



Intraoperative Monitoring Cerebral Blood Flow During the Treatment of Brain Arteriovenous Malformations in Hybrid Operating Room by Laser Speckle Contrast Imaging

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Background: Hemodynamic changes caused by hybrid surgery for brain arteriovenous malformations (bAVM) are usually related to long-term lesions from “blood stealing”. There are currently no viable low-cost, noninvasive procedures for assessing cerebral perfusion in the operating room. This study aims to investigate the use of intraoperative laser speckle contrast image (LSCI) software in AVM surgery.

Methods: In Zhongnan Hospital of Wuhan University, 14 patients who underwent surgery with LSCI were collected. To analyze the hemodynamic features of AVM and the influence on the peripheral cortex of AVM embolization and resection, we assessed the transit time between feeding arteries and drainage veins by intraoperative digital subtraction angiography (DSA). Meanwhile, LSCI was performed at pre-embolization, post-embolization, and after complete resection of bAVM.

Results: In this study, the transit time of bAVM before and after embolization was compared, the transit time before embolization was significantly shorter than that after embolization ($p < 0.05$). We also got good visualization of relative CBF, in addition, to flow imaging in the cortical vasculature round bAVM with LSCI. The flux of post-surgery was significantly higher than pre-embolization ($p < 0.01$).

Conclusion: Hemodynamic variable assessment plays an important role in the resection of AVM in the hybrid operative room and LSCI can be used to visualize and evaluate cortical cerebral blood flow to detect pathological hyperperfusion in real-time with a good spatial-temporal resolution in a sensitive and continuous, non-invasive mode.

Keywords: cerebral blood flow, Intraoperative cortical perfusion imaging, laser speckle contrast imaging, brain arteriovenous malformations, hemodynamics, hybrid surgery, preoperative embolization

INTRODUCTION

The treatment of complex brain arteriovenous malformations (bAVM) remains a challenge for neurosurgeons (1, 2). In the past decades, we have learned more about the anatomy of bAVM and made a great advance in therapy (2–5). Complete nidus obliteration is the only therapeutic treatment, while partial resection is neither efficacious nor prevents recurring bleeding (5–10). In

recent years, the combination of intravascular therapy and microsurgery in the hybrid operating room (hybrid-OR) seems to benefit the majority of patients by increasing the occlusion rate (1, 3, 6, 10–13).

Approximately 3–12.5% of patients with bAVM undergoing microsurgery have intracerebral hemorrhage (ICH) or severe edema, which may be caused by residual lesions or hemodynamic abnormalities after bAVM resection (14). Cerebral hyperperfusion plays an important role in the postoperative complications of bAVM. Cerebral hyperperfusion, which is characterized by a rapid increase in regional cerebral blood flow (CBF), results in the interruption of the automatic regulation function of the cerebrovascular system (15). Therefore, real-time vascular perfusion imaging and hemodynamic monitoring have become critical components of the excision of bAVM (5, 16).

Although indocyanine green videoangiography (ICG) (5, 17, 18) and intraoperative digital subtraction angiography (DSA) (13, 18) are able to assess arterial blood flow during neurosurgery, microcirculation, or cerebral perfusion cannot be showed. Laser speckle contrast imaging (LSCI) allows semiquantitative imaging of tissue perfusion (19–22). The lens radiates the laser to illuminate the investigated area, and the charge coupled device (CCD) camera captures the illuminated area in real time to create a two-dimensional color-coded blood flow map (23). Hecht et al. (20) demonstrated that intraoperative LSCI is feasible, safe, and effective in the process of neurosurgery.

This study was aimed to demonstrate hemodynamic changes after complete resection of bAVM and highlight the effectiveness and availability of intraoperative LSCI, which could continuously monitor normal cortical CBF during hybrid surgery in real-time.

METHODS

Patients

The study was approved by the local ethics committee of the (Zhongnan Hospital, Wuhan University) and a total of 14 patients with bAVM were admitted from May 2020 to October 2021. The data of the patients are shown in **Table 1**. All patients with hybrid surgery underwent bAVM embolization and microsurgical resection under general anesthesia according to the fixation scheme.

Laser Speckle Contrast Imaging

After imaging is illuminated by laser light, a random interference phenomenon called laser speckle occurs. The random speckle pattern, which is exploited by laser speckle contrast analysis, can be generated by irradiating the tissue with laser light and varies as blood cells move in the selected area (23, 24). When there is a high level of movement (fast flow), the dynamic pattern becomes more and more blurry and the contrast in the area decreases. As a result, low contrast is associated with high flow, while high contrast is related to low flow. The contrast image is processed

Abbreviations: bAVM, brain arteriovenous malformations; ICH, intracerebral hemorrhage; DSA, digital subtraction angiography; CBF, cerebral blood flow; LSCI, laser speckle-contrast imaging; AVTT, arteriovenous malformations transit time; NPPB, normal perfusion pressure breakthrough; ICG, indocyanine green videoangiography; hybrid-OR, hybrid operating room.

TABLE 1 | Summary of patients with AVM.

Patient	Age	Sex	Presentation	S-M grade	Location	Size/cm	No of LSCI	Transit time/ms		Operative time/h	Blood loss/ml	GCS of 7 days after operative	mRS
								Before	After				
1	44	M	Epilepsy	4	L, T	6.0*4.5*3.0	3	1,333	667	8	1,000	14	0
2	49	F	Neurological deficits	3	L, T	5.4*3.1*3.5	3	1,167	1,667	12	1,000	14	0
3	45	M	Epilepsy	3	R, F	5.0*3.0*3.5	3	1,333	2,167	7	100	13	0
4	38	M	Headache	5	L, P	6.5*7.0*4.5	3	1,000	1,333	12	1,500	15	0
5	16	F	Headache	3	R, F	5.0*3.5*3.0	3	1,667	2,333	6	300	15	0
6	25	F	Epilepsy	4	R, F	3.5*6.0*4.0	3	667	1,667	7	200	15	0
7	30	M	Headache	4	R, O	6.0*4.0*3.0	3	1,333	1,333	8	400	13	1
8	31	M	Headache	4	L, F	5.5*4.0*3.5	3	1,000	1,333	6	400	13	0
9	28	M	Headache	3	R, TO	4.0*3.5*3.0	3	1,000	1,667	9	1,500	11	2
10	11	F	Epilepsy	4	R, TO	5.0*4.0*4.0	3	1,667	1,500	11	800	15	0
11	10	M	Hemorrhage	4	L, Cerebellar	4.5*4.0*3.5	3	1,333	1,833	11	5,000	15	0
12	59	M	Hemorrhage	4	L, PO	6.0*5.0*3.5	3	667	1,667	10	7,000	15	0
13	53	M	Epilepsy	4	R, T	3.0*4.0*4.5	3	1,167	1,000	7	500	14	0
14	49	M	Epilepsy	3	R, T	3.5*4.0*3.0	3	1,000	667	6	600	15	0

R, parietal lobe; F, frontal lobe; O, occipital lobe; T, temporal lobe.

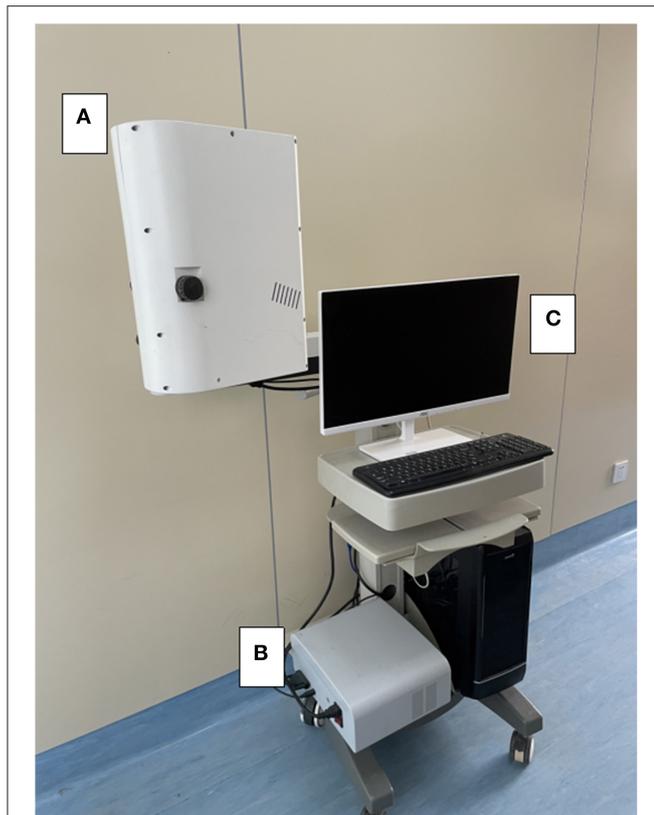


FIGURE 1 | Device settings for intraoperative laser speckle imaging. In the intraoperative setting of the laser speckle device, the laser imager (A) is fixed on the clamped joint and connected to the mobile trolley, allowing free positioning in the surgical area. (B) The standard USB and FireWire interface can be connected to the laser light source. The computer (C) for data recording.

to provide a color coded real-time image (flux image: red = high flow, blue = low flow), which is consistent with the blood flow velocity in the tissue, commonly referred to as “flux” (20, 25).

The laser imager (SIM BFI HR Pro, SIM Opto-Technology Co., Ltd, Wuhan, China, www.simopto.com) we used is conducted on a trolley by a rigid, extendable arm and attached with a mobile stand to allow versatile positioning over the interested imaging field. The imager was linked to a computer by a conventional universal serial bus (USB) and FireWire connections for data acquisition (Figure 1). The laser speckle imager was positioned 200 mm above and perpendicular to the exposed cortical region after craniotomy and durotomy. The laser penetration depth varies between 0.5 and 1 mm, depending on the optical qualities of the laser light and the sampled tissue (23, 26). The arbitrary perfusion unit CBF-Flux was used to record cortex perfusion using custom-designed data gathering software (SIM BFI measurement software, Version V2.0, SIMBFI HR PRO, CN). The mean flow in the observed region of interest (which can be any size or location) is computed and shown in real-time.

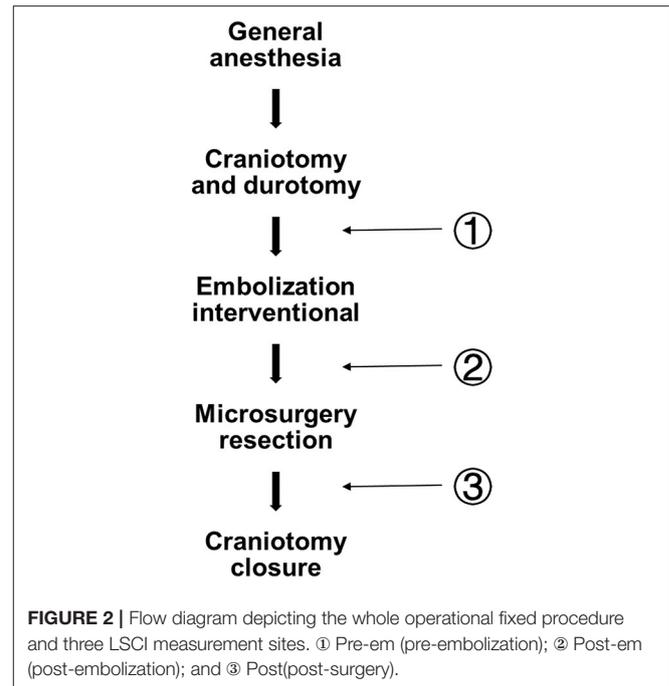


FIGURE 2 | Flow diagram depicting the whole operational fixed procedure and three LSCI measurement sites. ① Pre-em (pre-embolization); ② Post-em (post-embolization); and ③ Post(post-surgery).

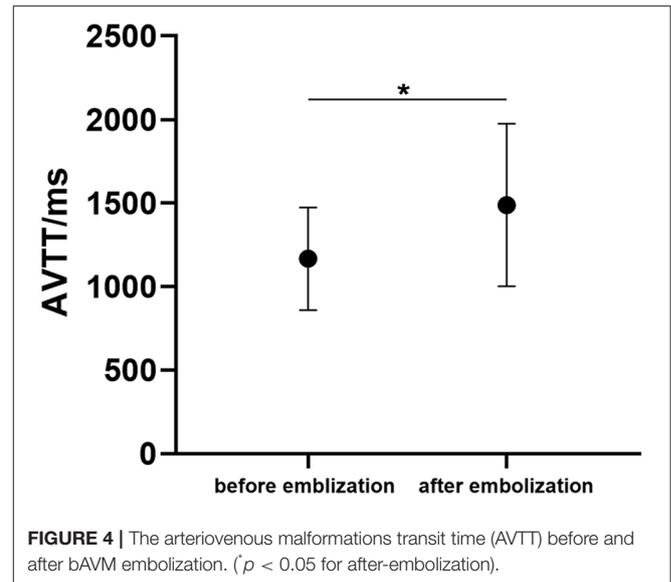
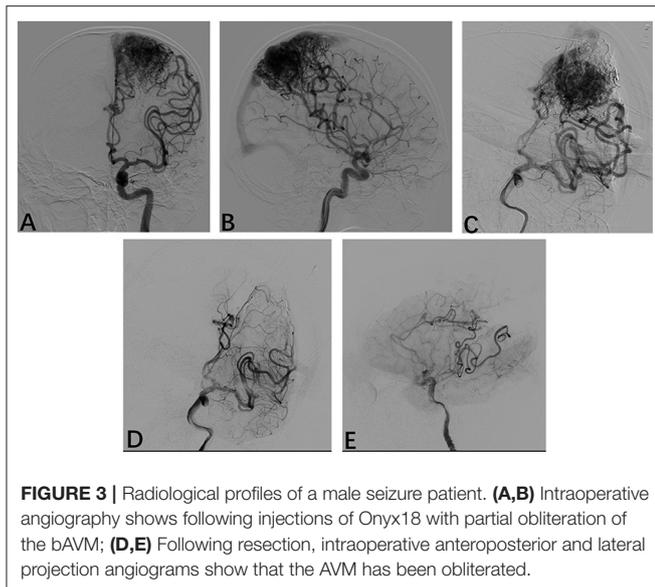
Operation

With the development of biplane angiography suite operation, the number of patients treated with hybrid surgery for bAVM has increased. The angiography system includes a vertical monoplane detector, a ceiling-mounted one (UNIQ FD20/20, Philips, The Netherlands), and an operational microscope (Pentaro, Carl Zeiss, Germany) in the operating room (10). Both bAVM resection and pre-surgical embolization were done at the one-stop stage in all. Under general anesthesia, endovascular embolization was conducted utilizing the biplane flat-panel angiographic suite with 3D reconstruction. Intraoperative DSA and LSCI are usually performed during the whole surgery (Figure 2).

Aseptic techniques were used throughout the procedure to provide a sterile environment. After craniotomy and durotomy, preoperative embolization was performed by using either n-butyl cyanoacrylate (Trufill, Cordis Neurovascular, Inc., Miami Lakes, FL, USA), ethylene-vinyl copolymer (Onyx 18 or 34, Medtronic, Inc., Minneapolis, Minnesota, USA). In hybrid surgery, surgical resection is performed without changing the patient's posture. After the excision of bAVM, DSA was used to evaluate the residual nidus. Arteriovenous malformations transit time (AVTT) was defined as the time required for blood to flow from the feeding artery to the drainage vein. During bAVM treatment, LSCI was performed at fixed at three measurement points (Figure 2): ① Pre-em (pre-embolization); ② Post-em (post-embolization); and ③ Post (post-surgery).

Statistical Analysis

Data are presented as mean \pm SD. Statistics were generated by GraphPad Prism for Win (Version 8.0f, GraphPad Software, San Diego, CA, USA). Comparisons between two groups (survey



scores) were achieved using the Student *t*-test. Two-tailed *p*-values < 0.05 were considered statistically significant.

RESULTS

Patient Characteristic

Our study enrolled 14 patients with bAVM who were considered suitable for hybrid surgery under general anesthesia. The demographic characteristics of the patient population are listed in **Table 1**. A total of 10 men and 4 women were enrolled, and the mean age was 34 years (range 10–59 years). Out of these, eight patients were diagnosed with grade 4 Spetzler-Martin bAVM, five patients were diagnosed with grade 3 bAVM, and 1 was diagnosed with grade 5 bAVM. The clinical presentation was hemorrhage in 14.2% of patients, epilepsy in 42.9%, headache in 35.7% of patients, and neurological deficit in 7.2%.

A total of 42 times LSCI were performed. All patients underwent DSA after resection, which showed that bAVM had been completely removed. A typical example is shown in **Figure 3**. All patients underwent a CT scan within 24 h after the operation to check for bleeding. Postoperative bleeding occurred in two cases.

AVTT During AVM Embolization

In hybrid surgery, all 14 patients underwent DSA at least three times. The present study analyzed the AVTT of bAVM before and after embolization. AVTT before embolization ($1,180.56 \pm 329.20$ ms) was significantly shorter than that after embolization ($1,597.22 \pm 429.11$ ms, $p < 0.05$, **Figure 4**).

Dynamics of LSCI During Perfusion Changes

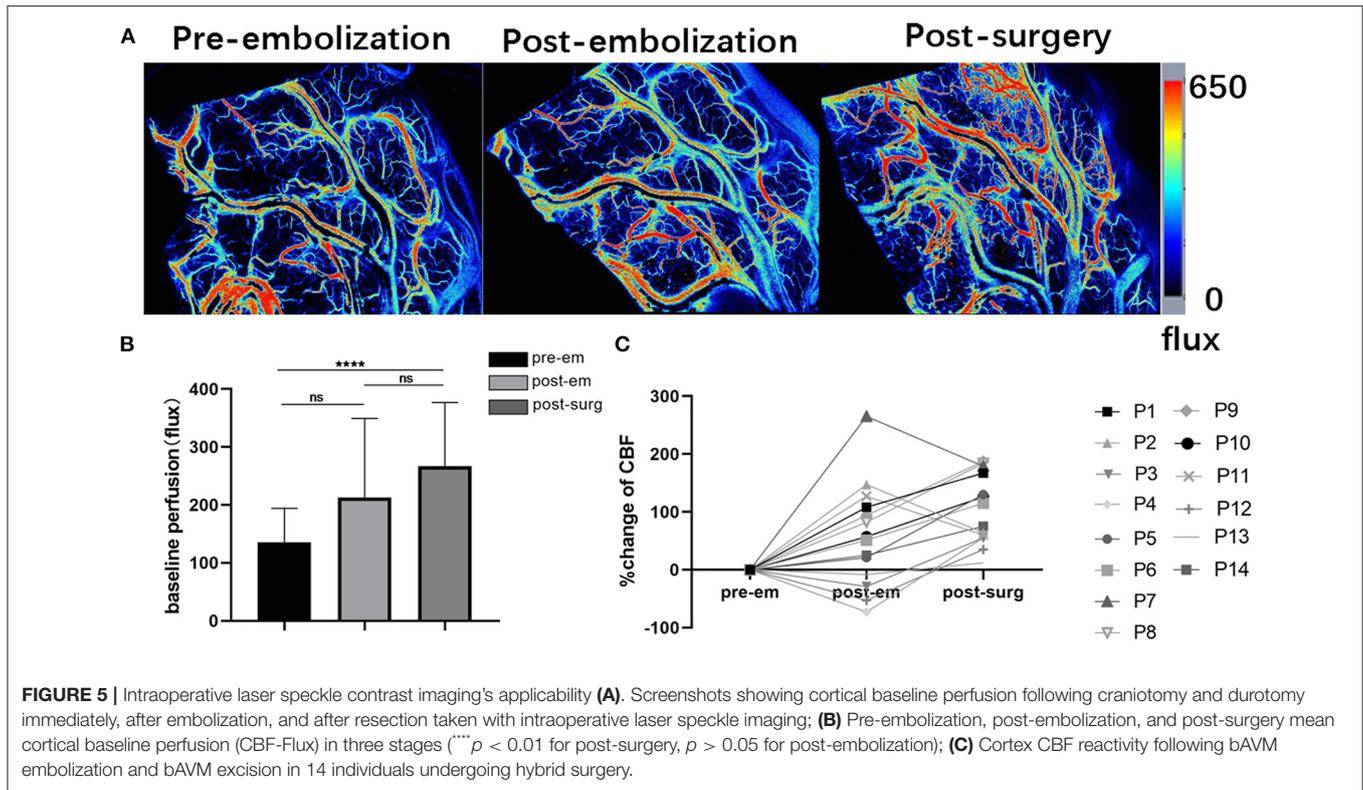
In each case, satisfactory CBF laser speckle patterns are obtained. This method accurately visualized blood

flow in the cortical arteries surrounding the bAVM (**Figure 5A**).

Baseline perfusion in the cortex was (135 ± 59 flux) before bAVM embolization, and cerebral flow in the cortex increased after embolization (223 ± 136 flux), although these differences were not significant. After bAVM resection, the perfusion was (267 ± 109 flux), and the cortical CBF flux increased significantly compared with that before embolization ($p < 0.001$, **Figure 5B**). In 14 patients who underwent hybrid surgery for bAVM, we could detect flow fluctuations in cortical blood flow during surgery (**Figure 5C**).

DISCUSSION

Hybrid surgery (microsurgical resection coupled with endovascular embolization) for bAVM has been proved to be safe and effective, with high rates of immediate, complete, and permanent bAVM obliteration (5, 6, 10, 12, 13, 27). Routine intraoperative DSA after microsurgical resection can identify the AVM remnant directly for one-stop resection (12, 27). Preoperative partial embolization of the malformation can assist in surgical positioning and decrease blood flow of the malformation, which contributes to minimizing the risk of intraoperative bleeding (28–31). However, after bAVM resection, excessive perfusion of adjacent cortical tissue and pathological increase of local intravascular pressure (32–34), may generate cerebral hemorrhage or edema, which worsens the postoperative course. Two possible causes for the hyperperfusion were proposed: (1) the microcirculation in the AVM area could not protect itself from the rapid increase of pressure from low to normal through automatic regulation reaction, resulting in the breakthrough of normal perfusion pressure (NPPB). This hypothesis is supported by the fact that there are significant differences between perinidal capillaries and other capillaries in the brain, which helps to prove that perinidal capillaries may be apt to rupture once bAVM is removed (5, 32). (2) Occlusive



hyperemia, the outcome of propagated thromboembolism in a dilated venous drainage system that became superfluous after AVM excision is occlusive hyperemia (35).

Our study suggested that the severity of postoperative hyperperfusion in the brain surrounding the resected AVM is locally distinct. Furthermore, the density of the cortical layer around vascular malformation was higher than that of normal cortical vessels. Asgari et al. (8) showed the removal of bAVM usually led to significant increases of SaO₂ in the cortical area around malformation, which indicated that the brain would suffer from congestive injury, primarily due to the excessive inflow of capillaries, which was used to be an ischemic area before the removal of bAVM.

The applicability of dynamic and noninvasive real-time monitoring of CBF in patients undergoing bAVM surgery by LSCI has been proven in our research, which involves a series of CBF changes related to bAVM resection. LSCI has been proved to be able to intuitively, effectively, and accurately reflect the changes in hemodynamics. The operation protocols were well managed in all the patients, and no adverse effects were found. Patient safety and image quality were not compromised by repeated measurements.

Intraoperative monitoring enhances the effectiveness of neurosurgery and the safety of patients. CBF remains the most important driver of tissue viability. However, there are no reliable means to evaluate it at present. Although many imaging methods for studying cerebral hemodynamics have been reported, such as positron emission tomography

(PET), SPECT, orthogonal polarization spectral (OPS) imaging, dynamic perfusion CT, or ICG-FLOW800 perfusion study (8, 17, 21, 36, 37), their intraoperative application is limited by immobilization, invasiveness, high financial, and personal costs.

Based on dynamic light scattering off moving particles, LSCI works as an optical blood flow visualization and quantification technique (erythrocytes). The camera records the speckle pattern, and the software computes the contrast of each pixel to create a color-coded map of CBF (20). At present, no data exists for direct cortex blood flow evaluation in patient with bAVM. LSCI has been used during intracranial surgery to map the motor cortex in awake craniotomy, identify cortical regions at risk of infarction after decompressive craniectomy, and show increased blood flow after arterial anastomosis (20, 38, 39). Through direct assessment of tissue perfusion, LSCI provides immediate functional feedback on cortical blood flow (20). Previously, Takeshita et al. (40) reported the value of SPECT in monitoring the changes in regional CBF after the removal of bAVM. They believe that SPECT plays a significant role in detecting the hyperperfusion of the area adjacent to the malformation. However, routine assessment of CBF using SPET is theoretically and financially difficult and has not been widely used. LSCI may be a non-invasive, cost-effective, and convenient method to detect the changes in normal tissue perfusion after resection, with high temporal and spatial resolution.

This present study found that the cortical flow index following bAVM removal is significantly higher than it was preoperatively. This may imply altered hemodynamics during bAVM surgery,

leading to the redistribution of blood flow into the capillaries of the surrounding cortex. In our data, three patients had a reduction in flux following embolization, as shown in **Figure 5C**. This may result from our surgical strategy. First, the target of embolization we chose might not be the main feeding artery of bAVM, but a tiny feeding artery. Therefore, there was no obvious change in perfusion of the cortex around the nidus. Additionally, when we finished embolization, the blood vessels experience vasospasm due to vessel “stimulation” caused by catheter manipulation during embolization. Although usually asymptomatic, it can lead to decreased blood flow and potentially poor recanalization in the region of the vasospasm (41).

Conger et al. (29) and Donzelli et al. (1) reported that preoperative embolization could reduce the size and grade of the bAVM so that patients with higher-grade lesions were able to be treated with curative microsurgery, thereby minimizing complications and improving outcomes. Our study showed that the transit time of bAVM is significantly longer after endovascular embolization than preoperative, implying that endovascular embolization decreases the nidus flow velocity, and minimizes the risk of intraoperative bleeding in microsurgery resection of high-grade bAVM. However, in the treatment of high-grade bAVM, especially Spetzler-Martin 5 bAVM, we need to pay more attention to the occurrence of hyperperfusion. Once we block the main feeding artery and partial nidus occlusion, there will be high perfusion in the area adjacent to bAVM. The increase in blood flow might be the initiator of intraoperative and postoperative bleeding. In this “outlier” patient, blood loss in microsurgery resection might decrease the “flux” value in CBF around malformation (**Figure 5C**).

Treatment of bAVM, including high-grade bAVM, requires hemodynamic evaluation (5). Previous studies (9, 17, 40, 42) suggested cerebral perfusion harassment by preoperative embolism could be measured with DSA, SPECT, or iFlow (parametrically color-coded angiography), which cannot instantly evaluate the flow dynamic and normal cortex perfusion. In our hybrid-OR, we manage endovascular treatment and microsurgical resection in one-stop. To ensure surgical safety and effectiveness, we routinely utilize intraoperative DSA and LSCI to monitor bAVM hemodynamic changes in real-time and prevent intraoperative bleeding. That could further help to reduce surgical complications and improve long-term outcomes.

Our research has some limitations. First, the sample size of surgical patients is not large enough. We need more clinical

data to reveal the usefulness of LSCI in monitoring cerebral hemodynamic change. Second, due to the limited depth of tissue penetration of LSCI, they may only evaluate superficial cortical perfusion. Furthermore, since the technology we used has not been incorporated into the surgical microscope, the operation must be paused while the LSCI device is positioned over the surgical field during the whole measurement interval.

CONCLUSION

The combination of embolization and microsurgical resection in hybrid surgery might be a safe and successful method for the treatment of bAVM. With high spatial-temporal resolution and good image quality, LSCI enables real-time dynamic imaging of blood flow within the cortical vasculature and assessment of cortical perfusion around the AVM at a low cost. LSCI can be used as a supplement for intraoperative CBF dynamic imaging to improve the quality of neurovascular treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was obtained from the Zhongnan Hospital of Wuhan University Ethics Committee (Kelun-2017005). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JC: conception and design of the study. TZ, ST, and KZ: data acquisition. ST, XL, and KZ: software. ST and YF: analysis and interpretation of the data. WZ, ST, YF, and JC: co-drafted the manuscript. All authors read and approved the final manuscript.

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