Antegrade Flow Across Incomplete Vessel Occlusions Can Be Distinguished From Retrograde Collateral Flow Using 4-Dimensional Computed Tomographic Angiography

Andreas M.J. Frölich, MD; Marios N. Psychogios, MD; Ernst Klotz, Dipl-Phys; Ramona Schramm, RN; Michael Knauth, MD; Peter Schramm, MD

Background and Purpose—In acute stroke patients with intracranial vessel occlusion, angiographic demonstration of antegrade contrast opacification distal to the occlusion site (termed the “clot outline sign”) has been associated with higher rates of vessel recanalization. We sought to determine whether antegrade flow can be demonstrated on time-resolved 4-dimensional computed tomographic angiography (4-dimensional CTA), whether it can be distinguished from retrograde collateral flow, and if it can be used to predict early recanalization.

Methods—Fifty-seven acute stroke patients with intracranial anterior circulation vessel occlusion were retrospectively identified. All patients had received a multimodal computed tomography examination including thin-section 4-dimensional CTA and subsequent digital subtraction angiography as part of an endovascular procedure. Pretreatment 4-dimensional CTA and single-phase CTA were assessed for presence of antegrade contrast opacification distal to the occlusion site. Digital subtraction angiograms were reviewed for preintervention Thrombolysis in Cerebral Infarction grade, presence of the clot outline sign, as well as postintervention Thrombolysis in Cerebral Infarction grade.

Results—On 4-dimensional CTA, evidence of antegrade flow was present in 11 of 57 cases (19.3%). Compared with angiography, 4-dimensional CTA predicted antegrade flow with 100% sensitivity and 97.9% specificity. Single-phase CTA offered 40% sensitivity and 87.2% specificity. Early recanalization occurred in 3 patients (6.5%) after intravenous thrombolysis (n=46); all demonstrated antegrade flow on 4-dimensional CTA.

Conclusions—Using 4-dimensional CTA, it is possible to noninvasively distinguish antegrade flow across a cerebral artery occlusion from retrograde collateral flow. Presence of antegrade flow on 4-dimensional CTA is associated with an increased chance of early vessel recanalization. (Stroke. 2012;43:2974-2979.)

Key Words: acute stroke ■ brain imaging ■ computed tomographic perfusion ■ thrombosis ■ vessel occlusion

In acute ischemic stroke patients, recanalization of an intracranial large vessel occlusion either with intravenous or intra-arterial thrombolysis and/or mechanical thrombectomy has been shown to improve outcomes and limit infarct growth.1–3 However, published recanalization rates vary considerably between different studies and used treatment modalities.3–5 emphasizing the need to establish predictors of successful recanalization to facilitate adequate patient selection. For endovascular procedures, the angiographic appearance of the occlusion site has been used as a predictor of recanalization success.6,7 In particular, angiographic demonstration of delayed antegrade contrast opacification distal to the occlusion site (referred to as “clot outline sign”) has been linked to improved recanalization rates after intra-arterial thrombolysis.8 With the recent advent of computed tomography (CT) scanners allowing volumetric perfusion CT examinations of almost the entire brain, time-resolved 4-dimensional computed tomographic angiography (4-dimensional CTA) of the cerebral vasculature can be obtained to noninvasively study cerebral hemodynamics.9–11 The purpose of this study was to determine whether antegrade contrast opacification across an intracranial vessel occlusion can be noninvasively demonstrated on 4-dimensional CTA, whether it can be distinguished from retrograde collateral flow, and if it can be used to predict early vessel recanalization.

Materials and Methods

Study Design

We retrospectively identified 57 acute ischemic stroke patients (January 2009–February 2012) from an Institutional Review Board-approved database who met the following inclusion criteria: (1) presence of a complete multimodal CT examination (MMCT) including nonenhanced CT of the head, single-phase CTA of the head and neck (spCTA), and thin-slice 4-dimensional CTA reconstructions of the head; (2) time from symptom onset <12 hours; (3) anterior circulation vessel occlusion on CTA; and (4) attempted endovascular recanalization. Exclusion criteria

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were incomplete coverage of the intracranial occlusive lesion on 4-dimensional CTA and presence of ipsilateral cervical internal carotid artery occlusion. We decided to exclude patients with ipsilateral internal carotid artery occlusion because proximal vessel manipulation and stent placement can affect the intracranial occlusion site through embolization and flow alteration. This may introduce an artificial discrepancy between MMCT findings and the initial intracranial digital subtraction angiography (DSA) series. For all patients in this study, spCTA and perfusion CT parameter maps were used to assess salvageable brain tissue and guide treatment decisions. The 4-dimensional CTA was reviewed retrospectively and was not used in making treatment decisions.

**Image Acquisition**

CT images were obtained on a 128-slice multidetector CT scanner (Siemens Definition AS+; Siemens Healthcare Sector, Forchheim, Germany). Scanning order was nonenhanced CT, perfusion CT, and, last, spCTA. Perfusion CT data were acquired using a periodic spiral approach consisting of 30 consecutive spiral scans of the brain (96 mm in z-axis, 2-second delay, 1.5-second mean temporal resolution) as previously described. To keep the amount of images manageable, perfusion CT data were reconstructed with a slice width of 1.5 mm every 1 mm (Kernel H20f, 512 Matrix) for 4-dimensional CTA, whereas spCTA data were reconstructed with a slice width of 0.75 mm every 0.4 mm. Biplanar digital subtraction angiograms were obtained during the endovascular procedure (Axiom Artis dBA; Siemens Healthcare Sector).

**Demographic Data**

Demographic and clinical data were obtained from patients’ medical records and included age, sex, time from symptom onset to CT, National Institutes of Health Stroke Scale (NIHSS) at presentation and discharge, modified Rankin Scale score at discharge as well as application of intravenous and/or intra-arterial recombinant tissue plasminogen activator. In patients with wake-up stroke, time last seen well was used as a substitute. When the time last seen well was not documented, symptom onset was defined as midnight when presenting between midnight and noon, and was defined as noon when presenting between noon and midnight.

**Image Analysis**

Thin-slice 4-dimensional CTA data were displayed for time-resolved analysis using a commercial dynamic analysis package (InSpace; Siemens Healthcare Sector). The presence of antegrade contrast opacification distal to the occluded vessel segment (antegrade flow) was assessed on 4-dimensional CTA using multplanar reformations and maximum-intensity projections in 3 orthogonal planes by 2 readers (with 2 years and 5 years of experience in neuroradiology, respectively) blinded to clinical and other imaging information. Cases of disagreement were settled by consensus. The 4-dimensional CTA Thrombolysis in Cerebral Infarction (TICI) grade was assigned in consensus. Single-phase CTA was reviewed by a third equally blinded reader (with >20 years of experience) who was asked to decide between either complete or incomplete occlusion of the target vessel. Biplanar DSA images obtained directly before endovascular intervention were assessed for TICI grade and the presence of the clot outline sign by a fourth reader (with 12 years of experience) blinded to the 4-dimensional CTA and spCTA data. Any increase in TICI from 4-dimensional CTA to DSA was classified as early recanalization. Final recanalization was assessed by TICI score on postintervention DSA images; successful recanalization was defined as TICI ≥2b. Time from symptom onset to angiographic recanalization (TICI ≥2b) was recorded.

**Statistical Analysis**

Diagnostic sensitivity and specificity of 4-dimensional CTA and spCTA for the detection of antegrade flow or early target vessel recanalization were calculated with DSA functioning as the standard of reference. Interobserver agreement between the 2 readers for 4-dimensional CTA was calculated using Cohen kappa. To assess the ability of 4-dimensional CTA to predict early and final vessel recanalization, the Fisher exact test was used. For early recanalization, only patients who received intravenous thrombolysis were included (n=46). Multivariate logistic regression was performed to assess the effect of age, baseline NIHSS score, and evidence of antegrade flow on 4-dimensional CTA on clinical outcome; patients were dichotomized into favorable (modified Rankin Scale score ≤2) and poor outcome (modified Rankin Scale >2). All statistical analyses were performed using Statistica (StatSoft Europe, Hamburg, Germany). The level of statistical significance was set at P=0.05.

**Results**

Among 149 consecutive patients who received endovascular treatment for acute ischemic stroke at our university hospital between January 2009 and February 2012, 71 patients with anterior circulation occlusions had thin-slice 4-dimensional CTA data available. After excluding patients with incomplete coverage of the intracranial occlusion on 4-dimensional CTA (n=1) and ipsilateral cervical internal carotid artery occlusion (n=13), data from 57 patients were available for final analysis. Patient demographic and clinical data are summarized in Table 1. Mean NIHSS score on presentation was 16 (range, 8–28). Mean time between symptom onset and MMCT was 184 minutes (8–624 minutes). The occluded target vessels were the terminal internal carotid artery (internal carotid artery, n=7) and the M1 (n=45) and M2 (n=5) segments of the middle cerebral artery. Forty-six patients received intravenous thrombolysis, which was initiated immediately after the MMCT examination. All patients received mechanical thrombectomy, and several different flow restoration and clot removal devices were used across the study population. In addition, intra-arterial application of recombinant tissue plasminogen activator was used in 36 patients (63%), most often after partial mechanical recanalization had been achieved. Three out of the 46 patients (6.5%) who received intravenous thrombolysis showed early recanalization on the initial DSA series. Final vessel recanalization status was TICI 0 or 1 in 7 patients (12%), TICI 2a in 13 patients (23%), TICI 2b in 12 patients (21%), and TICI 3 in 25 patients (44%). Sixteen out of 57 patients (28%) had a favorable outcome (modified Rankin Scale score ≤2). Twenty-eight patients (49%) showed at least a 4-point improvement on

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics.</th>
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<tbody>
<tr>
<td>N</td>
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<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Patients included</td>
</tr>
<tr>
<td>Mean age, y (range)</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td>Median NIHSS (range)</td>
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<tr>
<td>Mean time (min) from symptom onset to CT (±SD)</td>
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<tr>
<td>Occluded target vessel</td>
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<tr>
<td>Terminal ICA</td>
</tr>
<tr>
<td>M1</td>
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<tr>
<td>M2</td>
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CT indicates computed tomography; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation. M1 and M2 are segments of the middle cerebral artery.
Table 2. Diagnostic Accuracy of 4-Dimensional Computed Tomographic Angiography and Single-Phase Computed Tomographic Angiography for Detection of Antegrade Flow

<table>
<thead>
<tr>
<th>Detection of antegrade flow</th>
<th>Complete Occlusion</th>
<th>Outline Sign</th>
<th>Early Recanalization</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-dimensional CTA: antegrade flow</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>4-dimensional CTA: complete occlusion</td>
<td>46</td>
<td>0</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>spCTA: antegrade flow</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>spCTA: complete occlusion</td>
<td>41</td>
<td>5</td>
<td>1</td>
<td>47</td>
</tr>
</tbody>
</table>

Prediction of DSA outline sign or early recanalization

<table>
<thead>
<tr>
<th>Prediction of DSA outline sign or early recanalization</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-dimensional CTA</td>
<td>100.0% (72.3%–100.0%)</td>
<td>97.9% (88.9%–99.6%)</td>
</tr>
<tr>
<td>spCTA</td>
<td>40.0% (16.8%–68.73%)</td>
<td>87.2% (74.8%–94.0%)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CTA, computed tomographic angiography; DSA, digital subtraction angiography; spCTA, single-phase computed tomographic angiography.

Outline sign is evidence of delayed antegrade contrast opacification distal to an occlusion.

The NIHSS score at discharge. Eight patients died during their hospital stay (14%).

On 4-dimensional CTA, 11 out of 57 patients (19.3%) displayed evidence of antegrade flow (Table 2, Figure 1). Inter-rater reliability for the presence of antegrade flow was substantial ($\kappa=0.79$). When including patients with early recanalization (any increase in TICI score on DSA over 4-dimensional CTA), 4-dimensional CTA predicted DSA clot outline sign or early recanalization with 100.0% sensitivity (95% confidence interval [CI], 72.3%–100.0%) and 97.9% specificity (95% CI, 88.9%–99.6%). When excluding patients with early recanalization (n=3), 4-dimensional CTA predicted DSA clot outline sign with 100.0% sensitivity (95% CI, 64.6%–100.0%) and 97.9% specificity (95% CI, 88.9%–99.6%). For spCTA, 40.0% sensitivity (95% CI, 16.8%–68.7%) and 87.2% specificity (95% CI, 74.8%–94.0%) were observed for the detection of incomplete occlusions or early recanalization (Table 2). When excluding patients with early recanalization, spCTA yielded 28.6% sensitivity (95% CI, 8.2%–64.1%) and 87.2% specificity (95% CI, 74.8%–94.0%).

Baseline characteristics between patients with evidence of antegrade flow on 4-dimensional CTA and those with complete occlusions were similar regarding age (mean±standard deviation: 76.3±4.8 vs 70.7±13.7 years; $P=0.189$), presenting NIHSS score (median [range]: 13 [8–26] vs 16 [9–28]; $P=0.09$) and time from symptom onset to imaging (mean, 193±138 vs 179±141 minutes; $P=0.765$). Time from MMCT imaging to angiographically documented recanalization (TICI ≥2b) was significantly shorter for patients with antegrade flow (mean, 108±47 vs 146±44 minutes; $P=0.047$). Patients with antegrade flow were significantly more likely to achieve early recanalization after intravenous thrombolysis ($P=0.037$). There was no statistically significant correlation between antegrade flow and final vessel recanalization (TICI ≥2b; $P=0.41$).

On multivariate analysis, only NIHSS at presentation emerged as a significant predictor of favorable outcome ($P=0.0029$). Both antegrade flow on 4-dimensional CTA (odds ratio [OR], 5.13; 95% CI, 0.78–33.85; $P=0.0029$) and final recanalization TICI ≥2b (OR, 6.38; 95% CI, 0.74–54.88; $P=0.037$) were significant predictors of favorable outcome. Both 4-dimensional CTA and final recanalization TICI ≥2b were included in the model.

Figure 1. Antegrade flow. A, Coronal maximum intensity projection from single-phase computed tomographic angiography (CTA) in a patient with left-side hemiplegia demonstrates short-segment occlusion of the right middle cerebral artery (MCA). B, Early to late 4-dimensional CTA (left to right) demonstrates early opacification distal to the occlusion, extending more distally in an antegrade fashion (arrows). C, Serial right internal carotid artery injection digital subtraction angiography demonstrates slow antegrade opacification distal to the occlusion (arrows), confirming an incomplete vessel occlusion.
Furthermore, Doppler perfusion CT may be easily reproduced in centers already performing perfusion CT.

**Discussion**

The present study shows that 4-dimensional CTA obtained from a volumetric perfusion CT data set can be used to differentiate antegrade flow across intravascular thrombus (Figure 1) from retrograde collateral flow (Figure 2) with high sensitivity and specificity and substantial inter-rater agreement (Table 2). To our knowledge, this is the first study applying 4-dimensional CTA to noninvasively analyze incomplete vessel occlusions in acute stroke patients. The MMCT examination is an increasingly applied acute stroke imaging option, allowing detection of ischemic lesions and vascular pathology even in critical conditions. The 4-dimensional CTA can be easily obtained from volumetric perfusion CT without the need for additional contrast or radiation exposure; image reconstruction and loading takes an additional 175 seconds. Thus, the presented methodology can be easily reproduced in centers already performing perfusion CT.

Compared to 4-dimensional CTA, conventional spCTA seemed less well-suited for the assessment of incomplete occlusions, yielding an overall lower sensitivity (40% vs 100% for 4-dimensional CTA) and more false-positive results (6 vs 1; Table 2). The distinction between complete and incomplete occlusions on spCTA relies on indirect findings such as the length of the filling defect and the relative distribution of contrast material in the vascular bed distal to the occlusion site. Our results indicate that these findings, although certainly helpful, often may not allow an accurate distinction of complete and incomplete vessel occlusions. Interestingly, patients with antegrade flow may display strong opacification of the distal vascular bed, which on spCTA might be attributed to collateral flow only (Figure 1). Our findings suggest that both collateral flow as well antegrade flow contribute to opacification of the distal vascular bed in these patients and that the relative degree of contribution may not be easy to assess. Thus, applying angiographic grading schemes like the TICI scale to single-phase CTA or other static angiographic images has a certain risk of misjudging the strength of collateral flow because of the presence of incomplete occlusions. Interestingly, previous investigators have used the degree of collateral flow on spCTA to predict patient outcome and response to endovascular therapy. It would be interesting to know how many of the patients with good collateral on spCTA have antegrade flow and whether this may contribute to the CTA appearance of a densely opacified distal vascular bed. Although the assessment of vascular status and collaterals with CTA is certainly a desirable feature in stroke studies, this limitation should be kept in mind when applying scales like TICI in this setting. When comparing 4-dimensional CTA and spCTA, it should be kept in mind that spCTA offers coverage of the cervical and complete intracranial vessels. For this reason, in the clinical setting of acute stroke 4-dimensional CTA should complement rather than replace spCTA.

In our population, 11 patients (19.3%) displayed evidence of antegrade flow on 4-dimensional CTA and 10 patients (17.5%) had the clot outline sign or early recanalization on angiography. These proportions are well in agreement with previously reported values, confirming that antegrade flow across incomplete occlusions occurs in a substantial number of stroke patients. The presence of antegrade flow may have important clinical and prognostic implementations. Antegrade flow detected by angiography previously has been associated with an increased chance of vessel recanalization after intra-arterial thrombolysis. Furthermore, Doppler sonographic evidence of residual flow across thrombus has been linked to increased recanalization rates after intravenous thrombolysis. To date, relatively few other predictors of successful recanalization after intravenous thrombolysis have been established, including more distal occlusion site, absence of diabetes mellitus, and, recently, shorter clot length. If response to thrombolysis could be better predicted, then patient selection for more aggressive recanalization strategies including intra-arterial thrombolysis and mechanical thrombectomy might be improved.

Early recanalization after bridging intravenous thrombolysis (n=46) was significantly more likely and, in fact, only occurred
in patients with evidence of antegrade flow on 4-dimensional CTA (3 out of 8; 37.5%) vs those without antegrade flow (0 out of 38). Thus, our results support the hypothesis that incomplete vessel occlusions respond more favorably to intravenous thrombolysis, although our sample of patients with early recanalization is small (n=3). In fact, this surprisingly low rate of early recanalization (6.5%) supports recent reports showing low rates of early vessel reopening after intravenous thrombolysis in a larger patient sample. Previous studies on this matter have reported rates of complete recanalization between 17% and 46%, although recanalization was often assessed at later time points. Our comparably low early recanalization rate may be partly explained by some of the limitations of the present study. Because of the retrospective design, there is the risk of a considerable selection bias. All patients included had been selected for intra-arterial therapy, which likely results in an overall increased frequency of higher stroke severity and more proximal occlusions when compared with a less selected acute stroke population. Patients without available thin-slice 4-dimensional CTA reconstructions and those with cervical internal carotid artery occlusions were excluded. Patients received a range of different treatment options, including solely mechanical thrombectomy and combined intravenous thrombolysis and mechanical thrombectomy with different devices. The use of intravenous recombinant tissue plasminogen activator after the MMCT examination and before endovascular access, although allowing the analysis of early recanalization is a further limitation of our study because presence of the clot outline sign on DSA may be affected by thrombolysis. Interestingly, however, none of the patients who showed a complete occlusion on 4-dimensional CTA had the clot outline sign on DSA.

Ultimately, the goal of acute stroke imaging is to guide treatment decisions to improve patient outcome. The present study did show trends toward improved outcome depending on final recanalization and presence of antegrade flow without reaching significance. Given that early recanalization is an important predictor of outcome, we deem it possible that a larger sample size of patients with antegrade flow may reveal it as a predictor of favorable outcome. Because of the multitude of used treatment modalities, selection criteria, and the retrospective study design, clinical outcome in our study cannot be easily compared with previous studies of endovascular stroke therapy. Overall, patient outcome was approximately in agreement with the results reported in the Penumbra pivotal stroke trial, which was the device most commonly used in our study. However, compared with a more recent meta-analysis of patients treated with a bridging concept that reported good outcomes in 43% to 55%, we observed a somewhat discouragingly low proportion of good clinical outcome (28%) with a final partial or complete (TICI ≥2b) recanalization rate of 65%. Further assessment of the clinical efficacy of endovascular stroke therapy will rely on randomized prospective studies and was beyond the scope of the present investigation because of the limitations mentioned.

Thus, the main purpose of this investigation was to assess the accuracy of 4-dimensional CTA in studying incomplete occlusions. To further investigate the prognostic significance of incomplete occlusions and their response to intravenous and intra-arterial thrombolysis, a more homogenous study population would be desirable. It would be especially interesting to determine whether antegrade flow on 4-dimensional CTA has prognostic implications in a patient cohort treated solely with intravenous thrombolysis. However, because advanced stroke imaging (including 4-dimensional CTA) often is performed to triage patients to more aggressive endovascular treatment options, this study design may be more difficult to realize. Still, the present study provides evidence of an increased thrombolysis response rate and overall shorter time to recanalization in patients with antegrade flow. This information should be of value in stratifying patients toward a tailored treatment approach. However, further studies are needed to assess whether an improved response rate to intravenous thrombolysis may reduce the need for more aggressive therapies in these patients, or whether improved technical success and procedural outcome may make patients with antegrade flow ideal interventional candidates. Because clear evidence for the routine clinical use of endovascular therapy has yet to be established (most notably with the recent halting of the Interventional Management of Stroke III trial), antegrade flow should be further assessed because it may contribute to improved patient selection.

Conclusions
In summary, the present study shows that 4-dimensional CTA can be used to differentiate antegrade flow across incomplete vessel occlusions from retrograde collateral flow with high sensitivity and specificity. Diagnostic accuracy is improved compared with single-phase CTA, which often may not allow adequate distinction of the two conditions. Patients with antegrade flow may have a higher chance of early vessel recanalization after intravenous thrombolysis. The potential of antegrade flow on 4-dimensional CTA to serve as an imaging biomarker predicting response to therapy and patient outcome should be further assessed, especially considering that 4-dimensional CTA can be easily reconstructed from volumetric perfusion CT examinations without additional contrast or radiation exposure.

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References


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