Computed Tomography Angiogram Derived From Computed Tomography Perfusion Done with Low Iodine Volume Protocol Preserves Diagnostic Yield for Middle Cerebral Artery-M2 Occlusions

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Background: Computed tomography angiogram (CTA) derived from computed tomography perfusion (CTP) has been proposed to avoid addition of separate CT perfusion protocol for selection of large vessel occlusion in acute stroke patients. Previous studies have validated this technique for proximal large vessel occlusions. In this study, we test reliability for identifying M2 occlusions on CTA derived from CTP. *Methods:* Through a retrospective search of the institutional thrombectomy database, we identified 28 cases with M2-MCA occlusion, of which 24 met the inclusion criteria for analysis. An additional 20 cases without M2-MCA occlusion (either normal or M1-MCA occlusion) were randomly mixed in the database to reduce observer bias. The baseline images of the CTP study in these 48 cases were then independently analyzed by 3 readers with varying level of expertise. The digital subtraction angiography (DSA) images were also independently reviewed where available. The percentage of agreement among reviewers as well as the probability of agreement of the reviewers, when compared to the DSA findings was also calculated. *Results:* The observed agreement for the image quality amongst the 3 readers (n = 48) varied between 0.78 and 0.95 and tended to be higher for the M1 segment MCA and lower for distal M2-MCA. The observed agreements comparing 3 image reviewers versus DSA in M2 patients (n = 24) was 98% for identifying occlusion (95% CI 95%-100%), 94% for identifying proximal M2 occlusion (95% CI 88%-98%), and 91% (95% CI 84%-97%) and 90% (95% CI 83%-95%), respectively for correctly identifying inferior and superior branch of M2 occlusion. *Conclusion:* CTA data derived from CT Perfusion study preserves diagnostic yield for correctly identifying M2 occlusion.

Introduction

Mechanical thrombectomy has recently been established as the standard of care treatment for patients with anterior circulation large vessel occlusion (LVO) presenting within 24 hours of symptom onset, with the selection of patients presenting beyond the first 6 hours partly determined based on computed tomography perfusion (CTP) results.[1-7] These seminal randomized clinical trials focused largely on proximal vessel occlusion defined as intracranial internal carotid artery, middle cerebral artery (M1), or tandem lesion (IC + M1) except MR-CLEAN which had inclusion for M2 in design. Of note, a few patients enrolled in these randomized controlled trials were initially thought to have M1 occlusion, but later reclassified by the core radiology lab as having M2 occlusion. Infact, 94 patients out of 1287 had M2 occlusion, of which 51 were randomized in endovascular therapy arm.[1-5,8] Among the important reasons why there is lack of RCTs designed to answer the important question of "to intervene" or "not-to-intervene" on patients with M2 occlusion is the lack of sensitivity and specificity of initial diagnostic imaging that would accurately and reliably identify the M2 occlusions. The current American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend obtaining noninvasive intracranial vascular imaging during the initial evaluation of acute stroke patients to identify the patients with LVO, based on the available evidence, the guidelines also recommend obtaining perfusion imaging for patients presenting within the delayed window (Class I; Level of Evidence A).[9]

In light of the above mentioned evidence and guideline recommendations, CTP is increasingly used in selection of patients with suspicion of LVO, especially in patients with

known time of onset to more than 6 hours.[10] However, CTP in addition to computed tpmography angiography (CTA) could lead to further delay in initiating intra-arterial therapy. In addition to the additional time, there is also more contrast exposing patients to higher risk of renal dysfunction. CT angiography data derived from CT perfusion data has been proposed to avoid addition of separate CT angiography protocol for selection of LVO in acute stroke patients.[11,12] In fact, the use of anatomical information derived from the CTP data has previously been described to assess collateral scores, clot burden and retrograde filling of vessels.[12-14] Similarly, the utility of low dose anatomical CTP images to detect LVO has also been documented for the more proximal vessels. In a study by Frolich et al for example, the authors validated the use of this technique in proximal LVO like internal carotid artery, basilar artery (BA), and middle cerebral artery (MCA) M1 segment.[14] However, no prior studies have exclusively evaluated the accuracy and inter-reader reliability of this technique exclusively for M2 occlusions in acute ischemic stroke (AIS). This assumes further significance since technical advances in stroke care have led to technically successful MCA-M2 segment thrombectomy results in patients with AIS.[15,16] In this study, we sought to examine the accuracy and interobserver reliability for MCA-M2 occlusion on CTA derived from CTP (Fig. 1).

Methods

Patients

Our study was approved by the institutional review board. A retrospective search was performed from our neurointerventional stroke database from January 2015 to
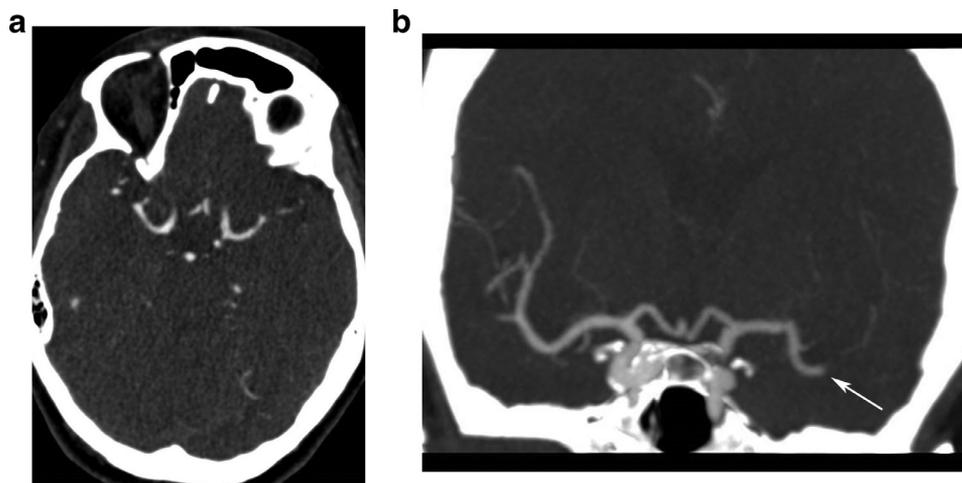

Figure 1. *Axial post contrast image (a) during peak arterial enhancement shows diagnostic image quality of the arterial vessels at the level of circle of Willis. The coronal MIP image (b), reconstructed at 10 mm thickness demonstrates the left sided occlusion (white arrow).*

July 2018 (n = 201). A total of 28 patients with suspected M2-MCA occlusion as indication for the study were identified. Of these, 1 patient had spontaneous recanalization at digital subtraction angiography (DSA), 1 had technically unsuccessful study and 2 patients had tandem proximal LVO. These patients were therefore excluded when comparing DSA and CTP derived CTA images. The remaining 24 cases had DSA confirmed M2-MCA occlusion and preintervention CTP study.

To reduce observer bias, we also included 20 additional cases for CTP-derived CTA analysis. These included patients with no LVO (n = 15) and M1-MCA occlusion (n = 5) and were randomly distributed among the M2-MCA occlusion patient dataset. All included patients without LVO had a negative follow up MRI within 24 hours of presentation. Overall, CTA data derived from CTP study was subjectively assessed for image quality in all 48 cases, while the concurrence of readers for diagnosing M2-MCA occlusion (compared to DSA) was evaluated in 24 cases.

Imaging Technique

Images were acquired on either a 128-(SOMATOM definition AS, Siemens AG, Forchheim, Germany) or 192-slice (SOMATOM Force, Siemens AG, Forchheim, Germany) CT scanner. CT imaging protocol included noncontrast CT brain followed by a dynamic spiral CT during contrast injection to cover the entire "volume" of the brain, referred to as volume perfusion CT (VPCT). The craniocaudal (z-axis) coverage for these scanners is 9.6 cm and 11.4 cm, respectively.

VPCT was performed after rapid injection (8 mL/s) of 40 cc nonionic iodinated contrast (Isovue 370; iopamidol 370 mg I/mL) followed by a 50 mL saline chaser at 8 mL/s using an 18-gauge peripheral IV. VPCT scanning parameters varied slightly between the 128-slice CT (80 kV, 190 effective mAs, rotation time 0.3 second, pitch 0.5, delay 2 second, acquisition 128 × 0.6 mm) and the 192-slice CT (70 kV, 200 effective mAs, rotation time 0.25 second, pitch 0.5, delay 2 second, acquisition 192 × 0.6 mm). Acquisition on both scanners included rapid sequential scanning following the contrast bolus, with 4 scans at 3 second intervals, followed by 15 scans at 1.5 second intervals, and another 9 scans at 3 second intervals (total 28 scans over approximately 60 seconds). VPCT data were routinely reconstructed with a slice width of 1 mm every 0.6 mm for all individual scans, resulting in 158 images per scan for the 128-slice CT and 190 images for the 192-slice CT.

Image Analysis

CTP-derived CTA and diagnostic cerebral angiogram were reviewed for the presence and location of arterial occlusion. Images were analyzed on a standard PACS workstation with capabilities to display the data in multiplanar reconstruction (MPR) and maximal intensity projections (MIPs) at different thickness, based on viewer preferences.

Three radiologists with differing levels of experience: 1 neuroradiology fellow, 1 fellowship-trained attending, and 1 certificate of added qualification in neuroradiology (CAQ) certified attending independently reviewed the randomized CTP exams. Each evaluator initially subjectively selected the temporal image series with the most robust large-vessel arterial enhancement. The selected series was then subjectively assessed for image quality across 10 vessel segments on a Likert-like scale (M1-MCA, Proximal M2-MCA superior and inferior division, Distal M2-MCA, superior and inferior, for both sides). CTP-derived CTA image-quality was subjectively evaluated by each radiologist using a scoring scale: nondiagnostic = 1, diagnostic with limitations = 2, diagnostic with minor limitations = 3, excellent = 4. Vessel occlusion was defined as abrupt cut-off of vessel signal without distal vessel enhancement on the ensuing time point (Image 1a,1b). If an occlusion was identified in a superior or inferior M2 branch, the occlusion was further subdivided as being proximal (<1 cm) or distal (≥1 cm) to the MCA bifurcation. All radiologists were blinded to the noncontrast CT, CTP perfusion maps as well as the DSA results.

The diagnostic cerebral angiograms were reviewed by an independent expert panel which included a neuroradiologist and neurointerventional expert who were provided with all imaging data without previous scores documented and co-reviewed all cases in consensus. The DSA readers were blinded to CT, CTP, and CTA results as well as patient information. Except for patients without LVO on CTP/CTA (n = 15), DSA study was attempted/performed in the remaining 33 cases and confirmed either M2-MCA occlusion (n = 24) or M1-MCA occlusion (n = 5). One case had spontaneous recanalization, 2 had tandem lesions and 1 was technically unsuccessful. IMS-III M2 branch occlusion was taken as a reference definition for grading intracranial occlusions.[17]

Statistical Analysis

All statistical analysis was conducted in R (v 3.5.3).[18] The lack of variability in the sample precluded assessment of Kappa scores for subjective image quality. Observed probability of agreement was therefore computed to measure agreement. Confidence intervals of the probability were computed via bootstrap with 500 iterations. For image quality, the percentage of agreement among the image reviewers was first computed for each patient at each location. Then the observed probability of agreement was computed as an average of the percentage of agreement across all patients for each location.

When comparing the image reviewers versus DSA for M2-MCA occlusions, the probability of agreement was computed for individual reviewers compared to the DSA. A pooled probability of agreement of all 3 raters against the DSA was also calculated (Table 1). Finally, the 3 rates were concatenated into 1 group, and compared with the gold standard DSA results to calculate Kappa scores.

Table 1. *Interobserver agreement on image quality of CTA derived from CTP*

	Observed agreement	95% CI lower	95% CI upper
Right M1	0.951	0.909	0.977
Left M1	0.938	0.886	0.970
Right M2 Prox Sup	0.889	0.848	0.939
Right M2 Distal Sup	0.826	0.780	0.886
Right M2 Prox Inf	0.931	0.879	0.962
Right M2 Distal Inf	0.889	0.856	0.947
Left M2 Prox Sup	0.882	0.841	0.932
Left M2 Distal Sup	0.785	0.742	0.841

Abbreviations: CTA, computed tomography angiogram; CTP, computed tomography perfusion.

Results

There was excellent observed agreement between the 3 readers in terms of subjective image quality, ranging between 0.78 and 0.95 for the analyzed vessel segments (Table 1). It tended to be higher for the M1-MCA (0.95, CI: 0.90-0.97) than for distal M2-MCA (0.74-0.84). Among all 3 readers, no study was scored as nondiagnostic.

Most of our patients with M2-MCA involvement had a proximal occlusion (23/24). When comparing the M2-MCA occlusions (n = 24), the observed agreements between 3 image reviewers versus DSA in M2 patients was 98% for identifying occlusion (95% CI 95%-100%), 94% for identifying proximal M2 occlusion (95% CI 88%-98%) and 96% for identifying distal M2 occlusion (95% CI 90%-100%). There was 92% (95% CI 85%-97%), and 90% (95% CI 83%-96%) agreement for correctly identifying inferior and superior branch of M2 occlusion, respectively.

When the 3 readers were compared as a single group with the DSA results, there was moderate agreement when identifying proximal versus distal M2-MA occlusion (κ: 0.47-0.55) and excellent agreement when identifying superior versus inferior division involvement (κ: 0.83-0.80).

Discussion

In this study, we report the diagnostic accuracy and inter-reader reliability of CTA data derived CTP in identifying MCA-M2 occlusion. Our study shows that CTA data derived from CTP carries high sensitivity, and specificity, and excellent inter-observer agreement in identifying M2 occlusion across readers with different levels of neuroimaging expertise. This is significant, since the readers were blinded to CTP perfusion maps, whose addition would likely have led to even better identification of the occlusion site and concordance among readers. In addition, all readers showed high agreement in terms of assessment of image quality, with none of the cases being classified as nondiagnostic by any of the 3 readers. It is also pertinent to note here that these results are achievable from the existing data and do not require any additional imaging time, radiation or contrast, or modification of the existing workflow.

When comparing the DSA findings and all readers for the M2 MCA occlusion, there was extremely high agreement in terms of presence or absence of occlusion (0.98, 95% CI 0.96-1). Interestingly, readers showed better correlation in terms of involvement of the superior or inferior division (κ 0.80-0.83) as compared to proximal versus distal occlusion (κ 0.47-0.55). This may be explained by lack of variability in the data since most patients had a proximal occlusion and also by the fact that the proximal and distal segments were based on a 1 cm difference in vessel involvement, which may be more subjective and difficult to evaluate in an occluded vascular segment.

In a study on natural history of intracranial occlusions, Lima et al have reported good outcomes (mRS 0-2) in 38.5 % (M1 occlusion) as compared to 54.2% (M2 occlusion) patients. The same study also reported poor outcome for 45.8 % patients with M2 occlusions (mRS > 3) as compared to 61.5% (M1 occlusion). Six-month mortality of 20.8% for M2 occlusions which again was similar to 23.1% in patients with M1 occlusion.[19] This significant morbidity and mortality makes it imperative that quick, safe, and effective management of M2 occlusions be pursued that reduces morbidity and possibly mortality in this patient population. As we further advance stroke management which have brought previously considered "distal" branches of MCA like M2 segments to be amenable to therapeutic advances, their rapid and reliable identification on the initial imaging becomes paramount.

There is no data on outcomes or safety of M2 occlusion who get endovascular therapy from the prior randomized trials as neither that was the aim nor the numbers significant for isolated M2 occlusions. In ad-hoc analysis of SWIFT, STAR, SWIFT-PRIME (total of 50 patients with isolated M2 occlusion) a few important features that stood out in comparison of M1 versus M2 group were lower ASPECT and higher NIHSS. A trend towards lower number of passes for M2 and equal reperfusion TICI greater than or equal to 2b for both groups were other important technical notes.[14] MERCI and Multi-MERCI trial (total of 28 isolated M2 occlusions) also show less number of passes for M2 versus M1 occlusion (2.1 versus 3.1; P < .001) better quality of reperfusion M2 versus M1 (82.1% versus 60.0% TICI II/III; P0.03). However, 40.7% achieved good outcomes (mRS 0-2) at 3 months.[20] This encouraging data from albeit a small number of patients enrolled in clinical trials have also encouraged comprehensive stroke centers to approach M2 occlusions in a more pragmatic way by deciding on multiple features that include NIHSS, time since onset, modified Rankin score, and age rather than just the anatomical site of occlusion.

Our results indicate that a standard CTA, followed by CTP in triage process can be safely replaced by a CTA derived from CTP while preserving sensitivity and specificity to diagnose distal occlusions like MCA-M2 occlusion. Even though this does not significantly change the time spent in the scanner (since most CTA studies on newer

scanner can be performed in less than 1 minute), it does significantly reduce extra-contrast dose for the CTA component and also reduces the radiation dose to the patient. Equally importantly, it can help standardize the imaging workup of patients with suspected AIS in the emergency room, since the time since last known normal may not always to clear. In such cases, the CTP study can serve as a single study to identify hypoperfused, nonviable tissue, as well as site of occlusion. CTA images derived from CTP data have been previously studied for proximal occlusions like MCA-M1 but diagnostic utility has not been studied in distal occlusions like M2.[12,14] It is noteworthy that the readers were blinded to the perfusion maps of the CTP study which may have further improved accuracy and reduced interpretation time in the real world setting. Another important takeaway from the study is that all readers showed moderate to excellent correlation with the DSA findings, regardless of the level of expertise, a finding that may reflect the robustness of this method.

Several studies have shown that the arterial phase of multiphase CTP has slightly improved vessel contrast compared to standard CTA, with the tradeoff of increased noise due to low-dose acquisition.[21] Several techniques have been developed to that may reduce image noise and produce higher quality vessel imaging from CTP. Our study demonstrates that arterial phase CTA data derived from CTP retains high sensitivity for identifying M2 vessel occlusion, obviating the need for additional postprocessing to generate timing invariant reconstruction.

Our study has few limitations. The main limitation of our study is derived from its retrospective nature and small sample size. Additionally, the study is limited by the fact that this was not a direct comparison between CTP-derived CTA versus traditional single phase CTA, and we only compared the sensitivity and specificity to DSA. Finally, tandem occlusion may limit contrast enhancement in the vessel distal to the proximal point of occlusion. This would then, in theory, limit evaluation of the more distal occlusion. Perfusion CTs are limited in scan volume based on detector width and rotational speed, with a z-axis in older generation scanners ranging from 2-4 cm and newer 320-slice scanner covering up to 16 cm.[22] This range is not sufficient for evaluating the extracranial vasculature to the aortic arch. However, there are several advantages of VPCTA over single-phase CTA. VPCTA is less susceptible to improper contrast bolus timing, given that multiple phases are acquired at the same time. Additionally, there is the potential to visualize collateral dynamics not seen in single phase studies, providing valuable prognostic information.[23]

Conclusion

CTA data derived from CTP study preserves diagnostic image quality and shows excellent correlation in terms of identifying presence or absence of occlusion as well as involvement of the superior or inferior division of M2-MCA. This may be helpful in providing the requisite CTA information, and may potentially obviate the need for extra contrast and radiation and allowing for a uniform workflow in the emergency setting.

Author Contribution

Details of contributions from individual authors with the complete list as follows:

1. Kaustubh Limaye- Study conceptualization, data acquisition, analysis and interpretation of data, drafting and revising the manuscript.

2. Adam Bryant- Study conceptualization, data acquisition, analysis and interpretation of data, drafting and revising the manuscript.

3. Girish Bathla- Study conceptualization, data acquisition, analysis and interpretation of data, drafting and revising the manuscript.

4. Biyue Dai- data acquisition, analysis and interpretation of data, revision of article for important intellectual content.

5. Sami Al Kasab- data acquisition, analysis and interpretation of data, revision of article for important intellectual content.

6. Amir Shaban- data acquisition, analysis and interpretation of data, revision of article for important intellectual content.

7. Edgar A. Samaniego- data acquisition, analysis and interpretation of data, revision of article for important intellectual content.

8. David Hasan- data acquisition, analysis and interpretation of data, revision of article for important intellectual content.

9. Bruno Policeni-Study conceptualization, data acquisition, analysis and interpretation of data, drafting and revising the manuscript.

10. Enrique Leira - data acquisition, analysis and interpretation of data, revision of article for important intellectual content.

11. Colin Derdeyn- Study conceptualization, data acquisition, analysis and interpretation of data, drafting and revising the manuscript.

12. Santiago Ortega-Gutierrez- Study conceptualization, data acquisition, analysis and interpretation of data, drafting and revising the manuscript.

Data Sharing

N/A.

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