Research Article

Application Value of CTA in the Computer-Aided Diagnosis of Subarachnoid Hemorrhage of Different Origins

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Received 5 November 2020; Revised 10 December 2020; Accepted 4 January 2021; Published 15 January 2021

Academic Editor: Yang Gao

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Subarachnoid hemorrhage (SAH) is difficult to detect because of its circulation through subarachnoid space, which leads to a high rate of missed diagnosis. Based on the above background, the purpose of this study is to study the application value of brain CT angiography (CTA) in computer-aided diagnosis of subarachnoid hemorrhage with a wide range of brain digital subtraction angiography as a gold standard. This paper collected images and related medical records of 111 patients with spontaneous subarachnoid hemorrhage receiving brain CTA and DSA examinations from February 2015 to November 2019 in the neurology department of our hospital. In contrast to the number, position, length, width, and neck width of the causative aneurysm detected by DSA, we evaluated the diagnostic results of CTA and evaluated whether there was statistical difference between the two detectives of intracranial aneurysms. The results showed that the area under ROC curve of subtraction CTA and conventional CTA was 1.000 and 0.818, respectively, which indicated that the former had better display effect on internal carotid aneurysm ($AUC > 0.9$), while the latter had medium value ($0.7 < AUC \leq 0.9$), and the difference was statistically significant ($z = 2.390, p = 0.017$).

1. Introduction

Subarachnoid hemorrhage (SAH) is a common neurological emergency and critical disease caused by vascular rupture of lesions at the bottom or surface of the brain. It can be divided into spontaneous SAH and traumatic SAH. Spontaneous SAH can be divided into primary SAH and secondary SAH. The incidence rate of primary SAH is 10% of all patients with acute stroke and third of the total acute stroke. The incidence rate is only inferior to cerebral infarction and cerebral hemorrhage. SAH caused by intraventricular hemorrhage, cerebral parenchymal hemorrhage, and subdural or epidural hematoma is called secondary SAH. In the 1990s, the WHO study showed that the annual incidence rate of intracranial aneurysms was about (2 ∼ 22.25)/10 million. The difference in incidence may be due to the difference of population, heredity, environment, and diet. China’s incidence is much lower than Japan, Europe, and the United States. Developing countries have a large population base and some regions are considered to be economically backward. It is also associated with factors such as lack of timely treatment for patients, lack of medical staff knowledge, and lack of equipment corresponding to hospitals. It is reported that about 12% to 15% of patients have died before hospitalization, so the incidence in China may be even higher.

The treatment of delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH) is difficult and still controversial. In Roman et al.’s study, xenon-enhanced computed tomography (XeCT) was used to evaluate the effect of therapeutic hypervolemia, hemodilution, and hypertension (HHH therapy) on cerebral blood flow (CBF) [1]. Subarachnoid hemorrhage (SAH) causes brain damage through the excitotoxicity of glutamate, which leads to excessive Ca2+ influx and initiates an apoptotic cascade. Memantine has been shown to reduce several
types of brain damage. Beaulieu et al.’s study aimed to explore the neuroprotective effects and mechanisms of memantine after subarachnoid hemorrhage (SAH). Memantine effectively protects the integrity of BBB in experimental SAH, saves neuronal damage, and improves the prognosis of the nervous system. Memantine has neuroprotective effects in experimental subarachnoid hemorrhage (SAH) and may help to combat brain damage caused by SAH in the future [2]. Garland et al. recently observed experimental subarachnoid hemorrhage (SAH) after early white matter damage, but its mechanism is unclear. Garland et al.’s study explored the potential role of matrix metalloproteinase 9 (MMP-9) in the destruction of the blood-brain barrier (BBB) and the formation of white matter. SAH was induced by intravascular perforation in adult male mice. MMP-9 plays an important role in these pathological processes and may become a therapeutic target for white matter damage caused by SAH [3].

In recent years, computed tomography angiography (CTA) and magnetic resonance angiography (MSA) have been used to evaluate intracranial aneurysms. When digital subtraction angiography (DSA) has the same specificity as traditional angiography (DSA), it should have the same specificity as digital subtraction angiography (DSA). In order to determine whether computed tomography angiography and magnetic resonance angiography can provide the necessary information for preoperative evaluation, Müller blindly compared the results of spiral CT angiography and MR angiography with the results of digital subtraction angiography and intraoperative findings. In addition, spiral CT is a fast, inexpensive, noninvasive inspection method, and it can be used as a reliable alternative to DSA in emergency situations that require immediate surgery [4]. The purpose of Linfante et al.’s study is to evaluate high-quality CT angiography (CTA), replace the possibility of digital subtraction angiography (DSA) in the treatment of ruptured saccular aneurysm, and perform early surgical clipping or coiling on the basis of CTA. The current high-quality CTA can formulate a reliable pretreatment plan for most cases of aneurysmal subarachnoid hemorrhage and greatly shorten the pretreatment evaluation time. If the CTA characteristics of a ruptured aneurysm are not satisfactory, additional pretreatment DSA is needed [5]. Lim’s study explores whether cardiac computed tomography (CTA) can predict all-cause mortality in symptomatic patients. Noninvasive coronary angiography is increasingly used to evaluate obstructive coronary artery disease (CAD) by CTA, while the results of coronary CTA are scarce. They used a group of symptomatic patients who underwent electron beam tomography, which can be followed up for a longer period of time (up to 12 years) compared with the current 64-slice multislice computed tomography study [6].

The innovation of this paper is as follows:

1. Medical institutions can optimize the diagnosis and treatment process of patients with spontaneous SAH and use CTA to evaluate the vascular condition of spontaneous SAH timely and accurately, which can correctly guide the selection of intervention measures for spontaneous SAH.

2. It can partly reflect the value of CTA in the diagnosis of spontaneous SAH in this region and promote the understanding of the diagnosis process of this disease.

### 2. CTA and Subarachnoid Hemorrhage

#### 2.1. Subarachnoid Hemorrhage

#### 2.1.1. Pathophysiological Factors

After SAH caused by aneurysm rupture, a series of changes in normal cerebral vascular physiology will occur, including the increase of intracranial pressure (ICP), the decrease of cerebral perfusion pressure (CPP), the decrease of cerebral blood flow (CBF), and the dysfunction of autonomic regulation. Finally, it leads to irreversible damage such as cell apoptosis and blood-brain barrier damage [9, 10].

#### 2.1.2. Elevated Intracranial Pressure

After aSAH, the increasing amount of bleeding will lead to the sharp increase of intracranial pressure. Other studies have shown that the rise of ICP is associated with obstruction of cerebrospinal fluid outflow, local or total vascular and nerve numbness, and dilation of small arteries in the distal part of the brain [11]. The rapid increase of intracranial pressure will lead to insufficient cerebral perfusion and oxygen supply, which will lead to a series of changes such as metabolic disorders, inflammatory reaction, and early and delayed cerebral ischemia [12, 13].

#### 2.1.3. Vasoconstriction

When an aneurysm ruptures, the brain tissue is separated from the arachnoid membrane by the blood rushing out from the vascular rupture, resulting in the mechanical traction of the arachnoid trabeculae attached to the artery, which makes the blood vessels begin to constrict. In addition, due to cell aberrations, formation of vacuoles, interruption of intercellular tight junction, and widening of intercellular space, vascular active substances directly contact with exposed smooth muscle cells, resulting in vasoconstriction; at the same time, a large number of vasoconstrictor substances are released after blood clot
fibrinolysis and platelet aggregation, which further aggravates the vasoconstriction [14, 15].

2.1.4. Decrease of Cerebral Blood Flow. Blood viscosity increases, vascular wall damage, microthrombosis, and platelet aggregation cause microcirculation occlusion of capillaries and reduce cerebral blood flow. Second, the decrease in cerebral blood flow is associated with vascular contraction, lack of blood volume (brain salt wasting syndrome, diuretic excess, etc.), and impaired autonomic nervous system (acidic brain tissue, hydrocephalus, vascular endothelial cell damage, etc.) [16]. A decrease in cerebral blood flow may also cause severe ischemic damage in brain tissue and may even lead to cerebral infarction [17, 18].

2.1.5. Dysfunction of Autonomic Regulation. Brain autonomic regulation refers to the ability of blood vessels in the brain to maintain cerebral blood flow through vasodilation or contraction within a certain range. When blood pressure is reduced due to insufficient blood volume, the autonomic function maintains constant cerebral blood flow through vasodilation. If the autonomic regulation function of the brain is destroyed, the cerebral blood flow will not be able to maintain a constant state.

2.1.6. Apoptosis and Damage of Blood-Brain Barrier. After SAH, high ICP, harmful components in blood, and acute CVS can lead to brain tissue and endothelial cell damage; in addition, in cerebral ischemia, the concentration of free radicals beyond local antioxidant capacity will also cause brain tissue damage and vascular membrane damage, resulting in cell apoptosis and blood-brain barrier damage [19, 20]. SAH patients are particularly prone to the disorder of water-and-electrolyte balance due to the abovementioned pathophysiological mechanisms, which further complicates the fluid management [21].

2.2. CTA Imaging Technology. CTA, as a minimally invasive cerebrovascular examination technique, uses intravenous contrast agent instead of arterial administration of DSA. At present, the spatial resolution of 64-row CTA is 0.4–0.7 mm. 3D-DSA was used as the reference standard. The specificity of CTA for intracranial aneurysms less than 3 mm can reach 90%–94%, and for aneurysms larger than 3 mm, the sensitivity is 96%–98% [22, 23].

CT is a kind of tomography equipment. Its disadvantage is that it cannot scan at any angle, and the original image can only provide cross-sectional information. In practice, it is often necessary to change the angle of observation in order to achieve the correct position for diagnosis. Therefore, CTA has been developed, and a variety of imaging methods have been developed, such as volume rendering (VR), maximum intensity projection (MIP), shaded surface display (SSD), multiplanar reformation (MPR), and curved planar reformation (CPR) [24, 25].

2.2.1. MPR Image. This is a relatively simple and direct reconstruction observation method. In the original volume data, the position and angle required for observation are found out through calculation, and the parallel layer data near the section are extracted according to a certain thickness and then displayed according to the 3D image rendering display mode. It should be noted that MPR images are usually NYP projection images observed from the cross section direction, but other projection methods, including volume rendering projection, are also applicable to MPR. Different forms of display can be achieved by using different rendering displays.

2.2.2. CPR Image. CPR is another way of level reorganization. It needs a known centerline along which the original volume data set is cut to form a curved surface. Then, expand the surface to display the centerline of the whole process in the result plane. The important significance of CPR is that it can display the whole centerline in a plane, and it is often used to display curved objects. The whole process of vascular lumen structure is often difficult to fully display in an MPR form oblique section plan. CPR can find the centerline of curved object, extend the curved surface in the original volume data intercepted by the centerline, and then display the object in a whole image. The results show that the information of each direction in 360° direction with the centerline as the axis can be observed completely. It provides a great help with disease diagnosis. CPR can reflect the whole process of curved organs and tissues. But it will produce a large space deformation in practical application. It should be selected according to the needs of diagnosis.

2.2.3. MIP Image. It uses the maximum value of CT value of all pixels on the projection line, which is a simple and rapid technology to display the whole body vascular system. It has good display effect for tissues with high CT value, such as bone, enhanced blood vessels, calcification, etc., but it is poor for tissues with relatively low CT value. Because MIP image is reconstructed from volume data, the lesion can be observed from different angles and positions. In addition, MIP images also have a good effect on the observation of calcification and stent. However, MIP images are also easily affected by high-density tissue structure, and the overlap of tissue images before and after the projection direction will lead to unclear spatial relationship, high CT value tissue blocks low CT value tissue, and other problems, so the overall observation of tissue structure is still limited.

2.2.4. SSD Image. This is a display method that one or several virtual light sources are projected on the isosurface to obtain the light and dark shadow on the surface of the isosurface, which shows the spatial stereoscopic sense of the object to be observed, so as to conform to the sensory effect of human vision. SSD can reorganize and display two-dimensional serial sectional images into three-dimensional models, thus providing a more intuitive way of spatial observation. SSD surface rendering is a real three-dimensional display method, which can show the virtual lighting model to simulate the effect of human observation of
space objects. SSD also has disadvantages: it mainly regards all objects as a closed range which is segmented by the surface. In the process of rendering, only its shape is considered, and the information of its internal voxel points is not considered. The relationship between the structure outline and the volume data is separated, and the corresponding image information is lost. In addition, because the surface is drawn according to the determined contour line, it is difficult to further modify and reprocess the three-dimensional image. Each processing needs to recalculate the equivalent surface, which is easy to form artifacts and affect the correct judgment of the three-dimensional shape of three-dimensional objects.

2.2.5. VR Image. VR is a 3D volume data visualization method based on projection algorithm, which is the most effective 3D imaging method at present. VR image combined with effective segmentation technology can be widely used in vascular and nonvascular diseases. VR image is mainly for the display of the shape; it can show the course of cerebral blood vessels and its relationship with the rest of the brain. The three-dimensional images obtained by VR keep the original voxel information, and the data of any volume, any plane, or any point in the original data can be obtained directly from the images, which is convenient for the observation of local tissues and the measurement of various values. In practical application, there are two kinds of three-dimensional postprocessing of VR image: one is the display of whole brain VR image; the other is more targeted to the display of intracranial artery structure VR image. VR images of the whole brain can directly show the relationship between the various parts of the brain, which plays an important role in the diagnosis of some cases. However, the disadvantage of whole brain VR image is that the display of complete brain, especially the display of skull, may block the course of intracranial artery and thus affect the observation of arterial lesions. At this time, image segmentation can be used to remove the tissue structure of the covered artery. However, in the case of complicated intracranial vessels, this processing will also encounter some problems, such as the distortion of important parts of the image, especially the image of the part entering the skull and the skull base, resulting in the omission of vascular lesions. In practical work, it is often necessary to combine two different VR images to meet the requirements of diagnosis.

3. CTA Check Experimental Design

3.1. Experimental Data Collection. Methods: from February 2015 to November 2019, 111 patients with spontaneous subarachnoid hemorrhage confirmed by brain CT scan or lumbar puncture were collected. A total of 111 patients underwent CTA and DSA. There were 33 males and 78 females with an average age of 56.1 years (range, 18–85 years). There were 56 cases of simple headache, 40 cases of headache with vomiting, 6 cases of coma, and 3 cases of oculomotor nerve paralysis.

3.2. Experimental Methods

3.2.1. CTA Examination. Siemens 64-row 128-slice spiral CT machine (SOMATOM Definition AS) was used to puncture the right middle elbow vein with 20 g indwelling needle. Both hands were placed on both sides of the body in supine position. The contrast medium was iohexol (350 mg/ml), and the injection dose was 55–80 ml, and the injection flow rate was 5 ml/s. The ROI was delineated at the aortic orifice level by contrast tracer technique. The trigger threshold was 110 HU and the delay time was 6.0 s. The scanning range was from the first cervical spine to the cranial crest (from foot to head). The X-ray tube collimator is 128 mm × 0.625 mm in width, 0.33 s in rotation time, 0.992 in pitch, 250 mm in FOV, 200–350 mAs in tube current, 1.0 mm in reconstruction thickness, and 0.5 mm in interval. The original data of DICOM were transmitted to mmwt workstation, and the images were processed by an unspecified CT doctor with double-blind method.

3.2.2. DSA Examination. After successful local anesthesia, the femoral artery was punctured by the Seldinger technique. The 5F sheath was inserted. Aortic arch angiography was performed with 5F “pigtail” catheter under the guide wire. The left and right internal carotid artery angiography and left and right vertebral artery angiography were performed with 5F “pigtail” catheter; 3D angiography of parent artery was performed.

3.2.3. Processing Images. After the CTA scan, data were transferred to geadw4.4 workstation, and the original data were reconstructed. The reconstruction methods mainly included volume reconstruction (VR), multiplanar reconstruction (MPR), maximum intensity projection (MIP), and curved planar reconstruction (CPR). Advantage workstation 4 was mainly used in DSA 3D workstation_ 3 system.

3.2.4. Analyzing Images. Arrange more than 3 attending physicians to evaluate and analyze CTA images. When analyzing, mainly check whether there is intracranial vascular disease. If there is intracranial aneurysm, determine the location of aneurysm and calculate the volume. If arteriovenous malformation is found, the location of drainage vein, feeding artery and abnormal vascular mass should be determined, and whether the lesion location is in the functional area should be determined. In case of moyamoya disease, the stenosis, occlusion, collateral vessels, and neovascularization of intracranial arteries should be observed.

DSA images for observation and analysis, mainly arranged in our hospital neurosurgeons in the process of surgical treatment, if necessary, were combined with CTA image observation results. DSA and surgical results were used as reference for all imaging data.

3.3. Experimental Statistical Methods. The positive predictive rate, negative predictive rate, false positive rate, and false negative rate of CTA were compared with those of DSA. The
clarity of the aneurysmal neck was compared with the row 2 test. All tests were performed with SPSS 22.0 statistical software, \( a = 0.05 \); when \( p < 0.05 \), the difference was statistically significant.

4. CTA Diagnosis Analysis of Subarachnoid Hemorrhage of Different Origins

4.1. CTA Inspection Results. 50 patients with SAH were examined by CTA. Results: 37 patients (40 aneurysms), including 36 cases of single aneurysm, 3 cases of two aneurysms, and 1 case of 3 aneurysms; the diameter of aneurysms ranged from 7 to 25.14 cases of anterior communicating artery (16 pieces), 13 cases of posterior communicating artery (9 pieces), 6 cases of bifurcation of middle cerebral artery (9 pieces), 2 cases of end of internal carotid artery (4 pieces), and 2 cases of basilar artery (2 pieces); according to the surgical classification method, there were 14 cases of anterior communicating artery (16 pieces), 13 cases of posterior communicating artery (9 pieces), 6 cases of middle cerebral artery bifurcation (9 pieces), and 2 cases of internal carotid artery (4 pieces). Among the 40 aneurysms, there were 3 giant aneurysms (larger than 25 mm in diameter), 6 large aneurysms (larger than 15 RNM and less than 25 mm in diameter), 23 general aneurysms (larger than 5 mm and less than 15 mm), 8 small aneurysms (less than 5 mm in diameter), 2 cases of arteriovenous malformation, and 1 case of moyamoya disease.

Experiments show that more accurate subarachnoid space estimation can be obtained based on CTA. Taking the relative coincidence degree as an example (its definition is as follows: the gold standard area of subarachnoid space is \( g \), the subarachnoid space area calculated by algorithm is \( a \)), and the test contrast accuracy of 69 sets of clinical data (30 SAH patients and 39 normal people) is shown in Figure 1.

The relative coincidence degree of subarachnoid space estimated by CT was \( 0.532 \pm 0.014 \) and that of subarachnoid space based on CTA was \( 0.625 \pm 0.013 \). The estimation accuracy based on CT was better than that based on CTA \( (p < 0.05) \).

4.1.1. Comparison of the Results of CTA and DSA. DSA examination results: there were 39 aneurysms (43 aneurysms), 34 single aneurysms, and arteriovenous malformations, including 1 case in the right temporal lobe, 1 case in the left occipital lobe, and 1 case in moyamoya disease; 8 cases were negative; CTA results: 1 case was misdiagnosed as aneurysm, 4 cases were missed diagnosis, and 10 cases were negative, as shown in Table 1.

Taking DSA results as the gold standard, the total diagnostic sensitivity of CTA was 94.29%, the specificity was 85.72%, and the accuracy was 92.85%. The specific values are shown in Figure 2.

Figure 2 shows the CT slice of a SAH patient and the result of algorithm recognition. It can be seen from the figure that the longitudinal fissure and lateral fissure with obvious hemorrhage can be correctly identified, but the tentorium cerebelli (arrow) cannot be identified due to the unobvious bleeding signal, so the sensitivity at the ROI level is low, while the sensitivity at the patient level is higher. The reason is that some ROI with small bleeding volume is omitted by the algorithm, but if the patient has a more obvious ROI, the patient will not be missed. What is missing is the quantification of the extent and extent of bleeding in the patient. On the other hand, if the patient has only the ROI with unobvious bleeding, it may be missed diagnosis, which is also a problem to be solved in further research.

4.2. Comparison of Display Effect of Subtraction CTA and Conventional CTA in SAH. The difference between conventional CTA and subtraction CTA in detecting aneurysms was that because of the occlusion of skull, four internal carotid aneurysms located at the base of skull were not detected by conventional CTA, and one of them was multiple aneurysms. In the other 4 cases, 4 internal carotid aneurysms of skull base could only show part of the tumor body by conventional CTA (3 cases showed that the part of aneurysm was less than half of the tumor body, and 1 case was more than half of the tumor body). The shape, size, and location of these aneurysms could be shown by subtraction CTA. The detection rates of subtraction CTA and conventional CTA were 100% and 63.64%, respectively. The display effects of the two methods were divided into four grades, and the ROC curve was used for paired comparison (as shown in Figure 3).

The area under the ROC curve (AUC) of subtraction CTA and conventional CTA were 1.000 and 0.818, respectively, which indicated that the former had better display effect on internal carotid artery aneurysm (AUC > 0.9), while the latter had medium value \( (0.7 < \text{AUC} \leq 0.9) \), and the difference was statistically significant \( (z = 2.390, p = 0.017) \). The AUC of subtraction CTA and conventional CTA were
1.000 and 0.956 respectively (as shown in Figure 4), and the difference was statistically significant (z = 2.072, p = 0.038).

The AUC of the number of aneurysms was 0.978 and 0.935, respectively; the difference was statistically significant (z = 2.070, p = 0.038). In order to make an accurate diagnosis of aneurysms in SAH, high-quality CTA images are needed. For the evaluation of image quality, it is suggested that the CT value of internal carotid artery after enhancement should be 340 HU to determine the image quality of subtraction CTA. Statistics show that for aneurysms less than 2 mm, the detection rate is 45% when the CT value is less than 340 HU, which is significantly lower than 75% when the CT value is greater than 340 HU; for the misdiagnosed and missed aneurysms, the CT value of internal carotid artery mostly exceeds 340 HU, which indicates that there are other factors that affect the accuracy of diagnosis, such as the location and size of aneurysm and the early filling of adjacent vein.

### Table 1: Comparison of inspection results between CTA and DSA.

| Project | Aneurysm | Arteriovenous malformations | Moyamoya disease | Negative | Total |
|---------|----------|----------------------------|------------------|----------|-------|
| CTA     | 37       | 2                          | 1                | 10       | 50    |
| DSA     | 39       | 2                          | 1                | 8        | 50    |
| Compliance rate (%) | 94.87 | 100.00                | 100.00           | 75.00    |       |

### 5. Conclusions

With the continuous innovation of spiral CT technology, the temporal and spatial resolution of CTA are also improved rapidly. The main advantages of CTA are small trauma, simple operation, fast scanning speed, and the whole examination process taking less time. After scanning, the original image can be processed quickly, and the preliminary
diagnosis can be made quickly; the risk of rebleeding and cerebral vasospasm is not increased. Because subtraction CTA is a noninvasive examination technique with high scanning speed, it can avoid the interference of cranial structure on the development of adjacent vessels and can be examined at any time 24 hours a day, so it is more and more widely used in the etiology search of SAH patients. In this study, subtraction CTA can be successfully completed, with no obvious adverse reactions, imaging time is short, and scanning and postprocessing are completed in a few minutes, for the treatment of patients to win valuable time.

In this study, the image quality of digital subtraction CTA was evaluated according to the presence or absence of the vein, which had an impact on the diagnosis and the clarity of the ophthalmic artery reflecting the filling state of the blood vessels. The results showed that the image quality was excellent in most cases and good in a few cases, which ensured the reliability of the analysis results; the other two cases had moderate image quality, which might be caused by the longer interval between plain scan and enhanced scan, the patient’s swallowing action during scanning, the instability of head fixation, and the late enhancement scanning time. To a certain extent, it increases the image post-processing time and the difficulty of detecting cerebral aneurysms. To avoid getting unsatisfied images, nurses can comfort patients patiently before scanning, such as explaining to patients that slight fever during contrast injection is normal; technicians should firmly fix the patient’s head before scanning, instruct them to avoid swallowing during examination, and accurately calculate scanning interval and delay time during scanning.

However, there are still some limitations in CTA: (1) at present, 64-slice CTA cannot present hemodynamic conditions such as blood flow direction and compensation in instantaneous state as DSA. (2) The innovation of CTA postprocessing technology requires higher requirements for readers’ experience in image processing. Some useful information can be lost when removing interference and redundant information. Therefore, it is greatly affected by subjective factors and is not as intuitive as DSA. (3) The examination still needs iodine contrast agent injection, which cannot be completely noninvasive, and there is still a risk for some patients with unknown allergic history. (4) Due to technical limitations, DSA is not as effective as DSA in displaying small vessels and perforating branches above grade 3, and it is easy to miss and misdiagnose distal micro aneurysms. (5) Compared with DSA, CTA cannot achieve synchronous diagnosis and treatment.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Acknowledgments

This work was supported by the National Key Research and Development Programs (2018YFC0807203) and College Key Scientific Research Projects of Henan Province (20B340001).

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