

Angiographic Reconstructions From Whole-Brain Perfusion CT for the Detection of Large Vessel Occlusion in Acute Stroke

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Background and Purpose—Multimodal CT imaging consisting of nonenhanced CT, CT angiography (CTA), and whole-brain volume perfusion CT is increasingly used for acute stroke imaging. In these patients, presence of vessel occlusion is an important factor governing treatment decisions and possible endovascular therapy. The goal of this study was to assess the value and diagnostic accuracy of angiographic thin-slice volume perfusion CT reconstructions for the detection of intracranial large vessel occlusion in patients with stroke.

Methods—Fifty-eight patients with acute stroke received nonenhanced CT, CTA, and volume perfusion CT. All images were obtained on a 128-slice multidetector CT scanner. CT angiographic axial and coronal maximum-intensity projections of the head were reconstructed from conventional CTA and from the peak arterial scan of the volume perfusion CT data set (4-dimensional CTA). Images were assessed for the presence of intracranial vessel occlusion. The distribution of ischemic lesions was analyzed on perfusion parameter maps.

Results—On CTA, 30 patients (52%) had a total of 33 occluded intracranial artery segments. Twenty-eight occlusions were identified on 4-dimensional CTA, resulting in an 85% sensitivity with a positive predictive value of 97%. When combined with an analysis of the perfusion parameter maps, sensitivity of 4-dimensional CTA increased to 94% with a positive predictive value of 100%.

Conclusions—In acute stroke, angiographic volume perfusion CT reconstructions may be a feasible option to detect intracranial arterial occlusion and evaluate patients for endovascular therapy. Sensitivity for detection of intracranial arterial occlusion can be increased by simultaneous assessment of perfusion parameter maps. Future studies should assess whether time-resolved 4-dimensional CTA may offer additional diagnostically relevant information compared with single-phase CTA. (*Stroke*. 2012;43:97-102.)

Key Words: brain imaging ■ CT perfusion ■ stroke ■ thrombosis ■ vessel occlusion

In acute ischemic stroke, rapid detection of the location and extent of infarction is essential for making treatment decisions. One of the diagnostic key elements guiding the therapeutic approach in the acute phase of an ischemic stroke is the presence or absence of intracranial large vessel occlusion (LVO). For patients with intracranial LVO, the prognosis is expected to be worse and different endovascular recanalization techniques have shown the potential to improve outcome, even outside standard time windows for intravenous thrombolytic therapy.¹⁻³ In addition, patients with LVO are less likely to benefit from intravenous therapy than patients with stroke without LVO,⁴ underlining the importance of detecting LVO as soon as possible. In a recent North American study, almost half of patients with acute ischemic stroke had an occlusion of a large intracranial artery.³ Although it cannot be inferred from this ratio that

every second patient with stroke will need endovascular treatment and indeed the number is likely to be significantly lower,⁵ diagnostic information on the presence or absence of LVO will still be one of the most important factors in making a decision for or against an endovascular approach in the acute setting. Considering that clinical scores such as the National Institutes of Health Stroke Scale often do not adequately predict the presence of LVO,⁶ urgent imaging of the intracranial vascular system has become a standard at many stroke centers.

Options for visualizing the intracranial vasculature are included in standard stroke imaging protocols, which are based either on multimodal CT or MRI imaging. Multimodal CT consists of nonenhanced CT, perfusion CT, and CT angiography (CTA) and is increasingly selected for diagnostic imaging in patients presenting with acute stroke.^{7,8} Some-

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what simplified, the rationale of this diagnostic protocol is to rule out or demonstrate hemorrhagic stroke or clearly visible large infarcts (nonenhanced CT), define the location and extent of ischemia and salvageable brain tissue (perfusion CT), and assess for a possible underlying vessel occlusion or other vascular pathology (CTA).

For the detection of acute LVO, CTA offers excellent sensitivity and specificity.^{9,10} It has previously been shown that angiographic reconstructions from perfusion CT acquisitions may offer image quality comparable to traditional CTA, although it has been stated that images were grainier and showed less detail.^{11,12} In addition, a recent study demonstrated good correlation for CTA and perfusion CT for vascular pathology with a reported sensitivity of 90% for all observed vascular changes (occlusion, stenosis, aneurysms, vascular malformations) in patients examined for suspected ischemic stroke or vasospasm.¹³ Another previous study was able to demonstrate good sensitivity and specificity for detection of the site of occlusion using the mean transit time parameter map on perfusion CT to indirectly infer the occluded artery segment.¹⁴ With the advent of CT scanners capable of continuously imaging almost the entire brain (9.6-cm z-axis coverage for the scanner used in this study, leading to the term “volume perfusion CT” [VPCT]), a plethora of anatomic vascular information is obtained with every VPCT scan. It has been shown that increasing the z-axis coverage of perfusion CT scans can improve the diagnostic sensitivity for detecting ischemic lesions.^{13,15} However, diagnostic evaluation of VPCT examinations typically focuses on functional abnormalities detected on the perfusion parameter maps such as cerebral blood volume, cerebral blood flow, mean transit time, and time to peak, whereas vascular reconstructions are not routinely obtained.

The present study aimed at assessing the diagnostic accuracy of thin-slice angiographic images reconstructed from 9.6-cm VPCT data sets (henceforward referred to as 4-dimensional CTA) in comparison with traditional single-phase CTA in the clinical setting of acute stroke. Specifically, the goal was to demonstrate the sensitivity of 4-dimensional CTA for the detection of occluded large intracranial artery segments that are potentially treatable with endovascular recanalization. In addition, we analyzed whether the joint assessment of perfusion parameter maps potentially increases diagnostic accuracy of 4-dimensional CTA.

Methods and Materials

Sixty-two consecutive patients (January to November 2009) presenting to our department for the evaluation of suspected acute ischemic stroke within 24 hours of symptom onset who received a complete multimodal CT examination were retrospectively identified for inclusion from a prospectively collected, Institutional Review Board-approved database. The only exclusion criterion was lack of a complete data set ($n=4$).

Images were obtained on a 128-slice multidetector CT scanner (Siemens Definition AS+; Siemens Healthcare Sector, Forchheim, Germany). Scanning order was nonenhanced CT, VPCT, and CTA. VPCT data were acquired using a periodic spiral approach (adaptive 4-dimensional spiral mode) consisting of 30 consecutive spiral scans of the brain (96 mm in z-axis, 2-second delay, 1.5-second mean temporal resolution) for a total examination time of 45 seconds after the injection of a short contrast bolus (Imeron 400; Bracco Imaging,

Konstanz, Germany). For VPCT (80 kV, 200 mAs, rotation time 0.3 seconds, maximum pitch 0.5, collimation $2^{\circ}64^{\circ}0.6$ mm), contrast volume was 36 mL at a flow rate of 6 mL/s followed by a 30-mL saline chaser at 6 mL/s. For CTA (120 kV, 120 reference mAs, rotation time 0.3 seconds, pitch 0.6, collimation $2^{\circ}64^{\circ}0.6$ mm), 65 mL of iodinated contrast was injected with a biphasic protocol (45 mL at 6 mL/s, 15 mL at 3 mL/s) followed by a 30-mL saline chaser at 3 mL/s. VPCT data were routinely reconstructed with a slice width of 5 mm every 3 mm for perfusion analysis and with a slice width of 1.5 mm every 1 mm for 4-dimensional CTA analysis (Kernel H20f, 512 Matrix). CTA data were reconstructed with a slice width of 0.75 mm every 0.4 mm. The thin-slice VPCT data were processed using a commercial dynamic analysis package (Volume Perfusion CT Neuro; Siemens) using automatic motion correction and a dedicated noise reduction technique for dynamic data.¹⁶ The peak arterial scan was determined by region of interest analysis in the proximal A2 segment. Finally, maximum-intensity projections in the axial and coronal plane (10-mm slice thickness, 3-mm interslice distance) were reconstructed from the CTA data set and from the peak arterial VPCT scan. All postprocessing was performed on a multimodality workstation (Siemens syngo 2010B; Siemens). For all patients in this study, functional perfusion data (ie, VPCT parameter maps) were used in making treatment decisions, whereas 4-dimensional CTA data were retrospectively analyzed and were not used to make treatment decisions.

A neuroradiologist (11 years of experience) and a fourth-year radiology resident evaluated all images for the presence of intracranial LVO in consensus blinded to clinical information. First, corresponding sets of axial and coronal 4-dimensional CTA reconstructions for the first half of the study population and CTA reconstructions for the other half of the population were provided. To reduce recall bias, the remaining CTA images of the first half and 4-dimensional CTA examinations of the second half of the study population were analyzed in randomized order after a break of 2 weeks. Vessel occlusion was defined as a focal loss of vascular opacity without distal vessel delineation. Specifically, the presence or absence of occlusion of the intracranial internal carotid artery, the proximal (A1) and distal (A2) segment of the anterior cerebral artery, the M1 and M2 segments of the middle cerebral artery, the P1 and P2 segments of the posterior cerebral artery, and the basilar artery were assessed. The intracranial vertebral arteries were frequently not covered by the 4-dimensional CTA scan range and were therefore excluded from analysis. In addition, image quality was rated on a 4-point scale (1, nondiagnostic; 2, diagnostic with limitations; 3, diagnostic with minor limitations; 4, excellent) assessing the visibility of the distal M2 segments. Relative distributions of vessel occlusions were obtained and diagnostic sensitivity, specificity as well as positive and negative predictive values of 4-dimensional CTA were calculated with CTA functioning as the standard of reference.

In patients with anterior circulation occlusion confirmed on angiography ($n=6$), biplanar angiographic images (Axiom Artis dBA; Siemens, Erlangen, Germany) were assessed for the presence of antegrade opacification distal to the occlusion. The corresponding 30 consecutive VPCT spiral scans were assessed by a different reader for opacification occurring in a retrograde fashion at the distal thrombus end.

Presence or absence of a perfusion deficit on the VPCT parameter maps was assessed in a separate reading session. Readers were presented with commonly used parameter maps (cerebral blood volume, cerebral blood flow, and time to peak) and were asked to assess the presence of an ischemic stroke (defined as a visual abnormality on cerebral blood volume and cerebral blood flow maps) and, if present, assign the perfusion deficit to 1 of the vascular territories defined previously. To assess whether the diagnostic yield of 4-dimensional CTA could be improved, raters were asked to re-evaluate the corresponding 4-dimensional CTA images for an underlying vascular occlusion in direct comparison with the perfusion parameter maps. The site of LVO was recorded and separate values for sensitivity, specificity, positive predictive value, and

Table 1. Overview of Occluded Vessel Segments in All Patients

Patients included	58			
Analyzed vessel segments	928			
Vessel Occlusion	CTA		4D-CTA	
Patients with intracranial LVO	30 (51.7%)		27 (46.6%)	
Total no. of LVOs	33		29	
Site of occlusion				
Intracranial ICA	8	14%	7	12%
A1	0	0%	0	0%
A2	0	0%	0	0%
M1	12	21%	11	19%
M2	9	16%	8	14%
P1	1	1.7%	1	1.7%
P2	1	1.7%	0	0%
Basilar artery	2	3.4%	2	3.4%

CTA indicates CT angiography; 4D-CTA, 4-dimensional CT angiography; LVO, large vessel occlusion; ICA, internal carotid artery; A1, A2, M1, M2, P1, P2, segments of the anterior, middle, and posterior cerebral arteries.

negative predictive value were calculated for the combined approach.

The Wilcoxon signed ranked test was used to compare the image quality ratings; $P < 0.05$ was used as the level of significance. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 16.0; SPSS Inc, Chicago, IL). Effective dose values were calculated by multiplying dose-length-product values with published conversion factors.

Results

Of 62 patients identified, 4 were excluded because of lack of a complete imaging data set. Fifty-eight patients were included for analysis. Mean age was 70.5 years (range, 30.3–88.5 years) and female-to-male ratio was 25:33. Median National Institutes of Health Stroke Scale score was 12 (range, 4–30; mean, 13.6). Time from symptom onset was available in 30 of 58 patients with a mean 242 minutes (SD, 142 minutes) between symptom onset and multimodal CT; the remaining 28 patients presented with unknown time of symptom onset <24 hours. The effective dose was 5.3 mSv for the VPCT scan, 1.1 mSv for the craniocervical CTA portion (20 cm from vertex), and 2.1 mSv for the remaining more caudal CTA range (15 cm).

Table 1 shows the number and site of occlusions detected by 4-dimensional CTA and CTA in the 928 vessel segments analyzed in this study. Of the 58 patients included, 30 (51.7%) had an occlusion of an intracranial artery segment on CTA. Three patients (10%) had an occlusion of multiple intracranial vessels. When assessing the presence or absence of intracranial large vessel occlusion, 4-dimensional CTA offered an 84.9% sensitivity and a positive predictive value of 96.6% when compared with CTA (Table 2; Figure 1). In addition, 9 patients had an occlusion of an extracranial artery and 5 patients had a cervical carotid stenosis without occlusion as described in the final multimodal CT diagnostic report. Subgroup analysis of patients with anterior circulation occlusion and catheter angiography ($n=6$) revealed collateral filling to the distal thrombus end in a retrograde fashion on

Table 2. Diagnostic Accuracy of 4D-CTA for Detection of Intracranial Vessel Occlusion

CTA vs 4D-CTA	Occlusion on 4D-CTA	Patent Vessel on 4D-CTA
Occlusion on CTA	28	5
Patent vessel on CTA	1	894
Sensitivity		84.85%
Specificity		99.89%
PPV		96.55%
NPV		99.44%
CTA vs Combined 4D-CTA and Parameter Maps	Occlusion on 4D-CTA	Patent Vessel on 4D-CTA
Occlusion on CTA	32	2
Patent vessel on CTA	0	894
Sensitivity		94.12%
Specificity		100.00%
PPV		100.00%
NPV		99.78%

CTA indicates CT angiography; 4D-CTA, 4-dimensional CT angiography; LVO, large vessel occlusion; ICA, internal carotid artery; PPV, positive predictive value; NPV, negative predictive value.

4-dimensional CTA in 5 cases (80%; Figure 2). None of these demonstrated antegrade flow across thrombus on angiography.

VPCT parameter maps (cerebral blood volume, cerebral blood flow, time to peak) showed an ischemic lesion in 36 of 58 patients (62%; Table 3). The second rating of the 4-dimensional CTA data with simultaneous access to the perfusion parameter maps led to a different final decision regarding LVO in 5 of 58 cases (8.6%). In 1 patient with an M2 occlusion, an additional A2 occlusion that had been missed on both CTA and 4-dimensional CTA in the initial rating was identified with the combined approach (parameter maps and 4-dimensional CTA together) and could be retrospectively confirmed on CTA. The overall sensitivity of the combined approach for detection of LVO was 94.1% with a positive predictive value of 100% (Table 2).

In our study population, the median National Institutes of Health Stroke Scale score was higher in patients with intracranial LVO (17; range, 6–30) than in patients without intracranial LVO (8; range, 4–24). Finally, the median quality rating on an ordinal scale from 1 to 4 was 4 for both CTA (mean, 3.74) and 4-dimensional CTA (mean, 3.70). There was no statistically significant difference in the observed image quality ($P=0.545$).

Although image quality ratings were comparable for both examinations, vessel contours appeared slightly sharper on CTA when directly compared with 4-dimensional CTA (Figure 1). This is almost certainly due to the significantly lower spatial resolution and sampling in the z-direction of the 4-dimensional CTA data as compared with the standard CTAs: 1.5 mm every 1.0 mm versus 0.75 mm every 0.4 mm. This is not a principal technical limitation, however, but rather due to the retrospective nature of our study. Images with the same z-resolution as in standard CTA can be reconstructed from the original VPCT raw data. Because the

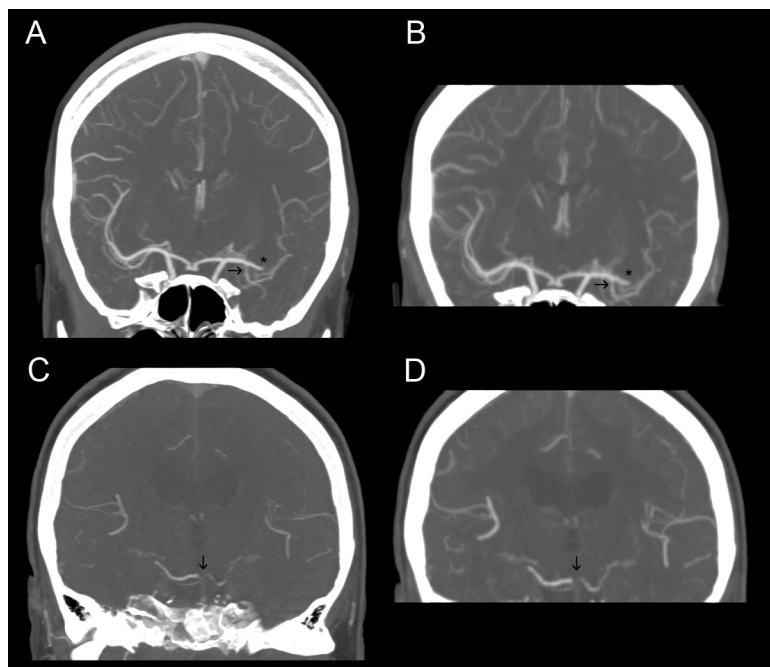


Figure 1. Examples of CTA and 4-D-CTA scans demonstrating intracranial large vessel occlusion. **A–B**, Coronal MIP reconstructions of CTA (**A**) and 4D-CTA (**B**) from a patient with a proximal occlusion of a left M2 segment (asterisk). In addition, there is faint proximal contrastation of a temporal M2 branch (arrow) consistent with subtotal occlusion. **C–D**, Coronal MIP reconstructions of CTA (**C**) and 4D-CTA (**D**) from a patient with distal basilar and proximal left posterior cerebral artery occlusion (arrow). CTA indicates CT angiography; 4D-CTA, 4-dimensional CT angiography; MIP, maximum intensity projection; M2, middle cerebral artery branch.

primary goal of this study was to assess large vessel occlusion, we had decided at the beginning of data acquisition to keep the number of 4-dimensional CTA images at a more manageable level (2850 versus >7000 per study).

Discussion

In patients presenting with acute stroke, multimodal CT is a widely available, robust, and comparatively inexpensive imaging modality, which allows detection of acute ischemia and vascular pathology. Obtaining angiographic 4-dimensional CTA reconstructions from VPCT may be an option to assess acute intracranial large vessel occlusion. The present study shows that arterial phase 4-dimensional CTA reconstructions offer image quality comparable to CTA and can be used to assess intracranial LVO in patients with stroke with high sensitivity and positive predictive value. Because 4-dimensional CTA is just another reconstruction of the VPCT data, it is easy to include into the routine diagnostic workflow.

Our data show that the diagnostic accuracy of 4-dimensional CTA can be improved by simultaneous assessment of the perfusion parameter maps. This combined approach further improved sensitivity (94%) and positive predictive value (100%) for the detection of LVO in comparison to CTA. In 1 patient with an occluded M2 segment, coexisting occlusion of the ipsilateral A2 segment had been missed

on both CTA and 4-dimensional CTA ratings alone and was only detected after an abnormality was seen on the perfusion parameter maps, underlining the use of VPCT to aid in stroke diagnosis.

Our results do not suggest, however, that standard CTA can be omitted. In the present study, 9 patients had an occlusion of a cervical artery not depicted in the used intracranial reconstructions, which may affect treatment decision regarding intravenous or endovascular thrombolysis. Figure 1 shows an example of basilar artery occlusion in which the extent of proximal involvement cannot be identified on VPCT because the scan volume was placed largely supratentorially, probably because an anterior circulation lesion was suspected clinically. Previous investigators have observed that in some patients, the dynamic attenuation of intracranial vessels over time may indirectly point to a more proximal site of vessel occlusion outside the VPCT scan range.¹³ We have made similar observations; however, we deem it unlikely that these indirect findings will provide enough diagnostic certainty to guide clinical decisions. Thus, cervical CTA including the carotid bifurcation will remain mandatory to detect relevant extracranial pathology and allow access planning for intra-arterial procedures. Increasing the VPCT z-coverage by approximately 5 cm over the roughly 10 cm used in our study would probably always cover the complete intracranial vasculature but would also increase the

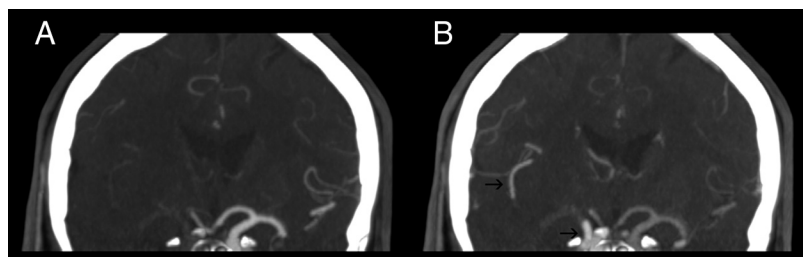


Figure 2. Early-arterial and late-arterial phases of 4D-CTA. Four-dimensional CTA images from a patient with right-sided carotid T-occlusion. **A**, Peak arterial phase demonstrating lack of opacification of the right ICA, M1, and M2. **B**, Late-arterial phase image shows delayed opacification of the distal ICA up to the proximal thrombus end as well as opacification of the distal M2 segments consistent with collateral flow. 4D-CTA indicates 4-dimensional CT angiography; ICA, internal carotid artery; M1, M2, middle cerebral artery branches.

Table 3. Distribution of Infarcts Observed on Whole-Brain Perfusion Parameter Maps

Distribution of Infarcts		
Patients with a perfusion deficit		36 (62%)
Territory of Perfusion Deficit	No. of Infarcts	Percent
ICA	6	10.3%
A1	0	0.0%
A2	1	1.7%
M1	14	24.1%
M2	10	17.2%
P1	1	1.7%
P2	0	0.0%
Basilar artery/infratentorial	4	6.9%

ICA indicates internal carotid artery; A1, A2, M1, M2, P1, P2, segments of the anterior, middle, and posterior cerebral arteries.

dose by approximately 50%, that is, approximately 2.5 mSv. The eye lenses would then always be in the primary beam, which we avoided by careful positioning and restriction to mostly supratentorial brain. Furthermore, the carotid bifurcation would still not be included and the dose-saving if the CTA would not cover the intracerebral vessels would be <1 mSv.

On the other hand, our study encourages examination of 4-dimensional CTA in cases in which CTA is degraded by motion artifacts or improper contrast bolus timing. Because our results indicate that peak arterial 4-dimensional CTA reconstructions already allow detection of intracranial LVO, future studies should explore the potential value of other 4-dimensional CTA phases (eg, early or late arterial), which can easily be reconstructed from the thin-slice VPCT data set (Figure 2). Indeed, we believe that time-resolved CTA may offer additional diagnostic information compared with single-phase CTA. The results of our subgroup analysis suggest that retrograde collateral flow can be demonstrated on 4-dimensional CTA. Consequently, it may be possible to differentiate antegrade flow across subocclusive thrombus from complete occlusion with retrograde filling, a distinction that previous investigators have shown to be challenging on conventional imaging.¹⁷ A larger sample size including patients with angiographically proven antegrade flow will be needed to investigate this hypothesis. For this purpose, use of a more refined scoring system, for example, the Thrombolysis in Cerebral Infarction score, may provide a more realistic depiction of vascular pathology including incomplete occlusions.

Four-dimensional CTA may also be valuable in assessing leptomeningeal collateral flow in patients with stroke. Recent studies have demonstrated that the degree of collateral flow may predict the success rate of revascularization measures as well as clinical outcome.^{18,19} Using 4-dimensional CTA, collateral flow could potentially be assessed in a manner more similar to traditional angiography and its usefulness in this setting should be further assessed. Four-dimensional CTA could also be helpful in depicting the localization and extent of intravascular thrombus, which has recently been used to predict the success of intravenous thrombolysis.²⁰

Finally, correlation of 4-dimensional CTA data with imaging and clinical outcome may show whether 4-dimensional CTA could be of value in selecting patients for intravenous or intra-arterial therapy and its possible role as an imaging biomarker should be further assessed.

In conclusion, 4-dimensional CTA is a promising additional option for the assessment of intracranial large vessel occlusion in patients presenting with acute ischemic stroke. Joint analysis of 4-dimensional CTA and perfusion parameter maps increases the sensitivity for detecting vessel occlusion. Complete visualization of the cervical vasculature by CTA or other modalities will usually still be required in most patients with stroke to detect coexisting extracranial pathology and 4-dimensional CTA is likely to complement rather than replace intracranial CTA in the foreseeable future. Additional research is required to maximize the diagnostic potential of 4-dimensional CTA in patients with stroke; especially promising applications include assessment of collateral flow, distinction of partial from complete occlusions, and delineation of intravascular thrombus.

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