Cerebrovascular Diseases

Stroke Spectrum

Cerebrovasc Dis
DOI: 10.1159/000526873

Received: July 1, 2022
Accepted: August 30, 2022
Published online: November 24, 2022

Angiographic Systems for Classifying Distal Arterial Occlusions

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Keywords
Distal arterial occlusion · Functional/imaging classification · M1 segment · M2 segment · Anterior temporal artery · Holo-temporal artery

Abstract
Background: Extensive randomized controlled clinical trials for endovascular thrombectomy in anterior circulation large vessel occlusions (internal carotid arteries and M1 segment of middle cerebral arteries) have been published over the past decade, but there have not been randomized controlled trials for distal arterial occlusions to date. Distal arterial occlusion randomized controlled trials are essential to decide on patient selection, imaging criteria, and endovascular approach to improve the outcome and reduce complications. ***Summary:*** The definition of distal arterial occlusion is however unclear, and we believe that a uniform nomenclature of distal arterial occlusions is essential for the design of robust randomized controlled studies. We undertook a systematic literature review and comprehensive analysis of 70 articles looking at distal arterial occlusions and previous attempts at classifying them as well as comparing their similarities and differences with a more selective look at the middle cerebral artery. Thirty-two articles were finally deemed suitable and included for this review. In this review article, we present 3 disparate classifications of distal arterial occlusions, namely, classical/anatomical, functional/imaging, and structural/calibre, and compare the similarities and differences between them. ***Key Messages:*** We propose the adoption of functional/imaging classification to guide the identification of distal arterial occlusions with the M2 segment starting at the point of bifurcation of the middle cerebral artery trunk/M1 segment. With regards to the anterior temporal artery, we propose that it will be considered a branch of the M1 and only be considered as the M2 segment if it is a holo-temporal artery. We believe that this is a practical method of classification in the time-critical decision-making period.

Introduction

Endovascular Thrombectomy in Distal Arterial Occlusions

Endovascular thrombectomy (EVT) for anterior circulation large vessel occlusions (LVOs) has been proven to significantly improve the functional outcome through multiple randomized controlled trials [1–5]; however, there are no studies to date looking at distal arterial oc-

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clusions (DAOs). The Highly Effective Reperfusion using Multiple Endovascular Devices (HERMES) collaborators performed a meta-analysis of 5 thrombectomy trials for LVOs and specifically looked into 130 patients with M2 segment occlusions and their outcome with thrombectomy [6]. The M2 segment was divided proximal and distal based on the location of the thrombus to the mid-sylvian point [6]. In patients with proximal M2 segment occlusions, 57.1% in the EVT arm compared to 37.7% in the control arm showed a favourable outcome with mRS 0–2 at 90 days ($n = 116$, adjusted OR 2.68, 95% CI: 1.13–6.37). When the dominant M2 segment was occluded, treatment favouring EVT was demonstrated ($n = 73$, adjusted OR 4.08, 95% CI: 1.08–15.48) for mRS 0–2 at 90 days [6]. Symptomatic intracranial haemorrhage (sICH) rates were 5.6% for EVT versus 2.1% for the control arm ($p = 0.10$) [6]. A meta-analysis of 12 studies on 1,080 patients with M2 occlusions demonstrated 58% of patients achieved functional independence at 90 days but with an increased odds ratio of sICH (OR 3.39, 95% CI: 2.31–4.98) [7]. In a pooled analysis of 3 randomized controlled trials and 2 prospective non-randomized studies, investigators examined M2 occlusions and showed improved clinical outcomes of EVT compared to medical management in patients with a perfusion mismatch profile (inverse probability of treatment weights OR 2.02, 95% CI: 1.08–3.78, $p = 0.029$), with no difference in those without mismatch (inverse probability of treatment weights OR: 0.71, 95% CI: 0.18–2.78, $p = 0.62$) [8]. In sum, these studies demonstrated potential benefits of EVT in M2 occlusions despite a possible increase in the rate of sICH.

Intravenous Thrombolysis in DAOs

The treatment of DAO with intravenous thrombolysis (IVT) is recommended as per current guidelines [9]. Although IVT in patients with demonstrable distal occlusion with either CT angiography or CT perfusion is an independent predictor of a favourable outcome compared to imaging negative patients [10], a recent analysis of 258 patients with DAO (72.1% receiving IVT) demonstrated that up to one-third of patients did not achieve functional independence (mRS 0–2), and half these patients did not achieve excellent functional outcomes (mRS 0–1) [11]. This exemplifies the need DAO randomized controlled trials to decide on patient selection, imaging criteria, and endovascular approach to improve the outcome and reduce complications. However, the definition of DAO is unclear, and we believe that a uniform nomenclature of DAO is required for the design of robust randomized controlled studies.

Review Methodology

For this review, we first formulated the research question "How to classify a distal arterial occlusion?" Among DAOs, we then focused on the middle cerebral artery (MCA), especially the distinction between the M1 and M2 segments. We proceeded to select and filter relevant articles from PubMed, Google Scholar, Embase, Scopus, and Web of Science databases using the keywords Distal Arterial Occlusion; Endovascular Thrombectomy; Large Vessel Occlusion; Medium Vessel Occlusion; Middle Cerebral Artery; M1 segment; M2 segment; Anterior Temporal Artery; and Holo-temporal Artery. More than 200 papers were published from 1981 to 2022 with these keywords, and these papers were collected and screened based on their relevance to our research question, narrowing it down to 70 articles that were reviewed in detail, with 32 articles finally being deemed suitable to be included in this review. We thoroughly reviewed these articles looking at DAOs and previous attempts at classifying them as well as comparing the similarities and differences between them with a more selective look at the MCA. In this review article, we present 3 disparate classifications of DAOs, namely, classical/anatomical, functional/imaging, and structural/calibre.

Classical/Anatomical Classification of Distal Arteries

Anterior circulation LVO includes the intracranial internal carotid artery (ICA) and the M1 segment of the MCA [1–5]. The MCA is classically divided into 4 segments which are M1 (sphenoidal) segment, M2 (insular) segment, M3 (opercular) segment, and M4 (cortical) segment [12]. There has been much discussion over the years on the specific distinctions of these segments and especially M1 and M2 (online suppl. Table 1; see www.karger.com/doi/10.1159/000526873 for all online suppl. material). Anatomically, the M1 segment starts at the origin of MCA at the bifurcation of the ICA and travels laterally, posterior to the sphenoid ridge and terminates at the genu which is the junction of sphenoidal and operculoinsular compartments of the Sylvian fissure [12]. Bifurcation of the MCA occurred proximal to the genu in 86% of the hemispheres studied [12]. The M2 segment continues from the genu, crossing the limen insulae, terminating at the circular sulcus of the insula followed by the M3 segment ending at the surface of the Sylvian fissure terminating as M4 segment which supply the cortices [12]. Multiple studies have shown bifurcation or trifurcation of the MCA occurs proximal to the genu with bifurcation, i.e., superior and inferior branches, being the commonest division of the MCA trunk [12–14]. Following dissection in cadavers, investigators [13] reported bifurcation rates of the MCA proximal to the genu at 82%, with 8% bifurcating at the genu, and 10% bifurcating distal to the genu, and another study of 350 patients showed 78.4% of MCAs divided before the genu, 19.2% at the genu, and 2.4% after the genu [15]. The MCA segment proximal to the genu regardless of its bifurcation/trifurcation status is still considered the M1 segment of the MCA (shown in Fig. 1a) [12–15]. One study looked at the natural history and outcome of 116 patients with M2 occlusions using the classical/anatomical classification system that did not receive EVT. Favourable outcomes (mRS 0–2) were seen in 43% (95% CI: 34–53%) of patients with a poor outcome in 57% (95% CI: 47–66%) with a mortality rate of 27% (95% CI: 19–37%) [16]. There are many anatomical variants of the MCA. The duplication of MCA and the accessory MCA are anomalous arteries present in individuals at 2–2.9% and 2.7%, respectively [17]. Duplication of the MCA occurs when the anomalous artery arises from the distal ICA and runs parallel to the MCA, whereas an accessory MCA occurs when the artery originates from the ACA [17]. The anomalous MCAs can be differentiated from the original MCA by either examining the bifurcation of the MCA (present in the dominant original MCA) or comparing the ICA bifurcation to the contralateral side [17]. If the two arteries reconnect distally, it is referred to as fenestration. Fenestrated arteries are rare, seen only in 0.7% of individuals [17]. Length of the M1 segments of the MCA is variable. Following studies using cadavers, investigators reported an MCA trunk mean length of 15 mm +/− 1.1 mm in the right hemisphere and 15.7 mm +/− 1.3 mm in the left hemisphere in 70 cerebral hemispheres that were studied [18]. Using similar approach in 50 cerebral hemispheres, investigators reported M1 segment mean length of 14.9 mm with a standard deviation of 1.2 mm [19]. A more recent study reported a mean length of the M1 segment of 20.6 mm with a standard deviation of 6.2 mm in 100 hemispheres and defined early bifurcation of the MCA as bifurcation occurring within 1

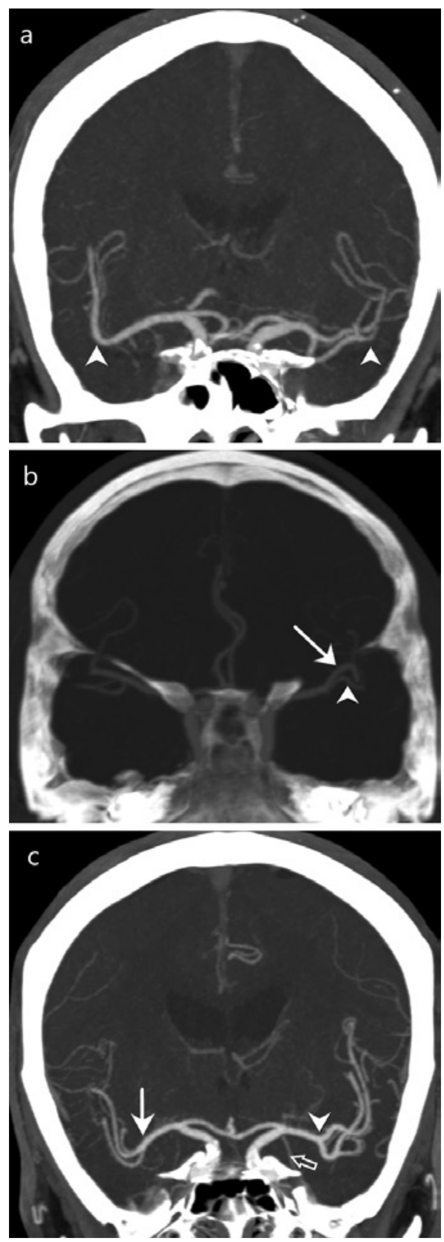

Fig. 1. a This image demonstrates the classical/anatomical classification system. The M1 segment of the MCA turns into the M2 segment at the genu. The left M1 segment/MCA trunk bifurcates before the anatomical genu compared to the left side (both anatomical genua indicated with arrowheads). The left MCA segment proximal to the genu and distal to the bifurcation is still considered as the M1 segment. **b** This image demonstrates the structural/calibre classification system. This system uses the dimensions of the arteries to decide on classifying it as an LVO or MVO. The MCA trunk/M1 segment falls into the large vessel category due to its diameter of 3.24 mm. The two left MCA segments distal to bifurcation are classified as large vessel (arrow) and medium vessel (arrowhead) due to the diameter being >2.0 mm and ≤2.0 mm respectively. **c** This image demonstrates the functional/imaging classification system. The left M2 segments take origin from the point of bifurcation (arrowhead) of the left M1 segment of the left MCA. The right M2 segments take origin at the point of trifurcation (arrow) of the right M1 segment of the right MCA. The left anterior temporal artery (clear arrow) is visualized taking origin from the posterior aspect of left MCA trunk but does not affect the M1 and M2 segment definition.

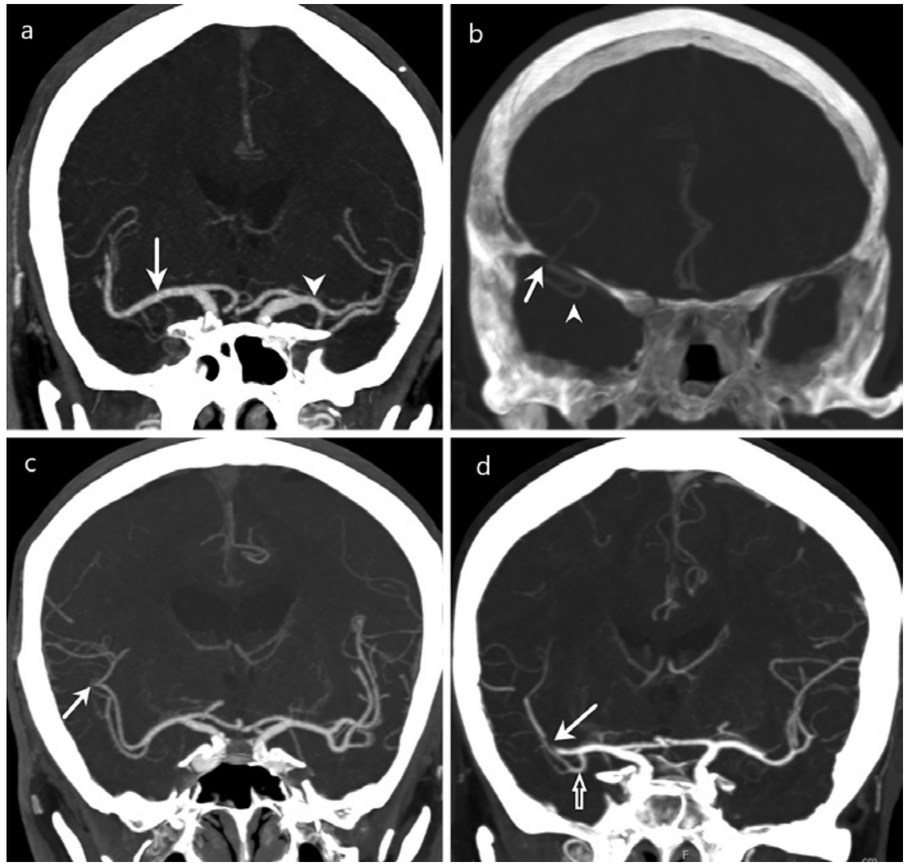

Fig. 2. a Early bifurcation (<10 mm from origin of MCA) of the left MCA with the left M1 segment measuring 7.92 mm (arrowhead). The right MCA bifurcates at the genu with the M1 segment measuring 25.68 mm (arrow). **b** Right proximal M2 segment occlusion (arrow) with the right anterior temporal artery (arrowhead) seen branching from the M1 segment of the right MCA. **c** Distal right M2 segment occlusion (arrow) with partial reconstitution of flow distal to the occlusion site. **d** Right M2 segment occlusion (arrow) with a right hTA (clear arrow) which further bifurcates. **d** Illustrates how each classification system would provide a different nomenclature for the occlusion site: classical/anatomical: this occlusion would be classified as and M1 occlusion as it occurs before the anatomical genu. Structural/calibre: This occlusion would be classified as an LVO as the diameter measured just proximal to the occlusion was 2.10 mm. Angiographic/functional classification: This occlusion would be classified as an M2 segment occlusion as the occlusion is distal to the origin of the hTA.

cm from the origin of MCA which was seen in 3% of the hemispheres [20]. An example of an early bifurcation is shown in Figure 2a. The MCA trunk then enters the lateral fissure where it bifurcates (72%), trifurcates (16%), or terminates as a primary trunk (12%) [19]. MCA bifurcation was found in 86.2% and trifurcation in 13.8% of the cases [15]. In summary, the classical/anatomical system is location specific, which means the points of demarcation are fixed and related to its surrounding structures, making this method of classification rigid. For example, the M1 segment continues as M2 at the genu, and this demarcation point is fixed for all patients. It does not consider individual variance of arteries like the anterior temporal or holo-temporal arteries (hTAs) and does not utilize the dimensions of the arteries to decide on proximal versus distal or large vessel versus medium vessel occlusions (MVOs) which are seen in the 2 systems discussed below.

Structural/Calibre Classification of Distal Arteries

Vessel occlusions in acute stroke can also be categorized as distal MVO (DMVO) or proximal LVO (PLVO) depending on its size and tortuosity/distance (shown in Fig. 1b, online suppl. Table 1) [21]. The Distal Thrombectomy Summit Group collaborators in their consensus statement proposed the terms PLVO and DMVO based on vessel tortuosity and vessel size. Vessels with lumen diameters measuring ≥2.0 mm such as the intracranial ICA (typical diameter, 3.8 mm), and the M1 segment of the MCA (2.7 mm) were categorized as large vessels, while vessels with lumen diameters ≤0.75 mm like the lenticulostriate artery (diameter 0.5 mm) were categorized as small vessels [21]. Therefore, the medium-sized vessels were defined as cerebral arteries with lumen diameters between 0.75 and 2.0 mm. M2 segments range in size from 1.1 to 2.1 mm in diameter. The dominant M2 segments may be similar to M1 in size (though still more distal and tortuous to reach), while the nondominant segments are similar to M3 and other much small arteries in size. The M3 segment (typical diameters at origin, 1.1–1.5 mm) and M4 fall directly in the medium-vessel category [21]. Distal cerebral arteries are differentiated from proximal cerebral arteries by longer travel distances and routes with increased tortuosity from the arterial puncture site with ≥1 additional branch steps compared to proximal arteries. Distal arteries also loop around neuroanatomic structures such as the insula and temporal lobe which increases the technical difficulty of reaching target occlusions and limits physical forces deliverable by an endovascular device [21]. Due to this variability, especially with the M2 segment, they suggested a more fluid or flexible categorization; PLVO and DMVO based on the size and tortuosity/distance or MVO and LVO only based on size or proximal vessel occlusion and distal vessel occlusion only based on tortuosity/distance to classify a segment of the vessel [21]. The structural/calibre system of DAO classifies vessel segments agnostic of spatial location and uses specific measurements/dimension of arteries to decide on size, tortuosity, and distance. However, it is onerous and tedious to perform in a time-limited setting, and this method would also be technically demanding for those with limited experience in image interpretation and measurements.

Functional/Imaging Classification of Distal Arteries

Angiographically, the start of the M2 segment of the MCA is defined as the vertical segment lying within the mesial margin of the sylvian fissure based on the course of the MCA changing from horizontal to vertical at the genu [22]; however, the Cerebral Angiographic Revascularization Grading (CARG) Collaborators, Stroke Imaging Repository (STIR) Revascularization working group, and STIR Thrombolysis in Cerebral Infarction (TICI) Task Force recommended that the definition of M1 segment should be from the first portion of the MCA up to the major bifurcation where it will continue as M2 in their consensus statement for acute ischaemic stroke (shown in Fig. 1c, online suppl. Table 1) [23]. In M1 segment occlusions, it was also recommended to divide the M1 segment into proximal and distal with the latter sparing the lenticulostriate branches [23]. The bifurcation of the MCA into superior and inferior divisions can be codominant or with one of the divisions being the dominant arterial supply [14]. The superior branch supplies the convexity of the frontal lobe and the inferior branch supplies the temporal lobe with dominancy depending on which branch supplies the parietal lobe/territory. Inferior division dominance was seen in 32% of patients, followed by superior division in 28%, and codominance in 18% of patients in this study [14]. The frequency of dominancy varied with one study showing dominant superior division in 26%, inferior division in 25.4%, middle branch in 4% (seen in trifurcation of MCA), and no domination/codomination in 44.6% of the cases [15].

Goyal et al. [24] coined the term medium vessel occlusion (MeVO) to include M2/3, A2/3, and P2/3 occlusion. MeVO of the MCA includes the M2 segment (from the main MCA bifurcation/trifurcation to the circular sulcus of the insula) and M3 segment (from the circular sulcus of the insula to the external/superior surface of the Sylvian fissure). As for the anterior cerebral and posterior cerebral arteries, MeVO includes the A2 segment (from the origin of the anterior communicating artery to the origin of the callosomarginal artery) and A3 segment (from the origin of the callosomarginal artery to the artery's posterior turn above the corpus callosum) as well as the P2 segment (from the origin of the posterior communicating artery to the point of entrance in the quadrigeminal cistern) and P3 segment (a segment within the quadrigeminal cistern) [24]. MeVO can be divided into primary and secondary MeVO as it can occur as primary occlusion, which has the same mechanism as LVO strokes or as a secondary occlusion when a fragment of the LVO embolizes to the distal artery either spontaneously or during treatment (IVT or EVT) [25]. One of the branches to note is the anterior temporal artery (Table 1) which typically arises at the mid-segment of M1 but can arise from M1 trifurcation or an M2 branch [14]. The vascular territory supplied by the anterior temporal artery can be occasionally variable. It may supply some parts of the eloquent posterior temporal cortex, especially if the middle temporal and/or posterior temporal arteries are small [26]. Khatri et al. [27] in their review of 886 cerebral angiograms concluded that the anterior temporal artery, re-

DOI: 10.1159/000526873

Table 1. Different classifications of M1 and M2 segments of the MCA

Type of classification	Authors (year of publication) [references]	M1 segment	M2 segment	Additional features
Classical/anatomical	Gibo 1981 [12]	Starts at the origin of MCA and terminates at the genu which is the junction of sphenoidal and operculoinsular compartments of the Sylvian fissure	Continues from genu terminating at the circular sulcus of the insula	
	Umansky 1984 [18]	From the origin of the main trunk at the ICA to its main divisions (bifurcation)	Secondary trunks which are the main divisions from the main trunks referred to as superior, middle, and inferior depending on the main divisions	
	Oo 2021 [20]	From the origin of the main trunk to the bi/trifurcation point or from the origin of the main trunk to the site of the first cortical branch in cases where there was no bi/trifurcation	From the point of bi/trifurcation to the cortical segments supplied by the cortical arteries	Early bifurcation was defined as the bifurcation occurring within 1 cm from the origin of the main trunk
Structural/calibre	Saver 2020 [21]	From the origin of the MCA and defined based on size and tortuosity/distance. Vessel diameter more than 2.0 mm is considered to be a large vessel	The M2 segment can be considered a large vessel especially in the dominant branch if the size is > 2.0 mm or a medium vessel if it is nondominant with the size is between 0.75 and 2.0 mm which can be similar to an M3	The distal cerebral arteries are distinguished by longer distances and more tortuous cumulative travel pathways from the arterial puncture site. Distal arteries have ≥1 additional branch steps than proximal arteries and also loop around neuroanatomic structures such as the insula and temporal lobe
Functional/imaging	Goyal 2016 [14]	From the origin to the site of bifurcation or trifurcation	From bifurcation/trifurcation to the circular sulcus of the insula/exit from the Sylvian fissure	Anterior temporal artery is not considered to be M2 unless the artery is large whereby it supplies territories beyond the anterior temporal lobe
	Zaidat 2013 [23]	From the first portion of the MCA until the major bifurcation	Continuing from major bifurcation however extent not mentioned	
	Khatri 2020 [27]	From the origin of the main trunk to the point of bifurcation of the sphenoidal segment – this point was noted by drawing a perpendicular line from the angiographic Sylvian point	Continuing from point of bifurcation of the sphenoidal segment however extent not mentioned	Early bifurcation was defined as the bifurcation occurring within 10 mm from the origin of the sphenoidal segment or the terminal ICA
		Further divided into "classic" when the bifurcation occurred at the genu and "non-classic" bifurcation occurred before the genu		The anterior temporal artery, regardless of its size, did not determine the MCA bifurcation pattern
	Tomsick 2016 [28]	1) From origin of main trunk of MCA to point of main bifurcation	1) Continuing from the main bifurcation however extent not mentioned	Anterior temporal artery is considered a branch of the M1
		2) From origin of main trunk to the origin of a holo-temporal or posterior temporal artery	2) If holo-temporal or posterior temporal arteries are present, continuation of the main trunk beyond this is M2 trunk	Holo-temporal artery and posterior temporal arteries taking origin from the main trunk are considered an M2 segment

MCA, middle cerebral artery; ICA, internal carotid artery.

gardless of its size, was not considered to determine the main MCA bifurcation pattern, whereas Goyal et al. stated that anterior temporal artery is not considered M2; however, if the artery is large, i.e., supplies territories outside those of the anterior temporal artery such as posterior temporal or low parietal region, it should be considered as M2 [14]. Another study defined the hTA/holotemporal M2 branch as an isolated branch of the M1 segment giving origin to the anterior temporal artery and arteries supplying the middle and posterior temporal lobes and possibly reaching the inferior parietal and temporo-occipital territories. The anterior temporal artery on its own is not considered an M2 branch even if it arises directly from the MCA trunk [28]. If the isolated branch arising from the M1 runs the similar course as the anterior temporal artery but is larger in size and supplying the mid and posterior temporal territories, it was termed as posterior temporal M2 branch. In the presence of an hTA or a posterior temporal artery arising from the MCA trunk, the continuation of the MCA trunk beyond the origin of these two vessels to the point of bifurcation was termed the M2 trunk which simulates the distal M1 segment [28].

The functional/imaging method of classification does not require complicated measurements or a relationship to the surrounding structures to define the segments. Its key difference from the other classification systems is the start of the M2 segment is at the point of bifurcation of the MCA trunk/M1 segment regardless of the length of the MCA trunk, and it also accounts for variants such as hTA and anterior temporal artery. This makes this system the most practical of the three systems which is important for time-critical decision-making.

Diagnostic Accuracy of DAO

Accurate interpretation of neurovascular imaging for the detection of DAO might be challenging for physicians or neurologists with limited experience in reading CTAs and MRAs in stroke patients, and this can result in misdiagnosis or mismanagement. A proximal M2 occlusion (shown in Fig. 2b) is often more easily identified compared to a distal M2 occlusion (shown in Fig. 2c) and M3 occlusions. A recent retrospective analysis looked at factors associated with erroneous detection of LVO with a single-phase CTA and found that non-neuroradiologists missed large vessel occlusions significantly more compared to neuroradiologists (OR: 5.62; 95% CI: 1.06–29.85; $p = 0.04$), and M2 segment occlusions were more than five times likely to be missed compared to distal ICA and/or M1 segment occlusions (OR: 5.69; 95% CI: 1.44–22.57; $p = 0.01$) [29]. The diagnostic accuracy and interrater agreement of MVOs was evaluated using single-phase and multiphase CTA. Interrater agreement for occlusion type was moderate for single-phase CTA ($k = 0.58$; 95% CI: 0.56–0.62) and improved to almost perfect agreement when multiphase CTA was used ($k = 0.81$; 95% CI: 0.78–0.83). Interrater agreement for detailed occlusion sites was moderate for single-phase CTA ($k = 0.55$; 95% CI: 0.53–0.56) and substantial for multiphase CTA ($k = 0.71$; 95% CI: 0.67–0.74). Diagnostic accuracy of MVO also improved with the multiphase CTA (86–89%) as compared to the single-phase CTA (57–61%) [30]. The diagnostic accuracy for detection of DAO with CT perfusion is significantly higher compared to that of CTA alone [31]. A study looking at 373 acute stroke patients (70 patients with DAO) demonstrated a sensitivity of 96.8%, specificity of 90.3%, and AUC >0.90 among all readers for detecting DAO using Tmax maps. This was significantly different compared to CTA with mean sensitivity of 70.7% and mean specificity of 87.5%. The diagnostic accuracy was significantly greater on Tmax alone compared to CTA ($p < 0.001$) [31].

The HERMES collaborators analysed five randomized controlled clinical trials of LVOs, two of which included M2 occlusions. Among those that included M2 occlusions, most were initially classified as M1 occlusions by the interventional neuroradiologists but were then reclassified as M2 occlusions by the core lab. This not only highlights the poor standardization of the M1 and M2 segments but informs us that a large number of M2 segments that were occluded were sizeable and proximal enough for experienced interventional neuroradiologists to consider them M1 segment occlusions [32].

Conclusion and Future Directions

We note the ongoing DAO trials such as the FRONTIER-AP, DISTAL, and DISCOUNT which will inform management of DAOs. However, a robust and reproducible nomenclature is essential to accurately dichotomize treatable occlusions into proximal arterial and DAOs. We propose the adoption of functional/imaging classification to guide the identification of DAOs with the M2 segment starting at the point of bifurcation of the MCA trunk/M1 segment. We believe that this is a practical method of classification in the time-critical decision-making period. This will also reduce the variance of definitions between interventional neuroradiologists/operators and core labs adjudicators in thrombectomy trials when defining the M2 segment. With regards to the anterior temporal artery, we propose that it will be considered exclusively a branch of the M1 and not an M2 branch on its own, hence not affecting the M1 and M2 segments definition. The hTA, if present, should be considered as an M2 branch (shown in Fig. 2d), i.e., supplying the entire temporal lobe and/or extra temporal territories with the anterior temporal artery arising from it. All other arteries originating from the MCA trunk should not be considered an M2 branch. The continuation of the MCA trunk distal to the origin of hTA should be referred to as the M2 trunk till the point of bifurcation or trifurcation. Figure 2d also depicts the variability in classification of an MCA occlusion using the 3 different classification systems and further emphasizes the need for a uniform classification moving forward.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

There were no conflicts of interest and ethical issues of note in this article.

Funding Sources

We did not receive any form of support in the form or financial aid or any other manner.

Author Contributions

Presaad Pillai drafted and revised the manuscript including acquisition and analysis of data for the work. Presaad Pillai also reviewed the final version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Bernard Yan, conceptualized, drafted, and revised the manuscript including acquisition and analysis of data for the work. Bernard Yan also reviewed the final version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Peter Mitchell, Thanh Phan, and Henry Ma conceptualized and revised the manuscript as well as contributed to acquisition and analysis of data for the work. Peter Mitchell, Thanh Phan, and Henry Ma also reviewed the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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