence of ischemic injury) and to report intraoperative data on the strategy in addition to changes in each monitoring technique, depending on aneurysm features. To our knowledge, this is the first study to describe this multimodal monitoring strategy.

MATERIAL AND METHODS

Clinical and Radiologic Data

Clinical, radiologic, and intraoperative data for patients undergoing microsurgical clipping of an intracranial aneurysm with a multimodal monitoring strategy based on NM, flowmetry with microflow probe, and ICG-VA were analyzed retrospectively. Patients undergoing surgery with monitoring based on only 1 or 2 monitoring techniques were excluded from the study. Patients were selected for surgical treatment versus coiling according to patient and aneurysm features after a multidisciplinary evaluation case by case preoperative and postoperative neurologic assessment was defined by neurologic examination. Hunt and Hess (H&H) grade and clinical focal deficits were registered. Aneurysm diameter was calculated on preoperative radiologic images. Postoperative evaluation was done immediately after surgery, during hospitalization, and 1 month after surgery. All patients underwent preoperative computed tomography angiography (CTA) or digital subtraction angiography (DSA). The occurrence of clip-related ischemic brain injury was evaluated by postoperative computed tomography (CT). When clinical deterioration or a neurologic deficit were recorded in the postoperative period, a new CT scan was always performed. If CT disclosed an ischemic injury, CTA/DSA and magnetic resonance imaging (MRI) were performed. Aneurysm exclusion and the patency of parent and perforating arteries were evaluated with CTA or DSA performed immediately after surgery. DSA was preferred over CTA in the postoperative period when dealing with a bleeding aneurysm or when CTA findings were unclear. Aneurysms were dichotomized to either a proximal group (internal carotid artery [ICA]-Ophtalmic, ICA-posterior communicating artery [P-comm], ICA-Choroidal, ICA bifurcation, anterior communicating artery [ACoA], A1, M1) or a distal group (middle cerebral artery [MCA] bifurcation and pericallosal artery) on the basis of different hemodynamic circulation properties[3,9] and higher (proximal group) or lower (distal group) risk of perforating arteries injury. Atheroma at the aneurysm neck or dome was detected and recorded intraoperatively.

Monitoring Techniques and Multimodal Monitoring Strategy

Neurophysiological Monitoring. Both motor and sensory pathways were monitored. To monitor MEPs, stimulation was made at the scalp with electrodes placed in C1-C2 (C3-C4) according to the 10-20 International System (I.S.). The two electrodes continuously stimulated the motor area during the intervention allowing "on-line" monitoring of the motor pathway. Stimulation was performed by means of a train of 4–5 stimuli lasting 75–500 µs with interstimulus intensity of 250–500 Hz and intensity suprathreshold (bandpass filter: low frequency filter, 10–100 Hz; high frequency filter, 500–2000 Hz). To monitor SSEPs, upper limb SSEPs were recorded by electric stimulation of the contralateral medianus nerve at the wrist. For recording from C3′ and C4′ according to the 10–20 I.S., lower limb SSEPs were recorded by electric stimulation of the contralateral tibial nerve at the medial malleolus. For recording from Cz′ and Fz according to the 10–20 I.S., stimulation occurred by means of an electric current to a single pulse at a frequency of 3 Hz and duration of 500 µs. Recording parameters were: 1) sweep 10 ms/div for lower limbs and 5 ms/div for upper limbs, 2) bandpass filter (low frequency filter, 20 Hz; high frequency filter, 300 Hz), and 3) Inactive Notch filter. Because general anesthesia can have an influence on intra operative neuro monitoring (IONM), a specific anesthetic protocol was followed. Total intravenous anesthesia, with a combination of propofol (6 mg/kg/hour) and remifentanil at a dose of 0.05–0.2 mcg/kg/minute was used. Propofol was titrated to levels that enable MEP generation. The use of muscle relaxants, such as rocuronium or cisatracurium, was reserved for endotracheal intubation. During surgery, neuromuscular blockers were not used unless they were required for patient safety.

Flowmetry. Vascular flow measurement was performed using the microvascular ultrasonic flow probe (Charbel Micro-flowprobe; Transonic System, Ithaca, New York, USA). This probe records blood flow through a flow sensing perivascular probe connected to an electronic flow detection unit. Using the principle of ultrasonic transit time, flow measurements appear as a digital display on the detection unit. Flow data were acquired in cubic centimeters per minute. Probes differed in size according to vessel diameter. Flow was measured in all the relevant vessels before clipping to obtain the basal flow, and immediately after clipping to exclude a flow drop and verify flow preservation. As previously reported by Amin-Hanjani et al.,[10] in the context of stable end-tidal carbon dioxide (CO_2) and mean arterial blood pressure values, a reduction threshold flow in after clipping measurement superior to 25% was indicative of vascular flow impairment requiring CR.[10]

ICG-VA. Intraoperative ICG-VA was performed using a surgical microscope (OPMI Pentero; Carl Zeiss, Oberkochen, Germany) equipped with a microscope-integrated near-infrared ICG-VA (Carl Zeiss, Infrared 800; Meditec, Germany). After intravenous injection of indocyanine green dye (ICG), the operating field is illuminated with near-infrared light.[11] Real-time angiographic images are displayed on a video screen and recorded. ICG-VA was performed every time after flow measurement after the clipping phase and after CR. The squeezing maneuver is based on a gentle pinch with a bayonet of the dome of a clipped aneurysm when ICG-VA demonstrates its apparent exclusion. The maneuver is positive when the sac is filled with dye after the dome pinch and indicates clip blades weakness or incomplete aneurysm exclusion.[12]

Monitoring Strategy. All 3 techniques were simultaneously applied in all cases in an integrated strategy as follows (Figure 1). NM was started from the beginning of surgery before craniotomy and continued until the end of the surgical procedure. NM was always set for both MEPs and SSEPs, but when MEPs monitoring was feasible, it was usually preferred over SSEPs. Sometimes, when clipping distal aneurysms, SSEPs were alternated with MEPs monitoring. Flowmetry was performed on vessels distal to the aneurysm before clipping (baseline data) and immediately after aneurysm clipping. ICG-VA was performed in all cases after clipping, and sometimes also before clipping when it was deemed necessary intraoperatively. After clipping, ICG-VA was always performed after direct inspection of clip blades over aneurismal neck, and when flowmetry and NM did not show flow reduction greater than 25% or evoked potential decrease. In this sense, the aneurysm remnant was assessed by ICG-VA only when arterial flow conservation (flowmetry) and brain function (NM) were assessed and deemed normal. Clip was repositioned when 1) flowmetry showed a flow drop greater than 25% from the baseline, 2) any EPs decrease was detected, and 3) ICG-VA showed a residual aneurysm or a flow decrease on distal arteries. Aneurysms were finally opened after clipping in all cases.

Statistical Analysis

Statistical analysis to compare categorical variables was performed using 2-sided Fisher exact test. Unpaired t test was used to

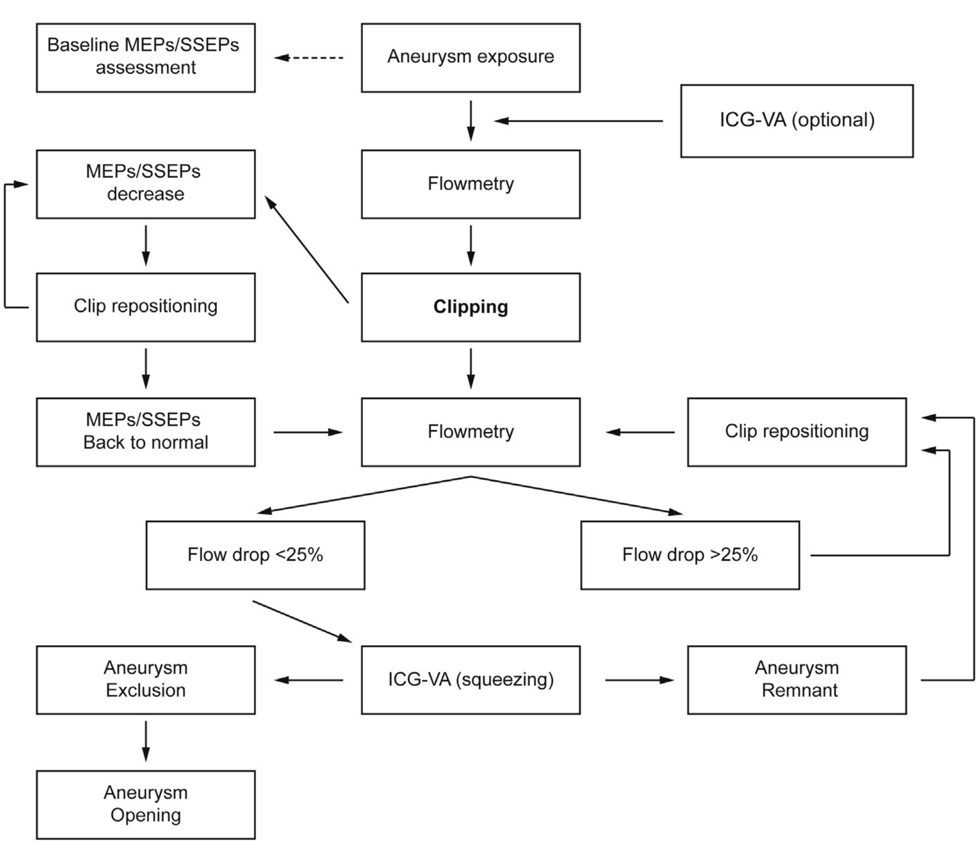

Figure 1. Decision-making process about clip repositioning based on monitoring data.

compare mean age in the atheroma and non-atheroma groups and standard deviation; $P < 0.05$ was considered significant.

Limitations and Weakness of the Study

We must point out some main limitations of our study. Our study was retrospective; this implies that there were potential sources of bias because of enrollment criteria for patients. The choice of treatment modality was a selection bias as well, because surgery was preferred over coiling in low-grade subarachnoid hemorrhage (SAH), and according to morphologic features and size of aneurysm (less favorable to coiling). In addition, IONM employment depended on the time of surgery (daytime vs. nightime), as IONM was not available at our department during the weekend and overnight. For this reason, most patients with unruptured aneurysms and a few with bleeding aneurysms were enrolled in the study. Another main limitation of the retrospective design of the study was the postoperative imaging performed. DSA and MRI, the gold standard techniques to detect respectively aneurysm remnant and ischemic events, were used only in select cases.

RESULTS

Patients and Aneurysms

Eighty-five patients underwent surgical clipping for 96 aneurysms at our Institution (Table 1) between February 2015 and April 2017, with a multimodal monitoring strategy based on NM (transcranial MEPs and SSEPs), flowmetry with a perivascular probe (Charbel Micro-flowprobe; Transonic System), and ICG-VA. The study included 57 female and 28 male patients (median age, 58 years). Fifty aneurysms were unruptured, and 46 were bleeding. All 46 ruptured aneurysms had a H&H grade less than 3. The aneurysm sizes was less than 7 mm in 37 patients, 7—12 mm in 46 patients, and 13—24 mm in 13 patients. Aneurysms were located as follows: 8 at the ICA bifurcation, 16 at the ACoA complex, 15 at the ICA-P-comm, 49 at the MCA bifurcation, 2 at the ICA-anterior choroidal artery, 2 at the ICA-Ophthalmic artery, 2 at the pericallosal artery, 1 at the A1, and 1 at the M1 segment (45 in the proximal and 51 in the distal group). Atheromas at the neck-dome of aneurysms were found intraoperatively in 26 cases (27% of total cases). The mean age of patients with atherosclerotic aneurysms was 65 years (SD ± 12.6 years) versus 55.8 years (SD ± 11.09 years) in patients without atheroma ($P = 0.001$). Among atherosclerotic aneurysms, 14 were detected in ruptured and 12 in unruptured aneurysms. Twenty-one atheromas were located at the MCA—2 at the ICA-P-comm, 2 at the ICA-Ophthalmic artery, and 1 at the ACoA. Postoperatively, CTA was performed in 65 while DSA was performed in 20 cases. In particular, DSA was performed in 20 SAH patients, while CTA was performed in 29 patients with ruptured aneurysms and in 36 patients with unruptured aneurysms.

Outcome

Aneurysm Exclusion Rate. Patients 95 out of 96 aneurysms were actually clipped; one case involved an unruptured anterior choroidal artery aneurysm and MEP disappearing twice during clip positioning; therefore, it was decided to stop clipping and opt for endovascular treatment. On postoperative CTA and DSA, complete aneurysm exclusion was achieved in 94 of 95 cases (98.9%). Indeed, an unexpected residual neck was detected by CTA in an unruptured P-comm aneurysm that did not present an atheroma intraoperatively. Finally, the exclusion rate was 100% in bleeding and 98% in unruptured aneurysms, 100% (26/26) among aneurysms with atheroma and 99.5% (68/69) among aneurysms without atheroma, and 100% (51/51) in distal and 97.8% (44/45) in proximal aneurysms. DSA detected no residual aneurysm (0/20), and CTA revealed a remnant in one patient (1/65; 1.5%).

Table 1. Patients and Aneurysms

Clinical Case Features	n (%)
Total number of aneurysms	96
Presentation	
Ruptured aneurysms	46 (47.9%)
Unrupted aneurysms	50 (52.1%)
Sex	
Male	28 (29.2%)
Female	57 (59.4%)
Neck-dome Atheroma	
Yes	26 (27.1%)
No	70 (72.9%)
Size	
<7 mm 11	37 (38.5%)
7—12 mm 18	46 (48.0%)
13—24 mm	13 (13.5%)
Aneurysm location	
Proximal group	45 (46.9%)
A1 segment	1 (1%)
Anterior communicating complex	16 (16.7%)
M1 segment	1 (1%)
ICA-posterior communicating	15 (15.6%)
ICA bifurcation	8 (8.3%)
ICA-anterior choroidal	2 (2.1%)
ICA-ophthalmic	2 (2.1%)
Distal group	51 (53.1%)
Pericallosal	2 (2.1%)
MCA bifurcation	49 (51%)

ICA, internal carotid artery; MCA, middle cerebral artery.

Clip-Related Stoke Rate. Postoperative studies in 10 cases documented a clip-related stroke (CRS; 10.4% of treated aneurysms; 11.7% of patients; Table 2). Two were symptomatic (2.08% of treated aneurysms, 2.35% of patients) and 8 were asymptomatic (8.32% of treated aneurysms, 9.41% of patients). CRS occurred in 15.2% of bleeding aneurysms and in 6% of unruptured aneurysms, in 7.69% of cases in aneurysm with atheroma and in 11.6% without

Table 2. Patients with Postoperative Stroke

		Causes of Clip Repositioning						
Patient Number	**SAH**	**EPs**	**Flowmetry**	**ICG-VA**	**Ischemic Territory**	**Postoperative Deficits**	**Aneurysm Location**	**Atheroma**
1	Yes	–	–	–	Hypotalamic	—	Bleeding ACoA + MCA bif	No
2	No	–	–	–	Fronto-orbitary	—	ACoA + MCA bif	No
3	No	–	+	–	Frontal M2	Motor	MCA bif	Yes
4	Yes	–	+	–	Frontal M2	Language	MCA bif	Yes
5	Yes	–	+	–	Frontal M2	—	MCA bif	No
6	No	–	+	–	Basal ganglia	—	M1	No
7	Yes	+	–	–	Basal ganglia	—	P-comm	No
8	Yes	–	–	–	Hypotalamic	—	ACoA	No
9	Yes	–	–	–	Hypotalamic	—	ACoA	No
10	Yes	–	–	–	Hypotalamic	—	P-comm	No

SAH, subarachnoid hemorrhage; EP, evoked potentials; ICG-VA, indocyanine green video angiography; ACoA, anterior communicating artery; MCA, middle cerebral artery; ICA bif, internal carotid artery bifurcation; P-comm, posterior communicating artery.

atheroma, and in 7.8% (3.9% symptomatic) of distal and 13.3% (0% symptomatic) of proximal aneurysms. A symptomatic ischemic event was recorded in 2% of bleeding and in 2% of unruptured aneurysms. In all cases, treated aneurysms exhibited an atheroma and belonged to the distal group. Regarding aneurysm location, distal aneurysm clipping had a 3.9% symptomatic ischemic event rate. Both cases of symptomatic CRS were in aneurysms of the MCA bifurcation. In the first case, a patient undergoing surgery for a left MCA aneurysm presented a postoperative aphasia caused by an ischemic injury in a frontal M2 branch territory arising 3 days after surgery. Flowmetry had intraoperatively detected a flow impairment (>25%) normalized after CR, although no MEP decrease was observed during surgery. A neck-dome atheroma was detected intraoperatively. Images produced by immediate postoperative CTA and DSA were normal. In the second case, a patient undergoing surgery for a right MCA aneurysm presented a hemiparesis caused by an ischemic injury in a frontal M2 branch that appeared thrombosed on postoperative CTA. A neck-dome atheroma was detected intraoperatively. Neither flowmetry nor NM disclosed functional or flow impairment during surgery. The 8 patients with an asymptomatic CRS (8.32%) underwent clipping for 1 MCA bifurcation aneurysm, 1 M1 aneurysm, 2 P-comms, and 4 ACoAs. In ACoA aneurysms, ischemic injury was detected in 3 patients in the hypothalamic region and in 1 patient in the fronto-orbital region. In MCA aneurysms, ischemic injury was detected in the frontal M2 in MCA bifurcation and in the deep ganglia in an M1 aneurysm. In P-comm aneurysms, ischemic injury was detected in the hypothalamus in 1 patients and in the basal ganglia in another. In one case of deep ganglia injury, a temporary MEP decrease was detected during clipping of a P-comm aneurysm that normalized after CR. Flowmetry detected a flow decrease (>25%) in 2 MCA aneurysms that normalized after CR.

Video

Video available at WORLDNEUROSURGERY.org

Intraoperative Data

Clip Repositioning. CR was performed 42 times (range 1–3 per patient) in 39 out of 96 treated aneurysms (in 40.51% of all aneurysms). CR was performed 10 times according to decreasing MEPs (10/42; 23.8% of all CRs), 24 times according to blood flow impairment (24/42; 57.1% of all CRs), and 8 times according to incomplete aneurysm exclusion on ICG-VA (after ICG 1/42, 2.4% of all CRs; after squeezing 7/42, 16.6% of all CRs). Among 39 aneurysms requiring CR, CR was due to MEP decrease in 9 patients (23.07%), flowmetry in 22 patients (56.41%), and ICG data in 8 patients (20.51%). Among all 96 treated aneurysms, CR occurred in 9.3% according to MEP decrease, in 22.91% according to flowmetry, and in 8.3% according to ICG data.

Neurophysiological Monitoring Data. Evoked potentials decreased in 11 patients: in 10 according to MEPs (Video 1) and in 1 according to SSEPs decrease during temporary clipping (thus not included among CRs) for a large, bleeding ACoA aneurysm. In this case, a temporary clipping of bilateral A1 yielded an SSEP decrease after 7 minutes; however, after temporary clip removal, SSEPs normalized. In 9 patients, the clip was repositioned and MEPs then normalized. In 1 patient, CR did not achieve satisfactory aneurysm exclusion without MEP decrease; therefore, the aneurysm was not clipped and was subsequently treated using an endovascular route. MEP decrease occurred during clipping of 7 unruptured and 3 bleeding aneurysms that were located at the carotid artery in 7 patients (2 ChoA, 1 ophthalmic, 2 P-comm, 2 ICA bifurcation; Videos 1 and 2), at the MCA bifurcation in 2 patients, and at the anterior cerebral artery in 1 patients (A1 tract). Atheroma was present in two aneurysms (7.69% of all aneurysms with atheroma). Among 10 patients requiring CR according to MEP decrease, no ischemic lesions were found postoperatively in 8 patients.

Clipping was not performed in 1 patient (see Outcome - Aneurysm Exclusion Rate). In 1 patient, an asymptomatic clip-related brain injury was recorded in an ICA-P-comm aneurysm in which the clip was repositioned after MEPs disappeared and MEPs returned to a basal state. However, even without any neurologic deficit, we found a capsular ischemic lesion. A subgroup of unruptured aneurysms had a higher frequency of MEP decrease in proximal aneurysms than in distal ones ($P = 0.04$). Finally, it is mandatory to consider that we never found irreversible MEPs deterioration but only 3 cases of reversible loss of MEPs. In the other cases, we recorded only an impairment of potentials. Moreover, we found some ischemic lesions in not assessable territories (hypothalamic). As a result, MEP specificity was 88.4% and negative predictive value was 0.9.

Flowmetry Data. Decreased blood flow was recorded in 24 patients—in 13 unruptured and in 11 ruptured aneurysms. Aneurysms were located at the MCA bifurcation in 22 patients, the ACoA complex in 1 patient (Figure 2), and at the pericallosal artery in 1 patient case. Atheroma was present in 17 aneurysms (65.3% of total aneurysms with atheroma). Among the 2 patients with postoperative impairment, decreased flow (decreased by 25% from basal flow) was documented in 1 patients, but it was baseline after CR flow; however, the patient developed hemiparesis. In the other case, no flow decrease was recorded. Among the other 23 patients in whom decreased flow was recorded, 1 patient developed an asymptomatic ischemic lesion of the caudate, and the other 22 patients did not exhibit any ischemic focus at postoperative radiologic examination. The rate of cases with blood flow decrease was significantly higher in distal than in proximal aneurysms (23/24 of cases; $P = 0.0001$). Moreover, alteration at flowmetry occurred more frequently in atherosclerotic than in nonatherosclerotic aneurysms ($P = 0.0001$). Concerning flowmetry (on 96 aneurysms), sensitivity, specificity, positive predictive value, and negative predictive value were 30%, 24.4%, 0.12, and 0.90 in detecting a postoperative ischemic event and 50%, 76%, 0.04, and 0.98 in detecting a postoperative symptomatic ischemic event, respectively.

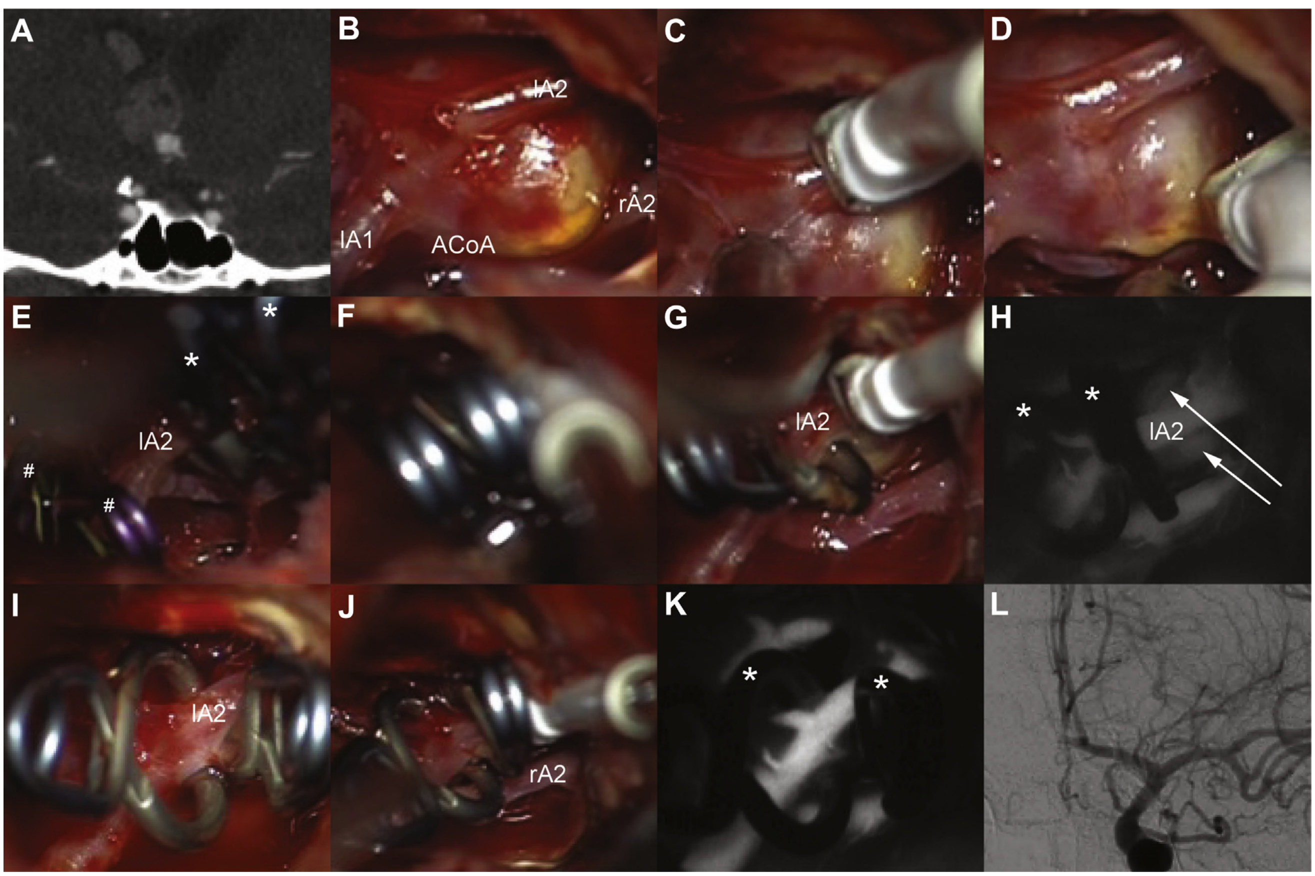

Figure 2. Anterior communicating artery bleeding aneurysm approached via a left frontopterional approach. (**A**) Preoperative coronal computed tomography angiography showing the ruptured aneurysm and the intraventricular bleeding. (**B**) Aneurysm exposure. (**C**) Left A2 flowmetry. (**D**) Right A2 flowmetry. (**E**) Aneurysm clipping with 2 fenetrasted clips (*asterisks*) bypassing the left A2 under bilateral A1 (#) temporary clipping. (**F**) Flowmetry of left A2 detects a flow drop greater than 25%. (**G**) Flowmetry of left A2 after clip repositioning (1 fenestrated clip over left A2 with larger ring) showed a flow drop less than 25%. (**H**) Indocyanine green video angiography showed an aneurysm remnant. (**I**) A second clip was positioned. (**J**) Flowmetry on both A2 is good. (**K**) Final ICG-VA did not show an aneurysm remnant. (**L**) Postoperative digital subtraction angiography, anteroposterior view. lA1, left A1 tract; rA2, right A2 tract; lA2, left A2 tract; ACoA, anterior communicating artery.

ICG-VA Data. ICG-VA implied CR in 8 cases according to incomplete aneurysm occlusion. A branch occlusion was detected in 1 case in which the clip was repositioned because a perforating artery occlusion was detected in an P-comm aneurysm with a simultaneous decrease of MEPs. Two aneurysms were unruptured, and 6 were bleeding. Aneurysm localization was 6 at the MCA bifurcation, 1 in the P-commA, and 1 in the ACoA complex. Residual aneurysm was detected in 1 of 95 cases (1.05%) with simple ICG injection after clipping, while the squeezing maneuver revealed a filling aneurysm in 7 of 94 cases (7.4%). The results of the squeezing maneuver were positive significantly more often in atherosclerotic aneurysms ($P < 0.05$) and in all cases of remnant neck on ICG-VA ($P = 0.0001$). Just one case of false-negative remnant neck was detected using postoperative CTA with an ICG-VA negative predictive value of 98.8% (interval confidence 95% ± 0.97). Regarding ICG-VA, we could calculated a negative predictive value of 0.98, as we found 1 false negative out of 95 cases corresponding to a P-comm aneurysm. Specificity of ICG-VA in detecting aneurysm exclusion rate in our series was 100%, without any false positive results.

DISCUSSION

Our Results and Data from the Literature

Ischemic accidents represent a severe complication during microsurgical clipping. In 2014, Park et al.[13] pointed out that the most common cause of unplanned re-exploration of the craniotomy following microsurgery for unruptured intracranial aneurysms is compromised distal blood flow. Moreover, intraoperative vessel compromise involves approximately 4%–12% of cases and may account for up 22.8% of total infarctions in patients with SAH.[14] In our study, the symptomatic ischemic rate was 2.08%, and the silent ischemic rate was 8.3%.

We reviewed the latest English-language literature on large series of aneurysms focused on this topic. In 2008, Krayenbuhl et al.[15] reported a symptomatic ischemic rate of 2% and a silent ischemic rate of 9.8% in 51 aneurysms (both ruptured and unruptured). Hammer et al.[7] found a permanent symptomatic ischemic rate of 7.6% in 281 clipped aneurysms. In a large series of 549 unruptured aneurysms, Moroi et al.[16] found permanent neurologic deficits in 2.2% of cases, whereas Buyon et al.[17] reported a 3.1% incidence of ischemic complications after microsurgical clipping of unruptured MCA aneurysms. In our series, ischemic injury occurred more frequently in proximal and in bleeding aneurysms, but a symptomatic ischemic event was reported more often in distal aneurysms (MCA bifurcation) and mainly in those with a neck-dome atheroma. Interestingly, bleeding and unruptured aneurysms (only low H&H grade aneurysms were enrolled in our series) had a similar CRS rate, even when symptomatic. A main concern of our study was the use of only postoperative CT to detect clip-related strokes; this could underestimate the silent ischemic events. A postoperative magnetic resonance - diffusion weighted imaging/susceptibility weighted imaging in all patients could have better disclosed any ischemic events. Aneurysm exclusion in the literature varies according to different series, but postoperative DSA showed residual filling of aneurysms in 2%–8% of cases.[18] Hammer et al.[7] reported a complete occlusion rate of 88.2% in 281 ruptured aneurysms. Our data are similar to those already published in the literature, but with a higher occlusion rate. We think that our monitoring strategy allowed us to safely maximize the aneurysm exclusion rate, which was 98.9% in our study and slightly lower (97.8%) in proximal (ICA) aneurysms. Regarding our data for aneurysm exclusion, it must be emphasized that angiography is much more sensitive in detecting residual disease. This consideration must be kept in mind regarding our study when exclusion data are compared with data from other authors.

Considerations on Intraoperative Data

Regarding flowmetry, literature data showed a major impact of this technique on prompt CR. In a series of 106 patients undergoing aneurysm clipping with intraoperative flow probe measurement, Amin-Hanjani et al.[10] found a CR rate of 25.5% with no unexpected large vessel occlusions on postoperative angiography and a sensitivity of 100% in detection of clinically significant vessel compromise. In only 1 case did the authors find occlusion of distal branches of the MCA resulting in stroke because of an embolic phenomenon after clipping a calcified ICA aneurysm. In this series, flow reduction occurred more often in aneurysms located in the basilar artery, MCA, AComA, and ICA terminus, and the authors concluded that the utility of flow probe measurements is highest in these aneurysm locations. However, the authors found unexpected residual aneurysm on postoperative angiography in 6.7% of 75 cases, thereby pointing to the lack of information on aneurysm remnant as the major limit of probe measurement as the only intraoperative monitoring tool.[10] In our series, flowmetry was particularly effective in detecting a flow decrease during clipping of atherosclerotic aneurysms ($P = 0.0001$). In both cases, symptomatic ischemia occurred after clipping of an MCA aneurysm, even if no flow drop was detected intraoperatively. In these cases, our explanation was in one case a thrombotic complication of a parent artery with a largely atheromatous aneurysm, whereas a collateral circle failure arising after surgery worsened a branch partially occluded during surgery in the other patient. Conversely, all 8 cases of asymptomatic CRS occurred in arterial territories fed by arteries too small to be evaluated by flowmetry. To our knowledge, this study is the first to show the role of flowmetry in a multimodal strategy. In this situation, flowmetry was more effective in detecting a flow decrease during clipping in distal ($P = 0.0001$) than in proximal aneurysms, probably because it is more difficult to measure perforators or small vessels than distal ones. Regarding NM, data from the literature report motor morbidity rates between 5% and 9% in aneurysm surgery.[19] Neuloh and Schramm reported new postoperative permanent motor deficits in 2 patients in a series of 100 operations and 10 new cases of transient paresis.[19] The authors emphasized the superior sensitivity of MEPs compared with SSEPs in detecting intraoperative events resulting from blood flow reduction. The sensitivity of MEPs to postoperative motor paresis was approximately 91%–100%. Moreover, the surgical strategy changed in 70% of cases because of MEP alterations, fourfold more frequently than in SSEP impairment.[19] A recent review article analyzed several studies of MEP-assisted vascular surgery demonstrating a positive predictive value for postoperative motor deficit of 1.0 in cases of permanent MEP loss. However, in transient loss of MEP, which is shown to be reversible in 50%—75% of cases, the positive predictive value for postoperative motor deficit is only 0.31.[20,21] In our study, NM was more effective in detecting a potentially dangerous clipping for brain function when treating a proximal aneurysm ($P < 0.05$) in close relationship with perforating arteries. Another interesting finding was that MEPs never decreased intraoperatively in all 8 cases of asymptomatic ischemic events recorded at postoperative imaging (see CRS, discussed earlier). In particular, no MEPs were shown in 6 patients in whom a hypothalamic ($n = 4$) or deep ganglia ($n = 2$) stroke was recorded postoperatively; this confirms that NM can avoid brain ischemia during clipping when function from the brain region fed by the occluded artery can be monitored. In 22 cases, we found an impairment of blood flow at flowmetry without MEP changes, and no SSEP decrease was reported in 2 cases of MCA aneurysms in which a flow drop was detected with flowmetry. As also suggested by others,[19] this might be due to the timing of flow checking. In fact, in our surgical schedule blood flow was assessed with flowmetry immediately after clipping when evoked potentials deterioration has not yet occurred. Our strategy may therefore imply earlier CR, thus reducing irreversible ischemic injury. Further study is needed to address this issue. We think that our study presented a high rate (10%) of false negatives and stroke. This result could probably be explained by the fact that we used this monitoring strategy to avoid direct inspection of clip blades in some cases, specifically when dealing with complex, deeply located, bleeding aneurysm. As a result, we probably underestimated potential clip-related stroke occurrence in such cases in which flow impairment could not be detected by our monitoring approach alone without direct inspection. As a matter of fact, among 10 patients with postoperative clip-related stroke (**Table 2**), a small artery (perforating in 6/7 patients) was occluded in 7 cases (70%). In all 7 patients, flowmetry could not be used to assess the flow because of the small vessel diameter, and NM could not be used to check the brain perfusion impairment because occluded artery was not feeding a motor pathway. We believe that what was clinically remarkable in our study was that clipping implied a clinically symptomatic stroke for only 2.08% of patients. Conversely, our monitoring strategy implied a high rate (8%) of asymptomatic strokes; this could be a limitation of our approach when direct inspection is not performed. In our study, ICG-VA proved a useful technique to reveal aneurysm remnant, in particular in atherosclerotic aneurysms ($P < 0.05$). We had only 1 false negative remnant neck in an ICA-P-comm aneurysm. As reported by Dashti et al.,[22] ICG-VA has limited ability to visualize the base behind the dome in deeply located aneurysms. In this case, we think that the squeezing maneuver, as described previously,[12] was confirmed to be effective in disclosing suboptimal aneurysm exclusion ($P = 0.0001$), mainly in atherosclerotic aneurysms ($P < 0.05$). Regarding the prevention of ischemic events, the sensitivity of ICG-VA has been reported to be about 94%.[23] De Oliveira et al.[14] reported 6.7% of postoperative perforating artery infarcts, whereas a recent study by Lai and Morgan[24] pointed out that the use of ICG-VA in aneurysm surgery reduces the incidence of postoperative ischemic complications from 7.7% to 3.3%. Moreover, they found that ICG-VA was critical in assuring the patency of small perforators in 9% of cases and helped to modify intraoperative strategies in 6% of cases. In our series, ICG-VA presented a low sensitivity in detecting vessel occlusion, but flowmetry was always performed before ICG injection, and MEPs decrease was usually reported before VA. Finally, it must be emphasized that the high rate of clip repositioning in our study based on ICG-VA data (8.3%) was largely dependent on the squeezing maneuver (87.5% of all CRs depending on ICG-VA data). The squeezing maneuver by testing clip blade force might reveal potential aneurysm rehabitation over time. However, we currently have no data to confirm our hypothesis. For this reason, 1,05% rather than 8.3% of clip repositioning should be compared with data reported by other authors on this specific issue.[22,24]

From a Multimodal to a Tailored Monitoring Strategy

We analyzed CR data to understand the impact of the single monitoring technique on the surgical strategy. In our study, clips were repositioned in more than 40% of cases according to MEPs, blood flow decrease, or incomplete aneurysm occlusion at ICG-VA. This rate is higher than reported in literature.[10,19] Our data show that a multimodal monitoring strategy implies a high CR rate. It is impossible to say whether an ischemic injury would occur in all cases if the clip was not repositioned, because collateral circulation compensation, sustained blood pressure, and other variables can prevent a potential ischemic event when a vessel is partially occluded. However, our study shows that the reported approach is highly sensitive at even minor clip-induced potential flow impairment. Our data partially address the issue of whether intraoperative monitoring is always needed and whether a multimodal monitoring strategy is required. In our series, both patients with a postoperative neurologic impairment had an atheroma; 56.4% of aneurysms requiring CR presented a neck-dome atheroma ($P = 0.002$), and 81.4% of aneurysms presenting an atheroma required CR. In this regard, Ohno et al.[25] observed that morbidity occurred in patients older than 60 years with atherosclerotic aneurysms in a series of 30 aneurysms, whereas Szelenyi et al.[4] claimed that the patient's age and atherosclerotic changes exacerbate postoperative morbidity. In fact, atheroma rigidity can lead to clip slippage with suboptimal aneurysm exclusion, the occlusion of a nearby perforating artery, or thromboembolic accidents during clipping. Atherosclerosis is known to impair vessel elasticity, making clipping more challenging. Retrospectively analyzing our data, we can argue that the different monitoring techniques used in our strategy yielded partially different data and addressed specific intraoperative issues. Indeed, the rate of cases with blood flow decrease detected by flowmetry was significantly higher in distal than in proximal aneurysms ($P = 0.0001$) and in atherosclerotic than in non-atherosclerotic aneurysms ($P = 0.0001$). Conversely, MEP impairment occurred more often in proximal aneurysms ($P = 0.04$). ICG-VA disclosed remnant aneurysms mainly in atherosclerotic lesions ($P < 0.05$). We can argue that the monitoring techniques used in our strategy are complementary, and this might account for our good results. On the other hand, because different monitoring techniques address different intraoperative issues based on aneurysm features, we can argue that the same outcome achieved with a multimodal monitoring strategy might be obtained by tailoring the monitoring strategy to individual aneurysm features. We plan to address this issue in the future.

CONCLUSION

Microsurgical clipping assisted by EPs, flowmetry, and ICG-VA as a unique strategy achieved a high rate of aneurysm exclusion with low morbidity in our study. Our results demonstrate that this multimodal approach has a major impact on surgical procedure, as demonstrated by the CR rate, triggering a tailored surgical strategy. Atherosclerotic aneurysms proved to be a peculiar entity with frequent blood impairment during clipping and an increased risk of morbidity. ICG-VA was demonstrated to be a useful technique to disclose remnant neck, and the associated squeezing maneuver was confirmed to be effective, particularly in atherosclerotic aneurysms. Flowmetry was more sensitive in distal and atherosclerotic aneurysms, and MEPs were more efficient in monitoring proximal aneurysm clipping. Multimodal monitoring tailored to individual aneurysm features could be the next step.

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