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# The Potential Value of 320-Row Computed Tomography Angiography in Digital Subtraction Angiography–Negative Spontaneous Subarachnoid Hemorrhage Patients

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**Objective:** This study aimed to investigate the clinical value of multiphase and multiparametric 320-row computed tomography (CT) in the long-term follow-up of spontaneous subarachnoid hemorrhage (SAH) with initially negative CT angiography (CTA) and digital subtraction angiography (DSA) results.

**Methods:** We retrospectively analyzed the clinical data of 35 patients with nontraumatic angiographically negative SAH results from February 2012 to December 2015. Regular follow-up was performed with 320-row CTA, CT venography, and CT perfusion.

**Results:** All patients received 320-row CT follow-up for 0.5 to 4 years. The diagnostic yield of the follow-up examinations was 4 of 35 (11.4%), 3 of 31 (9.7%), and 1 of 28 (3.6%) for the first, second, and third time points, respectively. Two patients were admitted to the hospital because of recurrent subarachnoid hemorrhage during the follow-up period and diagnosed with ruptured aneurysms.

**Conclusions:** Patients with SAH with negative findings in the first DSA examination require to follow up. Follow-up using 320-row CTA, CT venography, and CT perfusion allows for a noninvasive diagnostic test for cerebrovascular diseases with higher compliance and fewer complications when compared with follow-up using DSA.

**Key Words:** 320-row CT, spontaneous subarachnoid hemorrhage, DSA, follow-up

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Most (75%) of spontaneous subarachnoid hemorrhage (SAH) are caused by the rupture of an intracranial aneurysm.<sup>1–3</sup> In approximately 20% of SAH patients, digital subtraction angiographic,<sup>4</sup> and computed tomography (CT) angiographic evaluations all fail to identify an etiology for SAH, which is called angiographically negative SAH (AN-SAH).<sup>4–6</sup> Andaluz and Zuccarello<sup>6</sup>

reported that nonperimesencephalic SAH was associated with longer hospital and intensive care unit stays, higher complication rates, and worse outcomes than perimesencephalic SAH, and repeat digital subtraction angiography (DSA)<sup>7</sup> and/or CT angiography (CTA) are needed after AN-SAH. Sadigh et al<sup>4,8</sup> also reported that cervical spine and brain magnetic resonance imaging had extremely low diagnostic yields in AN-SAH, whereas DSA and CTA had higher diagnostic yields. Although DSA has been advocated as the criterion standard owing to its ability to identify smaller pathologies in cerebrovascular disease, it also increases the disease burden, hospital and intensive care unit stays, and DSA evaluation-related complications, as it is an invasive procedure. Bakker et al<sup>9</sup> also reported that repeat DSA is still warranted in patients with a diffuse nonperimesencephalic SAH and negative initial assessment, whereas the exact timing of the repeat DSA is subject to debate. Repeated DSA evaluations are not easily accepted by many asymptomatic SAH patients; thus, repeat DSA is less commonly used.<sup>4</sup>

As a result of the development of CT scanners and workstations, 3-dimensional (3D) CTA with helical scanning has been widely applied in cerebrovascular disease. An increasing number of studies have demonstrated that 3D CTA may be used as an alternative to DSA as a first-line imaging technique in patients with SAH and follow-up for AN-SAH.<sup>4,10,11</sup> The 320-row CT has a z-axis coverage of 16 cm that can be rotated by 0.5 mm for each layer of the same brain volume in the same direction. Unlike conventional CT, 320-row CT can perform continuous volume scanning to obtain CTA and CT venography (CTV) images and can quantify perfusion throughout the whole brain. The combination of CTA, CTV, and CT perfusion (CTP) better evaluates cerebral vascular morphology and provides visualization of dynamic flow, perfusion, and venous lesions as well as the motion of an entire volume at very short time intervals, which is important in a variety of cerebrovascular diseases with altered cerebral hemodynamics.<sup>12</sup> Patients are often more receptive to this approach than to DSA within less invasive, less expensive, fewer complications, and so on.<sup>13</sup>

The purpose of the current study was to investigate the clinical significance of 320-row CTA/CTV/CTP in the follow-up of 35 initial spontaneous AN-SAH patients from February 1, 2012, to February 1, 2016.

## MATERIALS AND METHODS

### Patient Selection and Study Protocol

This observational prospective study was conducted in the Department of Neurosurgery at Wuxi Medical College of Anhui Medical University, Chinese PLA joint services of the 904th Hospital (Wuxi Taihu Hospital). The protocol of the present study was approved by the Ethics Committee of Chinese PLA joint services of the 904th Hospital (YXLL-2012-008).

We conducted a retrospective review of prospectively collected data of patients who presented to our institution from February 1, 2012, to February 1, 2016, with nontraumatic SAH evidenced by

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The authors declare no conflict of interest.

All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This observational prospective study was conducted in the Department of Neurosurgery at Wuxi Medical College of Anhui Medical University, Chinese PLA joint services of 904th Hospital (Wuxi Taihu Hospital). The protocol of the present study was approved by the Ethics Committee of Chinese PLA joint services of 904th Hospital (YXLL-2012-008).

Informed consent was obtained from all individual participants included in the study.

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head CT or cerebrospinal fluid xanthochromia and an initial negative CTA or magnetic resonance angiography result. Then, DSA was performed within 48 hours. If the findings were negative, a 320-row CTA/CTV/CTP was performed 6 months after the presentation to identify a causative vascular etiology for the SAH (Fig. 1).

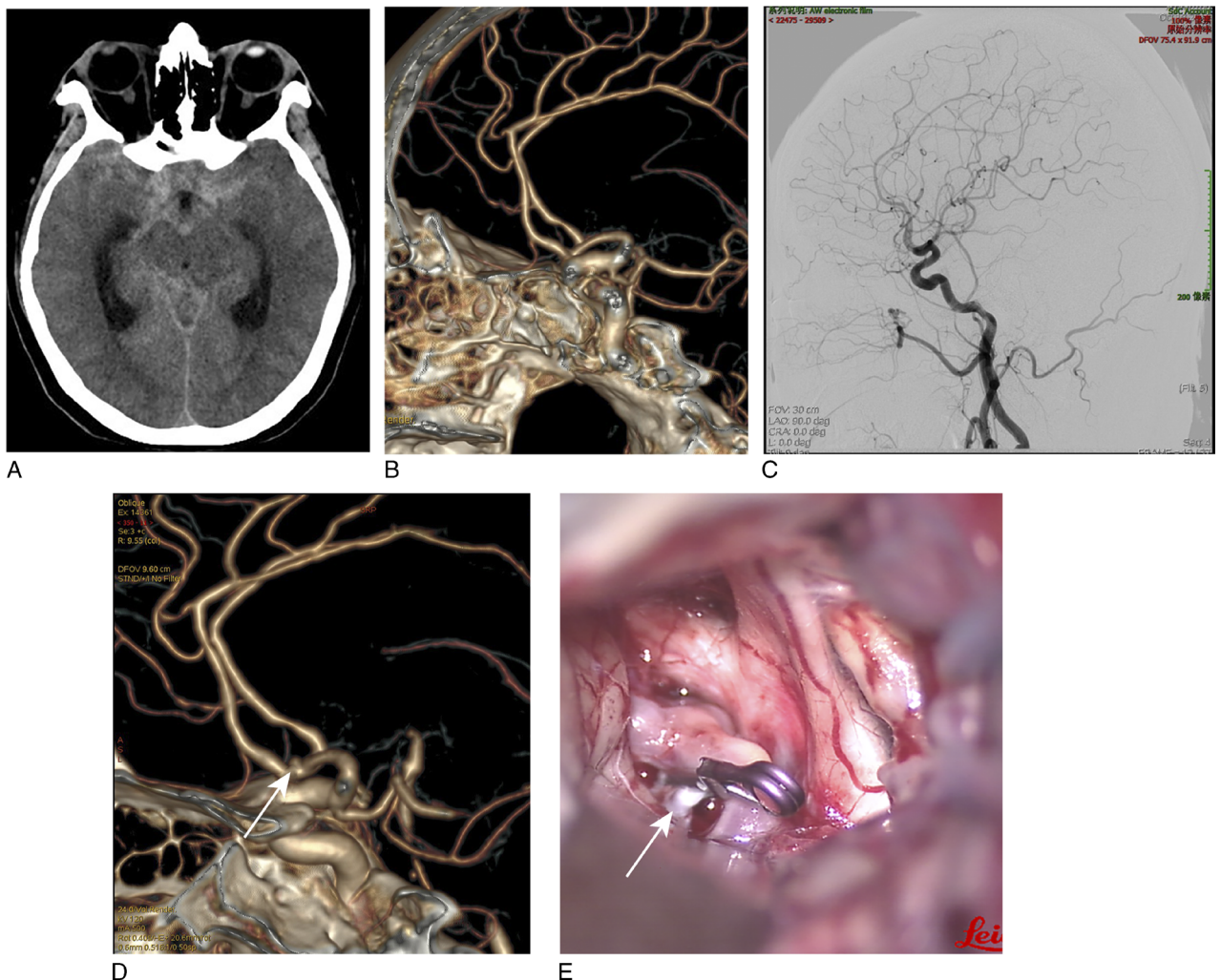
19 (54.3%) men and 16 (45.7%) women, with an average age of 54 years. All admitted patients were assessed using the Hunt-Hess Scale within 2 hours. The study included 16 patients with Hunt-Hess I, 16 patients with Hunt-Hess II, and 3 patients with Hunt-Hess III.

**Patient Population**

From February 2012 to February 2016, 750 patients with nontraumatic acute SAH were admitted to our clinical institutions (Wuxi Medical University of Anhui Medical University). We enrolled 35 (4.7%) patients who were diagnosed with AN-SAH. All patients present CTA and DSA examination at admission, and some patients present magnetic resonance angiography examination additionally. The second DSA examination at 2 weeks if the first DSA yielded a negative result. Then all patients present 320-row CTA/CTV/CTP at 6 months, 1 year, and 4 years of follow-up. There were

**Imaging Protocols**

Computed tomography angiography/CTV/CTP was performed with a 320-detector row volume CT scanner (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan) with a detector width of 160 mm. All patients were positioned supine with the head maintained in a neutral position during CT scanning to prevent motion artifacts.<sup>10</sup> The scan range covered from cervical vertebral body one to the calva (16 cm), with a slice thickness of 0.5 mm. Then, the CTA protocol was performed after a bolus injection of 55 mL of nonionic iodinated contrast agent (iopromide, 370 mg/mL of iodine, Ultravist) was administered into an elbow vein by using a double-cylinder



**FIGURE 1.** The case of a patient with diffuse subarachnoid hemorrhage was diagnosed without a history of trauma. A, The first CT examination in our hospital indicated diffuse subarachnoid hemorrhage, mainly located in the chiasmatic cistern and suprasellar cistern. B, The first CTA examination result was negative, and no intracranial aneurysm was found. C, The first DSA examination result was negative, and no aneurysm or vascular malformation was found. D, The first 320-row CT follow-up confirmed the presence of a very small communicating aneurysm (white arrow). E, Intraoperative image demonstrating the very small anterior communicating aneurysm (white arrow). Figure 1 can be viewed online in color at [www.jcat.org](http://www.jcat.org).

high-pressure injector (EZEM) at a speed of 4–6 mL/s, followed by 20 mL of physiological saline. The CT scanning parameters were as follows: gantry rotation speed, 0.35 s/r; width of the detector, 320 × 0.5 mm; beam pitch, 0; matrix, 512 × 512; field of view, 180 to 240 mm; 100 kV, 350 mA (nonenhanced image); and 100 kV, 300 mA (contrast-enhanced image).<sup>14</sup> Time series was as follows: 7- to 2-second delay to volume scan, 11-second arterial phase interval scan, and 1-second interval time, then 35- to 60-second venous phase interval scan and 5-second interval time.

**Postprocessing and CT Data Analysis**

Image postprocessing was performed by 2 experienced technicians. Computed tomography angiography images were subjected to multiplanar reconstructions, maximum intensity projections, and 3D volume rendering. Dynamic volume original data were reconstructed from 19 volume images based on a time sequence. Volume images were concurrently imported into the skull reconstruction software Clinical for Processing. CT Brain Analysis 4D directly obtained dynamic volume CTA images and whole-brain perfusion images including time to peak (TTP), mean transit time (MTT), cerebral blood volume (CBV), cerebral blood flow (CBF), and delay time.

**Imaging Analysis**

All images obtained were independently interpreted by an experienced (>10 years) neuroimaging physician and 2 neurosurgeons without other relevant clinical data or previous knowledge of the existence of intracranial aneurysms or the DSA results. The images were analyzed and the abnormal perfusion areas were confirmed, focusing on the morphological changes and blood flow within important blood vessels and their branches. If the conclusions were discordant, the physician and neurosurgeons discussed them together until an agreement was reached.

**RESULTS**

**General Results**

All patients underwent CTA, CTV, and CTP examinations. Four of the 35 first follow-up scans performed 14 days after the initial presentation were positive, including 3 very small intracranial aneurysms and 1 arteriovenous malformation (AVM). Of the remaining 31 patients who then underwent a 6-month follow-up scan, 3 were positive, including 1 with a very small intracranial aneurysm, 1 with an AVM, and 1 with moyamoya disease. The 1-year follow-up CT scan made no additional diagnoses. Of the 28 remaining patients, the 4-year follow-up CT scan found one intracranial aneurysm. During the 4-year follow-up period, 2 patients were diagnosed with aneurysms after recurrent bleeding. The first rebleeding the patient experienced was at 9 months, and at 6 months, the 320-row CT found a tiny aneurysm, whereas the patient refused the operation at that time. The second rebleeding the patient experienced occurred in the third year. All patients' conditions were intraoperative during microsurgery or endovascular therapy; all had a favorable prognosis after the operation (Table 1). No obvious adverse effects or complications were found after CT examination for any of the patients.

**Imaging Characteristics**

For the patient diagnosed with aneurysms, imaging characteristics of CTA were clear in 5, including the location, diameter, orientation, and distribution of the aneurysm, and the perforating artery. The 320-row CT follow-up provided extremely meaningful imaging data for clipping or endovascular embolization. Computed

**TABLE 1.** Four-Year 320-Row CT Follow-Up for Initial DSA Negative SAH

No.	First CTA	DSA (2 wk)	320-Row CT (6 mo)	320-Row CT (1 y)	320-Row CT (4 y)
1	—	—	ACoA	—	—
2	—	—	ACoA	—	—
3	—	—	AChA	—	—
4	—	—	AVM	—	—
5	—	—	—	ACoA	—
6	—	—	—	AVM	—
7	—	—	—	Moyamoya	—
8	—	—	—	—	R-PCoA
9	—	—	—	—	—
...	—	—	—	—	—
35	—	—	—	—	—

AChA indicates anterior choroidal artery; ACoA, anterior communicating aneurysm; R-PCoA, right posterior communicating aneurysm.

tomography angiography in both patients with AVM showed the shape, location of the supplying arteries, and the draining veins. Computed tomography angiography clearly showed the stenosis of the internal carotid artery and the tortuous vascular network around the arterial ring of the skull base in the patient with moyamoya disease; CTP clearly showed the phenomenon of blood theft, including regional normal CBV, delayed TTP, prolonged MTT, and decreased CBF, which provided important data for treatment.

**Radiation Dose**

The radiation dose of CTA/CTP has been a topic of debate in ethics and among scholars at home and abroad. Previous studies reported that the radiation dose of traditional 64-row CT scans and CTA-CTP combined examinations was approximately 9.6 to 11.4 mSv.<sup>14,15</sup> The 320-row CTA/CTV/CTP extended the sampling interval between the arterial phase and the venous phase, which significantly reduced the radiation dose. The radiation dose for whole-brain perfusion examination of 320-row CT has been reported in different studies within different views, but the range was 4.3 to 7.54 mSv.<sup>16,17</sup> In summary, compared with traditional 64-slice CT, 320-row CT can obtain more information.

**Case Illustrations**

**Case 1**

A 54-year-old woman presented with Hunt-Hess grade II spontaneous SAH. The initial CT demonstrated a diffuse subarachnoid hemorrhage that was located mainly in the prepontine cistern (Fig. 1A). Computed tomography angiography performed within 24 hours showed a normal result (Fig. 1B). The first DSA finding on day 3 was also negative (Fig. 1C). After discharge and follow-up, the first 320-row CTA examination at 6 months found a very small anterior communicating aneurysm (Fig. 1D). Then, the patient underwent clipping in our hospital, and intraoperative imaging confirmed the presence of the aneurysm (Fig. 1E).

**Case 2 (AVM)**

A 33-year-old woman presented initially with a 10-day history of headache, neck stiffness, and vomiting. The initial head CT findings were normal, but cerebrospinal fluid was positive, with

a higher percentage of red blood cells (no original data, patient statement). To further clarify the diagnosis, the patient was transferred to our hospital. Digital subtraction angiography was performed on the same day, with negative results (Fig. 2A). The patient was discharged after 7 days. Six months later, the first 320-row CTA showed anterior cerebral artery vascular malformation in the area supplying blood (Fig. 2B). Then, the patient underwent a craniotomy and resection of the artery vascular malformation (Fig. 2C). Postoperative pathological examination confirmed the presence of an AVM of the frontal lobe (Fig. 2D).

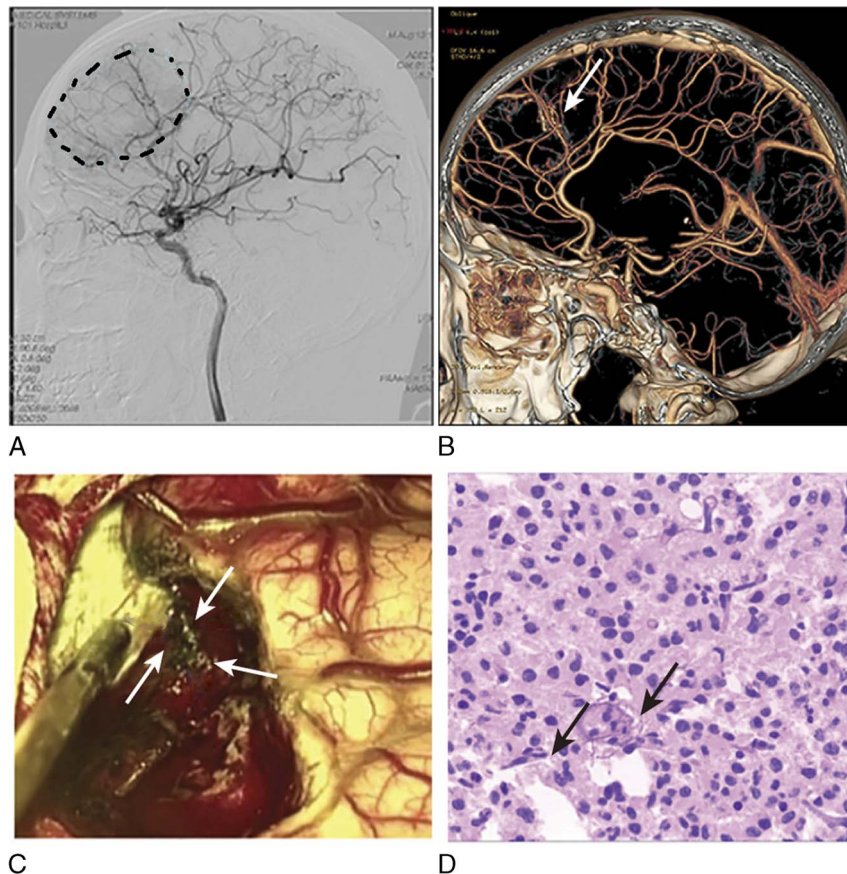
**Case 3 (Moyamoya Disease)**

A 40-year-old woman presented with sudden onset of headache and neck stiffness. The initial CT head demonstrated a local subarachnoid hemorrhage (Fig. 3A). The findings of CTA performed on the same day were reported as normal, and the findings of DSA performed the next day were also reported as negative (Fig. 3B). The patient was discharged after 5 days. One year later, the second 320-row CTA confirmed the presence of moyamoya disease on the right (Fig. 3C). Computed tomography perfusion examination showed that rCBV and rCBF were decreased, TTP was normal, and MTT was prolonged in the right cerebral cortex (Fig. 3D).

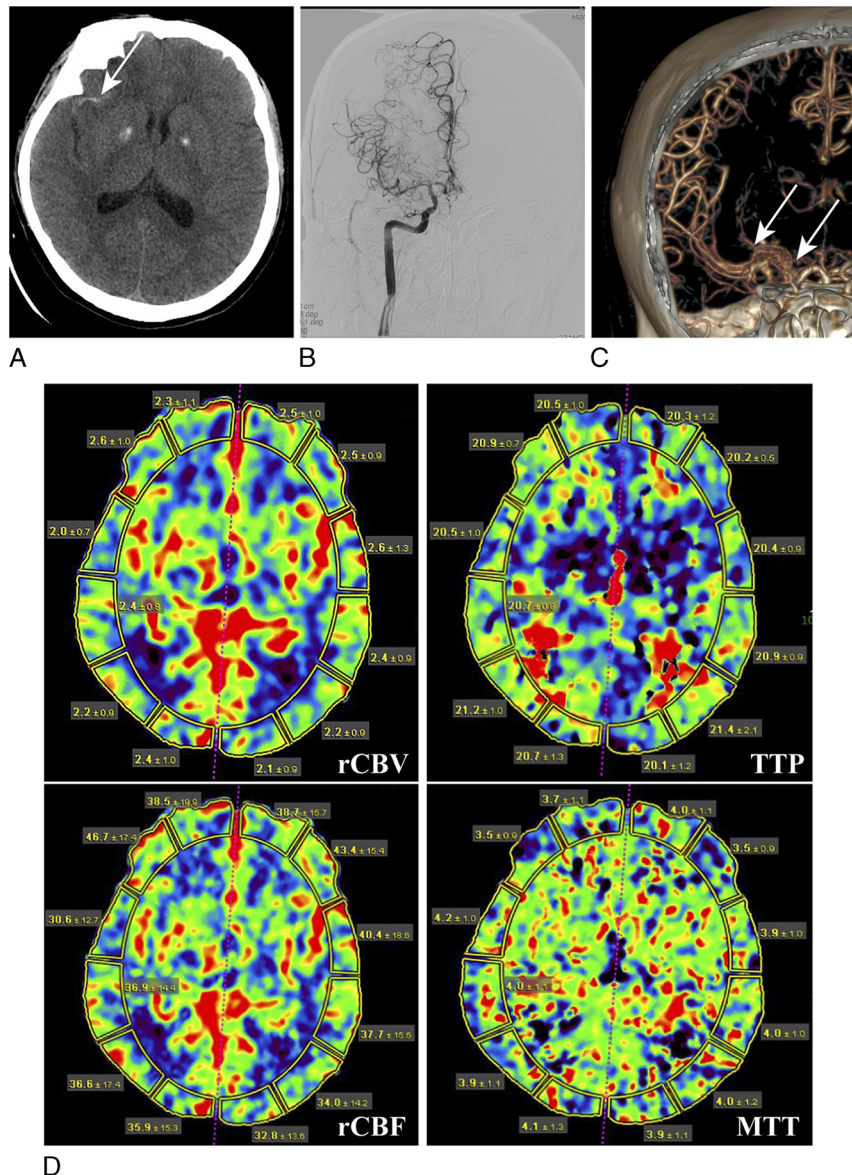
**DISCUSSION**

The results of our study showed that 320-row CTA examination is an efficacious and safe diagnostic method for follow-up in patients with AN-SAH. In addition, we found that early DSA missed the cause of SAH in at least 28.57% of our patients, with 80% of those patients receiving a diagnosis within 4 years before repeat hemorrhage by periodic follow up with 320-detector row volume CT scanning. Fontanella et al<sup>18</sup> reported that 5.1% of AN-SAH patients occurred rebleeding after follow. In the present study, we also found that 2 AN-SAH patients (5.7%) occurred rebleeding. Hence, a more aggressive follow-up timeline, such as every 2 years, may be needed.

Initially, DSA-negative SAH accounts for approximately 20% of all SAHs.<sup>4-6,19,20</sup> The main reasons for these false-negatives may be as follows: (1) intraneurysmal thrombosis, inflammatory changes in aneurysms, aneurysmal neck stenosis, and very small (<2 mm) size or bifurcation location; (2) cerebrovascular spasm preventing contrast agent from entering the aneurysm; (3) microarterial malformations and occult vascular malformations that break into the subarachnoid space but are not seen by DSA; (4) perimesencephalic SAH, with unclear etiology of this disease (the prognosis is good without special treatment, and DSA examination is negative); (5) bleeding from spinal vascular malformations, spreading along with the foramen magnum to the brain surface (CT manifestations



**FIGURE 2.** A patient with a small amount of subarachnoid hemorrhage in the frontal lobe was diagnosed at another hospital; the patient had no history of neurotrauma. A, The first DSA examination in our hospital yielded a negative result, and no obvious vascular malformations, aneurysms, or other vascular diseases were found in the frontal lobe bleeding area (black dotted line area). B, Six months later, the first 320-row CT scan indicated an AVM in the area supplying the anterior cerebral artery (white arrow). C, Intraoperative image demonstrating the AVM (white arrow). D, Postoperative pathological examination confirmed the presence of the frontal lobe AVM (black arrow). Figure 2 can be viewed online in color at [www.jcat.org](http://www.jcat.org).



**FIGURE 3.** A patient with no history of neurotrauma was diagnosed with a small subarachnoid hemorrhage in the right lateral fissure cistern at another hospital. A, The first CT examination in our hospital showed a small amount of bleeding in the right lateral fissure cistern (white arrow). B, The first DSA examination in our hospital yielded a negative result. C, The second 320-row CT scan was performed after 1 year and confirmed the presence of right moyamoya disease (white arrow). D, CTP examination showed that rCBV and rCBF were decreased, TTP was normal, and MTT was prolonged in the right cerebral cortex. Figure 3 can be viewed online in color at [www.jcat.org](http://www.jcat.org).

are typical subarachnoid hemorrhage, and DSA shows a negative finding); and (6) poor-quality technical equipment among other factors. The treatment strategy for DSA-negative SAH patients is often to repeat DSA examination, and surgical exploration is also a good choice for patients with poor-grade or intracranial hematoma. However, because DSA examination is an invasive and complicated operation, with more contraindications, complications, treatment costs, and longer hospital and intensive care unit stays, it is difficult for many patients to accept, which leads to a loss to follow-up. The 320-row CT examination is a simple, fast, and noninvasive diagnostic method.

In the present study, we found 5 intracranial aneurysms in 35 initial DSA-negative SAH patients after 320-row CTA/CTV/CTP, including 3 anterior communicating artery aneurysms, 1 anterior

choroid aneurysm, and 1 posterior communicating aneurysm. The diameters of the 5 aneurysms were 1.2 to 3.0 mm. The 320-row CTA/CTV/CTP not only clearly shows the size and location of the aneurysm through 4D-CTA technology but also shows its relationship to the parent arteries and the anatomy of perforating vessels of the parent arteries.<sup>15,21</sup> For the detection rate of 320-row CTA/CTV/CTP in intracranial aneurysms, previous literature reports that the specificity, overall sensitivity, and accuracy of 320-row CTA/CTV/CTP were similar to those of DSA; therefore, this technique can replace DSA as the first choice for noninvasive examination of SAH patients.<sup>12,22</sup> In addition, the other advantages of 320-row CT are as follows: (1) 4D-CTA can reconstruct the image at any angle and any plane, which clearly shows the aneurysm neck width, position, size, aneurysm orientation, and relationship with

the surrounding blood vessels; (2) 4D-CTA can clearly show the spatial structure between the aneurysm and the bone at the skull base and simulate the surgical approach, providing a complete assessment for surgical clipping of the aneurysm; (3) the assessment of the aneurysm responsible for bleeding among multiple intracranial aneurysms is also better than that of DSA; and (4) preoperative CT examination can better assess cerebral blood flow and determine whether cerebral vasospasm occurs, which is helpful for clinicians in the early diagnosis and treatment for these patients.

In the present study, 2 patients were diagnosed with an AVM, including one patient with an AVM located in the parietal lobe and another patient with an AVM located in the temporal lobe. Arteriovenous malformations mainly manifest as bleeding, seizures, and headaches, which can be life-threatening in severe cases. Digital subtraction angiography was recognized as the criterion standard for the diagnosis of AVMs. Four-dimensional CTA was used to dynamically display the condition of the blood supply arteries, draining veins, and vascular nests in these 2 AVMs, and the images could be reconstructed at any angle and plane. Thus, the morphology of the AVM and the structure of the surrounding blood vessels can be clarified and confirmed, which is conducive to preoperative evaluation. Arteriovenous malformations mostly present with hemodynamic changes in intracranial vessels. A single injection of contrast agent can be used to diagnose AVMs through 4D-CTA and provide preoperative evaluation or to assess the hemodynamics through CTP images to guide clinical treatment and predict prognosis. Many scholars believe that 320-row CTA/CTV/CTP can replace DSA for AVM diagnosis and subsequent follow-up.<sup>23,24</sup>

Follow-up diagnoses of moyamoya disease using 320-row CT in one patient show that the M1 segment of the left middle cerebral artery was occluded within the small reticular angiography at the distal end. Moyamoya disease is characterized by chronic progressive stenosis or the occlusion of the terminal portion and main branches of the bilateral internal carotid arteries.<sup>25</sup> Digital subtraction angiography is a commonly accepted method to evaluate the presence of collateral status; however, it is an invasive procedure.<sup>26</sup> Noninvasive 4D-CTA can identify dynamic images similar to DSA and can provide a visualization of the entire blood flow process from the early stage of the artery to the late stage of the vein. Four-dimensional CTA can reduce the number of missed diagnoses and misdiagnoses due to poor filling; 4D-CTA data can be arbitrarily rotated in 3D according to the needs of the clinician, and VR and MIP can be determined as required. Preoperative CTP assessment of brain tissue perfusion can better identify moyamoya disease and provide the basis for the choice of treatment.

## LIMITATIONS

The primary limitations of this study included the small number of patients and the retrospective nature of the study. A large, prospective, and multicenter trial is needed to confirm these findings. In addition, clinical data were missing in some patients who were not first admitted to our hospital.

## CONCLUSIONS

The 320-row CT examination including CTA, CTV, and CTP is also an accurate and promising method for the evaluation of cerebrovascular disease with advantages in the detection and characterization of aneurysms, AVMs, and moyamoya disease, especially for aneurysms small in size and near the skull base. This method has value in the short-term and long-term follow-up of DSA-negative SAH patients. The 320-row CT has the potential to replace DSA in the initial workup and follow-up for AN-SAH patients; a large, prospective, and multicenter trial is needed to confirm these findings.

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