Perfusion Imaging in Acute Ischemic Stroke

by

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Thesis Abstract

Background: Advancements in stroke imaging have allowed clinicians to more accurately select acute ischemic stroke patients for reperfusion therapies. This has moved patient selection from a time-based to an imaging-based paradigm. With few studies directly assessing the differences between various multimodal CT protocols, namely perfusion versus angiography, debate remains around the ideal imaging requirements for patient selection.

Methods: Patients in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial who underwent computed tomography (CT) perfusion imaging were analyzed for their perfusion patterns. The number and outcome of mismatch and non-mismatch patients was analyzed and compared against their angiographic profile. Then a direct comparison between perfusion (CTP) and angiographic CT imaging (CTA), specifically multiphase CTA (mCTA) was performed wherein imaging experts were given only the angiographic images and were tasked with identifying suitable patients for reperfusion therapy. These results were then compared against the semi-automated perfusion data obtained by the Apollo MIStar program.

Results: While most ESCAPE patients were found to have a penumbral pattern (90.6%), CTP identified non-penumbral patients that had a significantly poorer prognosis at 90 days. (mRS 0 – 2, 46% - 17%; p=0.041). In the direct comparison between CTP and mCTA, mCTA was relatively insensitive for a penumbral pattern (18.7%) with as many as 62.5% of large core patients being labelled as having moderate-good collaterals.

Conclusions: In both the ESCAPE analysis and direct perfusion-angiography comparison, perfusion imaging was superior in identifying target mismatch and non-mismatch patients who were likely to respond well and poorly to reperfusion therapies respectively. Perfusion imaging,

despite several limitations, allows for the most accurate and reliable selection of acute stroke patients.

Preface

This thesis is an original work by Robert Wannamaker. The research projects, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board: "CT Perfusion Versus Multiphase CT Angiography Comparison", Study ID MS2_Pro00071445, March 8, 2017. Chapter 3 of this thesis has been published as R. Wannamaker, T. Guinand, B.K. Menon, A. Demchuk, M. Goyal, D. Frei, A. Bharatha, T.G. Jovin, J. Shankar, T. Krings, B. Baxter, C. Holmstedt, R. Swartz, D. Dowlatshahi, R. Chan, D. Tampieri, H. Choe, P. Burns, N. Gentile, J. Rempel, A. Shuaib, B. Buck, A. Bivard, M. Hill, and K. Butcher, "CT Perfusion Predicts Poor Outcomes in a Randomized Trial of Endovascular Therapy" *Stroke*, vol. 49, No. 3, 1426-1433. I was responsible for the data collection and analysis as well as the manuscript composition. All authors assisted with the data collection and contributed to manuscript edits. K. Butcher was the supervisory author and was involved with concept formation and manuscript composition.

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Chapter 1 – Ischemic Stroke

Introduction

Ischemic stroke results from occlusion of a cerebral artery preventing perfusion of brain parenchyma. It is the leading cause of adult disability and third most common cause of death in Canada.[1,2] In 2013, approximately 405,000 Canadians (1.1%) were living with the effects of stroke, with an additional 13,000 deaths caused by strokes annually. With the aging population, these numbers are expected to increase. [3] Ischemic strokes comprise approximately 80 – 85% of all strokes, followed by intracerebral hemorrhage at 10 – 15 %. An acute ischemic stroke can have a variable presentation and prognosis based on many factors such as the etiology of the clot, location of the occlusions, the length of time the tissue is ischemic, the vasculature surrounding the occlusion or collateral blood flow to the ischemic tissue, and the history of the patient. These factors must be considered when deciding on treatment and predicting outcome.

Occlusion Characteristics

Thrombus Etiology

Two of the most common origins of an occlusion are cardioembolic, originating from the cardiac system and embolizing to a cerebral artery, and large-artery atherosclerotic, caused by stenosis and thrombotic formation in the blood vessels directly. [4] An embolism occurs when a clot originates in a different location than where the blockage occurs, such as what is seen in cardioembolic strokes. Atherosclerosis can also lead to an embolism when a clot breaks off from its origin and gets lodged into a distal, narrower blood vessel. It is important to discover the etiology of the stroke in order to determine whether further action needs to be taken in order to identify and treat other sources of clots through secondary stroke prevention. [5,6] Another key difference between clots besides origin is their composition, which can vary based on the stroke

subtype and age of the thrombus. [7] Fibrin-rich thrombi have more fibrin cross-linking and are more compact, making these clots more difficult to thrombolize, whereas fresher, red blood cell-rich thrombi have been found to respond more positively to thrombolysis. [8,9] This can greatly impact the success of therapy as a clot-busting agent may have decreased or no efficacy if the thrombus is too fibrin-rich.[10] Other factors such as calcification and size can have a significant impact on the efficacy of thrombolysis. [11] Understanding clot composition and etiology has a clear impact on both acute care and follow-up stroke prevention.

Occlusion Location

The location of the occlusion causing the ischemia can have a dramatic impact on clinical presentation, treatment decisions, and long-term prognosis. Clinical presentation is directly affected by the cerebral tissue experiencing ischemia, with symptoms ranging from motor and sensory impairments, language disturbances, impairments in consciousness, and memory deficits. Due to large overlap between vascular territories, however, clinical presentation remains only moderately reliable in stroke localization. [12] Anterior circulation strokes (ACS), involving either the internal carotid artery (ICA), the middle cerebral artery (MCA), or the anterior cerebral arteries (ACA) and their branches, have been more extensively studied compared to strokes in the posterior circulation (PCS) which include the basilar artery and posterior cerebral artery (PCA). This is due in part to the smaller occurrence of PCS (approximately 20%), along with the belief that PCS is associated with different risk factors, presentation, etiology, and prognosis, though some have challenged these assertions. [13] Within ACS, occlusions of the ACA are relatively rare (~3-5%) and have been less extensively studied regarding treatment effects and prognosis. [14,15] Due to the dramatically increased rates of reperfusion following mechanical

thrombectomy, proximal occlusions that are treated with endovascular therapy have higher rates of good outcomes 90 days following an ischemic stroke. [16]

Cerebrovasculature

Penumbra

Ischemia, the reduction of blood flow to brain parenchyma, is the primary consequence of an occluded blood vessel. The reduced blood flow prevents adequate blood perfusion in the capillary beds of the brain, therefore reducing the oxygen available to tissue. This hypoxic condition causes a failure in cells' electron transport chains, decreasing available ATP and leading to the failure of the Na^+-K^+ ATPase. This results in an influx of extracellular water into the cells and ultimately results in cell death. [17] The clinical presentation of stroke depends entirely upon the location of the ischemic territory, with symptoms ranging from language impairment to sensory and motor deficits. Ischemia is a dynamic process, with the length of time the tissue undergoes hypoxia being an important factor in whether the tissue will eventually infarct or not (Figure 1.1). [18,19] Infarction, or tissue death caused by ischemia, is also affected by the metabolic demands of the tissue undergoing hypoxia, along with the degree of blood flow reduction to the tissue and the state and amount of collateral blood flow to the affected tissue. During an ischemic event, some tissue may be receiving insufficient oxygen to function properly, but may still be viable for a certain time, given that blood flow is restored before infarction occurs (Figure 1.1). This salvageable tissue is the termed the penumbra, and is the key target of stroke therapies, as this tissue damage may be reversed. [17] Penumbral tissue can still cause clinical deficits and thus it is impossible to determine the degree of damage purely based on the onset time of the stroke and clinical presentation. More sophisticated imaging techniques have been developed to properly determine the extent of damage of an ischemic stroke.

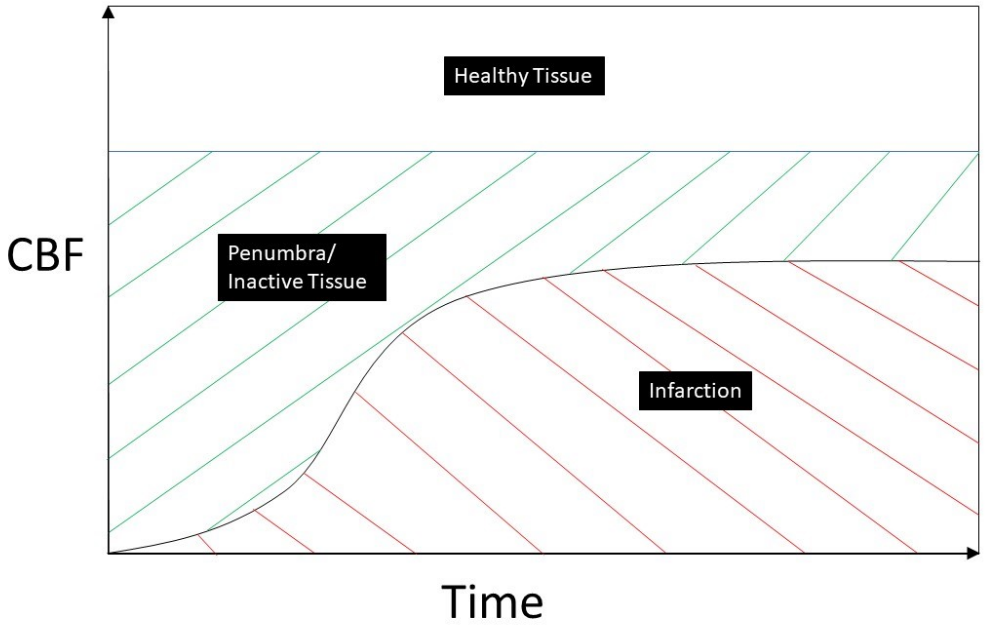

Figure 1.1 – The Relationship Between Cerebral Blood Flow and Time in Ischemic Tissue. **This Figure demonstrates the relationship between cerebral blood flow (CBF) and time during an ischemic event. There is a time-dependent threshold where the tissue changes from an electrically inactive but alive penumbral state to complete infarction. This figure highlights the time-sensitivity of acute ischemic stroke treatment, along with the necessity to be able to distinguish between penumbral and infarcted tissue as quickly as possible.**

Collateral Flow

An important factor that determines tissue salvageability is the extent to which alternative pathways can perfuse the affected tissue. Following an occlusion in the anterior circulation, leptomeningeal anastomoses, or pial collaterals, between the ACA and MCA have been found to contribute significantly to tissue prognosis. Good collaterals can prolong the time that a patient can have an occluded vessel and respond positively to thrombolysis. [20–22] This has become a target of imaging as patients with poor/no collaterals are unlikely to respond to treatment regardless of reperfusion of the tissue due to the extreme degree of hypoxia from a near complete ischemic state. Alternatively, the presence of moderate/good collaterals can be used as a

surrogate for blood flow imaging to approximate the presence of penumbral tissue. This has been used in large clinical trials in place of perfusion imaging. [23]

Risk Factors

Key risk factors for ischemic stroke include advancing age, atrial fibrillation, high blood pressure, and previous history of cardiovascular disease. Other factors that affect cardiovascular health can also increase the risk of stroke, including smoking, obesity, and diabetes or other diseases affecting glucose levels. [24]

Sex

There remains a sex difference in the mortality rate of stroke, due in part to the extended lifespan of women on average. Although men have an increased risk of having a stroke when age is controlled, the increased sex ratio with age in favor of women have caused an increased mortality and incidence rate of stroke in women, especially in older age. [25]

Age

Prevalence of stroke increases dramatically as patients age, with statistics from the American Heart Association estimating a prevalence ranging from 1.9-2.2% in patients aged 40 – 59 increasing to 14.0-15.8% in patients over 80. This is in large part due to increased risk factors affecting elderly populations, such as increased rates of both high blood pressure and atrial fibrillation. [26] The age of the patient has an impact on that patient's prognosis following an ischemic stroke. Older patients have higher rates of mortality and recurrent strokes, along with a significantly lower median survival time compared to younger patients. This increasing trend, however, is only true for patients over 40. Patients under 40 have mortality rates similar to patients over 70 years of age. [26]

Ethnicity

As various ethnicities will have different prevalence rates of the various risk factors, there is a significant difference in the incidence of all strokes and different types of strokes across different populations. Atherosclerosis, a key risk factor for ischemic stroke, has an increased prevalence in many Asian and African populations. This may not only translate to a different incidence of ischemic stroke between these patient populations but may also have a significant impact on treatment. Recent research suggests that due to the increased degree of stenosis in Asian populations, the risk of complications from treatment may be greater than the potential benefit from therapy. [27] These population differences need to be considered in both the clinical setting and when designing trials.

Secondary Complications

Hemorrhage

One of the primary concerns following recanalization of an occluded vessel is hemorrhagic transformation (HT) of the ischemic territory. As recanalization is the primary goal of treatment, HT is a common complication considered when deciding treatment. Although prediction of HT remains difficult, poor collaterals, severe hypoperfusion, and large cores at the time of recanalization are associated with higher rates of hemorrhage. [27–31] HT may be caused by several factors with the underlying pathophysiology not fully understood currently. Ischemia causes cellular and metabolic imbalances through disruption of the Na^+/K^+ ATPase that can affect the blood-brain barrier (BBB). Reperfusion injury, the resulting systemic effects of reperfusion including oxidative stress and inflammation, can lead to further BBB disruption that can cause edema and HT, in part through severe endothelial damage. [32–34] Furthermore, as ischemia

persists, the vasculature loses its ability to autoregulate cerebral blood flow. [35] Hyperemia through the infarcted tissue increases the likelihood of hemorrhage as the damaged blood vessels are unable to compensate and leakage occurs. HT can be classified as either a hemorrhagic infarction (HI), petechial hemorrhage with no mass effect, or as a parenchymal hemorrhage (PH), a hematoma with an associated mass effect. [36] Only PH is correlated with a poorer clinical outcome, occurring in approximately 3-7% of reperfusion therapy patients, and has become the safety measure of most stroke therapies. [16,37,38]

Treatment

tPA

Complete reperfusion remains the primary target of ischemic stroke therapy. Traditionally, this has been accomplished through intravenous injections of a recombinant tissue plasminogen activator (tPA) that converts plasminogen to plasmin, attacking fibrin-containing clots and allowing recanalization of occluded vessels. [39] Though use was initially restricted to within 3 hours of symptom onset, subsequent trials have found tPA to be safe within 4.5 hours and the drug remains the primary treatment for ischemic stroke patients. [38,40,41] Primary complications following tPA thrombolysis are reperfusion injury and hemorrhagic transformation, with the incidence rate of the latter increasing with later treatment and larger baseline infarct volumes. [33,42] The location of the occlusion can affect thrombolytic efficacy, with large vessel occlusions of the ICA having lower reperfusion rates compared to distal MCA occlusions. [43] One of the major drawbacks of tPA, besides variable efficacy based on the clot composition and location, is the systemic impact and multiple mechanistic pathways it has. While primarily a thrombolytic, research suggests that in different environments tPA can interact with many different substrates,

including NMDA receptors and various extracellular proteins, and may facilitate edema and cell death. [44] Intra-arterial administration of a thrombolytic agent, either alone or with mechanical clot retrieval, has been explored to increase the effects of the agent and decrease systemic effects with positive results. [45–47]

Other Thrombolytic agents

While tPA had been, until recently, the only thrombolytic agent approved for ischemic stroke patients, alternatives have been explored with different safety and efficacy profiles. Streptokinase and Urokinase were two of the first thrombolytics studied for use in acute ischemic stroke patients. While they both are cheaper than tPA and effective at degrading fibrin, their lack of localized specificity leading to increased fibrinogenesis has prevented any widespread use over tPA. [45,48] Tenecteplase (TNK), the only other thrombolytic agent approved for AIS patients, has a longer half-life, greater fibrin specificity, and decreased susceptibility to degradation, allowing for higher potency at smaller doses. [49] While it is still unclear whether or not TNK has superior efficacy compared to tPA, it has been found to have a similar safety profile and may have a larger treatment window at lower doses than tPA. [50–53]

Endovascular Therapy

Endovascular therapy (EVT), a mechanical thrombectomy approach, has emerged as a preferred therapy for select patients presenting with an acute large vessel occlusion (LVO) stroke. This treatment is associated with increased odds of independent recovery after stroke of 1.56 – 2.49 over standard medical care alone. [16,54–56] Seven recent trials since 2015 of EVT compared against standard of care alone demonstrated that EVT improves clinical outcome in patients selected with non-contrast CT (NCCT) and CT angiography or CT perfusion (CTP) (Table 1.1) up to 12

hours from symptom onset, considerably longer than the current guidelines for tPA (within 4.5 hours). This window was extended even further to within 24 hours in select CTP-selected patients. [57,58] This benefit is at least partially due to the high rates of reperfusion seen in EVT, with fewer systemic complications related to IV thrombolysis and no significant increase in symptomatic hemorrhage. [23,59–64] While endovascular therapy may be effective in PCS, most of the current prospective EVT trials have exclusively studied the treatment's impact in ACS. [16]

Table 1.1 – Recent Trials Comparing Endovascular Therapy to Standard of Care

Trial	Time from Symptom Onset	Good Functional Outcome (mRS<3)	Good Functional Outcome Odds Ratio	tPA in Intervention Arm	Reperfusion Rate (mTICI>/2b)	sICH
ESCAPE[23], 2015	12 hours	53%	3.1 (2.0 – 4.7)	120/165 (73%)	72%	3.6%
EXTEND IA[61], 2015	6 hours	71%	4.2 (1.4 – 12.0)	35/35 (100%)	86%	0%
MR CLEAN[62], 2015	6 hours	33%	2.2 (1.4 – 3.4)	203/233 (87%)	59%	7.7%
REVASCAT[59], 2015	8 hours	44%	2.1 (1.1 – 4.0)	70/103 (68%)	66%	1.9%
SWIFT PRIME[60], 2015	6 hours	60%	1.7 (1.2 – 2.3)	95/95 (100%)	88%	0%
THRACE[63], 2016	5 hours	53%	1.6 (1.1 – 2.3)	200/200 (100%)	69%	2%
PISTE[64] , 2017	tPA within 4.5 hours	57%	4.92 (1.23 – 19.69)	30/30 (100%)	87%	0%

(ESCAPE - Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA - Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial; MR CLEAN - Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS – modified Rankin Scale; mTICI – modified treatment in cerebral ischemia; PISTE - Pragmatic Ischaemic Stroke Thrombectomy Evaluation; REVESCAT - Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; sICH – symptomatic intracranial hemorrhage; SWIFT PRIME - Solitaire™ With the Intention For Thrombectomy as Primary Endovascular Treatment; THRACE - Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke, tPA – tissue plasminogen activator)

Time-Window Limitations

As previously discussed, the current standard of care for stroke treatment uses a treatment window of 4.5 hours for IV thrombolysis and 6 hours for EVT, although these windows may be extended with select imaging criteria based on recent findings. This creates a sub-population of ischemic stroke patients that are currently untreatable known as wake-up stroke patients. As the current standard is based on the time of symptom onset, and it is often unclear as to the time of the ischemic event in wake-up strokes, physicians are forced to use the time last seen well as a surrogate for the start of the stroke. This leads to a large population (15-25%) of stroke patients that fall out of the treatment window despite possibly benefiting from thrombolysis. [65] One of the issues with the time-last-seen-well model is that current research suggests ischemic events likely cause many patients to wake up and thus time-last-seen-well vastly over-estimates the length of time the patient underwent ischemia. [66] Furthermore, recent imaging work supports a tissue-based approach to treatment selection that would allow wake-up strokes with specific imaging patterns, namely a small established core with good collaterals or a significant amount of penumbral tissue, to be treated with relatively positive prognosis. [53,57,58]

Prognosis

The main target of ischemic stroke treatment is full recanalization and reperfusion of the brain parenchyma. Although recanalization, the removal of the occlusion and subsequent return of blood to a vessel, and reperfusion, blood perfusion returning to the affected area, often occur at the same time, reperfusion has been found to be a better predictor of both clinical and imaging outcomes and has thus become the primary target of treatment. [67] Achieving a Modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or 3, anterograde perfusion of at least half of the downstream ischemic territory, has been found to most strongly correlate with a good

prognosis (functional independence at 90 days), with earlier reperfusion increasing the likelihood of a good outcome. [68] Results from the recent HERMES meta-analysis which included trials with LVO patients with moderate strokes found that patients treated with current standard of care (tPA within 4.5 hours) had a mortality rate of 18.9% and functional independence rate of 26.5%. The functional independence was increased to 46.0% in EVT patients with no significant change in mortality or hemorrhage. [16]

Summary

Acute ischemic stroke, a leading cause of death and disability especially in elderly populations, costs the Canadian healthcare system billions of dollars annually. [69] The occlusion of an artery and resulting ischemia has substantial impacts on the brain parenchyma and can have variable etiologies and presentation, making diagnosis and treatment difficult. The clinical presentation is directly affected by the location and severity of the stroke, along with the length of time the tissue has been ischemic and the properties of the tissue. Therapy options for ischemic stroke continue to evolve, with multiple intravenous drug options being currently available along with mechanical removal of the clot in patients with a large vessel occlusion. Effective selection and treatment of stroke patients, whether through clinical manifestation, onset-to-treatment time consideration, or imaging patterns, have the potential to drastically reduce the cost of stroke while improving the overall prognosis of millions of patients. [70,71]

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Chapter 2 – Imaging in Stroke

Introduction

Neuroimaging has been used as the gold standard to diagnose stroke, differentiate hemorrhage and ischemia, guide treatment decisions, and predict prognosis. There are many different stroke mimics that can clinically present identical to an ischemic stroke which may account for up to 30% of "brain attack" patients. [1] While clinical presentation and time from onset has traditionally been used as a strong guiding factor in stroke treatment, neuroimaging has become an indispensable tool in stroke care for both establishing a differential diagnosis and deciding the treatment course in patients presenting with stroke-like symptoms. As research continues and the understanding of neuroimaging grows, moving to an imaging-determined tissue-based approach to patient selection could improve not only long-term prognosis but also increase the number of treatable patients, as currently less than 15% of acute stroke patients are treated, due in part to the narrow treatment window. [2] Selective therapy also lowers the overall cost of stroke on the healthcare system as it reduces the impact of disability following a stroke. [3,4] As thrombolytic therapy is expensive and increases hemorrhagic complications, selecting patients with the greatest benefit:cost ratio is essential. Finally, neuroimaging can give insights into the overall impact of the stroke and the treatment used, and the prognosis of the patient. These goals can be achieved through various imaging techniques that rely on different principles, from angiography versus perfusion imaging to computed tomography (CT) versus magnetic resonance imaging (MRI). Stroke clinicians use various combinations of these imaging tools to diagnose the clinical event, determine the etiology of the stroke, decide on the best course of action in treatment, and determine prognosis.

Non-Contrast Imaging

Non-Contrast CT

The first goal of a clinician when presented with a patient with stroke-like symptoms is establishing an accurate differential diagnosis that rules out stroke mimics and establishes whether the stroke is ischemic or hemorrhagic in nature. The first and most commonly used imaging tool, owing in large part to being relatively cheap, widespread, and quick to use, is non-contrast CT (NCCT). This uses X-ray beam attenuation to image brain parenchyma, with the degree of attenuation being directly proportional to the density of the tissue. [5–7] Due to the different densities between blood and brain tissue, NCCT can be used to quickly and accurately differentiate between intracerebral hemorrhage and an ischemic stroke with high reliability. Furthermore, as differences in water concentration creates variation in the density of brain parenchyma, NCCT is able to identify early ischemic damage as metabolic imbalances causes water to move intracellularly in dying cells. [8,9]

The Alberta Stroke Program Early CT Score (ASPECTS) is a qualitative grading system developed on NCCT that scores 10 different areas supplied by the middle cerebral artery (M1-M6, insula, caudate, internal capsule, and lentiform) on the presence or absence of early ischemic changes (Figure 2.1). ASPECTS has been used to predict the damage and prognosis of ischemic stroke patients in the hyperacute (6 hour) setting with mixed success. [10,11] While the ASPECTS system has been found to have a moderate ability to predict final infarct volume and clinical deficit on NCCT, with a strong correlation existing between ASPECTS and likelihood of good clinical outcome, several studies have shown that CT angiography (CTA) and CT perfusion (CTP) may be superior imaging tools to use with ASPECTS. [12–14] Additional limitations in the ASPECTS system exist that decreases its universality and accuracy. [15] The ASPECT regions are described on slices at the basal ganglionic and immediate supraganglionic level, which has led to

criticism that this only includes approximately 50% of the MCA territory.[16] The ASPECT score is in fact intended to reflect ischemic changes inferior and superior to these two levels, i.e. the entire MCA territory.[11] Although the ASPECT score can be used to quantify the degree of early infarction, scores vary with experience.[15] Any ischemic change within individual ASPECT regions should result in a decrease of 1 point, but this approach is not universally applied, particularly when only a portion of the region is affected. These differences in interpretation of ASPECT scoring rules likely contribute to the relatively poor inter-rater reliability in some studies.[14,17] Nonetheless, in experienced hands, inter-reliability of ASPECT scoring has been shown to be reasonable and predictive of outcome, as well as response to therapy.[11,15]

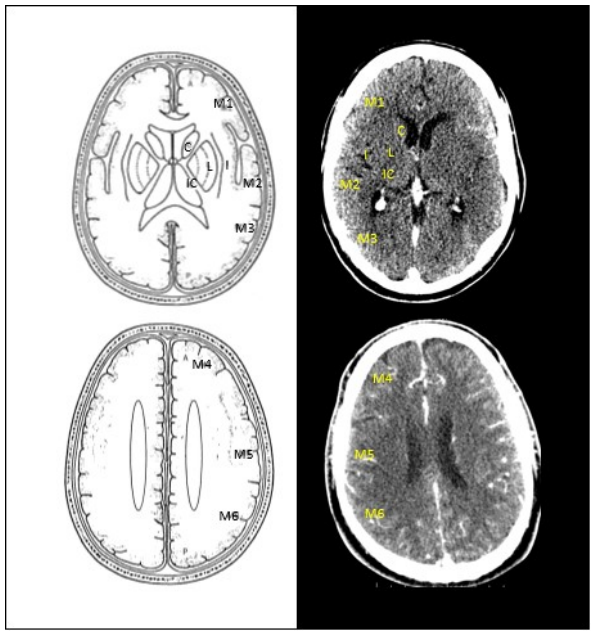

Figure 2.1. Alberta Stroke Program Early CT Score (ASPECTS) Template. A comparison of the ASPECTS system (left) in an acute ischemic stroke patient (right). ASPECTS is scored out of 10 based on 6 MCA cortical regions (M1-M6), the caudate (C), lentiform (L), internal capsule (IC), and insula (I). [10]

One explanation for the decreased accuracy of NCCT compared to other imaging techniques is the limited change in signal immediately following an ischemic event. [14] Within the first 3 hours from symptom onset, a critical time period for treatment, minimal changes can be reliably seen

on NCCT alone. [18] Additionally, early ischemic changes seen on non-contrast CT may not significantly impact the overall treatment of the patient. [19,20] When compared against MRI, specifically diffusion-weighted MRI (DWI), NCCT has only moderate sensitivity and specificity for ischemic lesions, making it a quick and easy but only moderately accurate tool. [21] Due to these limitations, although NCCT is still routinely used as a first response to diagnose an ischemic stroke, and 'frank hypodensity' is still considered an exclusion criteria for thrombolysis on NCCT, significant early ischemic changes on NCCT (more than 1/3 of the MCA territory) is no longer considered sufficient to withhold treatment. [22]

DWI

As discussed previously, immediately following an ischemic event, water moves intracellularly due to failure of the cells' ATPase. This results in restricted water diffusion in affected tissue. [23] MRI sequences that are diffusion weighted, such as DWI and maps of apparent diffusion coefficient (ADC), give fast and reliable images of infarction. Numerous studies have validated DWI as the 'gold-standard' for core imaging in both the hyperacute and the initial subacute (within approximately 1 week) setting over NCCT imaging. [21,24] This has led to DWI being used extensively in follow-up imaging to determine final stroke volume or for viewing smaller lesions not as easily detected on NCCT. As other factors can cause a hyperintense signal on DWI, such as the T2 shine-through effect whereby tissue with high T2 signal appears bright on DWI, ADC maps are used to confirm the signal is due to restrictions in water diffusion specifically. While DWI is accurate in the subacute phase of stroke, pseudonormalization may occur between 7-14 days after the ischemic event. ADC values begin to rise around 72-96 hours following ischemia, appearing normal approximately 7 days after the stroke due to cellular breakdown leading to extracellular edema. [25] Initially, DWI lesions will still be visible due to T2 shine-through in the

tissue, however as ADC values continue to rise, the DWI may appear normal 10-14 days following the event. [26] This pseudonormalization must be considered when viewing DWI several weeks following an ischemic stroke.

The limitations present with DWI, aside from considering pseudonormalization, largely concern the availability and speed with which an emergency patient can receive MR imaging. While some studies have found MR imaging to be effectively implemented in the hyperacute phase, the universality, speed, and simplicity of NCCT have prevented MR imaging to be used widespread in the hyperacute setting. [27]

Angiography

CT Angiography

After ruling out the presence of a hemorrhage or clear contraindication to treatment such as a stroke mimic (e.g. tumor) on NCCT imaging, angiography is commonly used to identify the presence and location of the occlusion. This is primarily accomplished using CT angiography (CTA), a CT technique that images the brain at a single time point as vessels are enhanced by an iodine contrast agent. This allows for a sensitive identification of a thrombus, along with an analysis of the carotid arteries and subsequent branches, aiding in identifying the etiology of the stroke. This scan can be performed immediately following a NCCT and adds minimal time to the procedure, allowing for a quick and efficient imaging of the cerebral vasculature. This further supports the diagnosis of stroke, adding validity over NCCT alone that symptoms are due to an ischemic occlusion. The absence of an occlusion, however, does not exclude the possibility of an ischemic stroke, for as many as 39% of stroke are not caused by CTA visible occlusions and may require further imaging. [28,29] These can be due to either small lacunar strokes, which account for

approximately 25-35% of ischemic strokes, or distal MCA occlusions too small to be visible on CTA. [30,31] In addition to the diagnostic value, the identification of the thrombus location can qualify the patient for endovascular therapy (EVT) provided a large-vessel occlusion (LVO) is present. The efficacy of EVT over tPA in LVO patients has been well documented and the quick, reliable identification of LVO patients can be extremely beneficial to this subgroup of ischemic strokes. [32] Finally, CTA gives some insight into the extent of the collateral circulation in patients, providing a moderately reliable predictor of response to treatment and infarct volume. Leptomeningeal anastomoses (Figure 2.2), or pial collaterals, between the ACA and MCA have been found to contribute significantly to collateral circulation following an MCA occlusion. [33–35] These collaterals are thought to increase the time tissue can withstand ischemia as they provide an alternative source of blood flow. The presence of good collaterals has been positively associated with a better outcome following reperfusion therapies and has become a more accurate measure of the extent of the ischemic core over NCCT alone. [36]

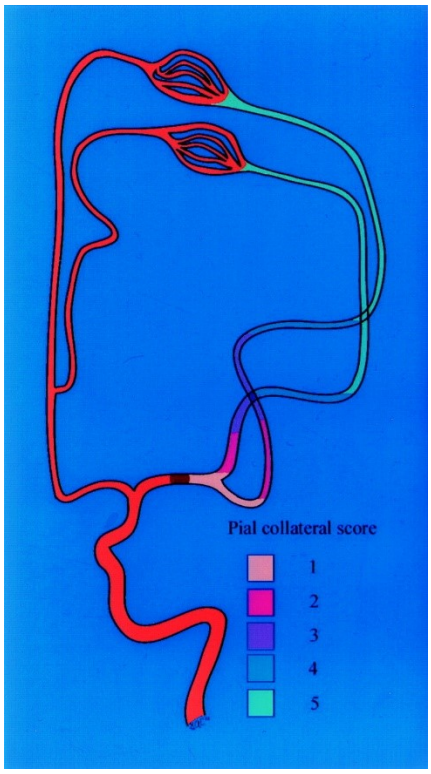

Figure 2.2. Collateral Flow Following an Occlusion. This figure highlights the path of leptomeningeal pial collateral flow and different degrees of collateral filling via leptomeningeal anastomoses from the ACA to the MCA following an M1 occlusion.[34]

Collateral Grading

The extent of collateral vessel filling on CTA can be assessed qualitatively, i.e. 'good' or 'poor'. As with all subjective assessments, inter-rater variability is significant and varies with experience.[37] A number of rating systems have been developed in an effort to standardize CTA assessment of collateral flow and improve the selection of patients for treatment (Table 2.1). These rating systems range from simple and fast methods of scoring collaterals to more complex systems that attempt to increase the accuracy of only selecting patients likely to respond well to therapy. Rating or scoring is based on the presence of vessel contrast opacification within the affected cerebral arterial territory. [36,38–41] Regional rating of collateral flow, based on an adaption of the ASPECT score, has also been proposed.[42]

Table 2.1. CT Angiographic Collateral Grading Systems for Acute Ischemic Stroke.

Kim[38] *	ASITN[43]	Miteff[36]	Maas[39] AND Rosenthal[44]	Lima[45]	Menon (ASPECTS)[42] **
Grade 0 • Absence of capillary blush in ischemic site	Grade 0 • No visible collateral	Poor • Superficial distal vessel filling	Grade 1 • Absent collaterals	Grade 1 • Less than contralateral side	Poor • Score of ≤ 10
Grade 1 • Collaterals to the periphery of ischemic site	Grade 1 • Slow collaterals to the periphery of the ischemic site	Moderate • Vessels seen at the Sylvian fissure	Grade 2 • Less than contralateral side	Grade 2 • Equal to contralateral side	Intermediate • Score of 11 - 16
Grade 2 • Complete irrigation of ischemic site via collaterals	Grade 2 • Rapid collaterals to the periphery of ischemic site and a portion of the ischemic territory	Good • Vessel filling in entire MCA distal to the occlusion	Grade 3 • Equal to contralateral side	Grade 3 • Greater than contralateral side	Good • Score of 17 - 20
Grade 3 • Normal, anterograde flow	Grade 3 • Slow but complete blood flow to the ischemic site		Grade 4 • Greater than contralateral side		
	Grade 4 • Rapid complete blood flow to the entire ischemic territory by retrograde perfusion		Grade 5 • Exuberant		

Table 2.1. CT Angiographic Collateral Grading Systems for Acute Ischemic Stroke. (continued)

Tan[46]	Yeo[40]	Demchuk (ESCAPE)[47]	Menon (CTA)[48]	Menon (mCTA)[48]	D'esterre[49] ***
Absent • absent collateral supply to the occluded MCA territory	Absent/Poor • Collateral supply filling <50% of ischemic site	Absent/Poor • collateral supply filling <50% of the occluded MCA territory	Grade 0 – Poor • no visible vessels in ischemic territory	Grade 0 – Poor • no visible vessels in ischemic territory	Poor 1. No washout 2. 2 phase delay of peak 3. 0 – 50% collateral filling
Poor • collateral supply filling ≤50% but >0% of the occluded MCA territory	Moderate/Good • Collateral supply filling ≥50% of ischemic site	Moderate • collateral supply filling ≥50% but <100% of the occluded MCA territory	Grade 1 – Poor • Few vessels visible in the occluded vascular territory	Grade 1 – Poor • Few vessels visible in the occluded vascular territory in any phase	Moderate 1. Delayed/incomplete washout 2. 1 phase delay of peak 3. 50 – 99% collateral filling
Moderate • collateral supply filling >50% but <100% of the occluded MCA territory		Good 100% collateral supply of the occluded MCA territory	Grade 2 – Moderate • Decreased prominence and extent and regions with no vessels in the ischemic territory of the affected hemisphere	Grade 2 – Moderate • 2 phase delay with decrease in extent and prominence **OR** • 1 phase delay with regions lacking any vessels	Good 1. Complete washout 2. No Phase delay of peak 3. Normal collateral filling
Good • 100% collateral supply of the occluded MCA territory			Grade 3 – Moderate • moderately reduced prominence and extent of pial vessels in the ischemic territory	Grade 3 – Moderate • 2 phase delay OR • 1 phase delay with significantly reduced number of vessels filling	
			Grade 4 – Good • Slightly reduced prominence and extent of pial vessels in the ischemic territory	Grade 4 – Good • 1 phase delay with normal prominence and extent	
			Grade 5 – Good • Normal pial vessel enhancement	Grade 5 – Good • Normal pial vessel enhancement, no delay	

* A score between 0 – 3 is assessed for 15 different vascular territories guided by the ASPECT scoring system

**Scores are given based on the ASPECT scoring system. M1 – M6, ACA, and the basal ganglia are given a score of either 0 (artery not seen), 1 (artery less prominent than contralateral side), or 2 (arterery equally or more prominent than contralateral side). The sylvian sulcus is also given a score of 0 (artery not seen), 2 (artery less prominent than contralateral side), or 4 (artery equally or more prominent than contralateral side).

*** A score between 1-3 is given for each parameter: delay, extent, and washout.

ACA – Anterior cerebral artery; ASPECTS – Alberta Stroke Program Early CT Score; CTA – Computed tomography angiography; MCA – Middle cerebral artery; mCTA – multiphase

Multiphase CTA

Conventional CTA uses a single time point, or phase, to assess the cerebral vasculature and collateral circulation based on the time with peak arterial contrast agent. Multiphase CTA (mCTA), a variation on conventional single-phase CTA (sCTA), acquires an additional 2 phases 8 seconds apart each. It has been developed to combat some of the limitations present in sCTA and provide a more accurate assessment of collaterals and infarct volume.[48,50] Proponents of mCTA claim that by using three different cerebrovascular metrics, (delay of filling, extent of filling, delay of washout), mCTA can be used to predict tissue fate similar to CTP ASPECTS quickly and with minimal technical applications necessary (Figure 2.3). [49] Limitations persist in mCTA that prevents widespread use, however. These limitations include decreased accuracy in the M1 and striatocapsular regions due to beam-hardening artifacts and difficulty interpreting vessel filling, an inability to rule out stroke mimics and small vessel occlusions, minimal use in PCA strokes, and minimal validation through randomized controlled trials (RCTs). [49] The most significant limitation of mCTA, however, is that it allows assessment only of the macrovascular vessels. In order to demonstrate changes at the tissue level, an assessment of the microcirculation is required. A subgroup analysis of the ESCAPE trial identified as many as 10% of patients that were included based on sCTA and mCTA criteria that did not meet CTP criteria, and who subsequently had larger final infarct volumes and poorer prognosis at 90 days compared to patients who did match CTP criteria. [51] Finally, as with sCTA, mCTA uses timing mechanisms to try and capture the arterial and venous phases in order to accurately assess filling delays. As these are not directly based off concentration curves, such as in CTP, the timing of the phases may be inaccurate and lead to improper assessments of collaterals and core volumes. This is especially true in patients with flow-limiting stenosis or poor cardiac function. [48]

DSA

While CTA is the most commonly used angiographic tool in the acute setting due to the widespread use of CT, the ease of use, and time efficient nature, there remains other options that are available that give additional information. Digital subtraction angiography (DSA) is a catheter-based iodinated contrast imaging tool that uses x-rays to look at the brain vasculature and is used in the process of endovascular therapy. Additionally, due to the subtraction of the mask image, recent research has looked at using DSA images to create perfusion maps, described below, providing an alternative to CTP (*In Press*). Furthermore, as DSA is used to guide EVT, it can provide a real-time assessment of not only the success of the recanalization, but whether reperfusion occurs or whether the patient is at a higher risk of hemorrhage due to severe, persisting hypoperfusion. While CTA will likely continue to be the primary angiographic tool as it can be run directly following the routine NCCT, additional research into DSA may provide a quantifiable prognostic tool that can be used directly following EVT.

Perfusion

Fundamentals

Based on previously discussed imaging methods, standard practice in the past has focused on qualitative evaluation of an ischemic event. Stroke treatment had focused on a time-based inclusion method for selecting patients for thrombolysis, using stroke imaging, whether through NCCT visualization of the ischemic core or angiographic visualization of the collateral status, as exclusion criteria for thrombolysis. This practice presents two key limitations to effective treatment. First, a time-based selection for thrombolysis excludes a large number of potential patients that could benefit from thrombolysis, namely patients with wake-up strokes and patients with large penumbras and slow evolving ischemic cores that are outside the treatment window Conversely, this practice may treat patients within the time window with completed infarcts that would not benefit from treatment,

regardless of their reperfusion status. Second, while qualitative imaging can give insights into vasculature status and infarct core volumes, these tools are both subjective and only moderately reliable. Due to these limitations, perfusion imaging has emerged as a potential means of accurately selecting potential patients for reperfusion therapies based on quantitative measures of perfusion and tissue status.

Perfusion imaging is based on non-diffusible tracer kinetics and the central-volume principle that relates cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) (MTT=CBV/CBF). Image acquisition is performed by imaging a contrast agent as it passes through the brain over time. Each perfusion imaging technique uses a unique contrast agent based on principles of that tool. Images are then post-processed by an imaging program to give quantitative perfusion values. In the program, a venous output function (VOF) and an arterial input function (AIF) are selected on the source images. CBV is used to normalize quantitative perfusion metrics and requires the selection of a pixel that is solely vascular, the VOF. The superior sagittal sinus is the most commonly selected VOF and used in CBV calculation as it is constant, large, and often orthogonal to acquisition. [52] The AIF is used to represents the contrast agent input into a region of interest (ROI). Knowing the contrast input into an ROI allows for the calculation of the residue function R(t), a time-concentration curve that is proportional to the CBF in that tissue. Finally, as often only a single AIF is selected, and thus not representative of an instantaneous injection into every ROI across the brain, mathematical models known as deconvolution models corrects for these errors and allows for an accurate estimation of perfusion in an ROI. Delay-corrected singular value decomposition (SVD) is a widely used model that has been found to accurately correlate with validated perfusion values for healthy patients using other techniques such as positron emissions tomography. [53] Using SVD, values for CBV, CBF, and MTT can be calculated using figure 2.3, with other values such as time-to-peak (TTP) and delay time (DT) also being able to be calculated from the graph (Figure 2.3).

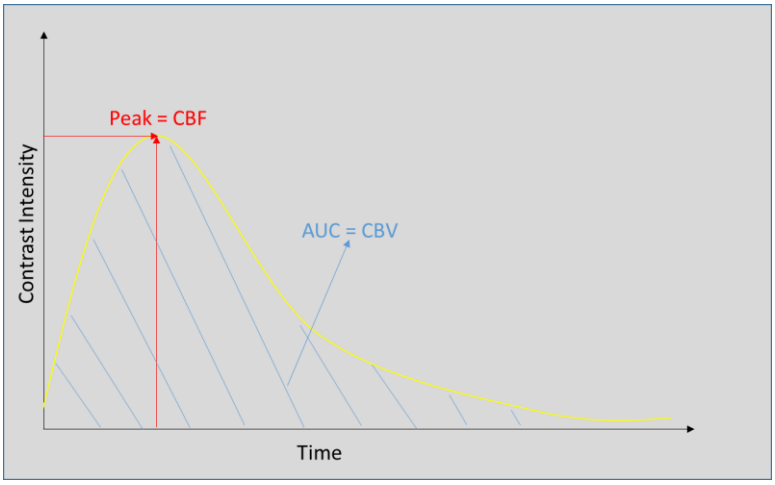

Figure 2.3. SVD Model of Perfusion. This model illustrates how CBF (red) and CBV (blue) are calculated by the R(t) curve for each pixel. CBF is calculated as the amplitude of the peak of the curve, whereas CBV is equal to the area under the curve (AUC).

CTP

Similar to the advantages of CTA, due to the widespread availability of CT and the ease of adding the perfusion scan following a NCCT, CTP remains the most dominantly used perfusion imaging tool. [54] CTP uses an iodinated contrast agent to image perfusion through the brain, a relatively safe and well-studied agent with low rates of life-threatening reactions from patients (~0.2%). [55] Accuracy and reliability of stroke diagnosis is improved with the addition of CTP over NCCT alone. [56] As discussed earlier, due to the large variability in the amount of tissue in each ASPECTS region, NCCT ASPECTS has large variability in terms of baseline core on CTP and final infarct volume. [57] Furthermore, early work comparing CTP to MRI has found that CTP has moderate/good accuracy at predicting final infarct size. [52,58] CTP has been effectively used in patient selection for tissue plasminogen activator (tPA), tenecteplase (TNK), and endovascular therapy (EVT). [59–63]

Patient selection is based on a target mismatch pattern of sufficient (>15 mL) penumbral tissue with a relatively small core that minimizes hemorrhagic transformation risk. Historically, a common

mismatch pattern of <70 mL of core ischemic tissue (core), >15 mL of salvageable tissue (penumbra), and a mismatch ratio of total perfusion deficit:core of >1.8 has been used. [64] The current definitions of core and penumbral tissue vary based on the program, with a commonly used threshold of DT>3 seconds for penumbral tissue and a double threshold of rCBF<30% and DT>3 seconds for core tissue. [65] The currently used target mismatch may not have the same accuracy and utility in all stroke patients, however. As seen in the Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) trial, core volume targets may change based on age, as older (>80 years old) patients have poorer prognosis than younger patients. Additionally, as the effect of more effective treatments such as EVT are yet to be fully understood, the currently describe thresholds for core tissue may overestimate what can be salvaged after successful treatment. Furthermore, as there is a delay between CTP image acquisition and treatment, the processed maps may be inaccurate at the time of therapy. This concept was proposed as one of the reasons why patients imaged and treated relatively later after stroke onset were able to achieve higher rates of good prognosis, as patients still presenting with a mismatch pattern so long after the ischemic event were unlikely to have significant change in degree of infarction between imaging and recanalization. [66] Finally, there may be cases where treatment is still preferred in the large core group, provided sufficient mismatch pattern is achieved, although a poorer prognosis relative to smaller core patients is still to be expected.[67] Regardless, target mismatch patterns have been shown to be an effective means of selecting patients for therapy outside the current standard of a time-from-symptom-onset based paradigm.

Several limitations of CTP hamper its widespread use outside of a research setting. First, as there are several different methods of deconvolution, variability in the total acquisition time, number of time points, and brain coverage, along with several different post-processing programs, a standard practice of CTP imaging has yet to be determined. This includes different methods of describing the

core/penumbra, such as using different combinations of CBV, CBF, MTT, TTP, and DT based on the mathematical model used. Second, while post-processing is semi-automated, AIF/VOF selection and correcting for patient motion can necessitate manual corrections which can delay treatment. Finally, the complications associated with radiation are increased with CTP, as the need for multiple scans over a period of time means CTP exposes patients to more radiation than NCCT or CTA. While the radiation received from a single CTP protocol are well below the thresholds for complications in most patients, and changing certain practices such as reducing the number of scans, increasing the time between scans, and using dose reduction functions have all been found to effectively reduce radiation without sacrificing accuracy, the increased radiation of CTP does remain a concern of many clinicians. [68,69] For these reasons, some argue faster, qualitative tools which require no post-processing such as CTA/mCTA are sufficiently accurate given their speed, although no direct comparison has described how mCTA compares to quantitative maps of CTP.

Perfusion-Weighted MRI

Contrast-enhanced perfusion-weighted imaging is possible on MR imaging (PWI) using a gadolinium contrast agent. Gadolinium (Gd) causes a decrease in signal intensity on T2* imaging directly due to its paramagnetic effects. Similar to CTP imaging, multiple images from the brain can be taken over time as the Gd travels through the vasculature, with each voxel having a change in signal intensity proportional to the concentration of Gd in that voxel. From these concentration curves, hemodynamic properties such as CBV, CBF, and MTT can be calculated to give perfusion values. While these values in PWI are often only relative values, due to the complex nature of the relationship between signal intensity and absolute concentration of Gd contrast, absolute values can be obtained by normalizing the values against either other imaging modalities or known values in the brain (e.g. Healthy white matter has a CBF of 22 mL/100 g per minute).

Several key limitations exist for PWI that have hampered its use in the clinical setting. First, as discussed with DWI, universality of CT imaging has hampered routine use of PWI in the hyper-acute stage over CTP. Second, PWI retains the same pitfalls of CTP post-processing, namely issues with delay and dispersion and differences in values depending on the deconvolution model used. Furthermore, properties of PWI related to MR add additional error, such as the previously discussed non-linear relationship between signal intensity and Gd concentration, along with varying T1 effects on signal. Finally, the contrast agent itself, Gd, has been associated in rare cases with nephrogenic systemic fibrosis, a severe and sometimes fatal reaction.[70] Due to the risk to patients, many MRI units now prohibit gadolinium administration unless the renal function is known, or if the glomerular filtration rate is <30 mL/min/1.73m^2, signalling proper kidney function.[71,72]

Arterial Spin Labelling

Arterial Spin Labelling (ASL) is an MRI technique developed to allow for perfusion MR imaging without the need for invasive contrast agent administration such as Gd. ASL involves paramagnetic labelling of water molecules in the blood of arteries supplying the brain, and when these labelled water molecules are exchanged into tissue at the capillary level, it gives a perfusion-weighted signal.[73] ASL takes paired images, a pre- and post-labelled image, when subtracted gives signal intensity proportional to CBF.[74] Though ASL is thought to give values of CBF, one study have shown that it more closely correlates with time-to-peak (TTP) values from PWI, suggesting that ASL-CBF and PWI-CBF are not measuring the same processes.[75] ASL has been found to have similar accuracy in the clinical setting at determining acute perfusion lesions as both PWI and CTP.[76]

ASL has several factors that makes it a superior technique to PWI. Not only does ASL not require the same invasive contrast agent that PWI requires, but it has been shown to more accurately identify tissue that has successfully reperfused. Penumbral tissue that has successfully reperfused may appear either

normal or hyperperfused on ASL and tissue that has not reperfused remains hypoperfused. Currently, hyperperfusion remains an area of interest to stroke researchers as the spatial and temporal properties of the hyperperfusion may predict the patient's prognosis. Hyperperfusion is thought to be due to a temporary loss of regulatory functions in the tissue to balance the increased blood flow following reperfusion. Within infarcted tissue, this hyperperfusion has been associated with an increased risk of hemorrhagic transformation.[77] In penumbral tissue surrounding infarcted tissue, however, some research suggests this hyperperfusion may be protective and be predictive of a more positive prognosis.[78] It is important to define hyperperfusion when using different imaging tools, however, as ASL looks at changes to CBF and does not account for compensatory changes in CBV which may lead to normal MTT values. This is in contrast to CTP where multiple factors, such as MTT and DT are used to describe perfusion. Additional research is clearly needed to allow physicians to more accurately determine subsequent treatment and prognosis for their patients.

One potential caveat of ASL imaging is the very short half-life of the labelled water molecules. As the molecules are magnetically labelled, they have decay with a T1 relaxation time of approximately 1-2 seconds. This can cause a significant underestimation of CBF and therefore an overestimation of hypoperfusion, with some research suggesting as much as a 30% overestimation when ASL was compared to optimal PWI thresholds.[75] Another potential limitation with ASL is a low signal to noise ratio (SNR) that can make accurate estimation difficult. This can at least partially be overcome by increasing the scan time and acquiring more paired images, increasing the field strength of the magnet, and using a pseudocontinuous ASL protocol instead of pulsed or continuous.[73,79] Finally, as mentioned earlier, it is important to remember that ASL only looks at CBF and thus gives a limited picture of parenchymal hemodynamics, especially when compared to the acute CTP. Due to these issues and the persisting lack of research interest into ASL, this imaging tool has yet to be adopted into routine clinical use.

Multimodal CT in Reperfusion Trials

Patients with a large ischemic penumbra and small infarct core are the ideal candidates for acute treatment, irrespective of time from onset.[80] Patient selection in stroke trials have evolved from utilizing simple non-contrast imaging alone to full multimodal CT (Table 2.2). The original thrombolysis studies did not use any blood-flow imaging as inclusion/exclusion criteria. A non-contrast CT was used largely to exclude patients presenting with ICH or extensive early infarction.[81–83] Despite this, the NINDS trials demonstrated the superiority of alteplase treatment within 3 hours of stroke onset.[81] This approach was later shown to be effective up to 4.5 hours after onset, albeit with an increased number needed to treat in the 3-4.5 hour window.[84] This reflects the large number of patients within 3-4.5 hours from symptom onset have penumbral patterns. The number of patients with penumbral patterns, however, reduces quickly as time progresses, with clinical symptoms being an imperfect marker of penumbral status. Recent perfusion studies utilizing CTP have demonstrated that there are a large number of non-penumbral patients even when imaged within 3 hours.[63,85–87] These same studies have shown that many patients have significant penumbral tissue persisting well beyond 3 hours after stroke onset, further demonstrating the limitation of a time-based approach to patient selection for reperfusion therapies

Table 2.2. Multimodal CT imaging Criteria in major stroke trials

Trial	Time Window	Intervention/ Control	Sample Size	Treatment Effect (Good Clinical Outcome) *	NCCT	CTA Required	CTP Required (Software used)	Advanced Imaging Criteria
NINDS[81]	0-3 h	IV Alteplase/placebo	333	+13%	✓			
ECASS[82]	0-6 h	IV Alteplase/placebo	511	+12%	✓			
ECASS 2[83]	0-6 h	IV Alteplase	800	+8.9%	✓			
PROACT[88]	0-6 h	Intra-arterial Pro-UK	105	+2%	✓			
ATLANTIS[89]	3-5 h	IV Alteplase	547	+8%	✓			
PROACT 2[90]	0-6 h	Intra-arterial Pro-UK	180	+15%	✓			
MELT[91]	0-6 h	Intra-arterial UK	114	+10%	✓			
ECASS 3 [84]	3-4.5 h	IV Alteplase	730	+7%	✓			
IST 3[20]	0-6 h	IV Alteplase	3035	+2%	✓			
IMS-3[92]	0-3 h	EVT/standard of care	656	+3%	✓			
ATTEST[93]	0-4.5 h	IV TNK/r-tPA	104	-3%	✓	**	**	
MR CLEAN[94]	0-6 h	EVT/ standard of care	500	+12%	✓	✓		LVO
REVESCAT[95]	0-8 h	EVT/ standard of care	206	+16%	✓	✓		LVO
EXTEND-IA[61]	0-4.5 h	EVT/ standard of care	70	+31%	✓	✓	✓ (RAPID)	LVO + Penumbra (Tmax >6 seconds); Core >70 mL

								(rCBF <30% AND Tmax >6 seconds); absolute difference of 10 mL between core and penumbra
SWIFT PRIME[96]	0-4.5 h	EVT/ standard of care	196	+24%	✓	✓	***	LVO
ESCAPE[47]	0-12 h	EVT/ standard of care	315	+22%	✓	✓		Moderate – Good collaterals (>50% of contralateral side)
THRACE[97]	0 -4 h	EVT/ standard of care	402	+11%	✓	✓		LVO
THERAPY[98]	0-4.5 h	EVT/ standard of care	108	+8%	✓	✓		LVO
PISTE[99]	0-4.5 h	EVT/ standard of care	65	+12%	✓	✓		LVO
NOR-TEST[100]	0-4.5 h	IV TNK/ r-tPA	1107	+1%	✓			
EXTEND-IA TNK[101]	0-4.5 h	IV TNK pre EVT	202	+13%	✓	✓	✓ (RAPID)	Penumbra (Tmax >6 seconds); Core >70 mL (rCBF <30% AND Tmax >6 seconds); Total at risk:core >1.8; absolute difference of 10 mL between core and penumbra
DEFUSE-3[62]	6-16 h	EVT/ standard of care	182	+28%	✓	✓	✓ (RAPID)	Penumbra <15 mL (Tmax >6 seconds); Core >70 mL (rCBF <30% AND Tmax >6 seconds); Total at risk:core >1.8
DAWN[63]	6-24 h	EVT/ standard of care	206	+33%	✓	✓	✓ (RAPID)	Group A: <21mL; Group B: <31mL; Group C: 31-51mL
EXTEND[†]	3-9 h	Alteplase/placebo	45	In progress	✓	✓	✓ (RAPID)	Penumbra (Tmax >6 seconds); Core >70 mL (rCBF <30% AND Tmax >6 seconds); Total at risk:core >1.8; absolute difference of

								10 mL between core and penumbra
TIMELESS††	4.5-24 h	IV TNK/placebo	456	In progress	✓	✓	✓ (RAPID)	Penumbra <15 mL (Tmax >6 seconds); Core >70 mL (rCBF <30% AND Tmax >6 seconds); Total at risk:core >1.8
TASTE†††	0-4.5 h	IV TNK/r-tPA	Estimated 700	In progress	✓	✓	✓ (MIStar)	Penumbra <15 mL (DT >3 seconds); Core >70 mL (rCBF <30% AND DT >3 seconds); Total at risk:core >1.8

*Good functional outcome was defined as an mRS of 0-2, except in the cases of the NINDS and PROACT trial that used an mRS of 0 – 1, and the IST trial that used an OHS of 0 – 2.

** CTA and CTP were acquired for retrospective analysis but were not used to guide randomization.

*** CTP required for the first 71 patients. CTP was encouraged but not required for final 125 patients to accommodate sites with limited CTP capabilities.

† EXTEND ClinicalTrials.gov number, NCT01580839

†† TIMELESS ClinicalTrials.gov number, NCT03785678

††† TASTE anzctr.org number, ACTRN12613000243718, sample size estimated due to adaptive trial design.

ATLANTIS - Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ATTEST - Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; CTA – computed tomography angiography; CTP – computed tomography perfusion; DAWN - Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention; DEFUSE 3 - Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; DT – Delay time; ECASS - European Cooperative Acute Stroke Study; ECASS II - Randomised Double-blind Placebo-controlled Trial of Thrombolytic Therapy With Intravenous Alteplase in Acute Ischaemic Stroke; ECASS III - European Cooperative Acute Stroke Study III: A Placebo Controlled Trial of Alteplase (Rt-PA) in Acute Ischemic Hemispheric Stroke Where Thrombolysis is Initiated Between 3 and 4 Hours 30 Minutes After Stroke Onset; ESCAPE - Endovascular Treatment for Small Core and

Proximal Occlusion Ischemic Stroke; EVT – Endovascular therapy; EXTEND - Extending the Time for Thrombolysis in Emergency Neurological Deficits; EXTEND-IA - Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial; EXTEND-IA TNK - Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke; ; IAT – aspiration thrombectomy; IMS-3 - Interventional Management of Stroke 3; IST 3 - Third International Stroke Trial; IV – Intra-venous; LVO – Large-vessel occlusion; MELT - Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial; MR CLEAN - Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS – modified Rankin Score; NCCT – Non-contrast computed tomography; NINDS - National Institute of Neurological Disorders and Stroke; NOR-TEST - Study of Tenecteplase Versus Alteplase for Thrombolysis (Clot Dissolving) in Acute Ischemic Stroke; OHS – Oxford Handicap Scale; PISTE - Pragmatic Ischaemic Stroke Thrombectomy Evaluation; PROACT - Prolyse in Acute Cerebral Thromboembolism; PROACT II - Prolyse in Acute Cerebral Thromboembolism II; rCBF – relative cerebral blood flow; REVESCAT - Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; r-tPA – tissue plasminogen activator; SWIFT PRIME - Solitaire™ With the Intention For Thrombectomy as Primary Endovascular Treatment; TASTE - Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation; THERAPY - Assess the Penumbra System in the Treatment of Acute Stroke, THRACE - Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke, TIMELESS - Prospective, Double-blind, Randomized, Placebo-controlled Trial of Thrombolysis in Imaging-eligible, Late-window Patients to Assess the Efficacy and Safety of Tenecteplase; Tmax – Time-to-maximum; TNK – Tenecteplase; UK – Urokinase

All of the successful EVT trials have been completed using CTA to demonstrate an LVO. In the five pivotal EVT trials, including over 1287 patients, only 78 were randomized outside 6 hours from symptom onset.[47,61,94–96] The majority of patients enrolled in the pivotal EVT trials were randomized and treated on the basis of a limited multimodal imaging criteria, requiring only the demonstration of an LVO and an absence of extensive early infarct changes on NCCT.

The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial used mCTA to assess collateral grades, requiring a moderate-good collateral grade for study inclusion.[47] The only LVO treatment trial that required a complete multimodal assessment was the Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial (EXTEND-IA) trial.[61] Eligible patients all had evidence of an ischemic penumbral pattern on CTP, in addition to an LVO, prior to randomization. Despite the trial's small patient sample relative to the other pivotal trials, treatment effect was the largest (31% absolute increased rate of functional independence over alteplase alone). Although not required, CTP was in fact obtained in many patients included in the other four HERMES trials. Retrospective analysis of the ESCAPE trial (138 of 316 patients underwent CTP) suggested that most patients had a penumbral pattern (90.6%).[51] Non-penumbral patterns were associated with a poorer outcome, although a response to EVT could not be ruled out, given the small number of patients. Another post-hoc analysis of seven major endovascular trials (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT, PISTE, and THRACE—acronyms defined in Table 2.2) included 591 of 1764 patients who underwent CTP prior to randomization to EVT/standard therapy.[87] Although this analysis suggested some treatment benefit, even in patients with large cores, the odds of independent recovery decreased by 23% with every 10 ml increase in the core

volume measured with CTP even in patients successfully treated with EVT.[87] Within 6 hours of onset therefore, CTP identification of large cores may help temper expectations of the response to EVT.

In patients presenting more than 6 hours after onset, the only available evidence for treatment with EVT is based on a complete multimodal assessment including CTP. The Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) trial randomized patients with acute ischemic stroke, CTA evidence of an LVO and salvageable brain 6-24 hours after symptom onset (Table 2.2). The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) trial included patients between 6 and 16 hours after onset with CTA evidence of an LVO and a CTP penumbral pattern. In both the DAWN and DEFUSE trials, an objective measurement of ischemic core volume based on pre-defined thresholds and an automated post-processing algorithm were used.[62,63]

Multimodal CT imaging incorporating blood-flow imaging has been demonstrated to be effective in extending the treatment window for intra-venous thrombolysis up to 9 hours. The Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial randomized patients with ischemic stroke between 4.5 and 9 hours of the last known well time (65% were wake up). Patients were randomized to alteplase or placebo. Alteplase significantly improved the odds of a good functional outcome in this relatively late time window (*In Press*).

Other MRI Techniques

Discussed in this chapter were the main MRI techniques used to look at perfusion, vasculature, and state of tissue infarction, techniques used routinely in clinical care or relevant to the projects in this thesis. There are other MR techniques available that, through utilizing different sequences, can look at different tissue properties often only used in a research setting. Magnetic resonance angiography is an MR technique that allows for the visualization of cerebral vasculature based on flow characteristics. Susceptibility-weighted imaging provides a highly sensitive tool for identifying hemorrhage, able to detect microbleeds often too small to be seen by routine CT imaging. Finally, fluid-attenuated inversion recovery (FLAIR) imaging is a T2-weighted sequence that can be used in the acute-subacute setting (after 4.5 hours) to look at infarction and gives some information on the age of the infarct as DWI positive/FLAIR negative lesions are likely within 4.5 hours of symptom onset. [102,103] While all these techniques can and are used in the clinical setting to a limited degree, they remain largely research tools to give further insight into an ischemic event.

Summary

Imaging of ischemic strokes is an important and constantly evolving field of study. Multiple methods can be used to image various properties of the brain, such as angiography versus perfusion, which gives varying insights into the state of the brain parenchyma. Each of these tools has various trade-offs, often between accuracy versus speed versus availability, and the acceptable combination of these three factors is constantly debated, especially in the case of patient selection for thrombolysis. Further research and improvements in clinical practice are needed to determine the ideal method of patient selection, as proper inclusion/exclusion criteria can both reduce long-term disability of patients and decrease the likelihood of complications to treatment. In the following chapters perfusion imaging is compared against CTA and mCTA,

exploring the differences in patient selection between the imaging techniques in an attempt to determine the ability of CTA/mCTA to identify CTP-established mismatch patients.

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Chapter 3 - CT Perfusion Predicts Poor Outcomes in a Randomized Trial of Endovascular Therapy.

Introduction

Endovascular thrombectomy (EVT) is the preferred therapy for appropriately selected patients presenting with acute large vessel occlusion (LVO) stroke. This treatment is associated with an increased odds of independent recovery after stroke of 1.56 – 2.49. [1–4] The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial demonstrated that EVT improves clinical outcome, relative to standard medical care, in patients selected with non-contrast computed tomography (CT), CT angiography (CTA) and optional Computed Tomography Perfusion (CTP).[5] A key inclusion criteria in ESCAPE was the presence of moderate to good collateral supply on CTA.

Acute measurement of the ischemic core and penumbra has been shown to be an accurate predictor of patient outcome in those receiving intravenous thrombolysis.[6] Typically, patients with penumbral patterns, that is a small ischemic core and a large penumbra, are thought to benefit the most from reperfusion therapy, while those with a large and established ischemic core are more at risk of hemorrhage and a poor clinical outcome with intravenous thrombolysis. However, with the advent of EVT, the clinical role of these measures needs to be reassessed.

CTP derived maps of regional cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit times (MTT), and delay time (DT) can be used to estimate the extent of core and penumbral tissue.[7,8] The estimated volume of penumbra measured with CTP has been shown to predict good outcomes in patients treated with reperfusion strategies.[9–12] Previous studies indicate that not only do non-penumbral pattern patients have a poorer prognosis than penumbral

pattern patients, but that CTP can be used to identify patients at an increased risk of hemorrhagic transformation.[6,13] However, complex post processing, variability in image acquisition capabilities, and a lack of standardization of perfusion thresholds have hampered routine clinical use.[14,15] Furthermore, the majority of CTP studies have been completed in patients treated with systemic thrombolysis alone. The utility of CTP in predicting outcome in patients undergoing EVT is unknown.

Although a large portion of the ESCAPE patients underwent CTP, these data were not required to randomize. Although NCCT and CTA were the preferred imaging modalities, alternative definitions of moderate-large core, based on subjective assessment of areas with low CBV and CBF seen on CTP maps were provided as guidance to investigators. [5] We tested the hypothesis that patients treated with EVT with CTP penumbral patterns have higher rates of good clinical outcome. The hypothesis that CTP can identify additional patients with large ischemic core volumes and poor prognosis, in whom therapy is likely to be futile, was also tested.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Population

Ethics approval was obtained at each site for the original ESCAPE trial. Where permitted, the consent process was deferred in cases where patients lacked the capacity to provide consent and a legally authorized representative was unavailable. Patients enrolled in ESCAPE had small infarct cores, defined as a non-contrast CT (NCCT) Alberta Stroke Program Early CT Score (ASPECTS) of 6-10. All patients had proximal anterior circulation occlusions with CTA

evidence of moderate to good collaterals as assessed by site investigators acutely. Patients were randomized to EVT therapy versus standard guideline-based care, including thrombolysis in eligible patients.[16,17]

Image Acquisition

Perfusion images were acquired at 13 sites, using site-specific protocols. Images were acquired using Siemens SOMATOM Sensation 64, Siemens SOMATOM Definition Flash, Siemens SOMATOM Definition AS, GE Discovery CT750 HD, GE Lightspeed VCT, Toshiba Aquilion ONE, and Philips iCT 128 scanners. Acquisition volume varied from 2.8 to 23.0 cm coverage, with slice thickness varying from 0.5 to 10.0 mm.

Image Analysis

All CTP images were post-processed centrally using the MIStar program (Apollo Medical Imaging Technology, Melbourne, Australia) with single value deconvolution with delay and dispersion correction to generate maps of and maps of CBV, CBF, MTT, and delay time (DT).[18] The perfusion deficit volume was defined using a threshold DT >3 seconds (DT3). The ischemic core was defined as tissue with a CBF of <30% inside the perfusion deficit. The penumbra was defined as tissue within the DT3 deficit which was not the ischemic core (i.e. CBF >30%).[6] A penumbral pattern was defined using the DEFUSE 2 criteria for 'target mismatch'; core volume <70 mL, penumbral tissue volume >15 mL, and a mismatch ratio of total perfusion deficit to core volume >1.8.[19]

Outcomes

The primary study outcome was good functional outcome at 90 days defined as a mRS score of 0-2. Secondary imaging outcomes were final infarct volume, infarct growth, and penumbral

salvage volume at 24 hours. Final infarct volume was measured using planimetric techniques (Quantomo (Cybertrial Inc., Calgary)[6] on NCCT images, or Diffusion-Weighted Magnetic Resonance images when available. Measurements were completed by imaging experts blinded to clinical information, as previously described. Infarct growth was calculated as the difference between baseline CTP ischemic core volume and the 24 hour infarct volume. [20] Penumbral salvage was calculated as the difference between the baseline perfusion deficit volume and the 24 hour infarct volume.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (IBM Corporation, 2014, NY). Differences in median final infarct volume, infarct growth, penumbral salvage, baseline ASPECTS, and 24 hour NIHSS improvement between groups were assessed with a one-way analysis of variance on ranks, followed by post-hoc tests. Differences in the frequency of good functional outcome between groups were assessed with Pearson's Chi Square test.

Results

Patient Population

Of the 316 patients randomized in the ESCAPE trial, 138 patients underwent CTP imaging. Ten patients were excluded due to patient motion leaving 128 patients in the final analysis, 116 (90.6%) of whom had penumbral patterns on CTP (Figure 3.1). Of the 12 non-penumbral pattern patients, 10 (83.3%) had baseline core volumes >70mL (large; Figure 3.2). Patients with penumbral and non-penumbral patterns had similar baseline clinical characteristics (Table 3.1). Median (IQR) baseline ASPECT scores of patients with non-penumbral patterns (9 (7 – 9.5)) and penumbral patterns (9 (8 – 10) were similar (p=0.179).

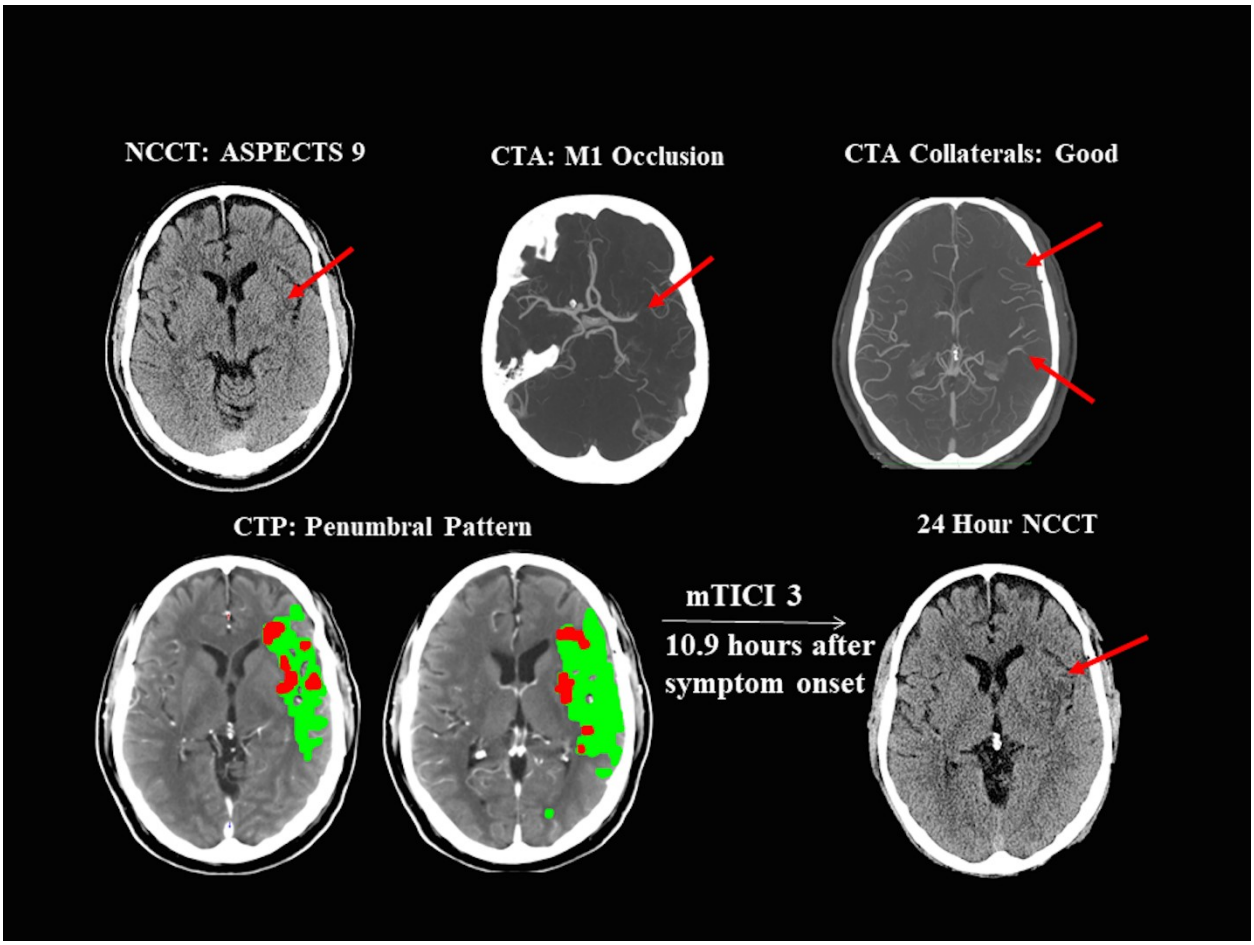

Figure 3.1: Target Mismatch Patient. Acute and 24 hour follow-up CT imaging in a 59 year old man treated with tPA, followed by endovascular therapy that resulted in full recanalization and modified Thrombolysis in Cerebral Infarction (mTICI 3) flow 10.9 hours after onset. Baseline non-contrast CT (NCCT) ASPECTS was 9. CT angiography (CTA) demonstrated good collaterals. CT perfusion (CTP) demonstrated a penumbral pattern (core (red) =18.5 mL; penumbra (green) =44.4 mL; mismatch =3.4). Follow-up non-contrast CT demonstrated minimal infarct growth (24 hour infarct volume=20.0 ml), and the day 90 modified Rankin Scale score was 2.

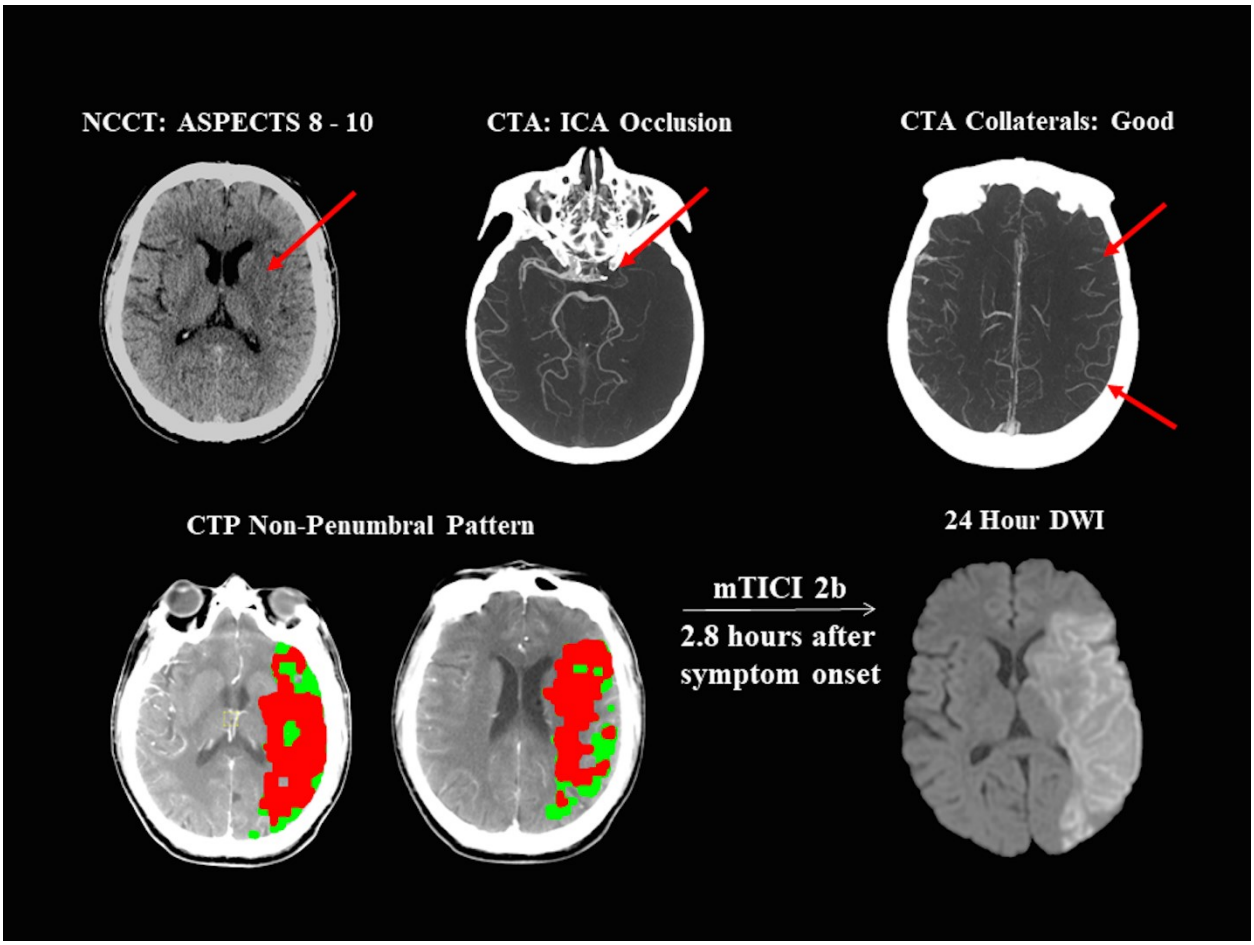

Figure 3.2: Non-Target Mismatch Patient. Acute CT and 24 hour follow-up diffusion-weighted magnetic resonance imaging (DWI) in a 59 year old man treated with tPA, followed by endovascular clot retrieval. Baseline non-contrast CT (NCCT) ASPECTS was between 8 (arrows) and 10 (core lab). Multiphase CT angiography (CTA) demonstrated good collaterals. CT perfusion (CTP) demonstrated a large core, non-penumbral pattern (core (red) =153.4 mL; penumbra (green) =59.9 mL, mismatch ratio=1.4). Despite successful endovascular therapy and recanalization with mTICI 2b flow 2.8 hours after onset, 24 hour DWI infarct volume was 278.0 ml, and the day 90 modified Rankin Scale score was 4.

Table 3.1. Baseline characteristics and outcomes in penumbral and non-penumbral pattern patients.

Variables	Penumbral Pattern	Non-Penumbral Pattern	p-value
No. of patients (%)	116 (91)	12 (9)	N/a
Age (IQR)	72.8 (59.8 – 82.9)	65.7 (56.6 – 83.6)	0.377
Female (%)	67 (58)	5 (42)	0.364
Median baseline ASPECTS (IQR)	9 (8 – 10)	9 (7 – 9.5)	0.179
Median baseline NIHSS (IQR)	17 (12 – 21)	20 (15 – 23)	0.201
Median baseline infarct volume (IQR) mL	16.1 (6.9 – 27.8)	103.2 (85.4 – 139.4)	**<0.001**
Median baseline penumbral volume (IQR) mL	85.1 (59.4 – 113.9)	88.8 (51.0 – 121)	0.909
Good collaterals (%)	102 (87.9)	5 (41.7)	**<0.001**

Moderate collaterals (%)	9 (7.8)	2 (16.7)	
Poor collaterals (%)	3 (2.6)	5 (41.7)	
Control/Intervention groups	58/58 (50% control)	9/3 (75% control)	N/a
No treatment	14	0	N/a
tPA- only	44	9	N/a
Endovascular only	18	1	N/a
Both endovascular and tPA treatment	40	2	N/a
Median final infarct volume (IQR) mL	19.0(6.0 – 48.0)	265.0 (32.5 – 338.0)	**0.001**
Median penumbral salvage (IQR) mL	80.0 (40.8 – 112.4)	-18.1 ([-111.0] – [62.6])	**0.011**
sICH (%)	1 (0.9)	1 (8.3)	0.179
Median core growth (IQR) mL	5.3 ([-4.6] – [28.7])	146.3 ([-3.2] – [171.6])	**0.024**

Median 24 hour NIHSS improvement (IQR)	6 (0 – 12)	2 ([-1] – [3.5])	**0.045**
Median 90 day mRS (IQR)	3 (1 – 4)	5 (3 - 6)	**0.003**
Good function outcome (mRS 0-2) (%)	53 (46)	2 (17)	**0.041**

(ASPECTS – Alberta Stroke Program Early CT Score; mRS – modified Rankin Score; NIHSS – NIH Stroke Scale; sICH – symptomatic intracranial hemorrhage; tPA – tissue plasminogen activator)

Collateral grades were assessed centrally by blinded raters in the core lab using CTA source images, including multiphase data in 85/128 (66.4%) of patients. Multiphase CTA was obtained in 75/116 (64.7%) penumbral and 10/12 (83.3%) non-penumbral patients. Eight patients (6.2%) were graded as having poor collaterals by the core lab, 5 of whom had a non-penumbral pattern. Of the 12 non-penumbral pattern patients, 5 were rated as having poor collaterals, 2 were rated as moderate and 5 were rated as good. Three patients with collaterals graded as poor had penumbral patterns. Median collateral grades were significantly lower in non-penumbral patients, (Table 3.1). Collateral grades did not differ between EVT treated and control penumbral patients (Table 3.2).

Table 3.2. Baseline characteristics and outcomes in penumbral pattern patients randomized to the EVT and control groups.

Variables	EVT	Standard of Care	p-value
No. of patients (%)	58 (50)	58 (50)	N/a
Age (IQR)	74.3 (60.9 – 82.4)	71.1 (59.1 – 83.4)	0.569
Female (%)	34 (58.6)	33 (56.8)	0.500
Median baseline ASPECTS (IQR)	9 (8 – 10)	9.5 (8 – 10)	0.589
Median baseline NIHSS (IQR)	15.5 (10.5 – 21.5)	17.0 (14.0 – 20.0)	0.199
Median baseline infarct volume (IQR) mL	15.5 (5.5 – 26.0)	16.3 (8.7 – 30.2)	0.285
Median baseline penumbral volume (IQR) mL	85.1 (53.9 – 115.5)	83.7 (62.2 – 111.6)	0.879
Good collaterals (%)	53 (91.4)	49 (84.8)	0.066

Moderate collaterals (%)	5 (8.6)	4 (6.9)	
Poor collaterals (%)	0	3 (5.2)	
Median final infarct volume (IQR) mL	11.0 (4.0 – 24.0)	32.0 (15.0 – 86.0)	**<0.001**
Median penumbral salvage (IQR) mL	84.2 (45.3 – 116.3)	59.2 (25.7 – 93.1)	**0.018**
Median core growth (IQR) mL	1.3 ([-6.7] – [9.9])	15.8 ([-1.0] – [52.5])	**0.001**
sICH (%)	1 (1.7)	0	1.000
Median 24 hour NIHSS improvement (IQR)	8.0 (4.0 – 12.0)	2.0 ([-1.0] – [11.0])	**0.002**
Median 90 day mRS (IQR)	2.0 (1.0 – 3.0)	30 (1.5 – 4.5)	**0.003**
Good function outcome (mRS 0-2) (%)	34 (56.8)	19 (32.7)	**0.009**

(ASPECTS – Alberta Stroke Program Early CT Score; mRS – modified Rankin Scale score; NIHSS – NIH Stroke Scale; sICH – symptomatic intracranial hemorrhage; tPA – tissue plasminogen activator)

Penumbral Patterns and Clinical Outcomes

Functional outcome data was available in 126 of 128 patients. Two patients, both of whom had penumbral patterns and were in the control group were lost to 90 day follow-up. Irrespective of treatment group, good functional outcome at 90 days was seen more frequently in penumbral than non-penumbral pattern patients (46% vs 17%, p=0.041; Table 3.1).

The median 90 day mRS was lower in penumbral patients (3(1–4)) than non-penumbral pattern patients (5 (3–6), p=0.003). The improvement in NIHSS scores between baseline and 24 hours was greater in the penumbral (6 (0–12)) than the non-penumbral pattern patients (2 ([-1]–[3.5]), p=0.045). Only 1 patient in each of the penumbral and non-penumbral groups developed symptomatic hemorrhagic transformation.

Penumbral Patterns and Radiographic Outcomes

Irrespective of treatment group, median final infarct volume in penumbral patients (19.0 (6.0–48.0) ml) was lower than that in the non-penumbral pattern patients (265.0 (32.5.0–338.0 ml), p<0.001). Infarct growth was also lower in penumbral (5.3 ([-4.6]–[28.7])) than non-penumbral pattern patients (146.3 ([-3.2]–[171.6]), p=0.024). Penumbral salvage volume was higher in the penumbral (80.0 (40.8–112.4)) than the non-penumbral pattern patients (-18.1 ([111.0]–[62.6]), p=0.011).

Effect of Endovascular Thrombectomy in Penumbral Pattern Patients

Of the 116 penumbral pattern patients, 58 were randomized to EVT and 58 were in the control group. Median time to groin puncture in the 58 EVT patients who underwent CTP was 172.0 [137.5 – 284.0] minutes, which was similar to that of the remaining 104 EVT patients (220.0 [148.0 – 323.0] minutes, p=0.073).

Despite similar baseline clinical and imaging characteristics, final infarct volume and core growth were both significantly lower in the EVT than the control patients (Table 3.2). By chance, the 12 non-penumbral pattern patients were disproportionately randomized between the EVT (3) and control groups (9), preventing meaningful analysis of the effect of EVT in these patients.

Within the penumbral pattern patients, good functional outcome occurred more often in the EVT (57%) than the control group (33%, p=0.009). Logistic regression indicated that good functional outcome in penumbral patients was predicted by EVT (OR=2.68, 95% CI 1.25 – 5.76; p=0.011). There was only 1 symptomatic hemorrhagic transformation in the penumbral group, in a patient treated with EVT therapy.

Effect of Recanalization

Of the 12 non-penumbral patients, 11 had follow-up vessel imaging permitting an analysis of recanalization rates. Five of 11 patients recanalized. Despite similar baseline characteristics in the recanalized and non-recanalized patients, final infarct volumes and 90 day mRS scores were similar (Table 3.3). In contrast, recanalization in penumbral pattern patients was associated with lower final infarct volumes and 90 day mRS scores.

Table 3.3. Baseline characteristics and outcomes in recanalized and non-recanalized patients with and without penumbral patterns.

		Recanalized	Non-recanalized	p-value
Non-Penumbral Pattern Patients	No. of patients (%)	5 (45)	6 (55)	N/a
	Median baseline core (IQR) mL	104.5 (91.8 – 109.7)	117.9 (81.3 – 179.7)	1.000
	Median baseline penumbra (IQR) mL	117.0 (98.6 – 125.0)	72.3 (50.6 – 103.3)	0.329
	Median final infarct volume (IQR) mL	259.0 (49.0 – 271.0)	335 (138.0 – 409.0)	0.247
	Median 90 day mRS (IQR)	4 (3 – 4)	6 (6 – 6)	0.177
Penumbral Pattern Patients	No. of patients (%)	71 (68%)	34 (32%)	N/a
	Median baseline core (IQR) mL	16.1 (6.4 – 24.0)	17.1 (6.2 – 37.7)	0.323
	Median baseline penumbra (IQR) mL	88.6 (61.2 – 113.9)	83.7 (59.9 – 116.9)	0.828
	Median final infarct volume (IQR) mL	11.0 (4.0 – 29.0)	32.0 (17.0 – 122.0)	**<0.001**

	Median 90 day mRS (IQR)	2 (1 – 3)	4 (2 – 5)	**0.001**

mRS – modified Rankin Scale score

Discussion

These results suggest that although perfusion imaging was not required to enroll patients in ESCAPE, most patients who did undergo CTP imaging did in fact have penumbral patterns. In addition, the presence of a penumbral pattern was associated with a better clinical and tissue fate prognosis, irrespective of treatment and recanalization. Prognosis was further improved by EVT therapy and early recanalization. Although the presence of a non-penumbral pattern was associated with a worse prognosis, a response to EVT/recanalization in this group of patients cannot be ruled out by the present data. Symptomatic hemorrhage was rare and not affected by CTP pattern or by treatment.

Patients in ESCAPE were selected using non-contrast CT and CTA images. Most patients in the five pivotal EVT therapy trials were selected on this basis.[5,21–24] Only the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND IA) trial included penumbral imaging patterns in the inclusion/exclusion criteria for all patients. Screening log data from EXTEND IA indicated that approximately 25% of patients were excluded on the basis of the CTP.[23] This appears to be slightly more frequent than the 10% of patients with non-penumbral patterns in our sample. This may be explained by the fact that poor collaterals, which were an exclusion criterion for ESCAPE, are likely to be associated with non-penumbral patterns. Our analysis was also completed in a non-randomly selected subset of the ESCAPE population.

In patients with proximal occlusions, the most common cause of a non-penumbral pattern was a large CTP-defined predicted ischemic core, not evident on non-contrast CT (Figure 3.2). Patients presenting with a non-penumbral pattern had similar baseline ASPECT scores to those with penumbral patterns. This was not unexpected, given the evidence for the limited sensitivity of non-contrast CT for detection of early ischemic changes.[25–28] The additional information provided by CTA source image collateral assessment likely limited the number of non-penumbral pattern patients in ESCAPE as well, although some patients with large cores evident on CTP were still included (Figure 3.2).

The promise of penumbral imaging is replacement of the therapeutic time window with one based on tissue status. To a certain extent, this was achieved by the ESCAPE trial, as well as the four other pivotal EVT studies, where the presence of penumbral tissue was inferred from CT and CTA collateral data. These trials have already expanded the intervention window from 4.5 to a minimum of 6 hours, with some support for treatment up to 12 hours. A small retrospective analysis of endovascular patient selection based on CT perfusion data indicated that treatment response in penumbral pattern patients was independent of onset to treatment time.[29] The recently published Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention (DAWN) trial results suggest that blood flow based selection can indeed be used to treat patients within 24 hours of their last known well time.[30]

The potential additional benefit of penumbral imaging is exclusion of patients who may not respond to therapy or even be harmed by intervention. In the present analysis, non-penumbral pattern patients were less likely to make independent recoveries, but a response to EVT cannot be excluded. A randomized study of patients with non-penumbral patterns is required to address this question definitively. Within ESCAPE, EVT patients in whom CTP was performed electively did not appear to suffer with respect to time to groin puncture. This suggests that CTP can be done efficiently when integrated into the workflow of acute stroke patients. There is also some evidence that non-penumbral patterns identified with CTP can identify patients at increased risk of hemorrhagic transformation.[6,13] In our present analysis there was no increased risk of hemorrhage in non-penumbral pattern patients, though the small sample size and the low frequency of the event requires a larger sample size to approach this topic with certainty.

This study has a number of limitations. Perfusion imaging was not required in ESCAPE. This analysis is therefore based on an incomplete and non-randomized sample of the larger trial population. Indeed, the disproportionate number of non-penumbral patients in the control group made it impossible to draw any conclusions about the effect of EVT in this group of patients. Similarly, the low total number of non-penumbral pattern patients (12) makes it difficult to definitively conclude outcome is worse in this group. This likely reflects the highly selected nature of the population, using the ESCAPE inclusion/exclusion criteria. In addition, it is possible that at sites where CTP was acquired, patients were excluded by investigators who felt that CT vendor maps revealed a non-penumbral pattern. Regardless, our data suggest that outcomes in patients with non-penumbral patients, particularly those with large ischemic cores, are generally worse than those with penumbra, irrespective of treatment. Another limitation is

the use of non-contrast CT as a follow-up imaging modality for many patients, which is inferior to diffusion-weighted MRI with respect to reliable final infarct volume measurement.[31,32] There is also variation in the CTP imaging techniques between centers, with a range of brain coverage (2.8 cm vs 23 cm). This may result in a reduced reliability of initial core and penumbral volumes at sites with incomplete lesion coverage. Finally, although an analysis of the effect of endovascular treatment on non-penumbral patients could not be completed, there may be cases where endovascular treatment is still preferred in the large core group, provided sufficient mismatch pattern is achieved, although a poorer prognosis relative to smaller core patients is still to be expected.[33]

Conclusion

The majority of ESCAPE patients who underwent CTP imaging had large penumbral patterns. Adding CTP based selection criteria may have resulted in exclusion of another 10% of patients who may be unlikely to benefit from reperfusion strategies. Patients presenting with a penumbral CTP pattern have a better prognosis than those with non-penumbral patients and also respond more favorably to EVT as well as early recanalization.

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Chapter 4 - Multiphase CT Angiography Predicts CT Perfusion Penumbral Patterns with Low Sensitivity and Specificity.

Introduction

Endovascular Thrombectomy (EVT) is the standard of care for large vessel occlusion (LVO) ischemic stroke.[1] The evidence for EVT within 6 hours is based primarily on patients selected using non-contrast CT (NCCT) and CT angiography (CTA).[2] More recently, the window for EVT has been expanded to 24 hours from onset, based on the evidence from two trials that utilized CT Perfusion (CTP) imaging to select candidates.[3,4]

Multiphase CT Angiography (mCTA) was developed in an attempt to obtain temporal information by tracking the bolus beyond the peak arterial phase. By repeating the CT acquisition in 1 mm slice increments following a delay of 7-8 s and another 7-8 s, images of the vasculature in the late arterial and venous phases can be obtained.[5] Although not required, mCTA use was encouraged in one of the pivotal 0-6 hour EVT trials.[6] Multiphase CTA (mCTA) in theory assists in differentiation of the ischemic core and penumbra. In the peak arterial phase, any hypoperfused tissue will demonstrate a lack of vessel opacification. Regions in which perfusion is delayed due to supply via collateral vessels, will demonstrate vessel opacification in the later phases only. In contrast, core regions will not opacify at any point of the mCTA acquisition.[5,7]

We aimed to compare mCTA to semi-automated CTP data to determine the predictive value of angiography for both target mismatch and large-core patients. We tested the hypothesis that mCTA ASPECTS will identify patients with penumbral patterns on CTP.

Methods

Patient Selection

Acute ischemic stroke patients presenting within 24 hours of symptom onset or time last known well underwent non-contrast CT (NCCT), CTP and CTA imaging at admission as part of routine clinical care. Patients were treated with IV thrombolytic and/or EVT as judged by the treating stroke physician per current standard of care guidelines.[8]

Imaging Acquisition

A whole brain CT (5mm slice thickness) followed by CTP with 40 or 80 mm coverage and 4 mm slice thickness was acquired every second over 45 s (80 kvp; 200mA/image). Iodinated contrast (40-50 ml) was be injected at a rate of 5ml/s. Extracranial and intracranial CT angiography (CTA) was performed after CTP with a separate iodinated contrast injection at 5ml/sec. Multiphase (mCTA) data was generated post-hoc using CTP source images. Three phases were used to create the mCTA dataset; peak arterial input determined from CTP time-density curves was the first phase, with two additional phases taken 8 s apart.

Image Analysis

All CTP images were post-processed centrally using the semi-automated MIStar program (Apollo Medical Imaging Technology, Melbourne, Australia) with single value deconvolution with delay and dispersion correction to generate maps of CBV, CBF, MTT, and DT.[9] Penumbral tissue was defined as tissue with a DT>3 seconds, and core was defined using a double threshold of DT>3 and rCBF<30% of the contralateral side. A mismatch pattern was defined as a core volume<70mL and a mismatch ratio≥1.8. [10] NCCT, CTA, and mCTA images were evaluated by

2 neuroradiologists (AT and HK) blinded to CTP and clinical data. These experts rated the Alberta Stroke Program Early CT Score (ASPECTS) of the NCCT, CTA, and each phase of the mCTA for every patient based on delayed filling and decreased extent of filling, representing decreases in blood flow and blood volume respectively. [7] Each rater also gave collateral grades for both the CTA and mCTA images (good, moderate, poor/absent). [6,11] An mCTA ASPECTS mismatch score was calculated based on the difference between phase 1, representing the total perfusion deficit, from the ASPECTS on phase 3, representing the baseline core volume. In cases of disagreement, a third, blinded rater (KB)adjudicated.

Outcomes

The primary study outcome was the sensitivity of the mCTA ASPECT scores for prediction of penumbral patterns. Secondary outcomes included the sensitivity of the mCTA ASPECTS mismatch pattern for prediction of large ischemic core patients, as well as specificity for both penumbra and large core. All outcomes were assessed in all stroke patients and separately in those with a large-vessel occlusion (LVO). We also compared mCTA ASPECTS mismatch scores to penumbral and core volumes, as well as collateral grades rated as good, moderate and poor/absent.[12]

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (IBM Corporation, 2014, NY). A standard receiver-operator characteristic analysis was completed. Differences in mCTA ASPECT scores, baseline CTP penumbral volumes, and baseline CTP core volumes were assessed with a Kruskal-Wallis analysis followed by post-hoc tests. Interrater agreement was assessed using a weighted

Cohen's kappa test. Correlation between CTP and mCTA ASPECTS scores was assessed using a Spearman rank correlation test followed by regression analysis.

Results

Between January 2016 and January 2017, 141 acute patients underwent multimodal CT, including CTP, CTA, and NCCT at admission for assessment of stroke symptoms (Figure 4.1). Four patients were excluded due to excessive motion on either the CTP and/or the CTA. Of the 137 remaining patients, 105 had a confirmed ischemic infarct on follow-up imaging (Table 4.1). Of the 105 confirmed stroke patients, 48 (45.7%) presented with a large vessel occlusion (LVO) confirmed on the CTA, 8 of whom had a large core (>70mL) on CTP (Table 4.1).

Of the 105 patients with a confirmed infarct on follow-up imaging, 31 (29.5%) were found to have a non-mismatch pattern on CTP, 14 of whom (45.1%) were LVO patients. Of the 74 mismatch patients, 34 (45.9%) presented with an LVO (Figure 4.2).

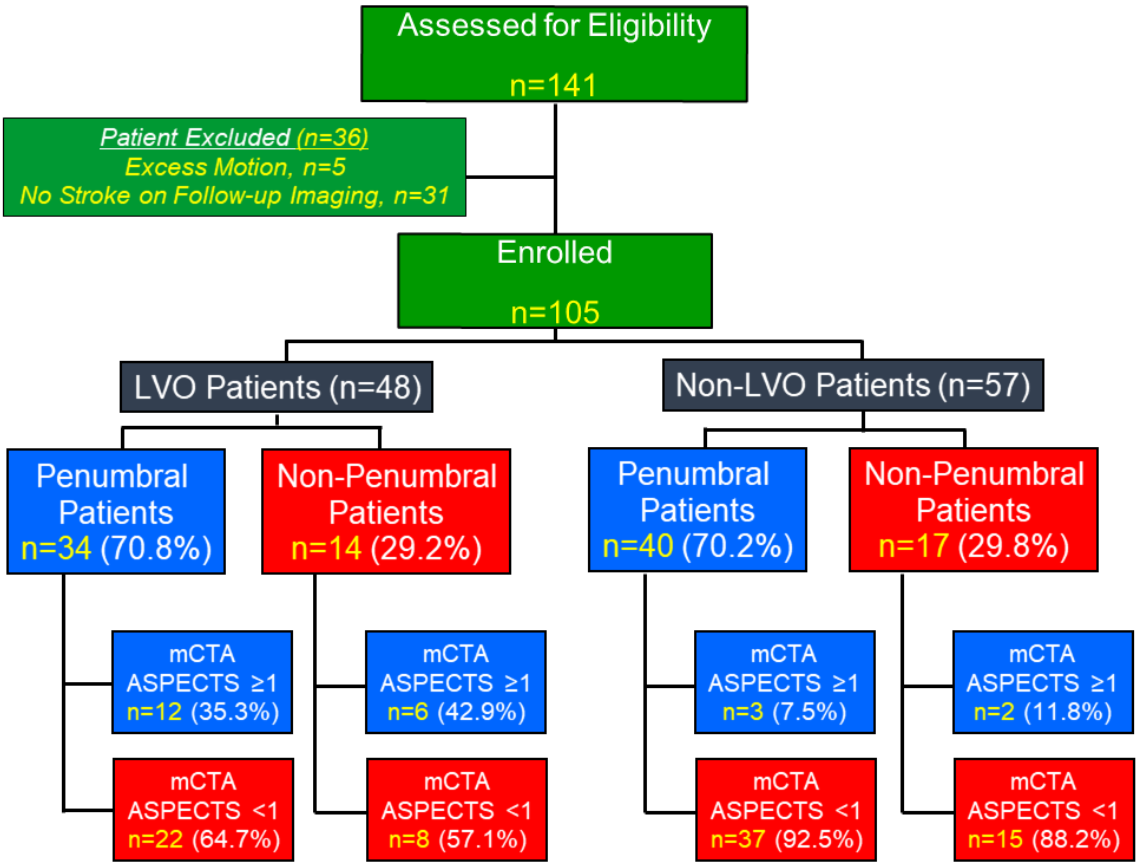

Figure 4.1. Study Patient Profile. ASPECTS – Alberta Stroke Program Early CT Score; LVO – large vessel occlusion; mCTA – multiphase computed tomography angiography.

Table 4.1:Baseline Characteristics of All Patients.

Variable	All Patients			LVO Patients		
	Penumbral (n=74)	Non-Penumbral (n=31)	p-value	Penumbral (n=34)	Non-Penumbral (n=14)	p-value
Large Vessel Occlusions (%)	34 (46)	14 (45)	0.557	n/a	n/a	n/a
Total Perfusion Deficit (IQR) mL	31.1 (13.6 – 85.3)	49.5 (12.5 – 106.6)	0.403	77.3 (36.1 – 104.5)	106.6 (78.8 – 130.6)	**0.010**
Baseline Core Volume (IQR) mL	9.3 (3.5 – 27.2)	34.9 (11.0 – 69.1)	**0.003**	21.5 (7.5 – 42.3)	69.1 (57.0 – 82.0)	**<0.001**

Baseline Penumbral Volume (IQR) mL	20.0 (9.3 – 45.2)	14.6 (1.3 – 35.2)	0.071	39.8 (20.5 – 61.7)	36.3 (26.9 – 43.4)	0.725
Median mCTA ASPECTS Phase 1 (IQR)	9.0 (5.5 – 9.5)	4.8 (2.5 – 9.5)	0.221	5.5 (3.8 – 7.8)	3.0 (1.0 – 4.0)	**0.001**
Median mCTA ASPECTS Phase 3 (IQR)	9.0 (6.5 – 9.5)	6.5 (3.5 – 9.8)	0.220	6.0 (4.5 – 8.3)	3.5 (2.5 – 4.0)	**<0.001**
Median mCTA ASPECTS Mismatch	0 (0.0 – 0.5)	0.2 (0.0 – 1.0)	0.800	0.5 (0.0 – 1.3)	0.5 (0.0 – 1.0)	0.566

(ASPECTS – Alberta Stroke Program Early CT Score; mCTA – multiphase computed tomography angiography

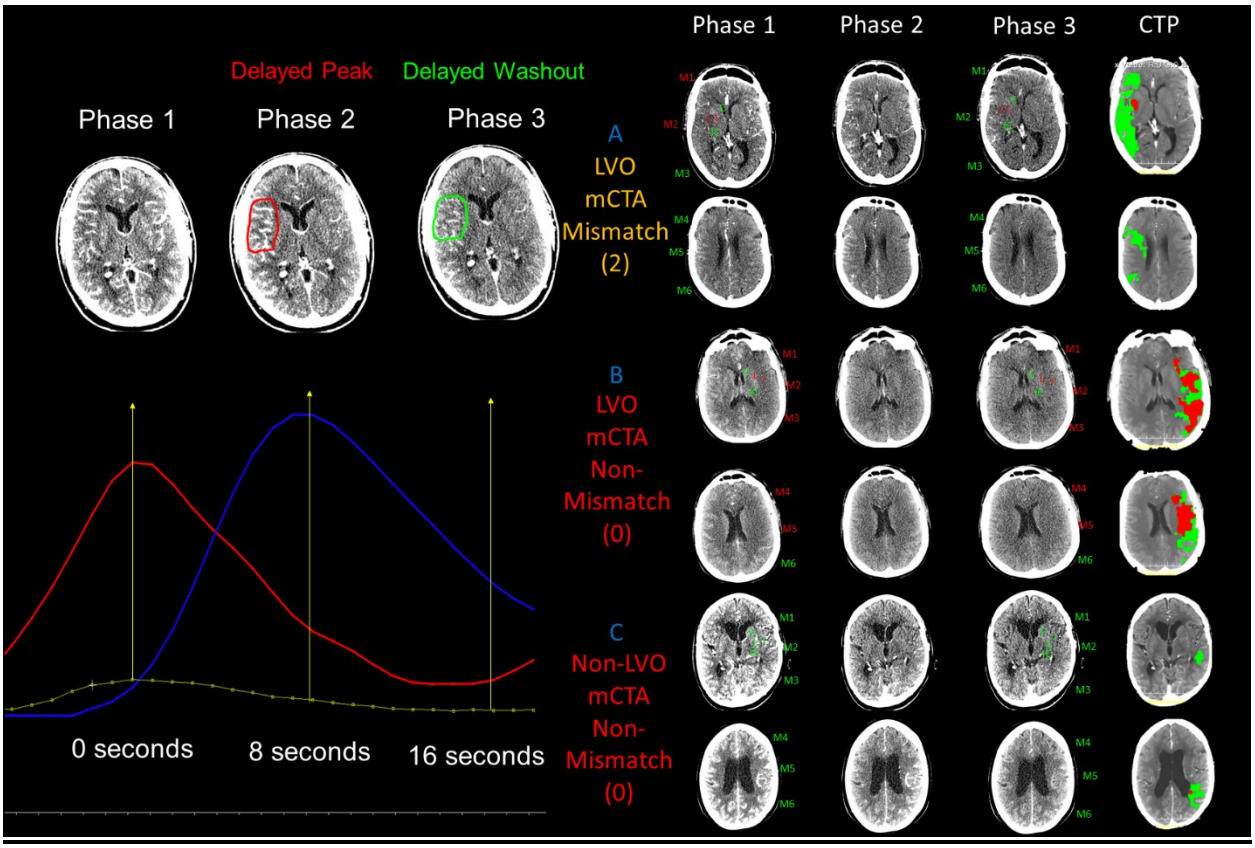

Figure 4.2. Multiphase CTA Images Derived from CT Perfusion Source Images. The peak arterial phase was defined as the first phase. The second and third phases were delayed by +8 and +16 seconds respectively. Images were scored regionally using the Alberta Stroke Program Early CT Score (ASPECTS). Affected regions are marked in red and unaffected regions in green. In the mismatch Large Vessel Occlusion (LVO) patient (A), the ASPECT score on phase 1 was scored 6 (lack of contrast opacification in M1, M2, lentiform, and insula). The ASPECT score improved on phase 3 to 8 (M1, M2 now opacified), and the mCTA mismatch score was 2. This was associated with a penumbral pattern on CTP (core = 3.6 mL, penumbra = 37.0 mL, mismatch ratio = 11.4). In the non-mismatch LVO patient (B), the ASPECT score on phase 1 was scored 3 (lack of contrast opacification in M1-M5, lentiform, and insula). The ASPECT score did not change on phase 3, remaining a 3, giving a mismatch of 0. This, however, was still associated with a penumbral pattern on CTP (core = 42.7 mL, penumbra = 33.6 mL, mismatch ratio = 1.8). In the non-mismatch non-LVO patient (C), the ASPECT score on phase 1 was scored 10 due to a lack of delay in peak filling of contrast. The ASPECT score did not change on phase 3, remaining a 10, giving a mismatch score of 0. This was also associated with a penumbral pattern on CTP (core = 0.1 mL, penumbra = 17.0 mL, mismatch ratio = 144.4).

mCTA ASPECT Scores (All patients)

The median (IQR) mCTA ASPECT score on phase 1 was 8.5 (4.5 – 9.5). The median (IQR) on phase 3 was 8.5 (5.0 – 9.5). The mCTA phase 1 ASPECT scores were inversely correlated with total perfusion deficit volumes (ρ = -0.801; p<0.001). Phase 3 mCTA ASPECT scores were inversely correlated with baseline core volumes (ρ= -0.775; p<0.001) (Figure 4.3).

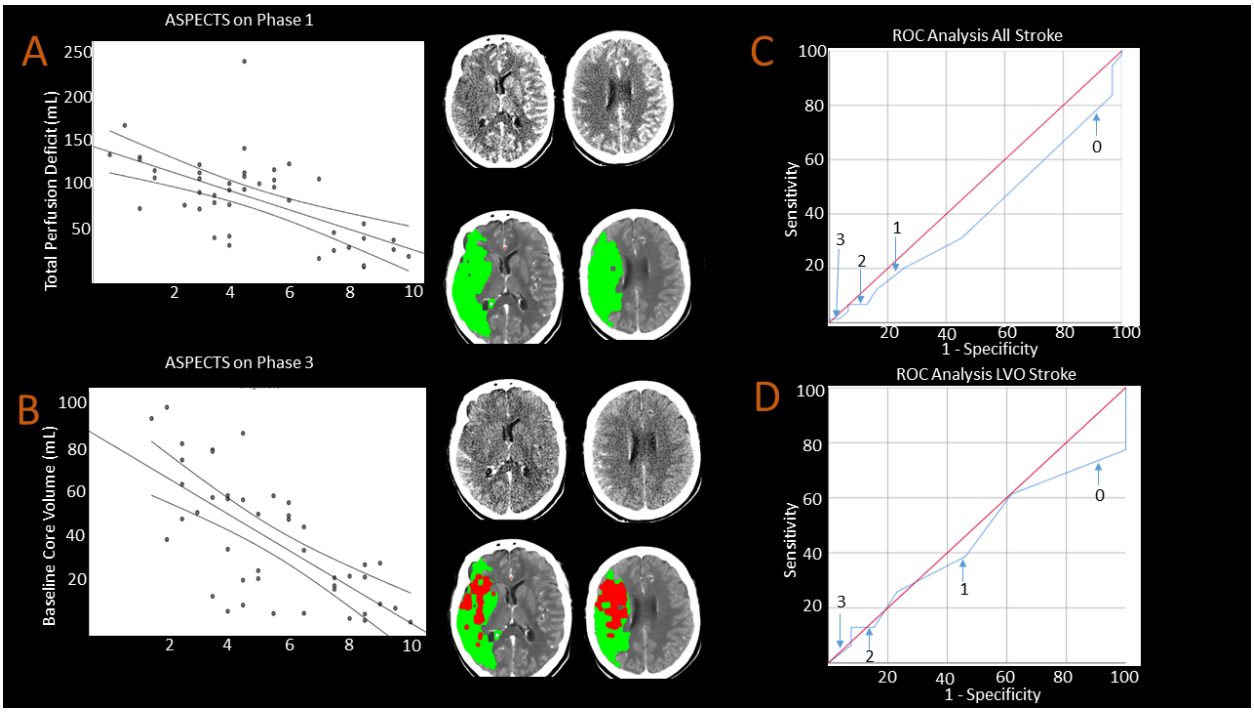

Figure 4.3. Multiphase CTA Compared to Quantitative CT Perfusion. In large-vessel occlusion (LVO) patients, mCTA ASPECTS (phase 1) was inversely correlated with (A) total perfusion deficit volumes (ρ= -0.577; p<0.001). mCTA ASPECTS (phase 3) was inversely correlated with (B) baseline core volumes (ρ= -0.682; p<0.001). The ROC curve for all patients (C) had an AUC of 0.402 (0.287 – 0.517). The ROC curve for LVO patients (D) had an AUC of 0.460 (0.285 – 0.635). At a mismatch score threshold ≥ 1 between phase 1 and phase 3 in LVO patients, the sensitivity was 38.7%, with a specificity of 53.8%, with a positive predictive value of 66.7% and a negative predictive value of 26.9%.

Between phases 1 and 3, 23/105 (21.9%) patients demonstrated a change in median mCTA ASPECT score of 1 or more. A change in 2 or more on mCTA ASPECT scores was seen in 9 (8.6%) patients, and a change in 3 or more was seen in 5 (4.8%) patients. The median mCTA ASPECTS mismatch score was 0.5 [0.0 – 0.5]. A mCTA ASPECTS cutoff ≥1, mCTA predicted a penumbral CTP pattern with a sensitivity and specificity of 18.8% and 71.4% respectively. The positive and negative predictive values were 61.9% and 26.3 % respectively with an AUC of 0.402 (0.287 – 0.517).

mCTA ASPECT Scores (Large Vessel Patients only)

In the 48 patients with an LVO, the median (IQR) mCTA ASPECT score on phase 1 was 4.5 (3.0 – 7.0). The median (IQR) was on phase 3 was 5.0 (3.5 – 7.5). The mCTA phase 1 ASPECT scores were inversely correlated with total perfusion deficit volumes (ρ= -0.577, $p<0.001$). Phase 3 mCTA ASPECT scores were inversely correlated with baseline core volumes (ρ= -0.682, $p<0.001$) (Figure 4.3).

Between phases 1 and 3, 18/48 (37.5%) patients demonstrated a change in median mCTA ASPECT scores of 1 or more. A change in 2 or more on mCTA ASPECT scores was seen in 6 (12.5%) patients, and a change in 3 or more was seen in 3 (6.3%) patients. In LVO only patients, the median mCTA ASPECTS mismatch score was 0.5 [0.0 – 1.3]. A mCTA ASPECTS cutoff ≥1, mCTA predicted a penumbral CTP pattern with a sensitivity and specificity of 38.7% and 53.8% respectively. The positive and negative predictive values were 66.7 % and 26.9 % respectively with an AUC of 0.460 (95% CI 0.285, 0.635).

Collateral Grades

Collateral grades were scored on both the sCTA and mCTA. The inter-rater agreement was moderate for both the sCTA (kappa=0.527; $p<0.001$) and mCTA (kappa=0.516; $p<0.001$). There were 6 cases where at least one rater scored the collateral grade as better on the mCTA, and 21 cases where the collateral grade was poorer on the mCTA. In the remaining 78 patients, there was no difference in collateral grades between the two modalities.

In 5/8 cases with large core on CTP (>70 ml), at least one rater scored the collaterals as moderate or good on mCTA. ANOVA indicated that median mCTA ASPECT score mismatch did not vary with collateral grade ($p=0.448 – 0.504$). ANOVA indicated that ischemic core volumes did vary with collateral grade ($p<0.001$).Post-hoc Kruskal-Wallis tests revealed good collateral grades were associated with smaller ischemic core volumes than those with poor and moderate collateral grades ($p<0.001$).

Discussion

Applying the ASPECT score to multi-phasic CT angiographic data derived from CTP source images, we were able to regionally quantify changes predictive of both the ischemic core and total area at risk. Early phase CTA images were correlated with the area at risk and late phase images the ischemic core. Although the calculated mismatch score was correlated with penumbral volume, the low sensitivity and specificity for penumbral patterns limit the clinical utility of this approach.

The ASPECT score has been previously applied to mCTA source images, albeit using a limited number of regions.[7] The investigators scored each of M2 – M6 ASPECT regions, which were assessed for contrast delay, extent, and washout.[7] Although the resulting 5 point score was complex, the authors proposed values corresponded to local perfusion pressure and provided information comparable to that obtained with CTP.[7] Delayed washout in the late CTA phase (phase 3) was associated with poorer outcomes, which contrasts with other rating systems in which late phase opacification was consistent with a good collateral pattern and improved response to therapy.[7,13,14]

In our study, we found that multiphase CTA changes the assessment of the collateral pattern in 11.1% of patients. The diagnostic yield of mCTA is improved when restricted to use in LVO patients only. However, even in this population, mCTA demonstrated differences between the first and subsequent phases only 21.7% of the time. While a change in ASPECT scores between phases was associated with penumbral pattern on CT, the predictive ability of the mismatch score was low.

Although we reconstructed a multiphasic CTA from CTP source data, this may not always represent the same images obtained using conventional CTA, followed by two delayed intracranial acquisitions.[5] We based the first phase on the peak of the tissue time density curve, which does not always correspond to the single phase CTA images acquired when contrast injection is triggered by bolus arrival in the aortic arch.[15,16] In fact, this represents a potential limitation of both sCTA and multiphase CTA, as originally described. In both cases, collateral flow can be incorrectly rated if the first phase images do not correspond to the tissue time density curve peak.

The poor performance of mCTA in identification of penumbral patterns in patients without LVO was not unexpected. Although inclusion of these patients in our study certainly biased the results in favor of CTP, this reflects the reality of every day acute stroke patient assessment. Patients with LVO represent a fraction of the acute stroke patient population. Multiphase CTA has been proposed as a tool that can be used to select patients for therapy with similar diagnostic accuracy as CTP.[5] Our results, however, suggest relying on an imaging modality that does not identify smaller volume infarcts will under-estimate the true number of potential responders to reperfusion therapies, particularly intravenous thrombolysis.

When assessment of mCTA performance was restricted to patients with an LVO, performance was improved. Certainly, there are patients in whom the perfusion changes are evident on both CTA and CTP, but assessment of the macrocirculation alone, as occurs with CTA, will always reduce sensitivity for detection of at risk and ischemic core tissue. In contrast, CTP provides a complete assessment of tissue perfusion at both the macrovascular and microvascular level.[17–19] We found that the mCTA mismatch score was only weakly correlated with penumbral and core volumes measured on CTP in both LVO and non-LVO patients. This is consistent with a recent study demonstrating a lack of correlation between collateral grades and penumbral volumes.[20]

One limitation of our study is the lack of outcome data. The highly variable treatment of our patient population, accrued during and after conduct of the pivotal EVT trials, confounds any assessment of outcome.[2] Regardless, the poor sensitivity of the mismatch score for CTP penumbral volumes makes it unlikely that this approach will predict tissue fate or clinical outcomes with any degree of accuracy.

Conclusion

Application of the ASPECT score to multiphase CTA images provides a surrogate marker of at risk, penumbral and ischemic core volumes. The low sensitivity and specificity of these scores for tissue volumes measured objectively with CTP limits the clinical utility of this diagnostic approach.

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Chapter 5 - Conclusion

Introduction

The goal of this thesis was to compare different techniques of computed tomography (CT) used in acute ischemic stroke treatment selection. We first sought to retrospectively analyze the CT perfusion (CTP) data from the ESCAPE endovascular stroke trial, comparing the CT angiography (CTA) based enrollment against thresholds established in CTP literature. We then sought to compare CTA directly to CTP on measures such as mismatch patterns and volume estimations. Both analyses included both single phase CTA (sCTA) and multiphase CTA (mCTA) as mCTA has been suggested as a more accurate, reliable tool that can be used in addition to sCTA in place of CTP. No direct comparison of mCTA to quantitative measures of CTP exists.

ESCAPE Trial

Since 2015, endovascular therapy (EVT) has emerged as an effective treatment for patients presenting with a large-vessel occlusion (LVO). [1] Not only does EVT achieve higher rates of reperfusion than standard medical care alone, namely tPA, but this can be achieved in an extended time-window in select patients than has been previously used for thrombolytic therapy. One of the main debates among stroke physicians, especially as we continue to extend the treatment window, is how best to select patients for therapy. The ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times) trial sought to compare EVT to standard of care using only non-contrast CT (NCCT) and CTA imaging to select patients for randomization.[2] Patients presenting within 12 hours of symptom onset and an absence of a large core on NCCT were

eligible for randomization. In lieu of perfusion imaging, the ESCAPE trial used good-moderate collaterals on either sCTA or mCTA as a marker of penumbral tissue, tissue that is electrically inactive but salvageable provided reperfusion occurs. [2] Collateral status had been used previously to identify patients with salvageable tissue who are likely to respond positively to therapy. [3] While collateral status was originally scored on sCTA, the development of mCTA has allowed for a more accurate analysis of collaterals as it provides additional phases to assess the delay and time-course of the collateral blood vessels. [4,5] Limitations of mCTA persist, however, as mCTA only acquires 3 time points and only looks at the macrovasculature, using blood vessels as a surrogate for perfusion status. This was supported by our retrospective analysis as, although most ESCAPE patients presented with a target-mismatch pattern on CTP, as many as 10% were non-mismatch patients. These patients had poorer rates of good clinical outcome and larger final infarct volumes, suggesting that CTA may be inadequate to exclude acute ischemic stroke patients for EVT.

Multiphase CTA versus CTP

As the ESCAPE trial analysis was studied retrospectively on study patients, we aimed to directly compare CTA, specifically mCTA, to CTP. While some work has compared mCTA to CTP ASPECT scoring, this was a limited analysis that did not use automated software for CTP to generate maps of penumbra and core volumes based on previously validated thresholds. [6] Based on established metrics of evaluating collateral status, we compared mCTA collateral scores to CTP-defined core and penumbral volumes. [2,3] While good collaterals were associated with smaller core volumes, there was no difference between the moderate and poor collateral status patients in terms of either core volumes or mCTA ASPECT mismatch scores in both all stroke patients and LVO-only patients. Furthermore, as many as 58% of patients with a non-penumbral

pattern on baseline CTP were rated as having moderate-good collaterals on mCTA. We then used the ASPECT scoring system to score the 3 phases of mCTA maps based on peak of flow, washout of contrast, and degree of extent of blood volume in affected tissue. As collateral flow may cause a delay in the contrast to reach the affected tissue, thus causing sCTA to overestimate core damage, the additional phases are thought to give a more accurate interpretation of core volumes. We compared ASPECT scores from phases 1 and 3, using this mismatch score as a surrogate for penumbral tissue. While there was a moderate correlation between phase 3 ASPECTS and core volumes and Phase 1 ASPECTS and total perfusion deficit, mCTA-defined mismatch was relatively insensitive to CTP-defined mismatch patient, preventing accurate identification of patients with salvageable tissue.

Limitations and Future Directions

While the comparison studies in this thesis have sought to compare CTA to CTP, and determine the utility of mCTA in acute imaging, these studies have had limitations. These limitations include having a small cohort of patients, approximately 100-150 patients, different methods of creating the maps of mCTA, and being retrospective analyses of trial data. To accurately determine whether sCTA and mCTA can reliably replace perfusion imaging in patient selection for reperfusion therapy, a larger comparison study is needed. This is evident in the ESCAPE study as the small number of EVT-randomized CTP patients prevented an analysis of the relationship between CTP and EVT. Furthermore, this study needs to accurately align with the imaging methods used to create mCTA. While our maps of mCTA were timed more accurately, using the concentration curves from CTP to ensure correct capture of each phase, this may not correlate with real-world data obtained using sCTA-based mCTA maps. Finally, both studies were based on a retrospective analysis of patient data. In the ESCAPE trial, approximately 40%

of randomized patients received CTP imaging as a part of their routine care. It is unknown how the use of CTP may have affected randomization decisions at each site. This includes the number of patients excluded solely based on CTP-imaging, thus possibly under-representing the percentage of patients that pass inclusion criteria for CTA but are non-mismatch patients on CTP.

While the studies discussed in this thesis looked at the clinical difference between patient selection based on CTA and CTP, the underlying physiology is not yet fully understood. Although collateral flow in ischemic tissue is associated with smaller final infarct volumes and better prognosis long-term, it is not fully understood when collateral flow begins to fail in relation to infarction. One proposed hypothesis for the reason we see moderate-good collateral flow in patients presenting with a large core or a non-mismatch pattern is that collaterals failure may be caused by the tissue infarction instead of the inverse relationship wherein the failing collaterals cause the infarction. This would potentially create a window where patients appear better on angiographic imaging than they are, with CTP being more accurate at predicting tissue status. Future studies may include multiple imaging time-points of CTA and CTP to compare how collaterals progress in relation to blood flow imaging. Increased radiation per scan, however, makes these studies difficult to perform in human patients.

The primary focus of these studies was the use of perfusion imaging in acute ischemic stroke care. One of the next key advancements in stroke imaging, discussed briefly in previous chapters, is utilizing arterial spin labelling (ASL) in the subacute setting of stroke. As MRI is already used in this setting to determine final stroke volume, the ability to add on a perfusion sequence that requires no contrast injection would allow for quick and relatively non-invasive

perfusion imaging post-treatment. This could be used to both predict adverse reaction to treatment and long-term prognosis regardless of therapy.

Conclusion

Advanced imaging in acute ischemic stroke patients is essential for a fast and reliable diagnosis, along with optimal patient selection for reperfusion therapies. As many different imaging modalities and techniques exist that look at different aspects of the brain, debate continues how best to utilize modern imaging in acute stroke care. Our studies support the argument that while angiographic CT imaging techniques, both singlephase and multiphase, are essential in confirming clot location and are moderately accurate in selecting ideal patients for reperfusion therapy, mismatch patients with relatively small baseline core volumes, they remain inadequate in supplanting CTP imaging as the gold-standard for patient selection. While further, large multi-site studies are needed to confirm the superiority of CTP imaging, it is already approved in EVT patients to extend the treatment window to 24 hours in select patients.

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