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EDITORIAL

Diagnosing carotid near-occlusion is a difficult task—but it might get easier

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Diagnosing carotid near-occlusion 1 is a difficult task – but it might get easier

In this issue, Manrique-Zegarra and co-workers present their comparison of CTA and DSA when diagnosing carotid near-occlusion [1]. As Manrique-Zegarra describes, this is a challenging diagnosis, but a relevant topic as separation of near-occlusion (especially those without full collapse, Fig. 1) and conventional stenosis affects management [1, 2]. Indeed, 30% of ≥ 50% are near-occlusions but they are often underdiagnosed [3–5]. Whether near-occlusion with full collapse (Fig. 2) should be identified and treated separately from without full collapse is debatable [6–8]. In this editorial, we will put these findings in a larger perspective, highlighting difficulties in image assessments and diameter measurements, and present a possible solution for future studies: postoperative angiography as a new reference test.

Current reference method—feature interpretation

Feature interpretation is arguably the current reference method as it was used to diagnose near-occlusion in the major RCTs [9] and in relevant prognostic studies [6], albeit Manrique-Zegarra did not use this approach [1]. Feature interpretation is performed by assessing various available features to determine if the distal ICA is small and if more proximal stenosis is the cause of the distal ICA collapse. The main difficulty is differentiating near-occlusion without full collapse from other causes of subtle distal ICA collapse, such as distal disease and anatomical variation (caused by an asymmetric circle of Willis, seen in 8% of people without steno-occlusive disease, Fig. 3) [10]. Feature interpretation has many advantages, such as allowing the assessor to use all available information in the exam. In our previous CTA analyses, we have focused on visual assessment of stenosis severity, distal ICA diameter, ICA side-to-side comparison, ICA-ECA comparison, and assessed Circle of Willis configuration (for the possibility of anatomical variants) [3–6, 8, 10–13]. Manrique-Zegarra assessed a limited version of this approach by visually assessing two features and using dichotomization [1]. We have previously assessed features on a spectrum (not dichotomized): A clearly "positive" or "negative" feature is weighted more in the analysis than barely "positive" or "negative" features. Furthermore, with the interpretation approach, one can work around non-existent features (such as severely calcified stenosis and contralateral occlusion) and avoid being fooled by misleading features (such as more severe contralateral near-occlusion and CCA stenosis causing both ICA and ECA collapse). Most features are similarly assessable in all modalities, but there are relevant differences: contrast propagation is easier with conventional angiography, and the side-to-side difference is easier with CTA and MRA.

However, while collaborating experts can achieve good inter-rater reliability for feature interpretation [11], the method requires experience and is reasonably not easily transferable between observers and centers. While many can learn and apply the method, it is questionable that it can be reliably applied outside centers with sufficiently dedicated radiologists, limiting the feasibility of routine practice. Also, it is difficult to know if one's feature interpretation matches what was done in the RCTs as the feature interpretation was done without clear criteria or thresholds. Given this lack of

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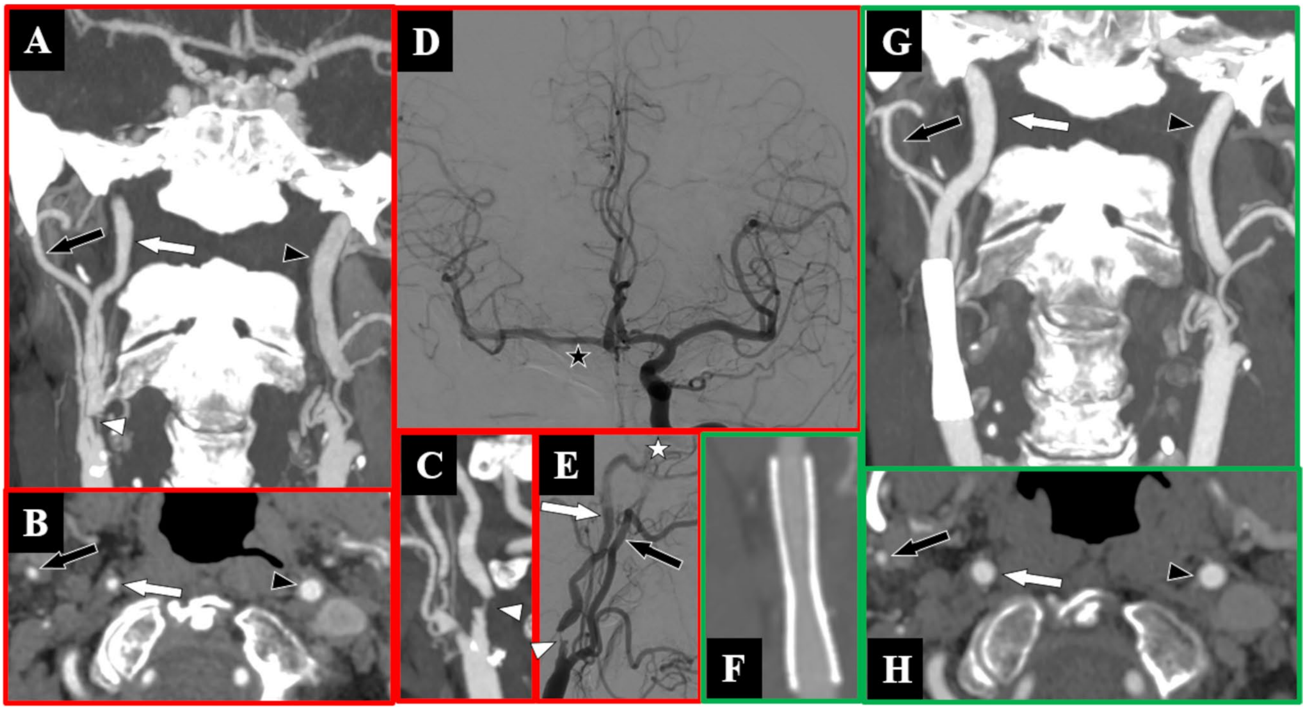

Fig. 1 A case with right-sided near-occlusion without full collapse. A–E (red frame) are before carotid stenting and F–H (green frame) are after carotid stenting, with a clear increase in ipsilateral distal ICA size. **A–C** Preoperative CTA. Beyond severe stenosis, the right distal ICA is smaller than the left ICA and similar to the ECA. However, distal ICA is otherwise a well-seen lumen. **D–E** Pre-stenting series. D shows spontaneous cross-filling collaterals from the contralateral injection, via anterior communicating artery (black star). E shows delayed contrast arrival in ICA (white star) compared to ECA and ICA and ECA of similar size. **F–H** Postoperative CTA. **F** Coronal thin slices, showing stent patency. **G** Coronal thick slices, both distal ICAs of similar size, larger than ECA. **H** Axial thin slices above the stent. White arrow: ipsilateral distal ICA. Black arrow: ipsilateral ECA. White arrowhead: stenosis. Black arrowhead: contralateral distal ICA

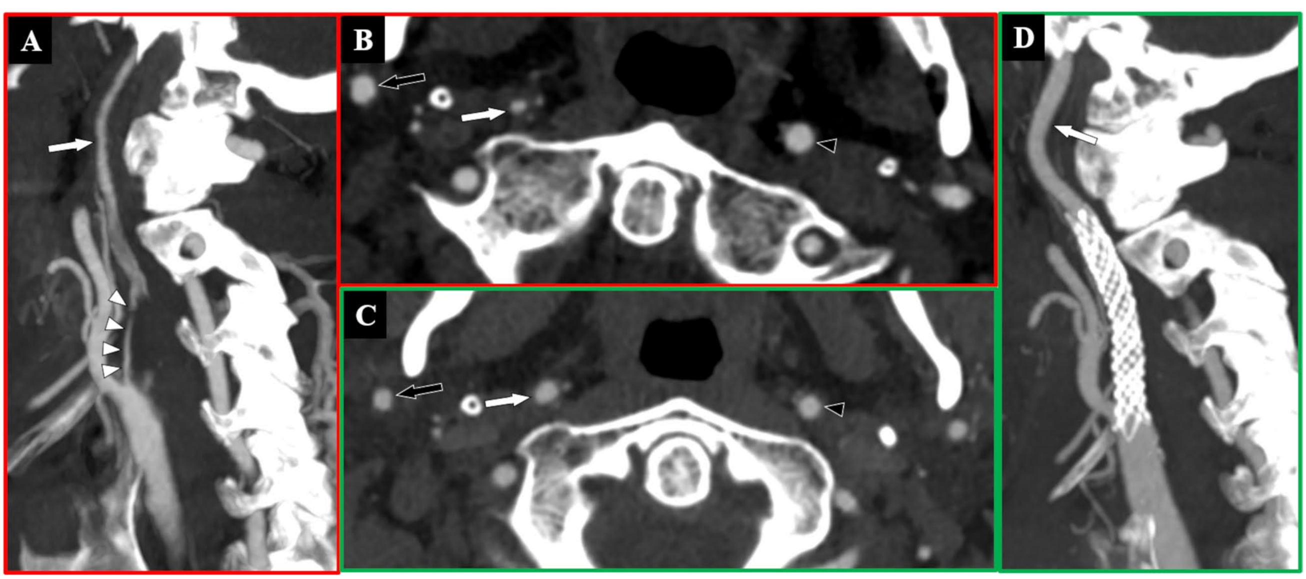

Fig. 2 A case with right-sided near-occlusion with full collapse. A–B (red frame) are of the distal ICA above the stenosis before carotid stenting and C–D (green frame) are also distal after carotid stenting, with a clear increase in ipsilateral distal ICA size. **A**, **B** Preoperative CTA. Beyond severe stenosis, the right distal ICA is smaller than the left ICA and similar to the ECA. The distal ICA is very small. **C**, **D** Postoperative CTA. The stent is clearly visible and patent. Both ICAs of similar size, larger than ECA. White arrow: ipsilateral distal ICA. Black arrow: ipsilateral ECA. White arrowhead: stenosis. Black arrowhead: contralateral distal ICA

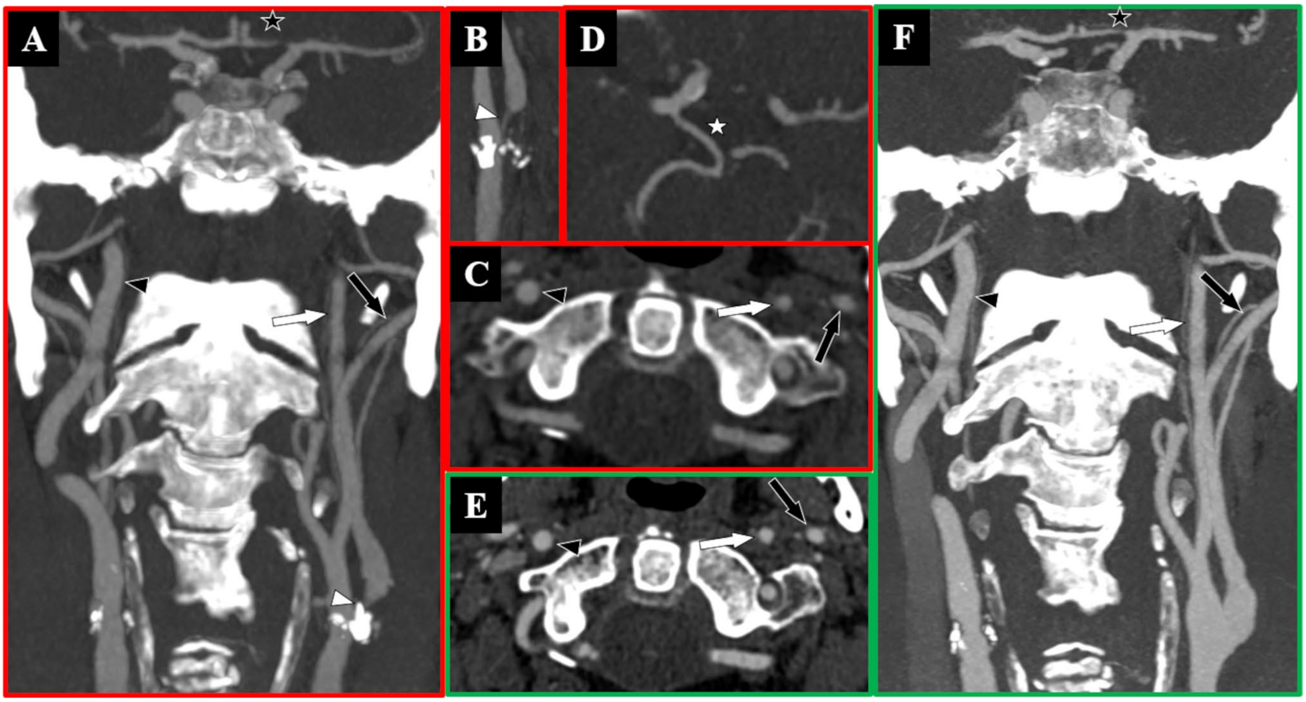

Fig. 3 A case with left-sided small distal ICA due to anatomical variation (a near-occlusion mimic). A–D (red frame) are before carotid endarterectomy and E–F (green frame) are after carotid endarterectomy, without a clear increase in ipsilateral distal ICA size. **A–D** Preoperative CTA. Beyond severe stenosis, the left distal ICA is smaller than the right ICA and similar to the ECA. Distal ICA is normal-appearing. **E**, **F** Postoperative CTA. Stenosis clearly removed and similar appearance in distal ICA, no clear increase. No additional stenosis could be noted. An anatomical variant, with left-sided A1 hypoplasia (black star) and right-sided fetal posterior communicating artery (white star)—both causing the right ICA to supply more brain tissue than the left ICA (explaining the difference in size). Two of two study observers mistook this case for a near-occlusion when assessed without access to the postoperative scan. White arrow: ipsilateral distal ICA. Black arrow: ipsilateral ECA. White arrowhead: stenosis. Black arrowhead: contralateral distal ICA

feasibility in routine practice, the use of feature interpretation for near-occlusion was arguably an error in the design of the large RCTs [9]. However, at the time of the RCTs, no relevant difference in outcome between near-occlusion and high-grade conventional stenosis was expected. Hence, the need for a feasible method to reliably diagnose near-occlusion in routine practice was not anticipated.

Current and past diagnostic studies

Four features to assess near-occlusion on conventional angiography (delayed contrast arrival, evidence of collaterals, ICA ratio, and ECA ratio) have been presented [9]. The suggested features on DSA have only been compared with feature interpretation in 32 of the cases from large RCTs, and having two or more criteria was 91% sensitive and 94% specific [9]. Manrique-Zegarra used this (≥ 2 DSA criteria) to define near-occlusion in their analysis [1]. With no clear thresholds, these RCT criteria are somewhat difficult to apply in routine practice. Also, inter-rater reliability was only good for some features in the RCTs [9].

Manrique-Zegarra assessed the four Bartlett criteria for CTA, which were based on the bilateral assessment of 134 cases with known or suspected carotid disease [1, 14]. Using feature interpretation as a reference, Bartlett found that combining distal ICA diameter ≤ 3.5 mm and ICA ratio ≤ 0.87 was 92% sensitive and 96% specific for near-occlusion [14]. The accuracy of the Bartlett criteria was seemingly validated when we assessed 358 cases with ≥ 50% stenosis: 4/4 criteria were 93% sensitive and 97% specific, and ≥ 3 criteria were 100% sensitive and 87% specific for near-occlusion, with feature interpretation as reference [4]. However, Manrique-Zegarra found that ≥ 3 features only had 75–82% sensitivity but similar specificity (87–90%) compared to near-occlusion defined as ≥ 2 DSA criteria [1]. Their two visual criteria seemed to have an even worse agreement with their near-occlusion definition [1]. The diameter assessments also had quite limited inter-rater reproducibility [1]. It should be highlighted that Manrique-Zegarra visually assessed and measured their CTAs blinded to the reference test [1]. In previous studies, interpretation and diameter measurements were done by the same observers on the same scan (not blinded) [4, 14]. Diameter assessments have many pitfalls, including varying artery size (even when well above stenosis), oblique sections, and fuzzy edges. Hence, the worse diagnostic performance and limited reliability of diameter-based assessment by Manrique-Zegarra are more likely to reflect routine practice than previous unblinded measurements. Also, for the visual CTA assessment, Manrique-Zegarra made no direct comparison of the 2 CTA makers and their DSA equivalent (only with the definition of near-occlusion as ≥ 2 of 4 DSA criteria). Hence, it is unclear if CTA differed from DSA due to actual differences between the modalities or the differences in approach. CTA is preferable to DSA for many reasons (including stroke risk, cost, and availability). However, diagnosing near-occlusion with CTA remains difficult: interpretation is arguably too difficult to be feasible, and Manrique-Zegarra shows that dichotomized visual assessment and diameter measurement have limited reproducibility and accuracy.

Commonly used ultrasound measurements cannot be used to diagnose near-occlusion when compared with feature interpretation [5]. In proof-of-concept studies, the possible usefulness of distal velocity on ultrasound and ICA flow on phase-contrast MRI has been suggested when compared with feature interpretation [12, 13]. Further research into these alternatives to anatomical methods should be pursued.

Issues with using feature interpretation as reference method in diagnostic studies

When comparing studies that have used feature interpretation, the possibility of differences in image interpretation makes differences in findings difficult to interpret. Example: A study of 635 northern European patients with ≥ 50% stenosis on CTA found that 10% had small distal ICA caused by anatomy [10], while a study of 198 Taiwanese patients with ≥ 70% stenosis on conventional angiography found 0% [15]. Was this difference in findings caused by differences in image interpretation, modality, or populations? In the current context—if two sets of criteria are created and do not align, why should one be trusted over the other?

Also, it seems reasonable to think of near-occlusion as an entity (as an idea): stenosis causing distal ICA collapse. The use of feature interpretation when assessing angiography is to strive toward this entity but does not define the entity. However, feature interpretation assessments are reasonably occasionally wrong compared to the entity (example below). Also, approximately 5% of cases with ≥ 50% have such divergent features that the cause of small distal ICA was unclear [10]. Such cases have been presumed to be conventional stenosis in prognostic studies [6, 9]. Some of these were the near-occlusion entity, some not, but no current method can tell the difference.

Postoperative artery diameter increase

At least 20 studies have anecdotally shown distal ICA diameter increase after stenosis removal in near-occlusion [16–37], i.e., the principle of causality between stenosis and distal ICA diameter is proven for near-occlusion. In cases with an anatomical cause of small distal ICA (asymmetric circle of Willis, the stenosis is just coinciding), stenosis removal should not result in a distal ICA diameter increase. It seems reasonable to diagnose near-occlusion as an entity by assessing distal ICA diameter with and without the stenosis. Occasionally, this is possible by comparison with a previous exam without stenosis (or at least without as severe stenosis). For many, a postoperative exam will be required. As postoperative exams can never be used to guide clinical decisions, the role would rather be to use the method as the reference in diagnostic studies.

We have started to use the postoperative method in a study approved by the regional ethics board in Umeå (all participants provided informed consent). Main results, assessing preoperative findings with postoperative-based diagnosis, will be presented when available. Initial experiences are the following:

- Most cases behaved as expected based on preoperative feature interpretation: in cases with small distal ICA diameter beyond the operated stenosis, the distal ICA diameter increased in most presumed near-occlusions (Figs. 1 and 2), not in most cases caused by anatomical variance, nor in most cases of conventional stenosis. However, feature interpretation was occasionally wrong (Fig. 3).
- In cases with two divergent features for a certain diagnosis, then distal ICA either increased or stayed the same. Thus, these could be diagnosed as near-occlusion or not for the first time.
- Occasionally, distal ICA diameter measurements slightly changed bilaterally in cases without visible diameter change on either side. Presumably caused by scan-re-scan differences, not the CEA. Thus, when assessing ipsilateral ICA diameter change, it should reasonably be controlled for change in contralateral ICA.

Future directions

Clinical studies assessing the outcome of conservative management for symptomatic near-occlusion without full collapse are warranted, either as single-arm or non-inferiority compared to CEA/CAS. For relevance, these studies must use a prespecified and reproducible method to diagnose near-occlusion without full collapses, such as a single threshold on a single modality. There is currently no such diagnostic method. A specific threshold for an artery size metric (on CTA), velocity metric (on ultrasound), or flow metric (on phase-contrast MRI) should be sought in diagnostic studies, and postoperative angiography could serve as the reference method in those studies. However, it should be expected that a mixed approach will be needed. Feature interpretation will likely be needed as a reference in clear cases of near-occlusion as these should not undergo surgery. The use of postoperative angiography will be limited to when surgery is performed. In cases where the near-occlusion diagnosis is unclear, postoperative angiography will be needed the most, and such cases are already likely to undergo surgery as the near-occlusion diagnosis should be sufficiently certain to withhold surgery.

Our suggestion is to move closer to the near-occlusion entity, beyond feature interpretation, when creating new diagnostic criteria. However, it is unclear if the low risk of recurrent stroke known from studies using feature interpretation will be applicable to all near-occlusion entity cases [6, 9]. The mechanism explaining why near-occlusion protects from future stroke compared to having conventional stenosis is not well established [2]. Even if this mechanism is not fully understood, it is presumably activated on a spectrum (not suddenly “on” or “off”). Thus, conservative management will be preferable to CEA only when reaching a sufficient point. Similarly, near-occlusion diagnostics is also on a spectrum: only when the distal ICA diameter reduction has reached a sufficient point can the diagnosis be set (regardless of approach). It is unclear which of these points occur “first” as a stenosis increases in severity. If the mechanism precedes diagnosis, then all diagnosed should get conservative treatment. If the diagnosis precedes mechanism, then near-occlusion cases close to the border with conventional stenosis will require CEA. Therefore, the results of future clinical studies should be critically analyzed for the possibility that near-occlusions bordering conventional stenosis still have a too high stroke risk for conservative treatment due to insufficient effect of the protective mechanism. If so, it would be reasonable to add a clinical decision threshold: separating near-occlusions without full collapse with a high risk of stroke (that reasonably need surgery) and near-occlusions without full collapse with a low risk of stroke that should be treated conservatively.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval Approved by the regional ethics board in Umeå, Sweden.

Informed consent All participants provided informed consent.

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