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Recent advances in imaging of acute ischemic stroke

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- CT angiography
- MR perfusion

Abstract

The need for early accurate diagnosis of AIS has motivated the development of new advanced imaging techniques for the early diagnosis of the condition and the selection of patients who might present outside the window for systemic thrombolytic therapy. During the last decade, the state of art imaging techniques has developed for the imaging of patients with hyperacute stroke including both angiographic and perfusion imaging. The imaging modalities, which are in widespread use in primary stroke imaging include; computed tomography and magnetic resonance imaging. Imaging can be categorized into structural imaging, vascular imaging and perfusion imaging. Important signs of early stroke on brain CT include; insular ribbon sign, the hypedense artery sign, and the development of hypo-attenuation lesions. MRI is more sensitive than CT for the demonstration of these lesions especially diffusion weighted images which are currently the gold standard for the evaluation of the extent of infarct core. Susceptibility weighted images are highly sensitive for the demonstration of hyperacute bleed within the infarct. CT and MR angiography are highly sensitive for the demonstration of large vessel occlusion which is very important for selection of patients for endovascular treatment. Perfusion studies can be performed using CT or MRI and are showing an increasing role in the identification of salvageable brain tissue (penumbra) and target mismatch between hypoperf used volume and infarct core, an important criterion for selection of patient who might benefit from endovascular treatment.

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INTRODUCTION

Ischemic stroke is a leading cause of death and long term disability worldwide. Following cerebral vascular occlusion about 1.8 million neuronal cells are injured each minute before perfusion is restored. Clinical outcome of patients with acute ischemic stroke (AIS) improves markedly if these patients have a reasonable volume of brain tissue that can be salvaged at presentation and they undergo early recanalization **(1).**

Intravenous recombinant tissue plasminogen activator (rtPA) is the mainstay of AIS treatment. Early treatment, within 3 hours of onset of symptom, is associated with best clinical outcomes. This window can be extended to 4.5 hours in some selected cases. Early imaging evaluation is essential in patients who are eligible for intravenous rtPA, for the proper selection of patients and to avoid delaying effective treatment **(2).**

Beneficial effect of endovascular treatment (EVT) with mechanical thrombectomy and a wider treatment window, beyond 4.5 hours, has been recently confirmed in AIS in 5 major randomized controlled trials. Advanced neuroimaging plays a major role in evaluating and selecting patients with AIS who may benefit from acute revascularization beyond 4.5 hours treatment window, i.e outside treatment window for systemic rtPA **(3).**

Pathogenesis of acute ischemic stroke

Acute ischemic stroke, is defined as a clinical condition characterized by sudden loss of neurologic function that results from the obstruction of blood supply to part of the brain **(4).**

AIS result from cerebral vascular occlusion. Ischemia results in cell hypoxia, failure of cellular energy mechanisms, intra-cellular edema and finally cell death**.** In addition, ischemia results in breakdown of the blood-brain barrier 4-6 hours after infarction leading to vasogenic edema, swelling of the brain reaching maximum at 72- 120 hours and resolving within next few weeks **(4).**

Ischemic penumbra & infarct core

The sudden occlusion of a cerebral artery results in hypoperfusion of corresponding cerebral territory supplied by that vessel. The affected area shows a severely hypoperfused central infarct core with irreversible damage (cerebral blood flow (CBF) $\leq$ 10 ml/100 g/min). The infarct core is surrounded by critically hypoperfused ischemic penumbra (tissue-at-risk) (CBF 10–20 ml/100 g/ min) where the injury can be reversed if prompt reperfusion occurs on time (Figure 1). With time the infarct core increase in volume at the expense of the penumbra.

The peripheral zone of tissue surrounding the penumbra is not at risk of infarction and is called zone of "benign oligemia' (CBF >20 ml/100 g/min) **(5).**

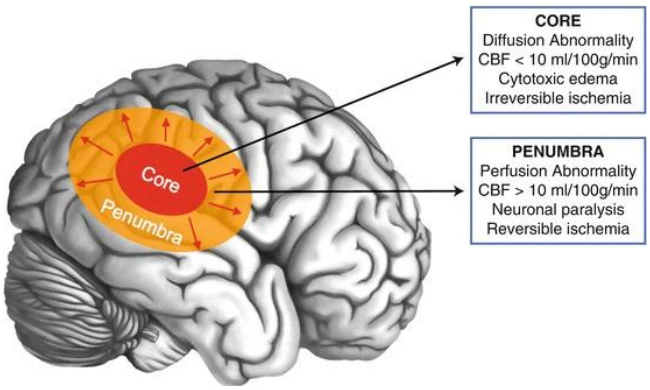

Figure 1: Schematic drawing of infarct core and penumbra (5).

Ischemic stroke classification

Large vessel occlusive disease: The atherosclerotic debris arising from carotid arteries in the neck is the main source of emboli occluding the large cerebral vessels with most of these emboli affecting the middle cerebral artery (MCA), followed by anterior cerebral artery **(4).**

Lacunar infarction: Lacunar infarctions are small, 5 to 15 mm lesions developing secondary to obstruction of thalamo-striate penetrating arteries as a result of small vessel atherosclerosis related to hypertension **(4).**

Cardioembolic infarction: Cardiogenic emboli, associated with atrial fibrillation or recent cardiac surgery, are a common source of repeated stroke constituting around 20% of AIS **(6).**

Watershed infarction: Watershed or border-zone infarctions develop at the distal areas between arterial territories and are believed to be due to severe hypoperfusion, such as in carotid occlusion or prolonged hypotension **(4).**

Hemorrhagic transformation of ischemic stroke: Hemorrhagic transformation of ischemic infarct is more common with larger infarct size and usually results from reperfusion of the ischemic cerebral tissue, either from recanalization of the obstructed artery or from the collateral blood supply to the affected area. **(7).**

Parenchymal imaging

Computed tomography (CT)

Non-contrast CT (NCCT)

Early findings (within 6 hours) of AIS on non-contrast CT (NCCT) scan, include loss of gray-white differentiation as a result of the increased water content from intra-cellular edema **(8, 9).**

Other early findings that might be seen in MCA infarction include; ill definition of the lateral margins of the insula, (insular ribbon sign) (Figure 2) and loss of density of the basal ganglia nuclei, such as the lentiform nucleus (vanishing basal ganglia sign) **(4).**

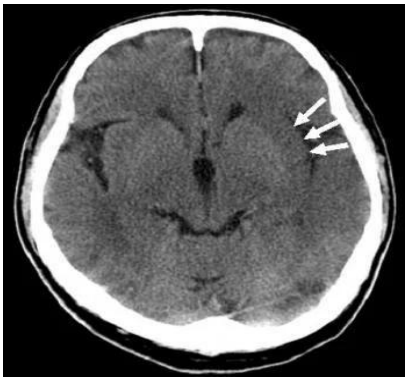

Figure 2: Insular ribbon sign. Loss of normal grey-white matter differentiation in the left insular cortex is noted (4).

Hyperdensity of cerebral arteries may be seen (dense vessel sign or dot sign); and are thought to result from acute intra-vascular thrombus or embolus. This sign can be seen in the MCA, basilar artery, and venous sinuses (Figure 3 & 4) **(4).**

After about 12-24 hours, well-defined wedge-shaped hypodense lesion, (Figure 5) mostly associated with mass effect may be seen. This finding is usually irreversible. Mass effect usually reaches its peak by about 3-5 days and disappears over the next several weeks **(5).**

Lacunar infarcts are seen as small, 5-15 mm hypodense lesions, typically seen at the subinsular regions, basal ganglia, thalami, capsular regions, and corona radiate **(4).**

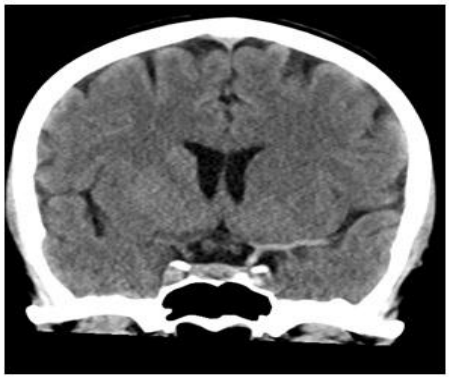

Figure 3: Dense left MCA sign (10).

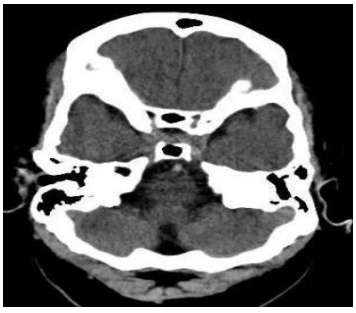

Figure 4: Dense basilar artery (dot sign) (4).

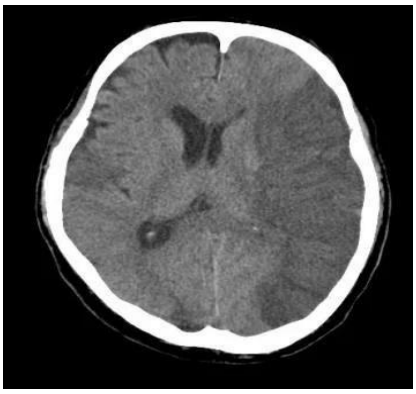

Figure 5: Left MCA infarction. Hypodense area of acute infarction of left MCA territory (4).

The hyperacute phase findings on NCCT can be very subtle. A high index of suspicion is needed during the interpretation of the examination. Characteristic findings highly suggestive of AIS include; hypodenseity of brain parenchyma, loss of gray-white differentiation, and effacement of cortical sulci **(4).**

Non-contrast CT scan obtained within 4-6 hours might be negative in 20%-30% of patients with AIS **(11).**

Quantification of Zone of Ischemia

The quantification of the volume of ischemic tissue is an important factor in guiding therapy. This is because larger infarcts, especially those larger than one third of the MCA territory, are more liable to bleed after intravenous rtPA **(4).**

The Alberta Stroke Programme Early CT Score (ASPECTS) is a 10-point scoring system used to quantify acute ischemia on NCCT according to the extent of ischemia of MCA territory.

The score is based on two sections; one at the basal ganglia level and the other section above that level. The ASPECTS divides the MCA territory into 10 areas; M1 to M6 inclusive, the caudate nucleolus (C), lentiform nucleous (L), insular cortex (I) and internal capsule (IC), and for each affected area a point is deducted. Accordingly, normal MCA territory scan would qualify for a score of 10 (Figure 6), and a patient with massive MCA infarction would receive a score of 0 (Figure 7). Patients with lower ASPECTS scores usually suffer from severe strokes and are more liable to develop symptomatic cerebral hemorrhage during treatment **(12, 13).**

ASPECTS evaluation gained increasing popularity after establishing EVT as an effective treatment for patients with LVO **(14, 15).** An ASPECTS score $\geq$ 6 was used as an inclusion criterion **(16).**

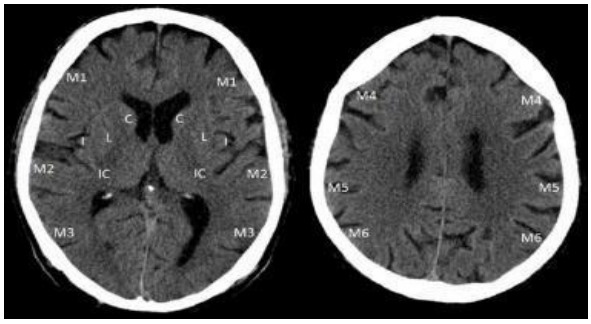

Figure 6: ASPECTS. Normal scan with a score 10 (4).

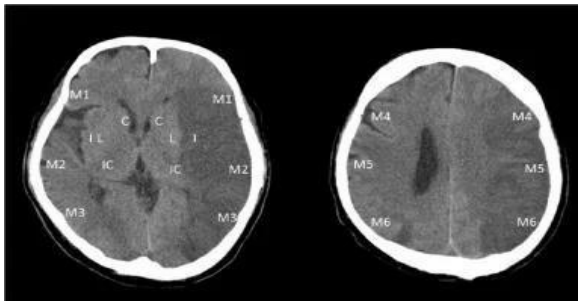

Figure 7: Left MCA infarction. ASPECTS score of 3 denoting large infarct core (4).

Automated Calculation of the ASPECTS:

The implementation of ASPECTS evaluation was found to suffer from poor interobserver agreement. Two available software have shown good results for automatic ASPECTS calculation within an acceptable timeframe, the e-ASPECTS software (Brainomix, United Kingdom) and the RAPID ASPECTS (iSchemaView, California) **(17-19).**

This is achieved by labeling each region as either normal or ischemic with the help of a machine learning algorithm. The use of e-ASPECTS software showed more accurate (Figure 8) results than human readers for the calculation of the size of the infarct in potential candidates for mechanical thrombectomy **(19-21).**

Magnetic Resonance Imaging (MRI)

Conventional MRI

Conventional MR imaging is more sensitive and specific than CT for the detection of acute cerebral ischemia within the first few hours. Typical MR findings include hyperintense signal on T2- Weighted images (T2WI), and Fluid Attenuated Inversion Recovery images (FLAIR), beginning approximately about 8 and 3 hours after symptoms onset respectively with loss of gray matter – white matter differentiation analogous to that seen on CT (Fig 9). T1-Weighted images (T1WI) may take longer time to demonstrate low signal. FLAIR images are more sensitive than T2 WI for the identification of AIS, with a sensitivity greater than 90% **(22-24)**

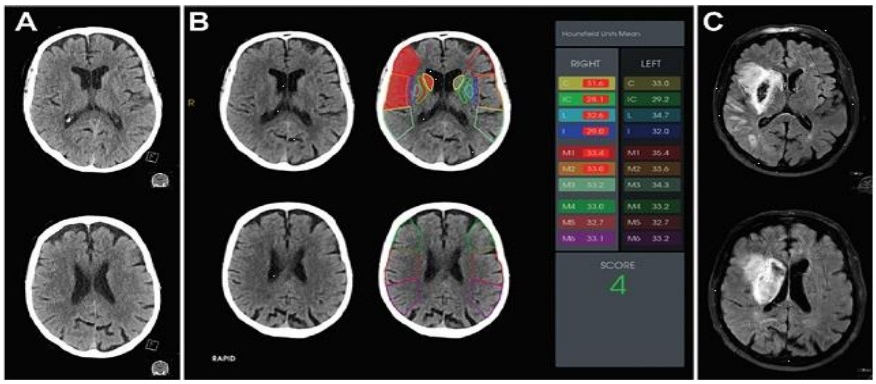

Figure 8: e-ASPECTS. Patient with right sided stroke. Two human readers showed ASPECTS score of 7 & 8 (A) while e-ASPECTS showed score of 4 (B) more in agreement with consensus ASPECTS score of 4 and FLAIR images score of 3 (C) (19).

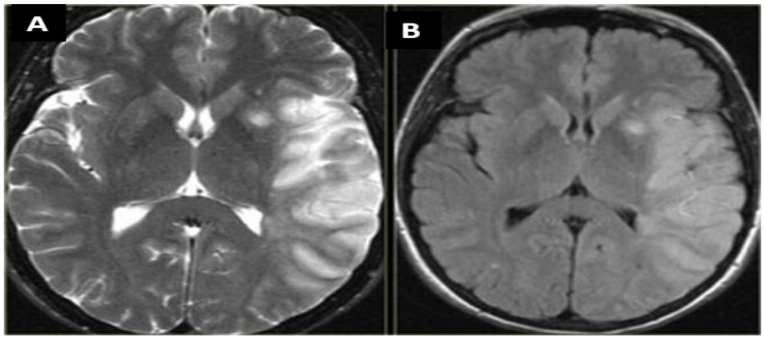

Figure 9: Left MCA acute infarction. (A) T2WI and (B) FLAIR images showing high signal of acute infarction involving the left MCA territory (24).

<u>Diffusion-weighted imaging (DWI):</u>

Diffusion-weighted imaging (DWI) is highly sensitive and specific, (88% to 100% sensitivity, 95% to 100% specificity) for the demonstration of AIS. DWI can detect the restricted motion of the molecules of water due to cytotoxic edema as early as 11 minutes after stroke onset **(24).** Restricted diffusion appear as area of high signal on DWI and low signal on the corresponding, apparent diffusion coefficient (ADC) maps (Figure 10) **(25).**

Hyperintense signal intensity is noted on DWI and decreased ADC values from about 30 minutes to 120 hours after symptoms onset (Figure 10); mildly hyperintense DWI signal with pseudonormal ADC values are seen around 7-28 days; and finally; low DWI signal with increased ADC values, characteristic of cystic encephalomalacia,

are seen several weeks to months in the chronic phase **(25).**

DWI may show high signal intensity for several weeks after onset of symptoms due to the predominance of T2-weighted effects, "T2 shine through", over the apparent diffusion changes **(26).**

DWI lesions are considered markers of irreversible ischemia and DWI is currently the gold standard imaging defining the extent of core infarct. An ADC value $\leq 620 \times 10-6$ mm 2 /s is considered the threshold for demonstration of core of infarct **(25).**

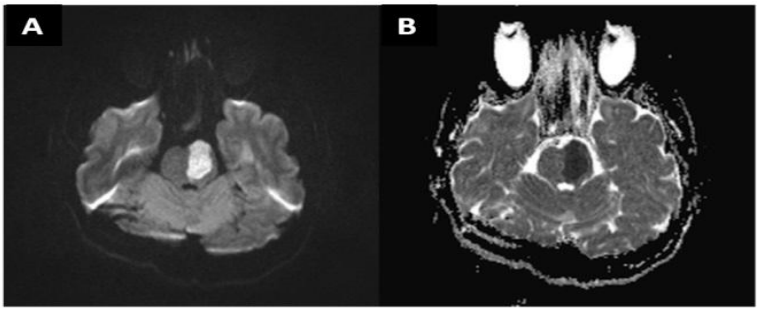

Figure 10: Pontine infarction. (A) DWI and (B) ADC map showing acute infarction of left side of pons (27).

Susceptibility weighted imaging (SWI)

Susceptibility weighted imaging (SWI) is very sensitive to inhomogeneities of the magnetic field such as those caused by paramagentic agents (deoxyhemoglobin) and ferromagnetic agents (hemosiderin) (25). Magnetic field inhomogeneities are shown as areas of signal loss or dropout on SWI. Although NCCT has been the gold standard imaging method for detecting acute hemorrhage for quite a long time, SWI has been shown to have similar accuracy to CT for the detection of hyperacute hemorrhage, and better than CT for the demonstration of chronic bleed **(28).**

Deoxyhemoglobin in an intra-vascular clot usually appear as a focus of low signal larger in size than opposite, due to "blooming" artifact, on SWI helping the localization of an occlusion "artery

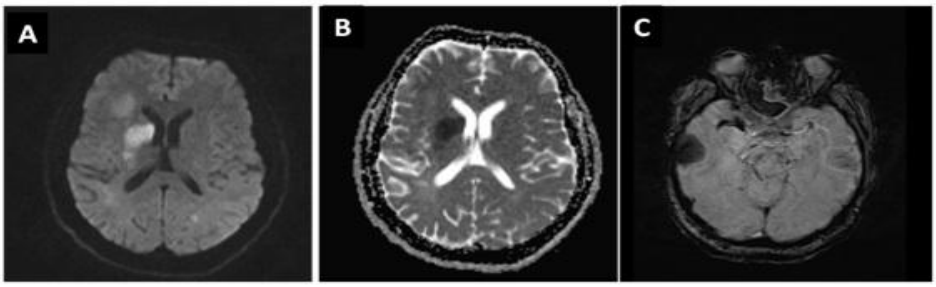

Figure 11: Artery susceptibility sign. (A) DWI, (B) ADC, and (C) SWI of a patient with right thalamic infarction showing blooming artifact of proximal right MCA denoting its occlusion (30)

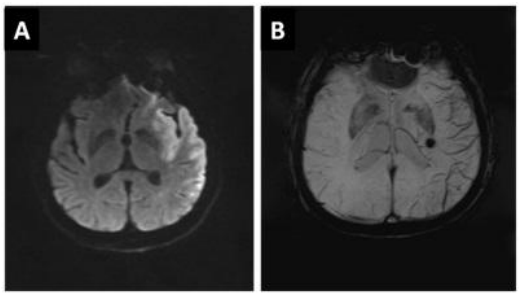

Figure 12: Cortical vessel sign. (A) DWI and (B) SWI of a patient with left MCA infarction showing prominent low signal cortical veins at left tempro-parietal region (30)

Susceptibility sign" (Figure 11) **(28, 29).**

Moreover, it was shown that as hypopoperfused tissue has a higher oxygen extraction, low signal veins with increased deoxyhemoglobin are usually seen draining the ischemic area on SWI. These veins can be seen either at the periphery of the brain "cortical vessel sign" or in the deep white matter transmedullary veins "brush sign" (Figure 12). This finding can help the identification of penumbra and showed strong correlation with increased risk of hemorrhagic transformation **(28, 29).**

Vascular Imaging

About 35-40 % of AIS is due to LVO. These patients have a 4.5 fold increase in mortality rate and 3 fold reduction in functional independence at 90 days follow up. Unfortunately evidence has shown that these patients respond poorly (4-44%) to systemic thrombolytic therapy **(31).**

The American heart association (AHA) emphasized the value of EVT for patients with internal carotid or proximal MCA occlusions (Level IA evidence) in their latest, 2019, guidelines edition. They also recommended that for those patients who qualify for EVT, noninvasive vascular imaging of the intracranial arteries is mandatory during the initial imaging assessment and it should be done as early as possible (Level IA evidence) **(32).**

CT angiography (CTA)

The role of CT angiography (CTA) in AIS is the detection of proximal vascular occlusion. CTA is very reliable for the demonstration of occlusion of large intracranial arteries, such as the internal carotid artery, proximal MCA trunk and basilar arteries (Figure 13) **(21).**

The sensitivity of CTA and MR angiography (MRA) as compared with conventional catheter angiography ranges from 87% to 100%, with CTA being more accurate than MRA **(22, 33).**

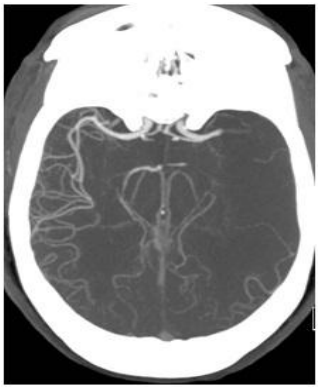

Figure 13: CTA showing occlusion of M1 segment of left MCA with poor collaterals (23).

Multi-phase CT angiography:

Single-phase CTA lacks temporal resolution; and consequently, pial collateral flow cannot be accurately evaluated using this technique **(34).** One drawback of collateral evaluation using single-phase CTA is the reliance on the assessment of one set of images in time. Thus, there is a risk patients with good pial collateral might be misidentified as having poor collaterals if the single-phase CTA scan is obtained early in the arterial phase **(35).**

Multi-phase CTA generates time-resolved cerebral angiograms of the brain vessels including three sets of images, in the late arterial, mid-venous and late venous phases. This technique is shown to be superior to single phase CTA for demonstrating pial collaterals (Figure 14) **(35).**

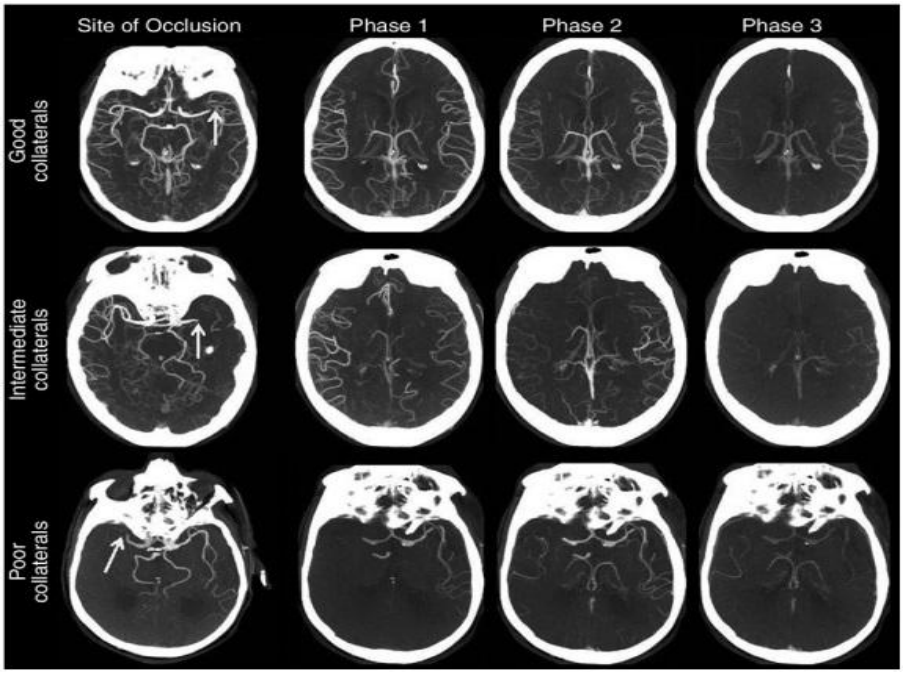

Figure 14: Multiphase CTA. Upper row: Left MCA occlusion with good collaterals. Middle row: Left MCA occlusion with intermediate collaterals. Lower row: Right MCA occlusion with poor collaterals (35).

Magnetic resonance angiography (MRA)

MRA may be performed using time of flight (TOF) or contrast-enhanced (CE) MRA techniques. TOF MRA depends on the reflection of signal from the proton in the blood flowing into the imaging plane while the stationary protons in adjacent tissue does not reflect any signal as they are saturated and appear dark. As a result the only signal on the final images appear to be representing the flow within the vessels. TOF MRA has the advantages of short acquisition time and high spatial resolution and is currently considered the preferred MRA technique for evaluating the intracranial arteries (Figure 15-top) **(29).**

On the other hand the combined assessment of both intra-cranial and extra-cranial vessels can be achieved using CE-MRA which relies on the imaging of a timed bolus of contrast.

The sensitivity of CE-MRA for intra-cranial stenosis is lower than for extra-cranial stenosis (Figure 15 - bottom) **(29).**

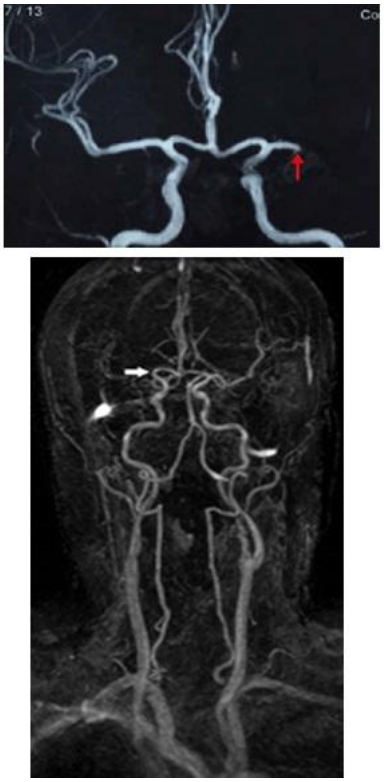

Figure 15: Top: TOF-MRA showing left MCA occlusion. Bottom: CE-MRA showing complete occlusion of the right MCA (29).

Perfusion Imaging

CT perfusion

CT perfusion (CTP) can help the identification of patients who might benefit from early EVT. CTP has shown high accuracy in the identification of patients not suitable for EVT, namely those with large infarct core or minimal salvageable tissue **(36, 37).** CTP is performed using sequential spiral CT scanning to ‘‘track’’ a single bolus of contrast material during its transition through the cerebral circulation. CTP can be used for the measurement of the following parameters; **(38).**

Cerebral blood volume (CBV): Volume of blood present on an imaging voxel measured as mL / 100 g parenchyma (Normal value : 5 mL/100g).

Cerebral blood flow (CBF): Volume of blood flowing through a voxel in a unit of time measured as mL / 100 g of parenchyma / minute (Normal value : 50 mL/100g/min).

Mean transient time (MTT): The mean time required by the bolus of contrast to transit through a given volume of brain, from the arterial to the venous circulation. It is measured in seconds.

Time to peak enhancement (TTP): The time period between the arrival of contrast intracranially and the time at which the contrast

reaches its peak concentration in a given region measured in seconds.

Time to maximum (Tmax): Time at which maximum value of residue function occurs and represents delayed arrival of contrast bolus.

Arterial and venous regions of interest (ROIs) are derived from the CTP source images to generate attenuation curves used to estimate the CTP parameters. The anterior cerebral artery and the superior sagittal sinus are usually used to obtain the arterial input and venous output functions respectively **(39).**

Evaluation of CTP maps is usually performed through visual inspection, for the demonstration of areas of core infarct and penumbra. Although visual inspection is fast and simple; qualitative methods are user dependent. Therefore, many centers advise cusing quantitative perfusion parameters as they are more accurate in demonstrating core infarct and penumbra. However, the protocols & guidelines for quantitative thresholds vary from one institute to another are very variable. Clearly defined standardized thresholds that can be used to guide therapy have not yet been established **(39).**

Normal perfusion:

Cases with normal perfusion (Figure 16), show bilateral symmetric values of all CTP parameters. The CBF and CBV are higher in the gray matter as compared with the white matter due to the normal physiologic differences between these tissues **(38).**

Acute ischemic infarction:

AIS diagnosis is made on CTP as corresponding to regions of reduced CBF and CBV, and increased MTT, TTP and Tmax **(38, 40).**

Infarct core: Shows matched decreases in CBF and CBV, with increased Tmax. Reduced CBF (<30% as compared to normal side), decreases in CBV (<30–40% compared to normal side), and increased Tmax > 6 seconds have been shown to best correspond to the infarct core (Figure 17) **(38, 40).**

Penumbra: Conversely, the ischemic penumbra demonstrates mismatched areas of abnormal perfusion – appearing as large areas of prolonged Tmax with smaller areas of only mildly reduced CBF where CBV is mildly reduced or relatively preserved (Figure 18) **(39).** Prolonged Tmax (> 6 seconds) reflects the fact that blood is taking alternative or (collateral) pathways to supply the ischemic territory. These findings are consistent with intact, yet stressed, cerebral vascular autoregulation. As a result, CBF is reduced but still >30% of the normal side, while CBV is 60% of normal. Tmax has been shown to be the most accurate CTP parameter describing salvageable penumbra. The penumbra is represented by total area of hypoperfused brain (Tmax > 6 seconds) minus infarcted core (CBF < 30%) **(38, 40).**

CT perfusion has been shown to be very valuable for the selection of patients who might benefit from EVT in an extended time window up to 24 hours. Target values for successful

reperfusion may be in constant evolution however the most accepted values at the present time are; a) Ischemic core volume < 70 mL, B) Target mismatch ratio > 1.8 and C) Mismatch volume > 15 mL **(3, 38, 40)**.

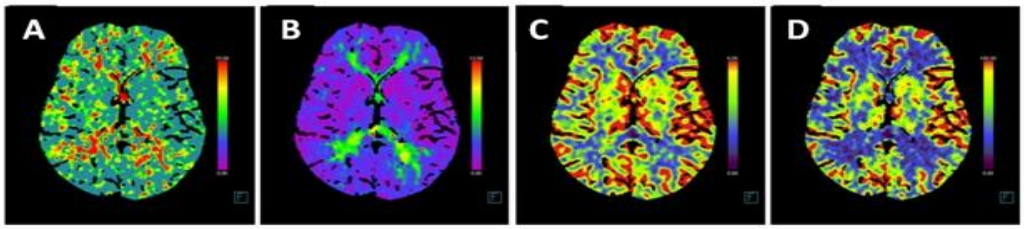

Figure 16: Normal brain perfusion. (A) MTT, (B) Tmax, (C) CBV and (D) CBF, demonstrate normal symmetric brain perfusion (38).

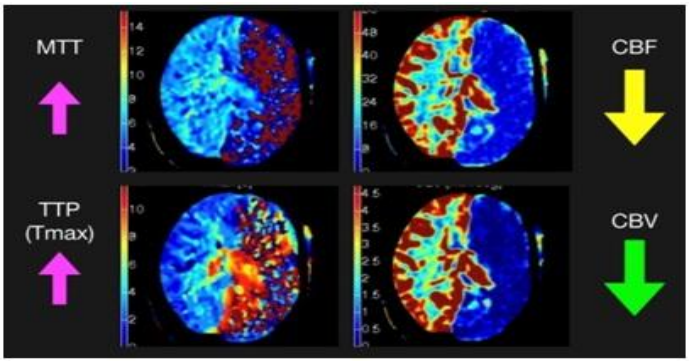

Figure 17: Infarct core. CTP showing left-sided MCA infarct without any salvageable penumbra. Matched abnormalities are noted as decreased CBF, decreased CBV and prolonged Tmax indicating infarct core (41).

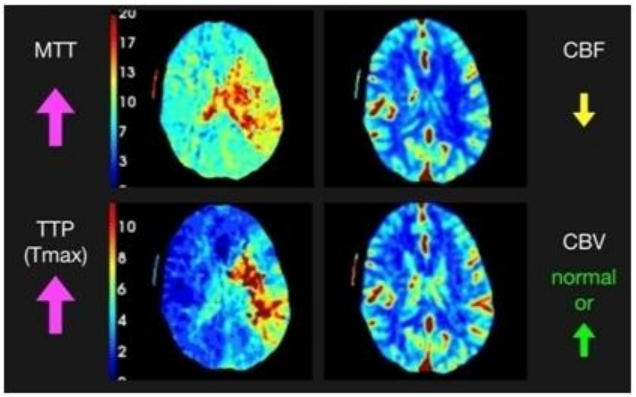

Figure 18: Penumbra. CTP showing left sided ischemic lesion with mismatched areas of prolonged Tmax larger than areas of mild reduction of CBF and normal or increased CBV indicating salvageable tissue (41).

MRI perfusion

The most common MR technique used for MR perfusion imaging (PWI) is dynamic susceptibility–contrast perfusion imaging (DSC-PI), which depends on acquiring maps of cerebral perfusion through tracking the first pass of a rapid bolus of contrast through the cerebral vasculature **(42).**

The MR signal decrease as contrast material transit through the infarcted area and returns to normal as it leaves this area. The data are used to generate a signal-time curve that is used to

calculate different perfusion parameters, similar to those with CTP. Most centers in USA consider MTT, TTP or Tmax as the best The infarction core can be demonstrated using parameters similar to the parametersr used in CTP. In addition the infarct core should correspond to the region of abnormality seen on DWI. Thus, the demonstration of tissue at-risk or penumbra may be represented as the area of mismatch between perfusion abnormalities and diffusion abnormalities (Figure 19) **(29).** For perfusion parameters for the demonstration of the infarct core and penumbra **(42).**

DSC-PI, a Tmax with a delay of > 6 s and >10 s is recently considered as a cut off thresholds for penumbra and infarct core respectively **(25).**
Although MR diffusion-perfusion mismatch may be slightly superior to CTP in demonstrating the infarction core and penumbra, CTP still has the advantage of being much faster and more readily available **(29).**

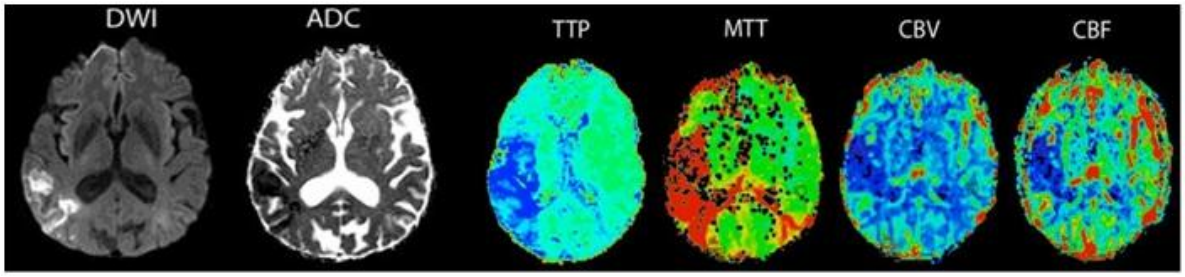

Figure 19: Penumbra. DWI and ADC map showing small infarct core of right posterior MCA territory. MTT/TTP maps showing the mismatch between the volume of ischemic hypoperfusion, compared with the volume of infracted penumbra (43).

Artificial Intelligence

Artificial intelligence (AI) is machine intelligence that imitates human brain processes. Stroke medicine is an ideal application for AI because of the extensive volume of images, data and multidisciplinary pathways used in establishing clinical decisions **(44).**

Machine learning identifies patterns of imaging information and can provide accurate diagnoses in many instances. The two main machine learning techniques include; supervised and unsupervised learning. Another more advanced technique is “deep learning” which uses multiple layers of artificial neuronal networks mimicking the human brain, **(45).**

AI techniques can be used in patients with AIS to help with; (1) automated diagnosis and (2) prognosis **(45).**

Diagnosis:

Automatic lesion segmentation is an important element in dealing with huge datasets of brain imaging **(45).** Machine learning techniques have shown promising results for lesion volume prediction using supervised lesion segmentation algorithm in T1WI in chronic stroke cases **(46).**
ASPECTS is one of the areas where machine learning showed early success. The ASPECTS was automatically assessed using the e-ASPECTS software which is a standardized, fully automated, ASPECTS scoring tool. The e-

ASPECTS showed excellent results when compared with results of human ASPECTS readings **(17).**

Successful attempts has been made using machine learning for the demonstration of the hyperdense MCA on CT with a sensitivity of 97.5% **(47).** In addition the automated segmentation of intracranial hemorrhage (ICH) has been found to be more accurate for the estimation of the cerebral hematoma volume than conventional measurement method **(48).**

Prognosis

The prediction of symptomatic ICH risk in AIS patients has been attempted recently using machine learning of CT images. The CT brain scan images of AIS patients along with clinical severity were used as inputs into a supervised machine (SVM) learning model to help in predicting the risk of symptomatic ICH and results were found to be superior to those of established neuro-radiologists **(49).**

Conclusion

The imaging work-up of patients suspected of having AIS has significantly evolved over the past few years following the validation of EVT and the establishment of a wider window for the treatment of patients with AIS.

NCCT remains the mainstay for diagnosis and selecting patients for systemic thrombolytic therapy. CTA / MRA play a major role for identification of cases with LVO who might benefit from EVT. Perfusion imaging and DWI – Perfusion mismatch is being increasingly used for the quantification of salvageable brain tissue for selection of patients for EVT up to 24 hours treatment window.

AI has shown initial promising trials for the automatic diagnosis and segmentation of lesions as well as for prediction of prognosis.

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