

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/116747>

Please be advised that this information was generated on 2022-08-23 and may be subject to change.

Article 25fa pilot End User Agreement

This publication is distributed under the terms of Article 25fa of the Dutch Copyright Act (Auteurswet) with explicit consent by the author. Dutch law entitles the maker of a short scientific work funded either wholly or partially by Dutch public funds to make that work publicly available for no consideration following a reasonable period of time after the work was first published, provided that clear reference is made to the source of the first publication of the work.

This publication is distributed under The Association of Universities in the Netherlands (VSNU)'Article 25fa implementation' pilot project. In this pilot research outputs of researchers employed by Dutch Universities that comply with the legal requirements of Article 25fa of the Dutch Copyright Act are distributed online and free of cost or other barriers in institutional repositories. Research outputs are distributed six months after their first online publication in the original published version and with proper attribution to the source of the original publication.

You are permitted to download and use the publication for personal purposes. Please note that you are not allowed to share this article on other platforms, but can link to it. All rights remain with the author(s) and/or copyrights owner(s) of this work. Any use of the publication or parts of it other than authorised under this licence or copyright law is prohibited. Neither Radboud University nor the authors of this publication are liable for any damage resulting from your (re)use of this publication.

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please contact the Library through email: copyright@ubn.ru.nl, or send a letter to:

University Library
Radboud University
Copyright Information Point
PO Box 9100
6500 HA Nijmegen

You will be contacted as soon as possible.

Timing-Invariant Imaging of Collateral Vessels in Acute Ischemic Stroke

Ewoud J. Smit, MD; Evert-jan Vonken, MD, PhD; Tom van Seeters, MD;
Jan Willem Dankbaar, MD, PhD; Irene C. van der Schaaf, MD, PhD; L. Jaap Kappelle, MD, PhD;
Bram van Ginneken, PhD; Birgitta K. Velthuis, MD, PhD; Mathias Prokop, MD, PhD

Background and Purpose—Although collateral vessels have been shown to be an important prognostic factor in acute ischemic stroke, patients with lack of collaterals on standard imaging techniques may still have good clinical outcome. We postulate that in these cases collateral vessels are present though not visible on standard imaging techniques that are based on a single time frame.

Methods—This study included 40 consecutive patients with acute ischemic stroke with a large-vessel occlusion. Standard computed tomography angiography (CTA, single time frame) and CT perfusion (multiple time frames) were obtained at admission and timing-invariant (TI)-CTA was created from the CT perfusion data. Clinical outcome data (modified Rankin Scale) were assessed at 3-month follow-up. Four experienced observers independently assessed collateral status twice on both standard CTA and TI-CTA in an independent, blinded, randomized manner. Collateral status was rated as good if $\geq 50\%$ and poor if $< 50\%$ of collaterals were present compared with the contralateral hemisphere.

Results—Collateral status was rated higher on TI-CTA (good in 84%) compared with standard CTA (good in 49%; $P < 0.001$). Thirty-one percent of patients with poor collateral status on standard CTA still had good clinical outcome. All of those patients, however, showed good collaterals on TI-CTA. All cases with poor collateral status rated on TI-CTA had poor clinical outcome.

Conclusions—Collateral vessels may not always be visible on standard single time-frame CTA because of delayed contrast arrival. Future prognostic studies in acute stroke should consider delay-insensitive techniques, such as TI-CTA, instead of standard single time-frame imaging, such as standard CTA. (*Stroke*. 2013;44:2194-2199.)

Key Words: CT ■ CT angiography ■ collateral ■ perfusion imaging ■ stroke

In acute ischemic stroke, cerebral blood supply is regionally challenged, typically as a result of arterial occlusion. In a subgroup of patients, however, sufficient blood supply may still be available to these challenged regions via collateral vascular pathways.^{1,2} This collateral blood supply, in particular via the leptomeningeal route, is an important and independent prognostic factor for patient outcome.^{1,3-5} Collateral blood flow is also an independent prognostic factor for successful thrombolytic therapy.^{3,6,7} Imaging of collateral blood supply can be divided in 2 main approaches: visualization of the collateral vessels directly or assessment of the effectiveness of collateral perfusion.⁸ Visualization of collateral vessels is typically performed using digital subtraction angiography, MR angiography, or computed tomography angiography (CTA). The effectiveness of collateral blood supply can be assessed using MR perfusion and CT perfusion techniques.^{9,10} From systematic review, it was concluded that imaging of collateral blood supply is still challenging, and that the most promising approach for routine assessment seems a multimodal CT or MR approach combining both vessel imaging and perfusion imaging.^{5,8}

Collateral grading on CTA has been shown to be a strong and independent prognostic factor for clinical outcome after acute stroke.^{4,6,11} In particular, the absence of leptomeningeal collaterals, also referred to as a malignant collateral profile, has been shown to be highly predictive for poor clinical outcome.¹² Surprisingly, however, patients with lack of collaterals could still have favorable clinical outcome in these studies. This indicates that either the current paradigm of collateral blood supply is not comprehensive or that collateral vessels are present but not visible on standard imaging techniques. The latter may be the case if contrast material has not yet arrived in the collateral vessels at the time of CTA or MR angiography acquisitions because of delayed contrast arrival via the collateral pathway. In contrast to these single time-frame angiographic imaging techniques, multiple low-dose scans are performed in CT perfusion after intravenous injection of contrast material. Generally, the CT perfusion source images are used to derive perfusion maps, such as the cerebral blood flow, cerebral blood volume, and mean transit time, but these images also contain information about the cerebral vasculature. Recently, a method

Received January 15, 2013; final revision received May 1, 2013; accepted May 6, 2013.

From the Departments of Radiology (E.J.S., E.-j.V., T.v.S., J.W.D., I.C.v.d.S., B.K.V.) and Neurology (L.J.K.), University Medical Center Utrecht, Utrecht, The Netherlands; Department of Radiology (B.v.G., M.P.), Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Correspondence to Ewoud J. Smit, MD, Department of Radiology (E01.132), University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail ewoudsmit@gmail.com

© 2013 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.111.000675

was presented to obtain CTA images from the CT perfusion source data that are insensitive to timing of contrast arrival.¹³ This technique is referred to as timing-invariant (TI)-CTA and displays maximal contrast enhancement over time. Because the CT perfusion source images cover the whole period from contrast inflow to outflow, collaterals should be visible on TI-CTA if present. TI-CTA, therefore, has the potential to display collateral vessels that are not yet visible on single time-frame imaging techniques, and may be a better predictor of clinical patient outcome.

The purpose of this study is to compare standard single time-frame CTA with TI-CTA for assessment of collateral vessels in acute ischemic stroke in correlation with clinical outcome.

Materials and Methods

Patients

Approval by the review board of the University Medical Center Utrecht was obtained. In our hospital, all patients who are admitted under the clinical suspicion of acute ischemic stroke undergo noncontrast CT, standard CTA, and CT perfusion imaging if they fulfill the following criteria: (1) admission at <9 hours after onset of neurological deficit (including patients who awaken with stroke symptoms if the time between going to sleep and admission is <9 hours) and (b) National Institutes of Health Stroke Scale score of ≥ 2 . Patients with known contrast allergy or kidney failure undergo only noncontrast CT scanning. For this study, we selected the records of all consecutive patients who underwent scanning at our center for the indication of stroke between July 2009 and October 2010. The inclusion criteria were as follows: acute occlusion of the middle cerebral artery or internal carotid artery (intracranial or extracranial part, including the bifurcation), and the availability of both CTA and thin-section CT perfusion images from the same study. The exclusion criteria were as follows: scans were performed on a scanner with <128 detector rows (for coverage in CT perfusion). Radiological assessment was made in consensus by experienced neuroradiology staff using noncontrast CT, standard CTA, and CT perfusion images. Follow-up modified Rankin Scale data at 3 months were collected for all patients by trained neurology staff.¹⁴ Good clinical outcome was defined as modified Rankin Scale ≤ 2 (independence in daily activities) and poor clinical outcome as modified Rankin Scale > 2 (dependence in daily activities or death).

Patients with acute stroke symptoms are admitted to our accidents and emergency department per ambulance, either directly or via a general practitioner. All patients are examined by a neurologist and sent for CT imaging. Patients first undergo noncontrast CT imaging to exclude hemorrhagic stroke. If appropriate, tissue-type plasminogen activator is prepared while additional CT perfusion and CTA imaging are performed. Intravenous tissue-type plasminogen activator is administered up to 4.5 hours after ictus, straight after completion of CT imaging. All patients stay at our stroke unit until clinically stable and, if necessary, are transferred to a rehabilitation center.

Imaging Protocol

All patients underwent standard CTA and CT perfusion imaging at admission, and TI-CTA was automatically derived from the CT perfusion data. All scans were performed on a 128 detector-row scanner (Philips iCT, Cleveland OH) using a previously described protocol.¹³ For CT perfusion, 40 mL of nonionic contrast material was injected into the antecubital vein. Scans were performed every 2 seconds during a total time period of 48 seconds and were started together with contrast material injection. For standard CTA, 50 mL of nonionic contrast material was injected into the antecubital vein. Timing of the CTA acquisition to the arterial phase was based on peak arterial contrast enhancement in the CT perfusion images. For the purpose of this study, the volume of CTA was manually clipped to the volume of the CT

perfusion data. The TI-CTA images were automatically reconstructed from the CT perfusion source images on a research workstation (iX Viewer; Image Sciences Institute, Utrecht, The Netherlands).¹³ TI-CTA provides angiography by displaying maximal enhancement over time with an additional noise-reducing filter in the temporal domain. The temporal filter ensures reduction of image noise at no loss of spatial resolution. Because of the choice of the temporal maximum this technique is timing invariant, which means that the maximal enhancement of a vessel is displayed independent of its contrast arrival time. Therefore, TI-CTA is not sensitive to delayed contrast material arrival in collateral vessels and thus should display collateral vessels if present. Typically, the time for reconstruction of TI-CTA from CT perfusion data is 24 seconds on a standard personal computer.¹³

Visual Assessment of Collateral Status

Four radiological observers (2 radiologists and 2 radiology residents with 11 (E.J.V.), 9 (I.C.v.d.S.), 5 (J.W.D.), and 3 (T.v.S.) years of experience in evaluating CTA examinations, respectively) visually assessed collateral status on all standard CTA and TI-CTA images. The observers were individually presented with a random sequence of images and were blinded with respect to patient information and imaging technique. To determine intraobserver variability, all images were evaluated twice by all observers in 2 separate sessions and after a 1-week interval. All 8 sequences (4 observers, 2 sessions each) were presented with different randomization.

Images were scored for the presence of collaterals in the territory of the middle cerebral artery compared with the contralateral hemisphere on a 4-point grading scale: (1) absent (0%), (2) $>0\%$ but $<50\%$, (3) $\geq 50\%$ but $<100\%$, (4) normal (100%).^{11,15,16} In addition, collateral grades were dichotomized to poor collateral status ($<50\%$ collaterals) and good collateral status ($\geq 50\%$ collaterals).^{11,15,16} Observers were provided with visual reference images from literature,¹¹ and the side of artery occlusion was presented alongside every scan.

Statistical Analysis

We compared collateral grades rated on standard CTA and TI-CTA images. Because it is our aim to investigate potential differences in visualization of collateral vessels between these CTA techniques, and because collateral grading is generally performed for outcome prediction, collateral grades were also related to clinical outcome.

To evaluate whether collateral grades are different for TI-CTA and standard CTA, we determined average collateral grades per CTA technique, and expressed these as the overall average with the range between observers (ie, range of the 8 observations of the 4 observers). A higher collateral grade indicates that more collateral arteries are visible on that CTA technique. Statistical equivalence was tested with a Wilcoxon signed-rank test for paired scores in the same patient (2 tailed, per observation).

Inter- and intraobserver agreement were determined for both the 4-point grading and dichotomized collateral status by using κ statistics. We calculated interobserver κ values for each observer pair (24 κ values) and intraobserver κ values for each observer individually (4 κ values). Inter- and intraobserver agreement were expressed as mean κ values with the range between observers. We used nonweighted κ statistics because the 4-point grading scale is asymmetrical (pointwise) and scores have very different clinical meaning (ie, poor: 0, 0–50; good: 50–100, 100%). A κ value of 0.81 to 1.00 indicated very good agreement; a κ value of 0.61 to 0.80, good agreement; a κ value of 0.41 to 0.60, moderate agreement; a κ value of 0.21 to 0.40, fair agreement; and a κ value of 0.20 or lower, poor agreement.¹⁷

To assess whether collateral grading on standard CTA or TI-CTA better correlates with clinical outcome, we calculated the odds ratios of collateral status for clinical outcome. These values were expressed as overall odd ratios with its 95% confidence interval (CI). Because the absence of collaterals has previously been shown to be predictive of poor clinical outcome,¹² we also compared the predictive value of absent (score 0%) and poor collaterals (score $<50\%$) for poor clinical outcome (negative predictive value). In addition, we compared the predictive value of good collaterals for good clinical outcome

(positive predictive value). The negative and positive predictive values were expressed as overall predictive values with the accompanying 95% CI and range between observers.

A *P* value of <0.05 was considered to indicate a significant difference. Statistical analyses were performed using SPSS software (SPSS, version 16.0; SPSS, Chicago, IL).

Results

Patients

Forty-five consecutive patients met the inclusion criteria and were selected from the clinical database. Of these patients, 3 were excluded because CT perfusion scan acquisitions were unsuccessful because of severe patient motion, and 2 were excluded because scans were performed on a CT scanner with <128 detector rows. The remaining 40 patients were included in this study. Patient characteristics are listed in Table 1.

Visual Assessment of Collateral Status

Tables 2 and 3 show the results of collateral grading. Overall, all observers rated collateral grades significantly higher with TI-CTA than with standard CTA in all scoring sessions (all *P*<0.001). On a case-by-case basis, TI-CTA was rated with higher collateral grades in 63% of cases (range between observers, 53%–75%), equal in 34% of cases (range, 25%–45%), and lower in 4% of cases (range, 0%–8%) compared with standard CTA. Collateral status was rated good in 84% of cases (range, 78%–90%) on TI-CTA compared with only 49% of cases (range, 35%–60%) on standard CTA (*P*<0.001). Of those patients rated with poor collateral status on standard CTA, 32% (range, 19%–45%) had good collateral status on TI-CTA. Figure 1A shows an example of collaterals that were not visible on standard CTA because of delayed contrast arrival. These collaterals were visible on TI-CTA (Figure 1B).

When scored on the 4-point scale, intraobserver agreement was moderate for both standard CTA ($\kappa=0.53$; range, 0.38–0.61) and TI-CTA ($\kappa=0.49$; range, 0.42–0.66) when it was scored on the 4-point scale. The interobserver agreement, however, was poor for both techniques (standard CTA: $\kappa=0.38$; range, 0.16–0.57; TI-CTA: $\kappa=0.39$; range, 0.19–0.68). With the dichotomized collateral status, the inter- and intraobserver agreement increased for both angiographic techniques. For TI-CTA, both inter- and intraobserver agreement were good ($\kappa=0.68$; range, 0.48–0.91 and 0.78; range, 0.69–1.00, respectively). For standard CTA, interobserver agreement was moderate ($\kappa=0.57$; range, 0.36–0.75) and intraobserver agreement was good ($\kappa=0.73$; range, 0.69–0.80).

The odds ratio for favorable clinical outcome by collateral status on standard CTA images was 4.0 (95% CI, 2.5–6.3). The odds ratio for favorable clinical outcome by collateral status rated on TI-CTA images could not directly be calculated because there were no cases with poor collaterals and good clinical outcome (division by zero). When calculating the odds ratio as if one patient with poor collaterals had good clinical outcome, the odds ratio would be 63.1 (95% CI, 8.6–463.8). In the absence of collaterals patients were likely to have poor clinical outcome for both standard CTA and TI-CTA (negative predictive value, 0.98 [95% CI, 0.86–1.00; range observers, 0.80–1.00] and 1.00 [95% CI, 0.68–1.00; range observers, 1.00–1.00], respectively). With poor collaterals rated on TI-CTA patients were also very

Table 1. Patient Characteristics

	(n=40)
Age, y, mean \pm SD	71.1 \pm 13.5
Male	20 (50%)
Prestroke mRS, median (IQR)	0 (0–0)
Time to CT, min, median (IQR)	99 (64–160)
NIHSS, median (IQR)	9 (4–17)
Intravenous tPA	32 (80%)
Thrombus location	
ICA	12 (30%)
MCA	38 (95%)
Pathogenesis	
Atherosclerotic plaque	21 (53%)
Cardioembolism	7 (18%)
Dissection	3 (8%)
Unknown	9 (23%)
Contralateral carotid stenosis (>70%)	2 (5%)
Clinical assessment at day 1	
Complete recovery	1 (3%)
Improvement, no complete recovery	17 (43%)
No improvement, no decline	14 (35%)
Decline	8 (20%)
Complications during hospitalization	
Hemorrhage after tPA	3 (8%)
Mass effect	1 (3%)
Additional stroke	2 (5%)
Unknown	1 (3%)
Poor clinical outcome	21 (53%)

Data are number of patients (unless indicated otherwise). Data in parentheses are percentage of cases (unless indicated otherwise). CT indicates computed tomography; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

likely to have poor clinical outcome (negative predictive value, 1.00 [95% CI, 0.91–1.00; range observers, 1.00–1.00]). With poor collaterals rated on standard CTA, however, only 69% of patients (negative predictive value, 0.69 [95% CI, 0.61–0.76; range observers, 0.64–0.75]) had poor clinical outcome (lower, *P*<0.05). In other words, with poor collateral status on standard CTA, 31% of cases still had good clinical outcome. All of these cases showed good collaterals on TI-CTA. Good collaterals, however, were a weak univariate predictor for good clinical outcome for both standard CTA and TI-CTA with positive predictive values of 0.64 (95% CI, 0.61–0.76; range observers, 0.59–0.71) and 0.56 (95% CI, 0.50–0.62; range observers, 0.53–0.61), respectively (similar, *P*>0.05). Figure 2 shows an example of poor collateral status on standard CTA and good collateral status on TI-CTA in a patient with good clinical outcome. Figure 3 shows an example of poor collateral status on both CTA techniques in a patient with poor clinical outcome.

Discussion

Although collateral grading on standard CTA previously has been shown to be a strong and independent prognostic

Table 2. Comparison of Collateral Grades Rated on Standard CTA and TI-CTA

Collateral Grades	Four-Point Grading Scale							Dichotomized Collateral Status		
	modified Rankin Scale							Clinical Outcome		
	Death				Normal			Collateral Status	Poor	Good
	6	5	4	3	2	1	0			
Standard CTA										
Absent (0%)	26 (2–5)	0 (0–0)	8 (1–1)	6 (0–2)	0 (0–0)	1 (0–1)	0 (0–0)	Poor	112 (7–22)	51 (4–11)
<50%	23 (1–5)	0 (0–0)	15 (1–3)	34 (2–6)	29 (2–6)	17 (2–3)	4 (0–1)	Good	56 (1–13)	101 (4–21)
≥50%	12 (0–3)	0 (0–0)	24 (1–4)	13 (0–3)	30 (1–6)	27 (1–6)	11 (1–2)			
Normal (100%)	3 (0–1)	0 (0–0)	1 (0–1)	3 (0–1)	13 (1–2)	19 (0–4)	1 (0–1)			
TI-CTA										
Absent (0%)	10 (0–4)	0 (0–0)	0 (0–0)	1 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)	Poor	50 (1–15)	0 (0–0)
<50%	15 (0–4)	0 (0–0)	9 (0–3)	15 (1–3)	0 (0–0)	0 (0–0)	0 (0–0)	Good	118 (6–24)	152 (10–28)
≥50%	30 (3–6)	0 (0–0)	20 (1–5)	20 (1–4)	44 (4–8)	25 (2–5)	9 (0–2)			
Normal (100%)	9 (0–2)	0 (0–0)	19 (0–4)	20 (1–3)	28 (1–5)	39 (3–6)	7 (0–2)			

The right part (dichotomized collateral status) shows the dichotomized scores and outcome of the left part (4-point grading scale). Collateral status: poor=absent or <50%, good ≥50% or normal; clinical outcome: poor=modified Rankin Scale >2, good=modified Rankin Scale ≤2. Data are reported as cumulative number of scores. Data in parentheses are ranges among observers. Four observers scored 40 cases twice, which resulted in 320 scores per CTA technique. TI-CTA indicates timing-invariant computed tomography angiography.

factor for clinical outcome after acute ischemic stroke, surprisingly, patients with lack of collaterals could still have favorable clinical outcome.^{4,6,11} We hypothesized that in these patients collateral vessels should be present but may not always be visualized by standard single time-frame imaging techniques as a result of delayed contrast arrival. We tested this hypothesis in patients with acute stroke with large-vessel occlusion using TI-CTA, a technique based on

multi-time-frame CT data, which is insensitive to delayed contrast arrival. We found that good collateral supply was indeed present in patients with good outcome, even if not visualized by standard CTA. Our study showed that standard single time-frame imaging techniques, such as standard CTA, are not adequately able to assess the presence of sufficient collateral supply: nearly one third of patients with poor collaterals on standard CTA had good clinical outcome.

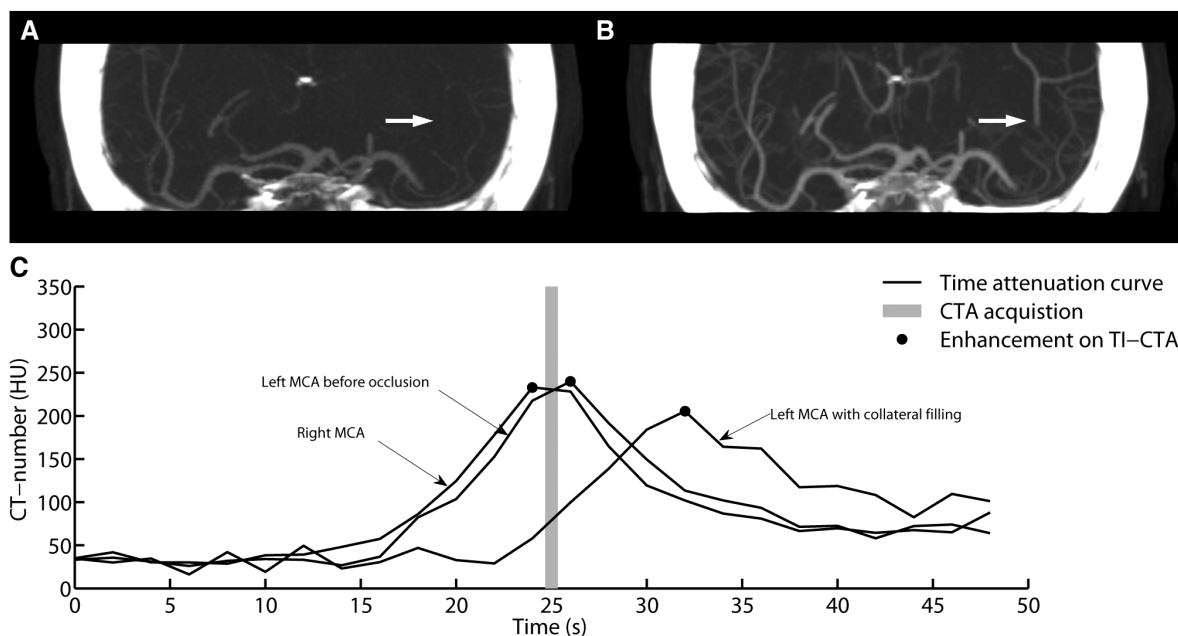


Figure 1. Delayed contrast material arrival in standard computed tomography angiography (CTA) and timing-invariant (TI)-CTA. Example of collateral vessels that are poorly visible on standard CTA (single time frame) because of delayed enhancement, but are well visible on timing-invariant CTA (maximum of multiple time frames) in a patient with acute left middle cerebral artery (MCA) occlusion and good clinical outcome (modified Rankin Scale=1). **A**, Standard CTA shows poor collateral status (arrow). **B**, TI-CTA shows collateral filling in the distal part of the left MCA (arrow). **C**, Time-attenuation curves show that contrast is delayed in the distal part of the left MCA and arrives after standard CTA acquisition (gray bar).

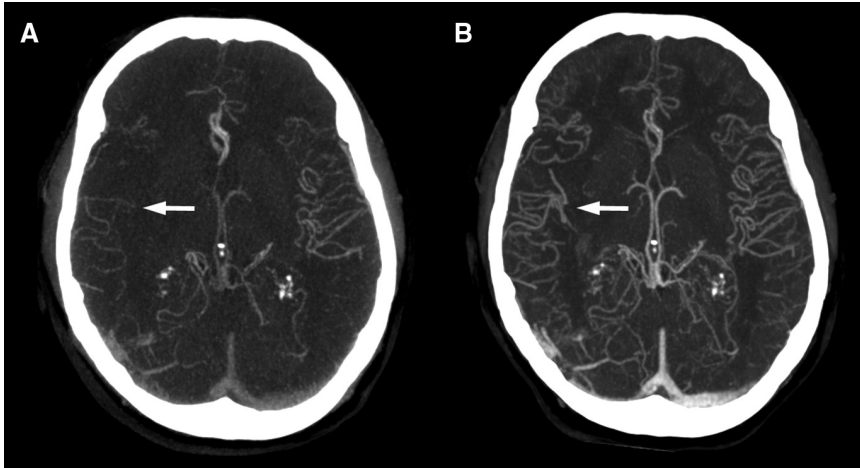


Figure 2. Standard computed tomography angiography (CTA) and timing-invariant (TI)-CTA images of a patient with acute right-sided middle cerebral artery occlusion and good clinical outcome (modified Rankin Scale=2). **A**, Standard CTA was rated with poor collateral status (arrow). **B**, TI-CTA was rated with good collateral status (arrow).

All of these patients, however, showed good collaterals on TI-CTA. We also found, in our small patient group, that all patients rated with poor collateral status on TI-CTA had poor clinical outcome at 3-month follow-up. Future prognostic studies in acute stroke should, therefore, consider multiframe techniques, such as TI-CTA, instead of standard single time-frame imaging, such as standard CTA.

This study intended to explore a potential weakness of current CT imaging techniques for collateral assessment in acute stroke and to provide a potential solution. We could show that TI-CTA was not only significantly superior for detecting collaterals, but also found that poor collateral status on TI-CTA had a high predictive value for poor clinical outcome. These results complement the previous finding that the absence of collaterals on standard CTA is highly predictive for poor clinical outcome.¹² Because the primary purpose of our study was to compare CTA imaging techniques, rather than a prognostic study to determine the absolute predictive values for clinical outcome, potential confounding factors, such as duration of symptoms or treatment, were not specifically assessed in a multivariate analysis. In addition, we did not correlate our findings to other imaging techniques, such as perfusion imaging, which has already been demonstrated to have strong association with favorable outcome.¹⁰ Collateral

vessel imaging may provide a different representation of the same pathological substrate. The predictive values found in this study should not be interpreted as absolute predictive values, but serve as a comparison of CTA techniques and may provide a direction for future research.

Our study compared standard CTA that is acquired during one time frame with TI-CTA, which integrates information over multiple time frames. In general, any technique that integrates information over multiple time frames can be expected to yield superior results to standard single time-frame techniques. The conclusion is likely also valid for contrast-enhanced MRI because it uses the same principle as CTA: acquisition of a single time-frame MR angiography data set is prone to miss collaterals with delayed enhancement, whereas information derived from multiple time frames should be superior.

Many grading scales are available for collateral status assessment in ischemic stroke.⁵ Recently, a systematic review of literature on collateral status assessment described 7 grading scales for CTA alone.⁵ In this study, we used collateral grading to compare CTA techniques and, therefore, chose a commonly used grading scale.^{11,15,16} Observer agreement of collateral grading scales is frequently not assessed or interobserver agreement is determined for 2 observers only.^{3,5,11,15,18,19} We calculated inter- and intraobserver agreement for 4 observers who scored all

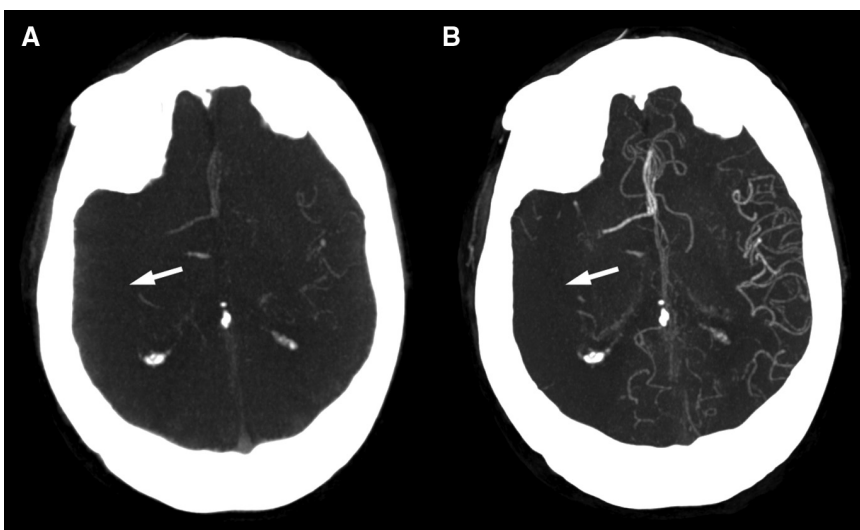


Figure 3. Standard computed tomography angiography (CTA) and timing-invariant (TI)-CTA images of a patient with acute right-sided middle cerebral artery (MCA) occlusion, who died a few hours after admission. **(A)** Standard CTA and **(B)** TI-CTA were both rated with poor collateral status (arrows).

Table 3. Comparison of Odds Ratios of Collateral Status for Outcome Prediction Between Standard CTA and TI-CTA

	Standard CTA	TI-CTA
NPV	0.69 (0.61–0.76)	1.00 (0.91–1.00)
PPV	0.64 (0.56–0.72)	0.56 (0.50–0.62)
Odds ratio	4.0 (2.5–6.3)	63.1 (8.6–463.8)*

Data in parentheses are 95% confidence intervals. NPV indicates negative predictive value; PPV, positive predictive value; and TI-CTA, timing-invariant computed tomography angiography.

*Estimated odds ratio calculated as if one patient rated with poor collateral status had good clinical outcome.

images twice, and found that, in particular, agreement among observers was low for the used 4-point scale. After dichotomizing to good or poor collateral status, in accordance with the literature, overall observer agreement became good. Therefore, we used dichotomized collateral status for the comparison of prognostic values between standard CTA and TI-CTA. Future prognostic studies should determine which grading scale provides the best prognostic value with good observer agreement for reliable use in clinical practice. In addition, future studies should compare the observer agreement of collateral grading to the observer agreement of other imaging techniques, such as perfusion imaging, to determine which imaging features are reliable for use in the general stroke population.

Our study had limitations. First, our study population was large enough to show significant differences between standard CTA and TI-CTA, but the number of patients was too small to establish CIs for outcome prediction using TI-CTA. Therefore, additional studies are required to determine whether the findings can be applied to the general stroke population. For instance, our study population included patients with large-vessel occlusion only and a relatively high proportion of patients received intravenous thrombolysis. In the general stroke population, there may well be patients with good clinical outcome but poor collaterals on TI-CTA. Second, our study population was not large enough to include perfusion imaging in the analysis. As several studies have previously compared perfusion imaging with collateral grading on standard CTA,^{3,4,8} we focused on the comparison of single time-frame CTA with TI-CTA. Future studies should investigate the correlation between collaterals on TI-CTA, CT perfusion imaging, and noncontrast CT imaging. Third, we could not compare our results with digital subtraction angiography, which is the reference standard for visualization of collateral vessels. Because collateral grading is generally used for prognostic research we evaluated collateral grading in relation to clinical outcome. Fourth, we calculated the observer agreement of collateral grading to demonstrate the reliability of our results, but could not assess its effect on outcome prediction in individual patients with stroke. High observer agreement is important for reliable outcome prediction in individual patients, and other imaging techniques may provide higher observer agreement particularly in small-vessel occlusions. Fifth, TI-CTA is currently not commercially available but can easily be implemented in commercial or research workstations.¹³

In conclusion, collateral vessels in patients with acute ischemic stroke may not always be visible on standard CTA because of delayed contrast arrival. TI-CTA displays collateral

vessels that are not visible on standard CTA. Poor collaterals status on TI-CTA has a strong correlation with poor clinical outcome in patients with acute stroke with large-vessel occlusion. Future prognostic studies in acute stroke should consider multiframe techniques, such as TI-CTA, instead of standard single time-frame imaging, such as standard CTA.

Disclosures

None.

References

- Liebeskind DS. Collateral circulation. *Stroke*. 2003;34:2279–2284.
- Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke*. 2006;37:979–985.
- Miteff F, Levi CR, Bateman GA, Spratt N, McElduff P, Parsons MW. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. *Brain*. 2009;132(Pt 8):2231–2238.
- Lima FO, Furie KL, Silva GS, Lev MH, Camargo EC, Singhal AB, et al. The pattern of leptomeningeal collaterals on CT angiography is a strong predictor of long-term functional outcome in stroke patients with large vessel intracranial occlusion. *Stroke*. 2010;41:2316–2322.
- McVerry F, Liebeskind DS, Muir KW. Systematic review of methods for assessing leptomeningeal collateral flow. *AJNR Am J Neuroradiol*. 2012;33:576–582.
- Kucinski T, Koch C, Eckert B, Becker V, Krömer H, Heesen C, et al. Collateral circulation is an independent radiological predictor of outcome after thrombolysis in acute ischaemic stroke. *Neuroradiology*. 2003;45:11–18.
- Bang OY, Saver JL, Buck BH, Alger JR, Starkman S, Ovbiagele B, et al; UCLA Collateral Investigators. Impact of collateral flow on tissue fate in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2008;79:625–629.
- Shuaib A, Butcher K, Mohammad AA, Saqqur M, Liebeskind DS. Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. *Lancet Neurol*. 2011;10:909–921.
- Köhrmann M, Schellinger PD. Acute stroke triage to intravenous thrombolysis and other therapies with advanced CT or MR imaging: pro MR imaging. *Radiology*. 2009;251:627–633.
- Wintermark M, Rowley HA, Lev MH. Acute stroke triage to intravenous thrombolysis and other therapies with advanced CT or MR imaging: pro CT. *Radiology*. 2009;251:619–626.
- Tan IY, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol*. 2009;30:525–531.
- Souza LC, Yoo AJ, Chaudhry ZA, Payabvash S, Kemmling A, Schaefer PW, et al. Malignant CTA collateral profile is highly specific for large admission DWI infarct core and poor outcome in acute stroke. *AJNR Am J Neuroradiol*. 2012;33:1331–1336.
- Smit EJ, Vonken EJ, van der Schaaf IC, Mendrik AM, Dankbaar JW, Horsch AD, et al. Timing-invariant reconstruction for deriving high-quality CT angiographic data from cerebral CT perfusion data. *Radiology*. 2012;263:216–225.
- van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607.
- Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. *Ann Neurol*. 2007;61:533–543.
- Soares BP, Tong E, Hom J, Cheng SC, Bredno J, Boussel L, et al. Reperfusion is a more accurate predictor of follow-up infarct volume than recanalization: a proof of concept using CT in acute ischemic stroke patients. *Stroke*. 2010;41:e34–e40.
- Altman DG. *Practical Statistics for Medical Research*. Boca Raton, FL: Chapman & Hall/CRC; 1991.
- Knauth M, von Kummer R, Jansen O, Hähnel S, Dörfler A, Sartor K. Potential of CT angiography in acute ischemic stroke. *AJNR Am J Neuroradiol*. 1997;18:1001–1010.
- Maas MB, Lev MH, Ay H, Singhal AB, Greer DM, Smith WS, et al. Collateral vessels on CT angiography predict outcome in acute ischemic stroke. *Stroke*. 2009;40:3001–3005.

Timing-Invariant Imaging of Collateral Vessels in Acute Ischemic Stroke

Ewoud J. Smit, Evert-jan Vonken, Tom van Seeters, Jan Willem Dankbaar, Irene C. van der Schaaf, L. Jaap Kappelle, Bram van Ginneken, Birgitta K. Velthuis and Mathias Prokop

Stroke. 2013;44:2194-2199; originally published online June 11, 2013;

doi: 10.1161/STROKEAHA.111.000675

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2013 American Heart Association, Inc. All rights reserved.

Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/44/8/2194>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>