

# Accuracy of CT Angiography for Differentiating Pseudo-Occlusion from True Occlusion or High-Grade Stenosis of the Extracranial ICA in Acute Ischemic Stroke: A Retrospective MR CLEAN Substudy

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## ABSTRACT

**BACKGROUND AND PURPOSE:** The absence of opacification on CTA in the extracranial ICA in acute ischemic stroke may be caused by atherosclerotic occlusion, dissection, or pseudo-occlusion. The latter is explained by sluggish or stagnant flow in a patent artery caused by a distal intracranial occlusion. This study aimed to explore the accuracy of CTA for differentiating pseudo-occlusion from true occlusion of the extracranial ICA.

**MATERIALS AND METHODS:** All patients from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) with an apparent ICA occlusion on CTA and available DSA images were included. Two independent observers classified CTA images as atherosclerotic cause (occlusion/high-grade stenosis), dissection, or suspected pseudo-occlusion. Pseudo-occlusion was suspected if CTA showed a gradual contrast decline located above the level of the carotid bulb, especially in the presence of an occluded intracranial ICA bifurcation (T-occlusion). DSA images, classified into the same 3 categories, were used as the criterion standard.

**RESULTS:** In 108 of 476 patients (23%), CTA showed an apparent extracranial carotid occlusion. DSA was available in 46 of these, showing an atherosclerotic cause in 13 (28%), dissection in 16 (35%), and pseudo-occlusion in 17 (37%). The sensitivity for detecting pseudo-occlusion on CTA was 82% (95% CI, 57–96) for both observers; specificity was 76% (95% CI, 56–90) and 86% (95% CI, 68–96) for observers 1 and 2, respectively. The  $\kappa$  value for interobserver agreement was .77, indicating substantial agreement. T-occlusions were more frequent in pseudo- than true occlusions (82% versus 21%,  $P < .001$ ).

**CONCLUSIONS:** On CTA, extracranial ICA pseudo-occlusions can be differentiated from true carotid occlusions.

**ABBREVIATIONS:** EVT = endovascular treatment; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; T-occlusion = occluded intracranial ICA bifurcation

Endovascular treatment (EVT) has been proved safe and effective in acute ischemic stroke caused by proximal intracranial occlusion if initiated within 6 hours of symptom onset.<sup>1</sup> The duration and success of EVT are influenced by the ease of access to the intracranial vasculature. In approximately 25% of middle ce-

rebral artery strokes, concomitant intracranial artery and ipsilateral extracranial ICA occlusion occurs, known as tandem occlusion.<sup>2</sup> A recent study that included patients with tandem occlusions reported a median procedure time of 88 minutes<sup>3</sup> versus 30 and 43 minutes in 2 randomized trials that excluded patients with tandem occlusions.<sup>4,5</sup>

However, not all tandem occlusions identified on CTA represent true occlusions of the extracranial ICA. True occlusion of the extracranial ICA is caused by atherosclerosis or dissection of the vessel wall. So-called pseudo-occlusions mimic occlusion on CTA in the acute phase of ischemic stroke, while the artery is patent on DSA during EVT.<sup>6</sup> The underlying mechanism of pseudo-occlusion of the extracranial ICA is sluggish or absent contrast flow caused by a distal occlusion of the intracranial vasculature. In these cases, CTA acquisition “outruns” the arrival of contrast material.<sup>6</sup> Contrast flow can also be impeded by an extracranial ICA stenosis located proximal to the level of apparent occlusion.<sup>7,8</sup>

The term “pseudo-occlusion” has also been used for chronic high-grade stenosis of the ICA with minimal distal flow.<sup>9,10</sup> This

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phenomenon is markedly different from pseudo-occlusion as an artifact of single-phase CTA, in which there is, in fact, no practically relevant carotid obstruction at all.<sup>6</sup> To our knowledge, 6 previous studies have described a total of 48 patients with pseudo-occlusions of the extracranial ICA in acute ischemic stroke. They reported that pseudo-occlusion occurs in 6%–15% of patients with acute ischemic stroke.<sup>6,11–15</sup> It was stated that pseudo-occlusion cannot be discriminated from true occlusion on CTA.<sup>13</sup> However, certain imaging characteristics may suggest pseudo-occlusion on CTA, such as an ipsilateral occluded intracranial ICA bifurcation (carotid T-occlusion) and good contrast filling of the carotid bulb followed by a gradual contrast decay in the ICA.

In the clinical setting, discrimination of pseudo-occlusion from true occlusion would improve estimation of the procedure time and intervention success by the operator. In case patients arrive late in their treatment window, time to overcome an extracranial ICA occlusion during treatment could be deemed too long for EVT to be beneficial to the patient. This could cause patients with unrecognized pseudo-occlusion on CTA to miss out on endovascular treatment that would have benefited them. Furthermore, better pseudo-occlusion recognition would enable more adequate planning and use of EVT materials such as guiding sheaths, percutaneous transluminal angioplasty balloons, and distal access catheters.

The aim of this retrospective study was to determine whether ICA pseudo-occlusion could be differentiated from atherosclerotic occlusion and dissection on CTA in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) dataset.

## MATERIALS AND METHODS

This study was a blinded retrospective analysis of the data from the randomized controlled MR CLEAN trial. MR CLEAN included 500 patients with acute ischemic stroke caused by occlusion of an intracranial artery of the anterior circulation, with an NIHSS deficit of  $\geq 2$  points, from 16 centers in the Netherlands.<sup>1,16</sup> After arterial occlusion was demonstrated on vessel imaging, patients were randomized for usual care only or usual care with the addition of EVT. Treatment was initiated within  $\leq 6$  hours from symptom onset. All imaging data were collected as part of MR CLEAN before the start of the current study.

### CTA Analysis

Three raters (O.A.B., J.B., M.K.) assessed all baseline CTA scans for the presence of apparent ipsilateral occlusion of the extracranial ICA, without knowledge of angiographic findings. Images were reviewed in the axial, coronal, and sagittal planes. Only CTA images were assessed; noncontrast CT was not evaluated in this study. Minimum requirements for CTA scans in MR CLEAN were a slice thickness of  $\leq 5$  mm, the presence of contrast in the intracranial vasculature, and depiction of at least the carotid bulb up to the circle of Willis. Median slice thickness was 0.9 mm (range, 0.5–2.0 mm), median scanner kiloelectron volt was 120 (range, 80–120), and the median number of scanner detector rows was 128 (range, 52–320). The total amount of injected contrast varied from 50 to 100 mL (median, 70 mL) with a median injection speed of 5.0 mL/s (range, 3.5–6.0 mL/s). Detailed CTA

scan protocols per participating center can be found in the Online Table. “Apparent occlusion” was defined as the absence of contrast enhancement in the extracranial ICA ipsilateral to the intracranial occlusion.

Two experienced interventional and diagnostic neuroradiologists (B.J.E., G.L.à.N.), who were also blinded to the angiographic findings, separately reviewed scans with apparent occlusions. They categorized all cases into 1 of 3 underlying causes: atherosclerotic occlusion, dissection, or suspected pseudo-occlusion.

**Atherosclerotic Occlusion.** If an apparent occlusion was located at the level of the carotid bulb, was sharply demarcated, and/or showed a clear presence of calcifications or plaque, this apparent occlusion was considered as most likely caused by atherosclerosis and classified as such.<sup>17</sup>

**Dissection.** If an apparent ICA occlusion was located above the level of the carotid bulb, without plaque or calcifications at the carotid bulb, and the occlusion was sharply demarcated on CTA, the occlusion was classified as most likely caused by a dissection. Furthermore, young patient age and widening of the ICA under the skull base could suggest the presence of a dissection.

**Suspected Pseudo-Occlusion.** Pseudo-occlusion was suspected if CTA showed a gradual contrast decay in the ICA above the level of the carotid bulb, in the absence of plaque or calcifications around the carotid bulb, and in the presence of a carotid-T or large M1-occlusion.

**Carotid T-Occlusion.** T-occlusion presence was determined to compare the prevalence in pseudo- versus true occlusion cases. If a carotid top or terminus was not filled with contrast on CTA, it was classified as a carotid T-occlusion. All cases with apparent extracranial ICA occlusion on CTA and available DSA imaging were reviewed.

### DSA Analysis

DSA images of cases with apparent occlusion on CTA were collected. To prevent recall bias, we gave the DSA images new patient identification numbers and rated them 6 months later than the CTAs. One rater (B.J.E.) reviewed all DSA images, checking for atherosclerotic occlusion or dissection. Contrast was injected in the common carotid artery and directly into the ICA in all cases. Dissection was confirmed in case of an irregular vessel wall (at the beginning of the procedure, before vasospasm could have arisen) with a tapering aspect of contrast leading up to an occlusion above the level of the carotid bulb that could not be passed with the guidewire or catheter. Atherosclerotic occlusion was confirmed in case of an abrupt, blunt contrast cutoff at the level of (or slightly above) the carotid bulb, with evidence of circumferential vessel wall involvement that could not be passed easily with a guidewire or catheter. If, despite an apparent occlusion on CTA, DSA showed only high-grade (90%–99%) atherosclerotic stenosis, the underlying reason for the apparent occlusion was deemed an atherosclerotic cause because the practical implications of atherosclerotic high-grade stenosis for EVT are similar to those of atherosclerotic occlusion. If DSA showed no occlusion, a low-grade stenosis, or an apparent occlusion that could be passed unhin-

dered with a guidewire or catheter, the apparent ICA occlusion on CTA was deemed a pseudo-occlusion.

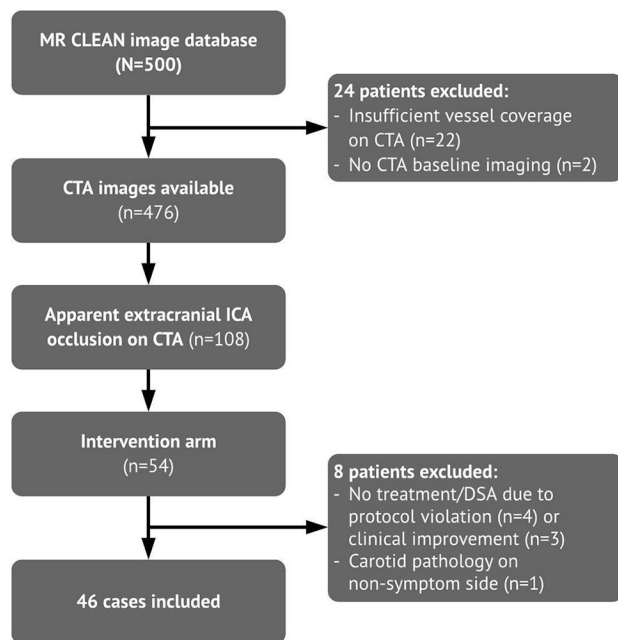
### Statistical Analysis

SPSS, Version 24 (IBM, Armonk, New York) and R, Version 3.2 (<http://www.r-project.org>) were used for the statistical analysis. Sensitivity, specificity, and positive and negative predictive values were calculated for detection of pseudo-occlusions, atherosclerotic occlusions, and dissections on CTA. DSA images were used as the criterion standard. Ninety-five percent confidence intervals were calculated using the Clopper-Pearson method for sensitivity and specificity and the asymptotic/adjusted logit intervals for predictive values. Interobserver variability of CTA-based pseudo-occlusion recognition was tested with the  $\kappa$  statistic and the Krippendorff  $\alpha$ , to control for the factor of random agreement. The Fisher exact test was used to calculate the statistical significance of the difference in T-occlusion rates in subgroups with and without pseudo-occlusions.

## RESULTS

### Patients

Figure 1 depicts patient inclusion. CTA images were available for 476 patients. The intervention arm of MR CLEAN com-



**FIG 1.** Patient-selection flow chart. *n* indicates number of cases.

prised 233 patients, of whom 216 had DSA images available for analysis.<sup>1</sup> Apparent extracranial ICA occlusion on CTA, regardless of the cause, was found in 108 patients. Forty-six of them had DSA images available and thus were included in the current study.

### CTA Analysis

Pseudo-occlusion was identified in 14/17 (82%) cases by both observers (Table 1). For observer 1, the sensitivity and specificity of CTA for identifying pseudo-occlusion were 82% (95% CI, 57%–96%) and 76% (95% CI, 56%–90%). For observer 2, these numbers were 82% (95% CI, 57%–96%) and 86% (95% CI, 68%–96%), respectively (Table 2). The  $\kappa$  value for interobserver agreement on pseudo-occlusions was .77 (95% CI, 0.56–0.97). The Krippendorff  $\alpha$  for interobserver agreement on pseudo-occlusions, atherosclerotic occlusions, and dissections was .77 (95% CI, .61–.90).

Dissection and pseudo-occlusion were most frequently not distinguished correctly from each other on CTA. For observers 1 and 2, respectively, 29% (6/21) and 22% (4/18) of suspected pseudo-occlusions turned out to be dissections. Conversely, 23% (3/13) and 20% (3/15) of CTA-diagnosed dissections turned out to be pseudo-occlusions (Table 1). Atherosclerotic pathologies were well-recognized, with a sensitivity of 92% (95% CI, 64%–100%) and 100% (95% CI, 75%–100%) for observers 1 and 2, respectively (Table 2).

Figure 2 shows examples of cases with matching classification of atherosclerotic occlusion, dissection, and pseudo-occlusion, respectively, on CTA and DSA. Figure 3 depicts examples of the most common misinterpretations: cases in which CTA suggested pseudo-occlusion, whereas DSA showed dissection, or CTA suggested dissection, whereas DSA showed pseudo-occlusion. An apparent occlusion located above the level of the carotid bulb, in the absence of extensive amounts of calcifications or plaque, is present in both dissections and pseudo-occlusions, making distinction of the diagnoses more difficult. However, dissections often show a less gradual decline of contrast in the ICA, more tapering of the vessel, and sometimes widening of the ICA contour under the skull base. Furthermore, the presence of carotid T-occlusion may contribute to identification of the right diagnosis.

### T-Occlusions

T-occlusions were present in 14 of 17 (82%) pseudo-occlusions versus 2 of 13 (15%) atherosclerotic cases and 4 of 16 (25%) dis-

**Table 1: Outcome of diagnoses on CTA for observers 1 and 2 versus final diagnosis on DSA**

CTA	DSA (No.)				Total No.
	Atherosclerotic Cause		Pseudo-Occlusion	Dissection	
	Occlusion	High-Grade Stenosis			
Observer 1					
Atherosclerotic occlusion	10	2	0	0	12
Pseudo-occlusion	0	1	14	6	21
Dissection	0	0	3	10	13
Total		13	17	16	46
Observer 2					
Atherosclerotic occlusion	10	3	0	0	13
Pseudo-occlusion	0	0	14	4	18
Dissection	0	0	3	12	15
Total		13	17	16	46

sections ( $P < .001$ ). Of all carotid T-occlusions, 70% (14/20) showed concomitant pseudo-occlusion.

T-occlusions were correctly recognized on CTA in all cases except 1. In that case, CTA showed a floating thrombus in the carotid siphon, which had possibly embolized into the carotid-T by the time DSA images were acquired. Two pseudo-occlusion cases did not show a carotid T-occlusion on DSA. In one, carotid T-occlusion was seen on CTA, and DSA showed an M1 occlusion.

The other case showed M1 and A1 occlusion on CTA, and M2 occlusion on DSA. Migration of the thrombus, possibly under the influence of IV tPA, could explain these cases.

### DSA Analysis

The prevalence of pseudo-occlusions in all patients in MR CLEAN with DSA imaging available was 8% (17 of 216 patients). Of 46 included cases with apparent occlusion on CTA, DSA showed atherosclerotic occlusion or high-grade stenosis in 13 cases (28%, of which 3 [7% in total] were high-grade stenoses) and dissection in 16 (35%). In 17 patients, no carotid occlusion or high-grade stenosis was found; therefore, 37% of apparent extracranial ICA occlusions on CTA were pseudo-occlusions (Table 1). These cases usually showed delayed or absent contrast filling of the vessel distal to the carotid bulb with an indistinct or oscillating contrast border on DSA.

**Table 2: Diagnostic accuracy measures for pseudo-occlusion recognition on CTA compared with DSA for observers 1 and 2**

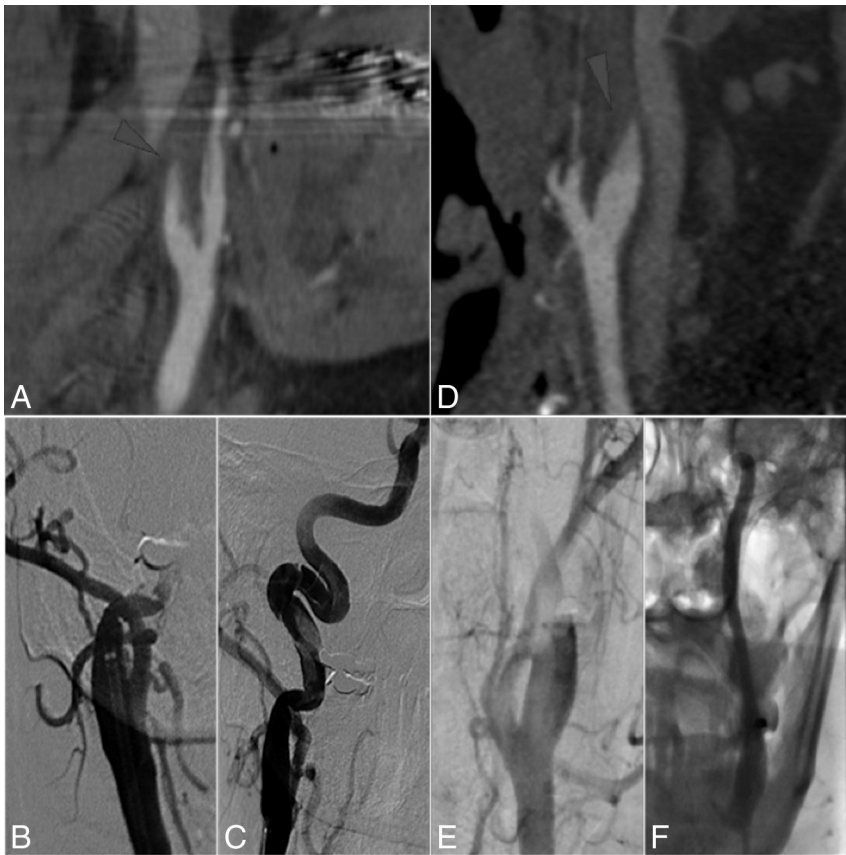
	Pseudo-Occlusion	Atherosclerotic Cause	Dissection
Observer 1			
Sensitivity (95% CI)	82 (57–96)	92 (64–100)	63 (35–85)
Specificity (95% CI)	76 (56–90)	100 (89–100)	90 (73–98)
PPV	67 (50–80)	100 (76–100)	77 (52–92)
NPV	88 (72–95)	97 (83–100)	82 (70–90)
Observer 2			
Sensitivity (95% CI)	82 (57–96)	100 (75–100)	75 (47–93)
Specificity (95% CI)	86 (68–96)	100 (89–100)	90 (73–98)
PPV	78 (58–90)	100 (77–100)	80 (57–92)
NPV	89 (75–95)	100 (90–100)	87 (74–94)

**Note:**—PPV indicates positive predictive value; NPV, negative predictive value.



**FIG 2.** Examples of carotid pathologies on CTA (upper row) and corresponding DSA (lower row). *A*, Atherosclerotic occlusion of the right ICA in a 79-year-old man. CTA shows extensive calcifications in the carotid bulb with a sharp contrast cutoff at the level of the bifurcation. *B*, DSA of the patient in *A* shows a sharp delineation of contrast at the level of the carotid bulb, and “shouldering,” a convex aspect of the contrast cutoff proximal to the occlusion. *C*, Dissection of the left ICA in a 44-year-old man. CTA shows a sharp, diagonal contrast cutoff above the level of the carotid bifurcation. *D*, DSA of the patient in *C* shows a gradual decline in vessel diameter also known as “tapering,” with a sharp contrast cutoff and irregular vessel wall. It was possible to pass the apparent occlusion with a guidewire, but not with a catheter. *E*, Pseudo-occlusion of the left ICA in a 51-year-old woman. CTA shows a gradual contrast decrease in the left ICA above the level of the carotid bulb (arrowhead) compared with a normal contrast density on the contralateral side, and an ipsilateral carotid T-occlusion. *F*, DSA of the patient in *E* shows a blurred contrast delineation above the level of the carotid bulb. A back-and-forth moving, “oscillating,” contrast border was seen. The apparent occlusion could easily be passed with a guidewire or catheter.





**FIG 3.** Examples of suspected dissection or pseudo-occlusion on CTA with a noncorresponding cause of apparent occlusion found on DSA. *A*, Dissection of the right ICA in a 65-year-old woman. CTA shows a blurred contrast cutoff above the level of the carotid bulb, suggesting pseudo-occlusion, without T-occlusion present. *B*, DSA of the patient in *A* shows major vessel wall irregularities and the impossibility of passing the occlusion with a catheter (*C*), indicating the presence of a dissection rather than pseudo-occlusion. *D*, Pseudo-occlusion of the left ICA in a 63-year-old man. CTA shows a sharp, diagonal contrast cutoff above the level of the carotid bifurcation, suggesting dissection, with T-occlusion present. *E*, DSA of patient in *D* shows a blurred contrast cutoff slowly moving upward and finally a patent ICA with intracranial carotid T-occlusion present (*F*), indicating pseudo-occlusion.

## DISCUSSION

The main finding of this study is that on CTA made in preparation for EVT, extracranial ICA pseudo-occlusion can be well-differentiated from atherosclerotic occlusion and reasonably well from carotid dissection. Additionally, in about one-third of patients with an apparent extracranial internal carotid occlusion on CTA in acute ischemic stroke, the artery is, in fact, patent on DSA during EVT. Finally, the prevalence of a carotid T-occlusion in patients with carotid pseudo-occlusion was high.

To our knowledge, there are no reports on the diagnostic accuracy of CTA on the etiology of apparent tandem lesions in acute stroke with proximal large-vessel occlusions. Previous research<sup>6,11-13</sup> reported the prevalence of pseudo-occlusions to be 6%–14%. However, these studies included cases in which high-grade extracranial ICA stenosis impeded contrast flow, and they considered them pseudo-occlusions as well.<sup>6,11-13</sup> Furthermore, previous studies found a high prevalence of carotid T-occlusions in pseudo-occlusion cases.<sup>11-13</sup>

We have introduced a CTA-based diagnostic approach that could differentiate pseudo-occlusion from true occlusion or high-grade atherosclerotic stenosis with high sensitivity and specificity. Imaging

characteristics suggestive of pseudo-occlusions were the presence of a carotid T-occlusion and a gradual contrast decline located above the level of the carotid bulb in the absence of atherosclerotic plaque or calcifications. The prevalence of pseudo-occlusions in MR CLEAN was in line with the findings in the studies above. Likewise, in our study, in most pseudo-occlusions, a carotid T-occlusion was present. In a minority of our patients, DSA showed high-grade atherosclerotic stenosis proximal to a gradual contrast decay in the ICA, similar to cases described before.<sup>6,11,12</sup> However, because high-grade atherosclerotic stenoses usually require a similar approach to atherosclerotic occlusions during EVT, in acute ischemic stroke, one could argue that these cases should be classified as atherosclerotic occlusions.

Several limitations to this study should be noted. First, we have no data on occlusion patterns and characteristics of patients who were not randomized. A selection bias might have occurred because local investigators might have opted not to include patients with extracranial ICA occlusions. Although this might have influenced the prevalence of apparent tandem occlusions in the study sample, it would not have affected the reported sensitivity and specificity measures. Besides, compared with other randomized controlled trials on EVT,<sup>4,5,18,19</sup> the number of patients with tandem occlusions included in MR CLEAN is relatively high.

Second, the initial selection of apparent ICA occlusions from the dataset was made by 3 researchers who were, though experienced, not certified radiologists. Carotid occlusions might have been missed. However, again this approach would not have affected the sensitivity and specificity numbers because apparent occlusion causes were determined by experienced interventional neuroradiologists.

Finally, this study showed the distinction between carotid dissections and pseudo-occlusions to be the most difficult to make. Both showed a contrast decline above the level of the carotid bifurcation in the absence of carotid plaque or calcifications. A possible discriminating characteristic is a sharp contrast cutoff in dissections versus a gradual contrast decline in pseudo-occlusions. This gradual contrast decline was previously described as the “midcervical flame-shaped extracranial ICA sign.”<sup>14</sup> However, contrast border appearance can be affected by bolus timing, scan acquisition, and low-grade proximal ICA stenosis. These factors may have influenced observers’ decisions on apparent occlusion classification and thereby sensitivity and specificity measures.

CTA scan timing may influence the occurrence and recognition of carotid pseudo-occlusion. Late-phase CTA scans may show a patent ICA by allowing slow contrast flow in the ICA to reach the actual intracranial occlusion. Determining optimal scanning conditions for pseudo-occlusion differentiation on single-phase CTA would require further research. Acquiring a second, late-phase scan after the initial CTA may be of additional value.

Other imaging modalities used in the acute setting of stroke may improve recognition of pseudo-occlusions. For example, 4D-CTA was recently shown to successfully identify slow flow causing pseudo-occlusions.<sup>13,20,21</sup>

## CONCLUSIONS

Extracranial ICA pseudo-occlusion can be well-differentiated from atherosclerotic occlusion and reasonably well from carotid dissection on CTA. The prevalence of pseudo-occlusion in the MR CLEAN trial was high. Several occlusion characteristics can raise suspicion for pseudo-occlusion on CTA, most importantly concomitant carotid T-occlusion.

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