Intraoperative real-time contrast-enhanced ultrasound angiography: a new adjunct in the surgical treatment of arteriovenous malformations

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Objective. The goal of this study was to combine the use of ultrasound contrast agents with intraoperative ultrasound techniques to identify intraoperatively a patient’s vascular anatomy, including feeding arteries and draining veins of an intracranial arteriovenous malformation (AVM).

Methods. The authors examined 12 consecutive patients with AVMs that had been diagnosed on the basis of preoperative findings on magnetic resonance imaging and digital subtraction angiograms obtained between September 2003 and December 2005. After each patient had undergone a routine craniotomy, a bolus of contrast agent was injected intravenously, and a real-time microbubble perfusion process was observed to identify the feeding arteries and draining veins of the AVM in a single cross-section. The so-called burst–refill technique was used to sweep the lesion in multiple sections and orientations to obtain information on the surrounding vascular anatomy, after which the findings were compared with those obtained during preoperative imaging.

Results. Intraoperative ultrasonography provided high-quality images in every case. Although plain imaging failed to show an identifiable AVM boundary, color Doppler flow imaging clearly delineated the shape and margin of the AVM. Nevertheless, neither mode of imaging enabled the surgeons to categorically distinguish between feeding and draining vessels.

The real-time perfusion process of microbubbles was first visualized 20 to 30 seconds after the SonoVue bolus injection, and the burst–refill technique made possible identification of the vascular anatomy of malformation lesions in multiple planes.

Conclusions. Using both an ultrasound contrast agent and the burst–refill technique provided a rapid, convenient, and precise way of locating AVM feeding arteries intraoperatively. The combined technique seems warranted in the intraoperative treatment of AVMs. (DOI: 10.3171/JNS-07/11/0959)

Key Words • arteriovenous malformation • intraoperative ultrasonography • ultrasound contrast agent

Although the last decade of the 20th century witnessed remarkable developments in sophisticated neurosurgery and imaging techniques, the intracranial AVM remains one of the most challenging lesions for neurosurgeons.4,20 Using imaging techniques such as MR imaging and DS angiography,9,17,22 we can determine the location of lesions and their vascular anatomy preoperatively. Nevertheless, after craniotomy and opening of the dura mater, surgeons frequently describe the visible portion of an AVM as the “tip of the iceberg.”15

Generally, the key to successful AVM surgery is obliteration of the feeding arteries early in the dissection.4,14,20 Intraoperative ultrasonography is sometimes useful in locating the AVM nidus, and color Doppler ultrasonography may help identify the vascular anatomy of the lesion.2,3,8,21,23 Because of the unique hemodynamics of this lesion, however, it is sometimes difficult to differentiate between lesion-associated arteries and veins or between feeding arteries and surrounding normal arteries by using a color or pulsed Doppler mode alone.

Since the introduction of ultrasound contrast agents in clinical diagnostics, the specific acoustic properties of microbubbles and their ideal hemodynamics have shown microbubbles to be powerful tools in the diagnosis of vascular diseases.3,6,17 Approximately the same size as erythrocytes, microbubbles do not normally disrupt the local environment and can serve as intravascular indicators when injected intravenously. Contrast agent–specific imaging with secondary harmonic imaging can show blood flow and the perfusion process in vessels in real time, thus enabling us to distinguish between the feeding arteries and draining veins of an AVM.

In this study, we applied ultrasound contrast agent–specific imaging and intraoperative ultrasound methods to seek and identify feeding arteries. In this paper, we describe our experiences with this combined method and determine if it improves the outcome of surgical treatment of such vascular malformations. Intraoperative ultrasound findings were compared with results obtained with preoperative an-
giographic imaging, the latter being the accepted standard of reference today.

Clinical Material and Methods

Patient Population

Ten male and two female patients, who underwent consecutive surgical procedures to treat AVMs between September 2003 and December 2005, were entered into the study. The patients ranged in age from 13 to 54 years (mean 24.5 years). None of them had undergone preoperative endovascular embolization. The AVM nidus ranged from 1.7 to 4.1 cm at the greatest diameter (mean 3.1 ± 0.8 cm) and the lesions were graded I, II, or III according to the Spetzler–Martin Scale.19

Imaging Studies

Written informed consent was obtained from all patients or their guardians in advance. Each patient’s pertinent preoperative imaging studies, including DS angiograms and MR images, were thoroughly reviewed before ultrasonography was performed. All ultrasound images were obtained using an Acuson Sequoia 512 unit (Siemens) and a planar 1- to 4-MHz phased-array probe. The transducer was covered with a specially designed sterile sheath. After we performed craniotomy and opening of the dura mater, we began direct-contact scanning while exercising extreme caution to minimize pressure injury. Visual images of the entire examination were continuously recorded on a hard disk in DICOM (Digital Imaging and Communication in Medicine) movie format.

The first step was gray-scale scanning; axial and sagittal sweeps provided orientation to intracranial and anatomical landmarks. Because this technique alone seldom clearly delineates the AVM, we used it in combination with the color Doppler method. Depth of focus, pulse repetition frequency, color gain, and image persistence in each patient were determined by the depth, size, and flow character of the lesion. Spectral Doppler ultrasonography was also applied to large vessels that appeared to be associated with the lesions, and the RI (systolic velocity – diastolic velocity/systolic velocity) was measured for these vessels.

Intraoperative ultrasound angiography was introduced at this point. The contrast agent SonoVue (Bracco) was injected intravenously. This agent is a sulfur hexafluoride–containing aqueous suspension that has between 108 and 5 × 108 phospholipid microbubbles per milliliter, 90% of which are 8 μm in diameter—small enough to pass through the pulmonary circulation. This suspension was obtained by adding 5 ml of normal saline to 25 mg of the powdered agent and agitating the mixture manually. A bolus of 2.5 ml of this suspension was administered within 10 seconds via a 20-gauge intravenous catheter inserted into the median cubital vein. The catheter was immediately flushed with 5 ml of saline after the injection to ensure that all the preparation had been administered.

Approximate positions of feeding arteries and draining veins could be determined from information obtained using preoperative imaging and intraoperative conventional ultrasonography—gray-scale, color Doppler, and spectral Doppler ultrasonography—but precise locations could not. We thus fixed the probe on the plane in which these vessels were deemed most likely to be found. The anesthetist administered a bolus injection of contrast agent while, at the same time, the operator switched the ultrasound device to contrast agent–specific imaging mode by using the pulse-inversion harmonic imaging technique (frequency 1.5 MHz; mechanical index 0.20) and started the timer and video recorder. The real-time process of contrast agent perfusion was clearly visible on the monitor within approximately 10 to 30 seconds.

To observe the real-time perfusion process in other planes, we positioned and fixed the probe on those planes once the concentration of contrast agent became stable. High-pressure (that is, high-mechanical-index) ultrasound waves radiated outward to destroy all the microbubbles within the target field. To produce these high-pressure sound waves, we set the ultrasound device to a color Doppler mode. After the ultrasound device was set back to the contrast agent–imaging mode, in a matter of seconds the reperfusion process was visualized in the appropriate scanning plane.

The probe was controlled by the neurosurgeon in charge of the operation. An experienced physician who was operating the ultrasound device advised the surgeon on how to perform the ultrasound sweep. After data acquisition, the neurosurgeons and this physician together analyzed the video to determine the exact position of the feeding arteries and draining veins. This position was then compared with that determined from preoperative imaging results.

Postoperatively, we performed conventional DS angiography in 11 of the 12 patients and compared the findings with those obtained intraoperatively.

Results

All 12 AVMs were located in the cerebral hemispheres—six on the left side and six on the right. Four of the lesions were located in the frontal lobe, two in the parietal lobe, one in the occipital lobe, and five in the temporal lobe. Ten patients made a good recovery; of the remaining two patients, one subsequently experienced a moderate disability (hemiparesis) and the other patient was lost to follow-up after discharge from the hospital. No intracranial infections or normal perfusion pressure breakthrough was reported postoperatively. The patient with hemiparesis had a Grade III AVM and during long-term follow-up displayed complete resolution of his symptoms.

Intraoperative ultrasonography produced high-quality images in all the patients. Gray-scale mode provided important information on normal surrounding landmark structures such as the lateral ventricle, falx cerebri, and brainstem. Color Doppler flow imaging clearly delineated the shape and margin of the AVMs. Using color Doppler flow imaging and the pulsed Doppler technique, we quickly distinguished normal arteries from abnormal vessels. Nevertheless, distinguishing between feeding arteries and draining veins was difficult, as discussed in Illustrative Cases.

In the contrast-enhanced ultrasound angiography mode, the perfusion process of microbubbles could be observed in real time approximately 20 to 30 seconds after the bolus injection of SonoVue. The burst–refill technique enabled us to identify the vascular anatomy of malformation lesions in multiple planes.

In general, compared with preoperative DS angiography

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and/or MR imaging, all the feeding arteries of the 12 lesions could be depicted clearly. Moreover, in nine of 12 cases the draining veins were also clearly visualized. In the remaining three cases, clear visualization of the draining veins was not possible due to their location on the cortical surface. The use of a low-frequency probe made it difficult to depict superficial draining vessels. However, because of their superficial position, direct visualization was possible on opening the dura.

Although the duration of ultrasound scanning (inclusive of conventional examination, contrast angiography, and co-analysis of video) was not accounted for, we estimate that it was a mere 15 minutes. The total time for surgery was reduced due to the prompt identification of vascular anatomy.

Postoperative DS angiography and 3 to 18 months of follow-up review confirmed complete resection of 11 of the 12 AVM lesions. One patient declined to participate in follow-up and subsequent contact with this patient was lost after discharge from the hospital.

Illustrative Cases

Figure 1 illustrates the case of a 54-year-old man referred to our institution with a 5-year history of intermittent epilepsy. Magnetic resonance imaging revealed a hematoma with an abnormal vascular configuration in the right frontal lobe, and DS angiography confirmed the lesion to be an AVM. Microsurgery was guided by intraoperative ultrasonography.

A direct-contact ultrasound scan was performed after craniotomy. Although the lesion was barely visible in grayscale mode, the brainstem and the skull—two relative landmarks—were clearly visualized and the shape and margin of the AVM was clearly delineated in the color Doppler images (Fig. 2). Spectral Doppler imaging was applied to the vasculature around the nidus to assist in differentiating normal cerebral arteries from those of the AVM. The RI of the vessels in the lesion, 0.34, was lower than that of normal arteries, but spectral Doppler signals from the AVM vessels did not help distinguish the feeding arteries from the draining veins because the RIs and peak velocity values of these vessels were similar (Fig. 3).

The microbubble perfusion process appeared on the monitor about 24 seconds after the contrast agent was injected. The feeding arteries clearly visualized in the arterial phase confirmed the location of the lesion. We also observed the flow of contrast agent into the draining vein in the early venous phase (Fig. 4). According to the imaging principle of pulse-inversion harmonic imaging, however, we suggest that all signals generated in the contrast agent-specific imaging mode arise from microbubbles and that signals from other tissues can be ignored. We used the burst–refill technique to perform multiplane sweeps to identify clearly the vascular anatomy of this malformation (Fig. 5).

Figure 6 shows ultrasonograms of two similar lesions. The vascular anatomy of these lesions could be clearly depicted intraoperatively by using microbubbles.

Discussion

Arteriovenous malformations are lesions defined by the presence of arteriovenous shunting through a nidus of coiled and tortuous vessels connecting feeding arteries and draining veins. Because no capillaries connect these vessels, arterial circulation must flow directly into the venous circulation, producing the characteristic hemodynamic changes of increased blood flow velocity and decreased hemodynamic resistance. All the clinical presentations of AVMs—hemorrhage, epilepsy, and neurological deficit, for example—are based on these pathophysiological mechanisms.

Although endovascular embolization and stereotactic radiosurgery have been used to treat these lesions for the past 10 years, microsurgery remains the mainstay of AVM treatment. In general, excision of the AVM ideally proceeds through well-defined stages as follows: the AVM is identified, the superficial feeding arteries are eliminated, and the superficial portion of the nidus is circumferentially dissected. The apex is then dissected and the vascular pedicle divided. We thus conclude that a thorough understanding of the vascular anatomy of the AVM and, specifically, knowledge of the location of feeding arteries and draining veins is essential for intraoperative treatment.

Unfortunately, there are fewer intraoperative imaging techniques than sophisticated preoperative ones. Four concepts seem to represent the options: a neuronavigation system; interventional MR imaging; intraoperative DS angiography; and ultrasonography, which requires only a small, sterile, draped scan head in the field, rendering real-time 2D scanning available when needed.

Intraoperative ultrasonography has been used for many years and is an efficient imaging adjunct to neurosurgery. Our experience with intraoperative ultrasonography over a period of approximately 10 years has shown us the value of its real-time results. The ability to depict real-time anatomical data during a surgical procedure is a valuable surgical adjunct, one that even affects decisions made during surgery. It is a rapid and effective way to localize and characterize diseases of the brain.

In the 12 cases reported here, conventional ultrasonography provided rapid localization of the AVM nidus. Because of the unique hemodynamics of this arteriovenous shunt,
however, it is difficult to distinguish feeding arteries from draining veins. Some authors\textsuperscript{2,8,15,21} have reported that duplex scanning can differentiate between lesion-associated arteries and veins or between feeding arteries and peripheral normal arteries by using the RI, peak systolic velocity, and directional information. However, in our study, spectral Doppler was seen to be of little help because the draining veins had arterialized and their spectral Doppler waves presented as those of arteries. This is shown in Fig. 3.

Owing to the emergence of contrast agents and the ease with which they are administered, we can now try this technique in seeking and identifying feeding arteries intraoperatively, as stated previously. Microbubbles of encapsulated gas possessing strongly nonlinear properties led to the introduction of harmonic imaging, which differentiates echoes of microbubbles in the capillary bed from those in avascular tissue. Although insonated tissue responds primarily at the fundamental frequency, resonating microbubbles cause the scattering of echoes at multiples of fundamental frequency called harmonic frequencies. By selecting the ultrasound frequency required to preferentially detect echoes from microbubbles while suppressing those from solid tissues, we achieved specialized harmonic imaging, known as contrast agent–specific imaging. Furthermore, a new harmonic imaging method, the pulse-inversion harmonic perfusion-imaging technique, was developed to improve image quality while reducing contrast agent–specific artifacts.\textsuperscript{3,6} This method can provide an angiogram-like view of AVM vessels in real-time imaging. Fortunately, this real-time angiospecific imaging enabled us to observe the microbubble perfusion process and to distinguish feeding arteries from draining veins.

Results obtained in these 12 cases indicate that the microbubble perfusion process in the brain is the same as that of contrast-enhanced computed tomography scanning proceeding from artery to tissue to vein. Although the AVM displays a unique characteristic hemodynamic change, in fact microbubbles do follow this perfusion pattern. Because ultrasonography provides results in real time, is always readily available, and presents no radiation danger, it is an optimal intraoperative guidance tool. Moreover, it is appropriate for intraoperative application, even when used in combination with contrast agents. In situations in which surgeons have doubts after an ultrasound examination, they can review the video records stored on the hard disk and review and analyze the vascular anatomy carefully.

The major problem encountered with the method described here was that the real-time perfusion process could be observed in only two dimensions, whereas the AVM is a 3D lesion. Thus a single image contains a relatively small quantity of information. This is a serious problem in contrast agent–specific imaging. To counter this issue, we used
one of two options: 1) repeating the bolus injection whenever observation of a new section was required, or 2) using the burst–refill technique. The former method is a time-consuming process; whenever we wanted to observe a new dynamic perfusion process, we had to wait until most of the microbubbles in the tissues disappeared. In addition, although this method apparently requires lesser amounts of contrast media with each bolus injection, the overall cumulative amount is significant and possibly harmful to the patient.

To overcome this limitation, we took advantage of another characteristic of microbubbles. Above a certain pressure threshold, microbubbles burst or collapse and are destroyed on sonication. We could thus send a pulse of high-pressure sound waves to clear the microbubbles within the insonation field. The difference in the concentration of contrast agent would then bring about a new refill process of microbubbles, allowing us to observe the perfusion process in multiple sections. By contrast, although this method required a great amount of contrast agent in one bolus injection, it actually saved the overall consumption and scan time of the contrast agent.

We solved this problem satisfactorily by using the burst–refill technique and were able to obtain multisection sweeps. Based on our experience, we state that an intraoperative 2.5-ml bolus injection of ultrasound contrast agent is effective in many situations and the high recovery rate in this patient group (10 of 12 patients) proved it was a safe procedure. Pulmonary circulation, nitrous oxide anesthesia, and positive-pressure ventilation do not appear to be significant limiting factors for the harmonic imaging of intravascular microbubbles. Further, SonoVue can persist intravascularly for approximately 3 to 5 minutes, depending on the weight of the patient and the frequency at which the burst–refill technique is applied; this is a sufficient time to complete a multidirectional sweep. As this is a pilot study, no comparison was made of the effectiveness of a bolus injection and a continuous injection. Additional study is required to find a better method of administration.

One should bear in mind that this technique also has some shortcomings. Some surgeons complain that the ultrasonograms are hard to interpret and that inability to demonstrate precise spatial localization can be confusing during surgery, even though professional examiners could interpret them. Further development of a real-time 3D ultrasound technology might enable neurosurgeons to interpret ultrasonograms more easily. Another problem with intravenous contrast-enhanced ultrasound angiography is the resolution of its images, which being lower than that of DS angiography may increase the probability of overlooking an arterial aneurysm within a lesion.

**Conclusions**

Intraoperative real-time contrast-enhanced ultrasound angiography is a powerful tool in AVM resection. Instead of the bulky C-arm of a DS angiography system, one need only apply the convex ultrasound transducer to the dural surface when ultrasound angiography is used. The definite advantages of ultrasonography over other imaging modalities are its availability, portability, and low cost.

**FIG. 4.** Ultrasongsgrams displaying the real-time perfusion process of the microbubbles. The perfusion process was visualized in the contrast agent–specific imaging mode 24 seconds after the bolus was injected.  a: Microbubbles first flowing into a feeding artery (arrow).  b: Microbubbles flowing into the lesion.  c: Microbubbles finally flowing into a draining vein (arrow). WS = Willis circle.

**FIG. 5.** The process of refilling with microbubbles after transmission of a pulse of high-pressure sound waves. These three images are similar to those in Fig. 4, except that they were obtained after all microbubbles had been destroyed by a pulse of ultrasound energy. Arrows indicate the feeding artery and draining vein.
Fig. 6. Intraoperative contrast-enhanced ultrasound angiography findings.  a: Image obtained in a 26-year-old man with an AVM in the left frontal lobe. After administration of a bolus injection of contrast agent, the feeding artery can be seen clearly (arrow), but its draining vessel is too superficial to be depicted by a 1- to 4-MHz probe.  b: Image obtained in a 34-year-old woman with a lesion in the left parietal lobe. The feeding artery can be clearly seen in the contrast agent-specific imaging mode (arrow).

References


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