Applications of CT Perfusion indices in estimating early core growth in ischemic stroke

by

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Abstract

Computed Tomography Perfusion (CTP) is a rapidly acquired minimally invasive mean to assess brain perfusion dynamics, collaterals and infarct growth in acute ischemic stroke (AIS). It helps differentiate expected stroke evolution and speed of core growth after arterial occlusion.

The goals of this research were to determine: 1) Evaluation of means to differentiate rate of core progression in AIS and usefulness of hypoperfusion index (HI), 2) Evaluation of performance of CTP HI in medium and large - vessel occlusions (MeVO and LVO respectively) in early and late time windows, to assess infarct growth in patients with AIS, and 3) Association of cerebral small vessel disease (SVD) to HI as an imaging marker of infarct growth in patients with LVO AIS.

We have shown that: 1) Estimation of progressors by definition inclusive of M2 occlusions and HI seem to be more comprehensive and can estimate rate of infarct growth with good sensitivity and specificity. External validity of these methods however requires further study. 2) HI is able to estimate the initial rate of core progression in acute ischemic stroke in patients with both MeVO and LVO comparably up to 24 hours of onset, likewise in early and late windows. Patients with HI > 0.5 have a fast rate of infarct progression that is on average ten times that of slow progressors. Further evaluation of HI however is needed to determine whether it could aid in the selection, triage and management of stroke patients treated with reperfusion therapy. 3) Advanced SVD is associated with higher HI, thus higher chances of early infarct growth in patients with LVO AIS. This can potentially support the hypothesis that increased burden of SVD is an imaging biomarker for impaired circulatory reserve and infarct growth. Future studies should explore how HI relates to SVD and can better predict micro-circulatory failure.

In summary, this research has shown the utilization of hypoperfusion index as a promising tool that can help better triage and select patients with AIS for reperfusion therapy and understand the mechanisms contributing to differential infarct growth in patients with AIS.

Keywords: *Stroke, ischemia, CT perfusion, hypoperfusion index, core progression, infarct growth, small vessel disease, large vessel occlusion, medium vessel occlusion, fast and slow progressors*, *collaterals, micro-circulation*

Preface

This thesis is an original work by Ali Zohair Nomani. The research project which this thesis is a part of, received research ethics approval from the University of Alberta Research Ethics Board, Project name "Genomics of stroke and neurological diseases", No. Pro00066577, October 24, 2016. This dissertation contains both under publication and unpublished work, which is original work of myself, and appropriately cited work of others.

Chapter 1 is an introduction to stroke, stroke imaging and CT perfusion in context of acute ischemic stroke. The literature review in chapter 1 and writing has been done by me.

Chapter 2 of this thesis is being submitted to a peer-reviewed journal as a brief communication as "How to define fast and slow progressors in ischemic stroke". It is an evaluation and comparison of various methods to ascertain core growth in patients with acute ischemic stroke and potential benefits of hypoperfusion index. The project design, data collection and analysis, and composition of manuscript have been done by me and reviewed by Dr Glen C. Jickling for edits.

Chapter 3 of this thesis is under peer-review process for publication as an original article as "Relationship of hypoperfusion index to core progression in medium and large vessel ischemic stroke". It is a prospectively investigated application of hypoperfusion index and its ability to estimate core progression in medium and large vessel occlusion ischemic stroke up to 24 hours of stroke onset. Chapter 3 was designed by me and Dr Glen C. Jickling. Data collection and analysis was done by me with assistance from Joseph Kamtchum-Tatuene. The manuscript was composed by me. Dr Jeremy L. Rempel, Dr Thomas Jeerakathil, Dr Ian Winship, Dr Khurshid A. Khan,

Dr Brian H. Buck and Dr Ashfaq Shuaib helped with edits to the manuscript. It was reviewed by Dr Glen C. Jickling for concept reformatting and manuscript finalization.

Chapter 4 explores the relationship between small vessel disease and hypoperfusion index with the hypothesis that patients with severe cerebral small vessel disease are more likely to have a higher hypoperfusion index and thus faster core growth in patients with large vessel occlusion ischemic stroke. It is being submitted to a peer-reviewed journal as an original article as "Advanced small vessel disease is associated with hypoperfusion index in large vessel occlusion acute ischemic stroke". Chapter 4 was designed by me and Dr Brian H. Buck. Data collection, processing and analysis was done by me with assistance from Noman Ishaque. The manuscript was composed by me and reviewed for edits by Dr Brain H. Buck, before been finalized by Dr Glen C. Jickling.

Chapter 5 is a review discussion of practical applications of CT perfusion indices, conclusion and future directions in assessment of infarct growth. Literature review and concluding analysis in chapter 5 have been done by me and reviewed by Dr Glen C. Jickling.

Dedication

This work is dedicated to my beloved parents and my wife, for their love and support, and from whom all I have learnt the way of life …

Thank you!

Acknowledgements

I would like to express my sincere gratitude for the unequivocal support and unmatched dedication of my supervisor and mentor, Dr Glen C. Jickling, from whom I take inspiration of "following the path of knowledge despite all odds". I am grateful to him and acknowledge the assistance provided by his laboratory for collection of data and acquisition of ethics approval. I would also like to thank my mentors including Dr Khurshid A. Khan, Dr Ashfaq Shuaib, Dr Brian H. Buck, Dr Ian Winship, Dr Jeremy L. Rempel and Dr Thomas Jeerakathil for their endless support, kind and understanding spirit and wisdom …. thank you all!

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List of abbreviations

CTP: Computed Tomography Perfusion

HI: Hypoperfusion Index

HIR: Hypoperfusion Intensity Ratio

AIS: Acute Ischemic Stroke

LVO: Large Vessel Occlusion

MeVO: Medium Vessel Occlusion

ACLVO: Anterior Circulation Large Vessel Occlusion

CT: Computed Tomography

NCCT: Non-Contrast Computed Tomography

SVD: Small Vessel Disease

EPVS: Enlarged Peri-Vascular Space

DWMH: Deep White Matter Hypodensities

PVWMH: Peri-Ventricular White Matter Hypodensities

CTA: Computed Tomography Angiography

CBF: Cerebral Blood Flow

CBV: Cerebral Blood Volume

MTT: Mean Transit Time

TTP: Time to peak

PACS: Picture Archiving and Communication System

DICOM: Digital Imaging and Communications in Medicine

TIA: Transient Ischemic Attack

ICA: Internal Carotid Artery

ACA: Anterior Cerebral Artery

MCA: Middle Cerebral Artery

HERMES: Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials

DEFUSE 3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3

DAWN: DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo

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: Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial Using Intravenous Tenecteplase

TIMELESS: Thrombolysis in imaging eligible late window patients (4.5-24 hours) to evaluate the efficacy and safety of tenecteplase

DIRECT MT: Direct Intra-arterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals

ESCAPE: Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times

MR CLEAN: The Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands

SWIFT PRIME: Solitaire ^{TM} with the Intention for Thrombectomy as Primary Endovascular Treatment

REVASCAT: Revascularization with Solitaire FR device vs. best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within 8 hours of symptom onset trial

RACECAT: Direct Transfer to Endovascular Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory

SELECT: Optimizing Patient Selection for Endovascular Treatment in Acute Ischemic Stroke

NIHSS: National Institutes of Health Stroke Scale

ASPECTS: Alberta Stroke Program Early CT Score

mRS: modified Rankin Scale

EIGR: Early Infarct Growth Rate

IVT: Intra-Venous Thrombolysis

EVT: Endo-Vascular Thrombectomy

NINDS: The National Institute of Neurological Disorders and Stroke

ECASS: European Cooperative Acute Stroke Study

rtPA: recombinant tissue Plasminogen Activator

FDA: Food and Drug Administration

TOAST: Trial of Org 10172 in Acute Stroke Treatment

MRI: Magnetic Resonance Imaging

DW-MRI: Diffusion Weighted Magnetic Resonance Imaging

RAPID: Rapid processing of perfusion and diffusion

AutoMIStar: Apollo Medical Imaging Technology

TICI: Thrombolysis In Cerebral Infarction

MM: Medical Management

ICH: Intra-Cranial Hemorrhage

NNT: Number Needed to Treat

aOR: adjusted Odds Ratio

Chapter 1

Introduction: Stroke and infarct growth

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1.1. Ischemic stroke:

Ischemic stroke is a major cause of neurological morbidity and mortality across the globe. [1] It is the third main cause of death and the leading cause of long-term disability. [2-9] The major causes of ischemic stroke are occlusion of cerebral arteries either by a cardiac or non-cardiac embolus or by thrombus formation in atherosclerotic vessel walls. [5, 7] Studies of cerebral blood flow measurement have revealed that after occlusion of an artery there is region of brain that is threatened but viable and is called "ischemic penumbra". [10-12] The time till this zone would remain viable is called "therapeutic time window". [3, 4, 6, 8, 10] The tissue which gets irreversibly injured is known as "core" or "infarct". [3, 4, 10, 13, 14] Though degree of occlusion, presence of collaterals and extent of spontaneous reperfusion can vary, studies have consistently shown that reperfusion within 3-4.5 hours of arterial occlusion using intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT) up to 24 hours will limit the size of infarct and halt infarct growth. [15, 16] This scientific dictum resulted in origin of the unique idea of "time delay" from onset which has been defined as time it takes from stroke onset to initiation of acute medical intervention. [11-20]

Advances in stroke research have made complete reversal of disability and prevention of early death from stroke a reality. [1, 5, 12, 16, 19, 20] There was no definitive treatment available to counter deficits from acute ischemic stroke (AIS) until late 1980's. [21] The first randomized controlled trial to revolutionize the treatment of ischemic stroke was The National Institute of Neurological Disorders and Stroke (NINDS). [22-25] This trial was a large, placebo-controlled trial of intravenous recombinant tissue plasminogen activator (rt-PA) versus placebo in patients with acute ischemic stroke who were treated within first 3 hours of stroke symptom onset. [22] It was carried out in two parts. 1) Part 1 (n=291) assessed changes in neurologic deficits 24 hours after the onset of stroke.

2) Part 2 (n=333) assessed whether treatment with alteplase resulted in sustained clinical benefit at 90 days assessed by modified Rankin Scale (mRS). NINDS was able to show that thrombolysis within 3 hours of stroke onset can potentially benefit patients by early recanalization of occluded artery with a robust number needed to treat (NNT) of ~ 8. [22]

NINDS was followed by evaluation of alteplase in European population. Three AIS trials were conducted using variable doses of alteplase. By using different time windows, The European Cooperative Acute Stroke Study (ECASS) III showed benefit of alteplase up to 4.5 hours from onset of stroke with NNT of ~ 20. [16, 23-25]

Another trial was conducted by the Japanese to assess the efficacy of alteplase in their population. [26] They showed that a dose of 0.6mg/kg was just as efficacious and safe as the original dose of 0.9 mg/kg, which was used in the NINDS trial. [26] A further exploration of time windows beyond 4.5 hours was conducted by researchers in Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial which showed sustained benefit of thrombolysis in people with favorable brain imaging up to 9 hours from stroke onset. [27]

Thrombolytic therapy is now an approved treatment for acute cerebral ischemia within 4.5 hours of onset and is used selectively by stroke neurologists for extended window thrombolysis given its potential benefits. [6, 12, 25, 27] However, the benefit from this treatment rapidly declines over time. [28-33] Intravenous administration of rtPA is currently the only food and drug administration (FDA) approved drug for thrombolysis in acute ischemic stroke. [28-36] However given a substantial proportion of patients with AIS have large vessel occlusions (LVO), the number of patients benefiting from it has been small. [11, 12, 14, 21, 29, 34, 37, 38] Even with extended window up to 9 hours, a handful of AIS patients qualify for thrombolysis. [27]

Following the results of Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) meta-analysis in 2015, endovascular thrombectomy has been adopted as the standard of care for recanalization of Anterior Circulation Large Vessel Occlusion (ACLVO). [38-40] The number needed to treat for such patients is quite robust and ranges from a mere two to four. [38] Initial evidence by HERMES meta-analysis from five randomized trials namely - Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE), The Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN), **:** Solitaire [TM] with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME), Revascularization with Solitaire FR device vs. best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within 8 hours of symptom onset trial (REVASCAT) and Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial (EXTEND IA), supported LVO recanalization within 6-8 hours of stroke onset. [38] This was however extended up to 24 hours after the results of extended window thrombectomy trials i.e., DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3), were published. [39-41] Endovascular thrombectomy has substantially improved stroke outcomes and has changed the perception of how physicians see stroke as a “somewhat manageable to completely reversible” pathology, that can profoundly reduce disability and death from AIS. [12, 20, 21, 30, 37-40]

Earlier thrombolysis as well as thrombectomy are both associated with lower risk of subsequent complications, including symptomatic intracranial hemorrhage (ICH). This is because

early recanalization is mechanistically associated with lesser chances of complete disruption of blood brain barrier at the site of infarction. [8, 10, 13, 14, 15, 27] Because of the vital importance of rapid reperfusion, worldwide stroke guidelines recommend that hospitals complete the evaluation of patients with acute ischemic stroke and initiate thrombolysis within 30-60 minutes of patient arrival to the thrombolysis capable center. [4, 6, 8, 29-31] However, studies have demonstrated that less than one-third of patients presenting with acute ischemic stroke even in the developed world are treated within the guideline recommended door-to-needle time. [29-32, 34, 42-44] This quality control measure has improved minimally over time due to the inherent nature of stroke presentation, identification, assessment and need for imaging before instituting reperfusion strategies. [44] Prior research shows that stroke care is most effective when integrated into a collage of explicit goals i.e., strong collaboration, interdisciplinary teams, a patient focused organizational culture, logical triaging, intelligent use of ground and flight transfers, and logistically feasible and geographically beneficial transport strategy. [44-48]

1.2. Etiology of acute ischemic stroke:

Ischemic stroke occurs because of a sudden impedance or total lack of adequate blood supply to part of the brain. [15-18] This initiates a cascade of tissue injury which grows quickly over time unless salvaged by restoration of blood supply to the respective part of brain. [10-12, 17, 18] Pathophysiology of stroke is defined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification which categorizes etiology of AIS into following major categories. [49]

a. Large artery atherosclerosis (embolus/ thrombus)
b. Cardio-embolism (high/ medium-risk)
c. Small vessel occlusion (lacunae)

d. Stroke of other determined etiology
e. Stroke of undetermined etiology
    i. Two or more causes identified
    ii. Negative evaluation
    iii. Incomplete evaluation

Common risk factors for AIS are the same as for cardiovascular diseases in general, including uncontrolled high blood pressure, uncontrolled diabetes mellitus, tobacco smoking, being overweight or obese, dyslipidemia, prior history or family history of cardiovascular disease and atrial fibrillation. [50-52] The American Heart Association/American Stroke Association recommends controlling or optimally treating these risk factors in order to prevent or reduce future chances of stroke. [51, 52]

1.3. Anatomy of cerebral vasculature and effects of occluded blood supply:

Brain vasculature is majorly divided into anterior and posterior circulation, that join at base of the brain to form the circle of Willis as shown in figure 1.1. [53, 54] For anterior circulation, the left common carotid artery originates from arch of aorta while the right common carotid arises from right brachiocephalic trunk. The common carotids bifurcate into internal carotid artery (ICA) and external carotid artery. The external carotid artery supplies the neck, face and scalp. The internal carotid gives off the anterior cerebral artery (ACA) and terminates into middle cerebral artery (MCA). The middle cerebral artery begins as a continuation of ICA and subsequently divides into M2, M3 and eventually cortical branches (M4-6). [53, 54-56] The ACA communicates with other ACA via anterior communicating artery and leads to A2-5 distally. [54] Other major branches of carotid include the anterior choroidal and the ophthalmic artery. [54] The posterior circulation originates

from two vertebral arteries that usually arise from the subclavian arteries and join to form the basilar artery. The basilar artery divides into two posterior cerebral arteries which are joined to anterior circulation via the posterior communicating arteries. [53, 54] The major communicating connections between anterior and posterior circulation are known as primary collaterals and serve as alternate bypass channels to perfuse brain tissue via substitute pathway for blood supply to the brain when an artery gets occluded. [54, 55] In addition, each of these major vessels is joined via some bypass channels via cortical pathways called pial or leptomeningeal collaterals, to both internal and external carotid systems. These conduits successively have decreasing diameter and eventually at the point of anastomosis have a caliber quite comparable to capillaries. [54, 55] Some of the branches from these arterial circuits however terminate into vessels with no bypass anastomosis. These are called “end-arteries”. Occlusion of these end-arteries leads to perforator type infarcts. [54, 55]

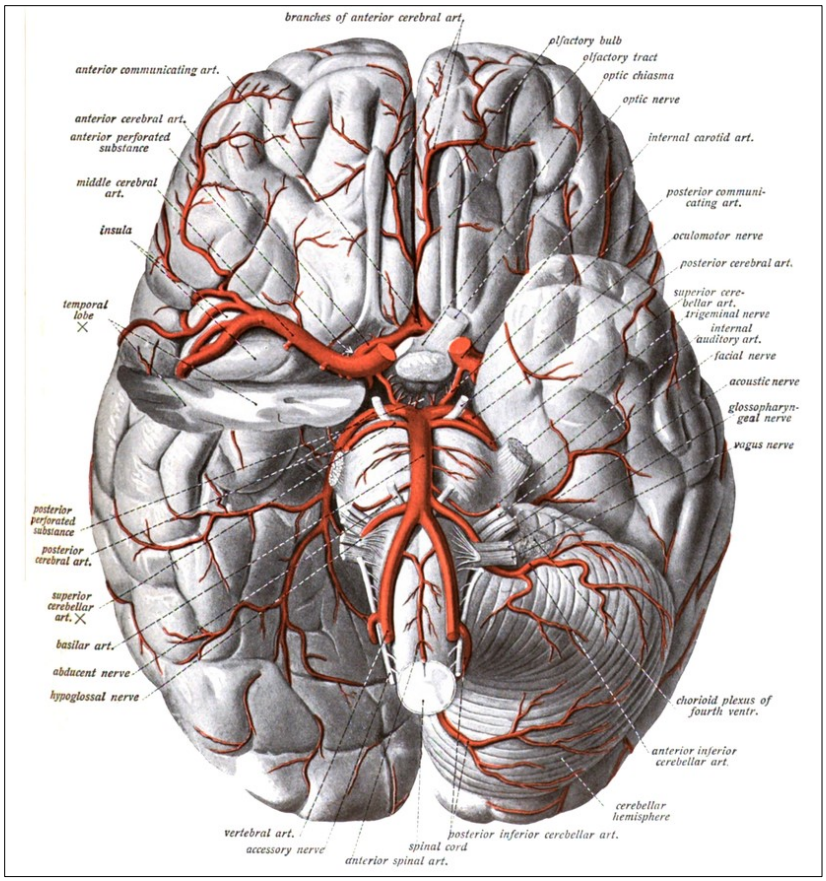

Figure 1.1. Anatomy of cerebral arterial system. Adopted from: 20th U.S. edition of Gray's Anatomy of the Human Body. [53]

With occlusion of an intracranial cerebral artery, brain tissue ceases to function because of deprivation of oxygen. [57-60] Injury to brain tissue can begin as soon as 60 to 90 seconds of impeded blood flow. After a few hours, brain usually suffers irreversible injury, possibly leading to death of the tissue, i.e., infarction. [59, 60] That is why fibrinolytics such as alteplase are given only until early hours since the onset of the stroke. [57, 58] As oxygen or glucose supply becomes depleted in ischemic brain tissue, the production of high energy phosphate compounds such as adenosine triphosphate stalls. The adenosine triphosphate dependent pumps necessary to maintain ion and

chemical gradients across cell membrane therefore fail which leads to cell death. This sets off a vicious cycle of irreversible brain cell injury and eventual liquefaction. [57-60]

One of the major contributors towards this injury is the cytotoxic effects of certain excitatory neurotransmitters like glutamate. [57-60] Under normal circumstances, the concentration of glutamate outside the cells of the nervous system is low. This is mediated by the uptake carriers, which are powered by the concentration gradients of sodium across the membrane. As soon as energy supply is cut-off, undesired release of glutamate into extracellular space leads to N-methyl-D-aspartate receptor mediated influx of calcium which activates enzymes that digest the intracellular proteins, lipids and nuclear material. In addition, calcium influx empowers failure of mitochondria, with further energy depletion and thus programmed cell death. [57-60]

Ischemia also induces production of oxygen free radicals and reactive oxygen species. These radicals are toxic to both intracellular and extracellular components via redox signaling. [58-60] While this ischemic cascade is universal for any tissue type, vulnerability of brain to ischemia is profoundly hazardous due to limited respiratory and circulatory reserve. Ischemia and infarction result in loss of structural integrity of brain tissue and blood vessels, partly through the release of matrix metalloproteases that break down collagen, hyaluronic acid, and other elements of connective tissue. The loss of vascular structural integrity results in a breakdown of the protective blood brain barrier that contributes to cerebral edema, which can cause secondary progression of the brain injury and continued growth of early infarcted tissue. [57-60]

1.4. History and clinical examination:

The symptoms of brain ischemia reflect the strategic anatomical region of the brain undergoing blood and oxygen deprivation. [61-64] Ischemia within the arteries branching from

the internal carotid artery may result in symptoms such as visual impairment in one or both eyes, weakness or paralysis in one arm or leg, or entire side of the body. Ischemia within the arteries branching from the vertebral arteries at the back of the brain may result in symptoms such as dizziness, lightheadedness, drop attacks, vertigo, double vision, weakness on both sides of the body, impaired awareness, difficulty speaking and articulating, and/ or the loss of coordination and balance. [61, 63] The symptoms of brain ischemia range from mild to severe; and are usually graded on a standardized scale namely National Institutes of Health Stroke Scale (NIHSS), which ranges from 0-42. Strokes with NIHSS ≤ 5 are usually called as "minor strokes"; (table 1.1.). [61-63]

Table 1.1. National Institutes of Health Stroke Scale (NIHSS). Re-illustrated - Adopted from Runde. [61]

NIH STROKE SCALE SHEET (Circle the Patient's Score)

LOC	0 = Alert, keenly responsive 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond 2 = Not alert, requires repeated stimulation to attend, pain to move 3 = Responds with reflex motor, posturing, unresponsive, not movement, etc.	**Limb Ataxia Out of Proportion to Weakness (test both arms FTN legs HTS)**	0 = Absent, global aphasia, complete hemiplegia 1 = Present in 1 limb 2 = Present in 2 limbs UN = Post-angio maintain straight leg, amputation, joint fusion, explain:_____
Month Age	0 = Answers both questions correctly 1 = Answers one question correctly, intubated but follows command 2 = Answers neither question correctly, aphasic, stuporous, coma	**Sensory on Face/Arms/Legs (use pin or noxious)**	**Don't test on hands/feet** 0 = Normal, no sensory loss 1 = Mild to moderate sensory loss, can tell touch 2 = Severe to total sensory loss, not aware of touch, coma, or quadriplegic
Open/Close Eyes Open/Close Good Hand	0 = Performs both tasks correctly without coaching 1 = Performs one task correctly, even if weak 2 = Performs neither task correctly	**Best Language (describe picture, name objects, read sentences)**	0 = Normal, no aphasia 1 = Mild to moderate aphasia, can be understood 2 = Severe aphasia, much is not understood, excess listener work 3 = Mute, global aphasia, no usable speech or auditory comprehension, follows no 1 step commands, coma **Alternate method if unable to read: repeat words/ sentences, object recognition after feeling object in hand**
Best Gaze Horizontal (voluntary or Doll's)	0 = Normal 1 = Partial gaze palsy, can be overcome by finger tracking/head turning 2 = Forced deviation or total gaze paresis, not overcome by the oculocephalic maneuver	**Dysarthria (clarity of articulation, read or repeat words)**	0 = Normal 1 = Mild to moderate dysarthria, some slurring, speech understood 2 = Severe, so slurred to be unintelligible UN = Intubated, or other physical barrier explain:_____ **If patient is aphasic, judge only the spontaneous words**
Visual Fields (upper, lower quadrants)	0 = Normal, no visual loss, or regards/looks at moving fingers 1 = Partial (upper/lower quadrantopia) hemianopia, visual extinction 2 = Complete hemianopia 3 = Bilateral hemianopia, blindness	**Extinction or Inattention, Neglect (test face and arms with bilateral simultaneous stimulation)**	0 = No abnormality 1 = Personal inattention or extinction to bilateral stimuli in any one of the senses (vision, tactile, auditory, spatial or personal) 2 = Profound inattention or extinction to more than one sense, may not recognize own hands or orients to only one side of space
Facial Palsy (show teeth, raise eyebrows, close eyes,use noxious stimuli)	0 = Normal, symmetrical movement 1 = Minor asymmetry, ↓ nasolabial fold 2 = Partial paralysis lower face 3 = Complete paralysis 1 or both sides, upper/lower face (absence of facial movement in the upper and lower face)		
Motor Arm	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain:_____ **5a. Left Arm** 0 1 2 3 4 UN **5b. Right Arm** 0 1 2 3 4 UN	**TOTAL NIH STROKE SCALE SCORE** _____ **(Don't count any UN's in score)** **DATE** _____ **TIME** _____ **EXAMINER** _____ **MD or RN (NIH Stroke Scale trained)** **Please check appropriate box to indicate time this NIHSS completed:** ❑ **Admit (or at time of Code 3 Stroke initiated)** ❑ **24 hours** ❑ **Discharge** **PLACE IN H&P/CONSULT SECTION OF CHART.**	
Motor Leg	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain:_____ **6a. Left Leg** 0 1 2 3 4 UN **6b. Right Leg** 0 1 2 3 4 UN		

The symptoms from occluded artery in the brain can last from a few seconds to a few minutes or extended periods of time. A transient deficit that usually lasts less than an hour and by conventional definition does not exceed 24 hours is called a transient ischemic attack (TIA). [65] If the brain becomes damaged irreversibly and infarction occurs, the symptoms may be permanent, and can usually be seen subsequently on gold standard imaging for AIS i.e., diffusion weighted magnetic resonance imaging (DW-MRI). [65, 66] Figure 1.2. shows the clinical examination of a patient with one of the many features of stroke presentation, i.e., arm drift.

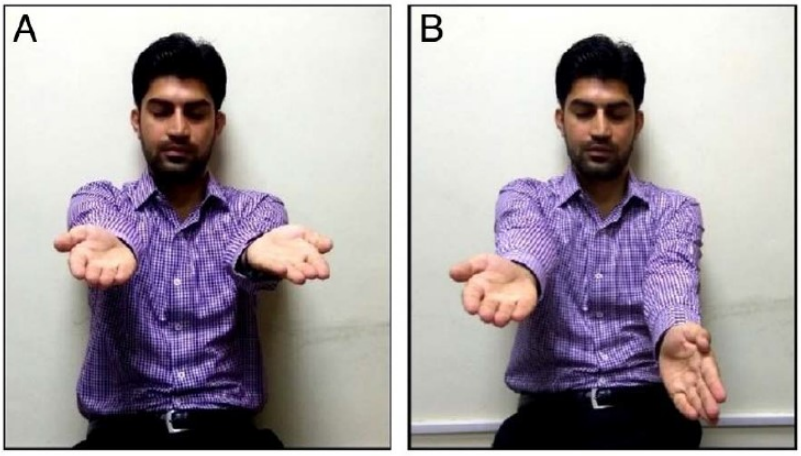

Figure 1.2. Clinical examination in acute stroke. Bedside clinical signs of stroke; **A:** patient simulation with no stroke has his arms held in an extended position with eyes closed. **B:** patient simulation with stroke displaying left arm drift. Adopted from Nomani et al. [51]

1.5. Dynamics of acute ischemic stroke and failure to sustain ischemia:

Early vessel recanalization and cerebral reperfusion is the goal of acute stroke therapies. [67, 68] It is the most effective mean to salvage penumbral tissue and improve clinical outcomes. [67, 68] The dynamics of acute ischemic stroke are complex (figure 1.3.). [51] Stroke evolution is affected

by both intrinsic as well extrinsic factors before restoration of blood supply to the brain. With occlusion of a cerebral artery, inherent reserve of autoregulation within the brain is able to sustain the ischemia and prevent irreversible infarction for only a period of time. [51, 59, 60] Few of the factors that predict viability of brain to sustain ischemic injury include time from stroke onset, time to recanalization, presence or absence of large vessel occlusion, carotid T-occlusion, variability of blood pressure, cardiovascular risk factors and resilient capacity of auto regulation. Over the last decade, extensive research into predictors of infarct growth and stroke outcomes have revealed that there may be other factors besides those mentioned above which can substantially contribute to infarct growth despite uniformity of well-known risk factors. [51, 69, 70] Collateral failure has been shown to be one of the robust predictors of final infarct volume and functional outcome after stroke onset. [55, 59, 60]

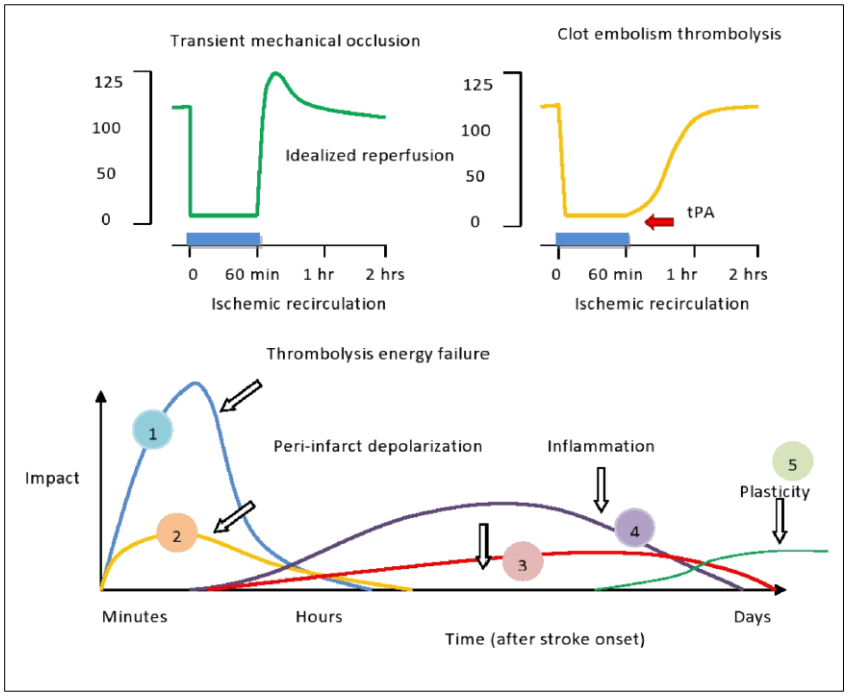

Figure 1.3. Process of tissue damage and possibility of time dependent salvageability of hypoperfused brain tissue after onset of ischemic stroke. Adopted from Nomani et al. [51]

A major contribution to infarct growth after arterial occlusion is due to collateral failure, both primary and secondary. [59, 60, 69] The primary collaterals being anterior and posterior bypass channels within the circle of Willis contribute a retrograde blood flow to the area of the brain supplied by the occluded artery. On the other hand, secondary collaterals, also known as pial or leptomeningeal collaterals, are smaller bypass channels running over the cerebral cortices that serve as secondary pathways of retrograde blood flow to the area supplied by the occluded vessel. [54, 55, 58, 59] The difference in baseline collateral status between patients and the dynamics of their timely recruitment in acute phase of an arterial occlusion is still not completely understood. [55] Collaterals may open up with the acute occlusion of major conduits. [55] However, the speed and extent of this recruitment as well as duration of sustained alternative blood supply depends upon the collateral reserve and possibly chronic stenosis of intracranial vasculature. [55, 59, 60, 69-71] There are various other factors speculated to be related to individual collateral status including genomic variability. [71] In the acute phase after stroke onset, the collaterals in some people can readily open and can save the hypoperfused tissue till the time reperfusion is achieved. In others, they may remain closed leading to lack of tissue resilience to tolerate brain ischemia. [55, 58, 59] Depending upon the status of these collaterals, patients either can progress slowly into their stroke with gradual growth of their infarct from stroke onset or can rapidly progress to completion of infarct in the whole hypoperfused territory. [70-73]

Predicting collateral status is challenging. Similarly, when and how these collaterals will fail is hard to anticipate. [59, 60, 69, 71, 72] It is virtually impossible to know the status of intracranial collaterals in a person unless and until they have some type of vessel related brain imaging performed to assess and quantify these collaterals. [55, 59, 72, 73]

1.6. Imaging for acute ischemic stroke:

The most commonly employed neuroimaging method for the evaluation of acute stroke is a non-contrast computed tomography (NCCT) scan without the administration of contrast material. [74] It is indeed the only study that is mostly required before the administration of intravenous rtPA. This is because at the time of advent of stroke treatment following results of NINDS and ECASS III, NCCT was the primary mode of evaluating stroke and thus was the major imaging technique used across major stroke trials. [16, 22-25] Over the course of years, it has been shown that NCCT might be sufficient at least for delivery of rtPA within 4.5 hours of stroke onset without the need of advanced imaging. [75] Sometimes NCCT can be predictive of LVO as well (figure 1.4.). [75]

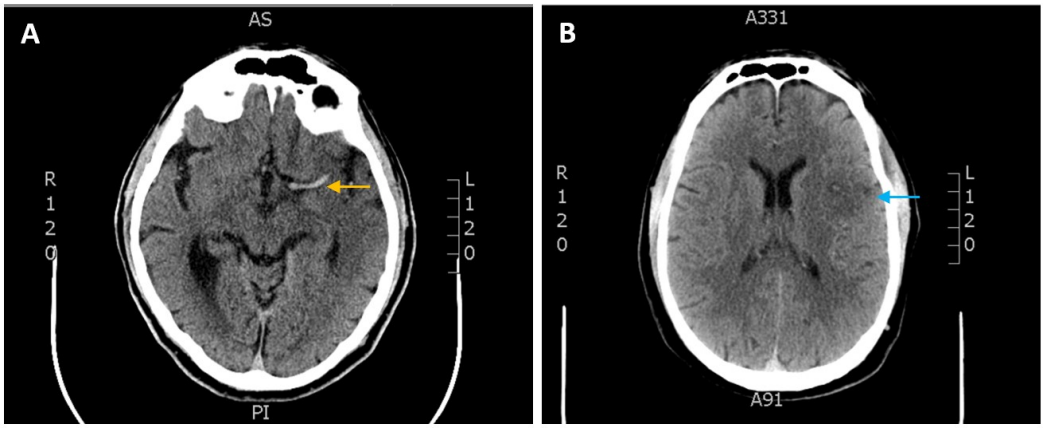

Figure 1.4. Non-contrast CT signs in acute ischemic stroke. A: Dense Middle Cerebral Artery sign (left), shown by yellow arrow. **B:** Sulcal effacement in territory of left Middle Cerebral Artery, shown by blue arrow.

For LVO, early window thrombectomy requires identification of the occlusion on angiography. [38] However, the basis of extended window treatments including thrombolysis as well as thrombectomy, especially beyond 6 hours, were originally based on advanced dynamic imaging

i.e., Computed Tomography Perfusion (CTP). [27, 39, 40] Physiological neuroimaging with Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) has the potential for significantly improving stroke treatment and has been adopted quite extensively nowadays for treating non-conventional NINDS, ECASS III and HERMES cohorts. [76]

CT and MR imaging are widely available and provide information on the state of the brain parenchyma, the vessels, and brain tissue perfusion in patients with AIS. [74, 76] Many institutions have the capability to perform either one or both imaging techniques. The treatment strategy for AIS patients relies on the capability of a facility to perform IVT or EVT. [67, 68, 75] The major question to formulate a treatment plan depends up on the need for thrombolysis or thrombectomy including imaging exclusion for intracranial hemorrhage and large established infarct on NCCT, and the presence or absence of large vessel occlusion. [22-25, 38, 74, 75]

1.7. Identification of large vessel occlusion:

The outcome of AIS depends on the size of the affected territory. Hampered blood flow to one of the major arterial regions will produce profound neurological symptoms followed by a large infarct if not reversed. [75-77] The therapeutic strategy may also depend on the size of the occluded artery. [38-41] For example, a thrombus within a proximal large vessel like middle cerebral artery will usually not be completely lysed by the administration of alteplase. The percentage of vessel recanalization for a distal MCA might reach as much as 65-70% with alteplase as opposed to a proximal MCA occlusion which can hardly exceed 15-20%. The successful recanalization strategy for such occlusions is usually accomplished using EVT. [27, 38-40] In setting of AIS, the most frequently used imaging technique to visualize LVO is CT angiography (CTA). It provides high-

quality images for both the head and neck vessels and guides treatment strategy. Alternative ways to assess LVO include conventional angiography and MR angiography. [78]

1.8. Advent of endovascular treatment strategies beyond LVO: Large versus Medium vessel occlusion:

Traditionally, EVT has been assessed in patients of AIS with LVO, including ICA and M1 branch of MCA. [38-41] However, with sophisticated access catheters, clots in distal vessels like M2, M3 [medium vessel occlusion (MeVO)] and other distal vessels can be approached and retrieved. [56] In fact, MeVO is being actively studied for potential benefits of recanalization with EVT and thrombolysis in several recent stroke trials. [56] The classification of MeVO as proposed by Goyal et al is shown in table 1.2. [56] Figure 1.5. shows an example of LVO and MeVO.

Table 1.2. Proposed definition of medium vessel occlusion. Adopted from Goyal et al. [56]

Proposed definition of MeVO	**Both A and B need to be applied**
Anatomical: Occlusion in one of the following vessel segments (A)	
	M2 segment (from main MCA bifurcation/ trifurcation to the circular sulcus of insula)
	M3 segment (from the circular sulcus of the insula to the external/ superior surface of the sylvian fissure)
	A2 segment (from the origin of the anterior communicating artery to the origin of the calloso-marginal artery)
	A3 segment (from the origin of the calloso-marginal artery to the artery's posterior turn above the corpus callosum)
	P2 segment (from the origin of the posterior communicating artery to the point of entrance of the quadrigeminal cistern)
	P3 segment (segment within the quadrigeminal cistern)
Functional: substantial clinical deficit (one of the following) (B)	
	NIHSS ≥ 5
	NIHSS < 5 with disabling deficit

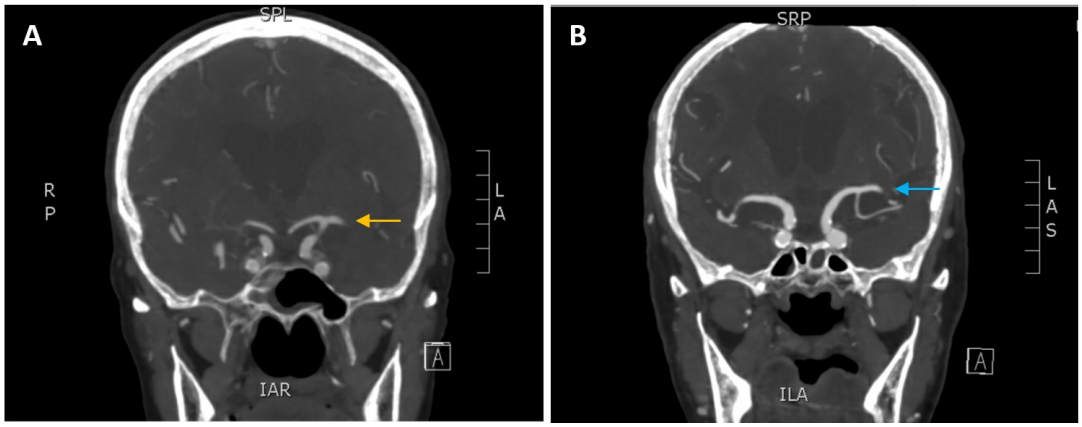

Figure 1.5. Large and medium vessel occlusion on CTA. A: Large vessel occlusion; left Middle Cerebral Artery M1 occlusion (yellow arrow)**. B:** Medium vessel occlusion; left Middle Cerebral Artery M2 occlusion (blue arrow).

1.9. Hypoperfused brain tissue:

The single most important marker of functional outcome in AIS patients is the absolute size, location and the proportion of completed infarct within an affected arterial territory. Usually, patients with infarct or core volumes ≥ 70 mL in the anterior circulation are likely to have poor stroke outcomes. [39, 40, 79, 80] Identifying the irreversibly injured brain tissue rapidly and reliably is one of the most vital factors that dictates eventual outcome. [79, 80] While diffusion MRI is the best indicator of severe cerebral ischemia or core at its earliest stage, acquiring MRI in acute setting is not always feasible. [74, 76] The infarction core can be estimated by certain NCCT methods as well. However, a clearly visible infarct marked by hypoattenuation on the NCCT takes some time to show up on the scan and may not be readily identifiable (figure 1.6.). [74, 75, 81] In contrast, infarct on MRI is much easily discernable but with the tradeoff of feasibility, cost and availability (figure 1.7.). [74, 76]

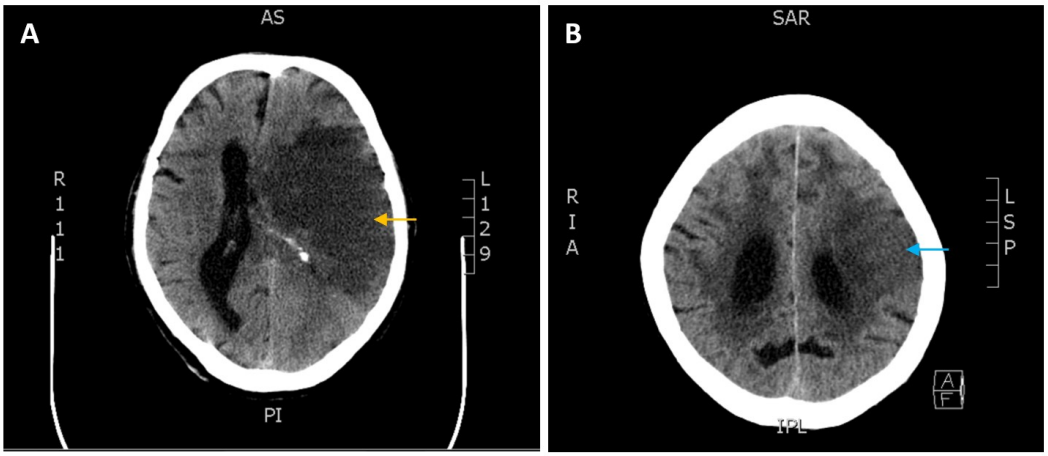

Figure 1.6. Middle Cerebral Artery infarct: at 16-18 hours from stroke onset. **A:** Large left Middle Cerebral Artery M1 occlusion infarct with midline shift (yellow arrow). **B:** Left Middle Cerebral Artery M2 occlusion infarct (blue arrow).

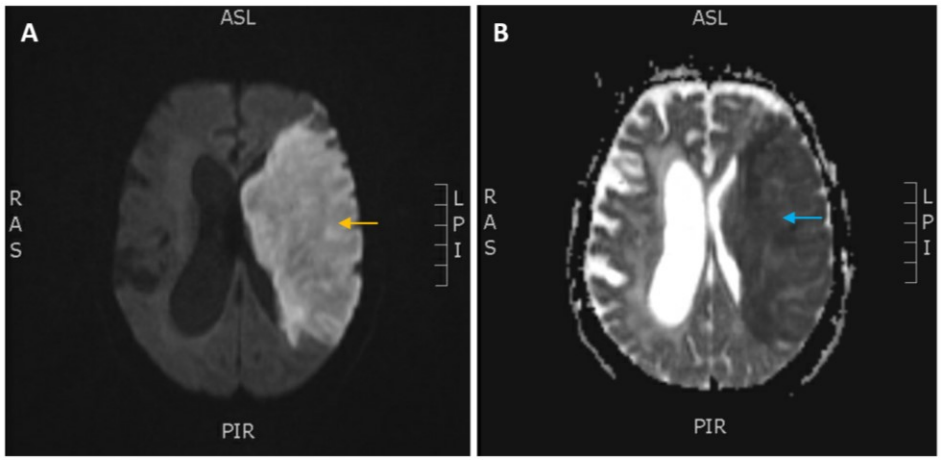

Figure 1.7. Infarct on MRI. MRI- brain showing left sided Middle Cerebral Artery infarct. **A:** Diffusion-Weighted (yellow arrow). **B:** Apparent Diffusion Coefficient (blue arrow).

The best CT-based marker for identifying the infarct or core is a low-blood-volume or flow abnormality identified in cerebral blood volume/ flow perfusion map studies using CTP. [81]

1.10. Computed tomography perfusion:

Perfusion imaging unlike anatomical visualization of vessels on CTA or conventional angiography, performs functional evaluation of brain tissue vascularity. [81] It acquires serially obtained brain images after intravenous injection of an iodinated contrast that assesses temporal changes in brain tissue density over time, i.e., dynamic study. [82-84] The rapid and convenient acquisition of CTP source images and quick postprocessing has made CTP one of the most attractive and frequently growing imaging technique in the last decade. [81-84]

Once the contrast bolus is injected, it gets distributed into two phases based on intravascular and extravascular compartments. The first phase enhancement is due to contrast in the intravascular space lasting approximately first 40-60 seconds. [81, 83, 85-87] The second phase results from distribution of contrast from intravascular to extravascular compartment. In short, first phase enhancement is based on blood flow and volume, whereas second phase is dependent up on vascular permeability to the contrast. With sophisticated mathematical modeling and prediction, tissue perfusion is thus evaluated accurately and quickly. [81-85]

Dynamic contrast enhanced CT is based on multi-compartmental tracer kinetic model. This means that it is performed by monitoring the first pass of an iodinated contrast agent bolus through cerebral circulation. [81, 85] The contrast agent bolus causes transient increase in attenuation that is linearly proportional to the amount of contrast in a given region of interest or pixel. This principle is used to generate time-attenuation curves for an arterial region of interest, a venous region of interest, and within each pixel (figure 1.8.). The perfusion parameters then can be calculated by employing mathematical modeling and visualized on color maps (figure 1.9.). [85]

Most analytical methods evaluate the change in signal intensity as a function of time on a voxel-by-voxel basis using the original source images. [84] The time required for the maximal signal

intensity change within a voxel after the infusion of the contrast bolus marks the estimation of time to peak (TTP). Measurement of the slope of signal intensity change on the attenuation curve is an approximation of cerebral blood flow (CBF), whereas the full width of the signal intensity-change curve at half of maximum value is an approximation of the mean transit time (MTT). The area under the signal-intensity change-time curve is proportional to the cerebral blood volume (CBV). [84, 85] An alternative strategy to TTP is calculation of time to maximum peak of residual tissue function known as Tmax. These CTP parameters are estimated in quantitative measures as follows:

CBF: Flow rate through vasculature in tissue region (mL per 100g/ min) [81-86]

CBV: Volume of flowing blood within a vasculature in tissue region (mL per 100 g) [81-86]

MTT: Average time taken to travel from artery to vein (seconds) [81-86]

TTP: The time from the beginning of contrast material injection to maximum concentration of contrast in the region (seconds) [81-86]

Tmax: Time to maximum peak of residual tissue function (seconds) [81-86]

The evaluation of brain perfusion can be described using the central volume principle, i.e., CBF = CBV / MTT. [81, 83, 85]

The clinical application of CTP imaging in acute stroke is based on the hypothesis that the tissue at risk shows either (a) Increased MTT with moderately reduced CBF and normal or increased CBV or (b) increased MTT with markedly reduced CBF and moderately reduced CBV. The infarcted tissue shows severely decreased CBF (<30%) and CBV with increased MTT. [81, 82, 84, 86]

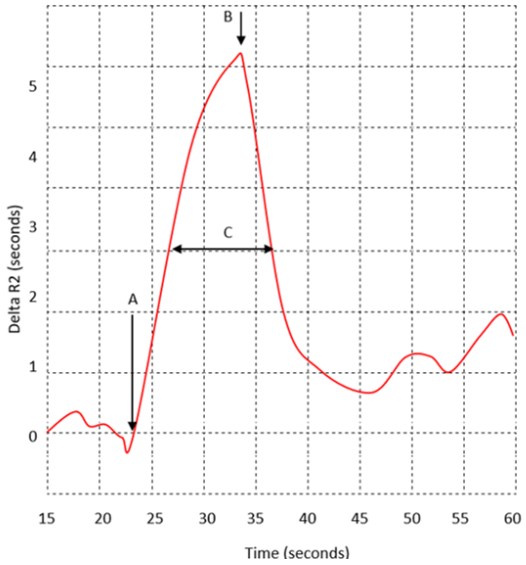

Figure 1.8. Tracer measurement over time: (Time-contrast attenuation curve). A is time of onset of contrast upslope, B depicts the peak of contrast attenuation and C shows an estimation of MTT i.e., full width of the signal intensity-change curve at half of maximum value. Re-illustrated - Adopted from Basavaiah. [85]

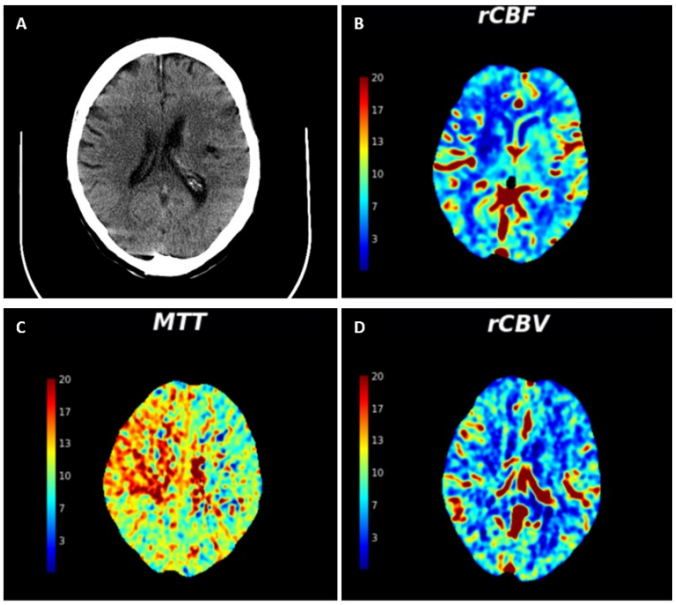

Figure 1.9. Perfusion source maps. A: Non-contrast CT Head, **B:** Cerebral Blood Flow map, **C:** Mean Transit Time map, **D:** Cerebral Blood Volume map.

The two most commonly used CTP imaging techniques are dynamic contrast material enhanced perfusion imaging and perfused blood volume mapping, with the former being used most often for clinical purposes. [81, 83, 85] CTP parameters can be analyzed by: 1) Compartment analysis, or 2) Deconvolution analysis. Both methods are based on attenuation data acquired through estimation of tissue vascularity; the latter using arterial input and correcting for inter-patient variations in bolus related geometry. [81, 85]

The compartmental model can be either single or dual. The single compartment model uses Fick's principle i.e., tissue perfusion is based on the principle of conservation of mass within the system. This means a maximal slope or the peak height of the tissue concentration curve is normalized to the arterial input function. [85] The dual compartment model on the other hand is based on Patlak analysis. This means that the rate of tissue uptake of a tracer from the vascular space is determined by using the value of tracer concentration in tissue and blood. In other words, it quantifies the passage of contrast from intravascular space into extravascular space. [81, 85]

The deconvolution method requires a separately measured arterial input function, which allows computation of a residue function describing the fraction of a hypothetical instantaneous contrast bolus that would remain at each time after injection. [85] The deconvolution method is not based on unrealistic assumptions about venous outflow and uses lower intravenous infusion rates. [86] Using this method, MTT is calculated by performing a deconvolution of the regional (tissue) time-attenuation curve with respect to the arterial time-attenuation curve i.e., arterial input function. CBV is calculated by dividing the area under the time-attenuation in a parenchymal pixel by the area under the time-attenuation curve in the arterial pixel. The central volume equation is then used to obtain the CBF. Moreover, there is visual assessment of the venous time-attenuation normalization of perfusion parameters as it helps correct the data for partial volume averaging. [81,

[85] Commonly used selected artery to define region of interest is the anterior cerebral artery and the vein used is the superior sagittal sinus (figure 1.10.). [81-87]

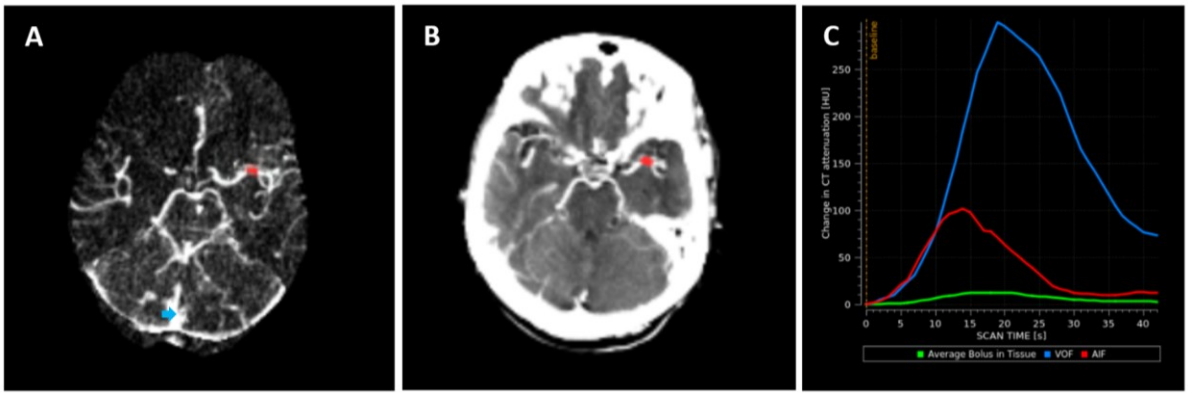

Figure 1.10. CT perfusion inputs and curves. A: Venous output (blue), **B:** Arterial input (red), **C:** Arterial (red) and venous (blue) graphs and tissue bolus (green)-appropriate curves.

1.11. CT perfusion metrics - Core and penumbra; mismatched and matched profiles:

Based on different perfusion parameters, there are several metrics defined using CTP. Core is defined as the already dead or infarcted tissue. It is usually estimated by cerebral blood flow with the value of less than 30% marked as ischemic core (figure 1.11). [81-85] Penumbra defines whether there exists a clinically significant volume of hypoperfused brain that is still viable but at profound risk of death. The area that is hypoperfused out of the area of core is the mismatch and the penumbra is usually defined by time to peak of greater than 6 seconds i.e., Tmax > 6 seconds (figure 1.11). [81, 82] The difference between the penumbra and core gives the mismatch and a profile with significant difference between penumbra and core is called a mismatch profile (figure 1.12). The ratio of penumbra to core is known as the mismatch ratio. [81, 82-84] If the core and penumbra substantially match each other with no clear area of mismatch, the profile is called a matched defect (figure 1.12). [81, 85]

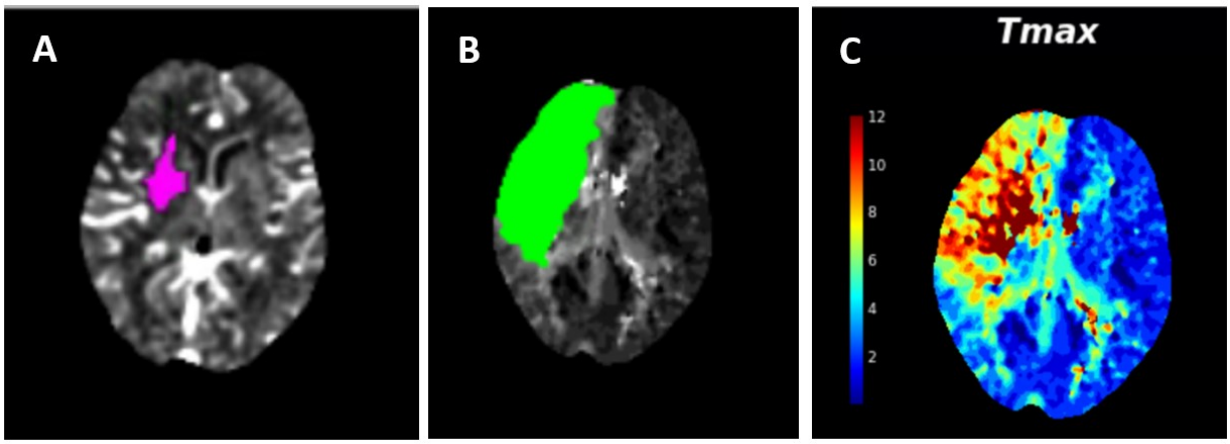

Figure 1.11. Perfusion parameters of core and penumbra: right Middle Cerebral Artery M1 occlusion stroke. **A:** Core (purple), **B:** Penumbra (green), **C:** Tmax perfusion deficit (color coded bar on left side for Tmax in seconds).

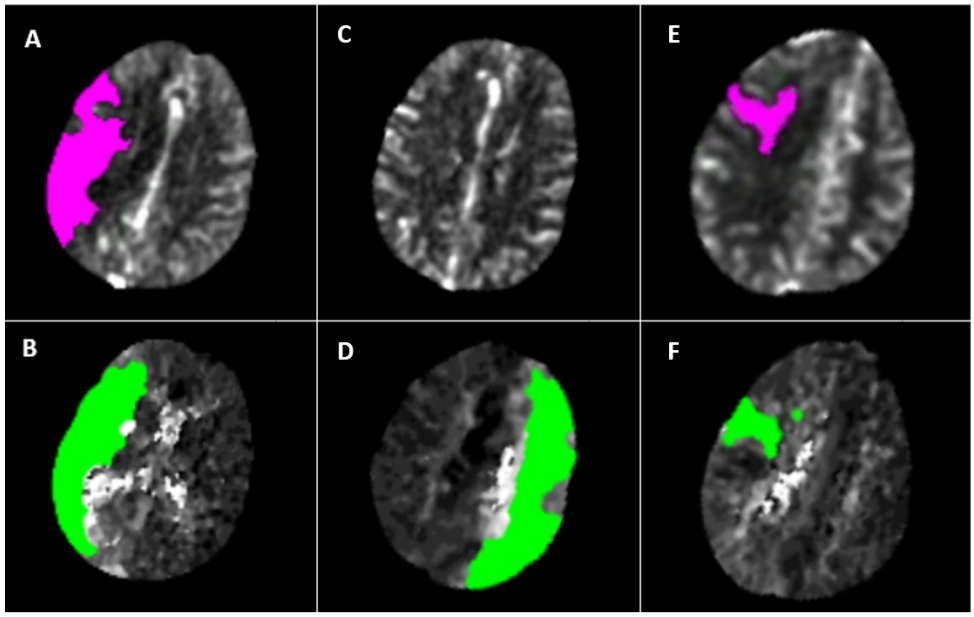

Figure 1.12. Automated CT Perfusion maps; RAPID: *A and B* - Patient 1: 72 year old male with right M1 occlusion at 1.6 hours from onset of symptoms and NIHSS 21. Core 78 mL (A), penumbra 111 mL (B), mismatch 33 mL, mismatch ratio 1.4. No thrombolysis. Thrombectomy

done. 90 day mRS 6 (matched defect). ***C and D*** - Patient 2: 74 year old female with left M1 occlusion at 12.4 hours from onset of symtpoms and NIHSS 6. Core 0 (C) mL, penumbra 148 mL (D), mismatch 148 mL, mismatch ratio > 1.8. Thrombectomy done. 90 day mRS 0 (mismatch profile). ***E and F*** - Patient 3: 79 year old female with right M2 occlusion at 2 hours from onset of symtpoms and NIHSS 7. Core 9 mL (E), penumbra 14 mL (F), mismatch 5 mL, mismatch ratio 1.5. Thrombolysis done. No thrombectomy. 90 day mRS 4 (matched defect). Purple represents core in top row scans, green represents penumbra in bottom row scans.

A quick visual analysis for color changes that are indicative of perfusion deficits or with a more tedious measurement of perfusion parameters within region of interest placed in multiple regions (using automated softwares), makes clinical CTP use very attractive and a clinically feasible modality for acute stroke imaging. [81, 86-89]

Without early recanalization, the core gradually expands to include the at-risk penumbra. [81] With initiation of tissue death (infarction), inflammation follows and results into added contribution towards infarct growth as shown in an inflammatory model in figure 1.13. [82]

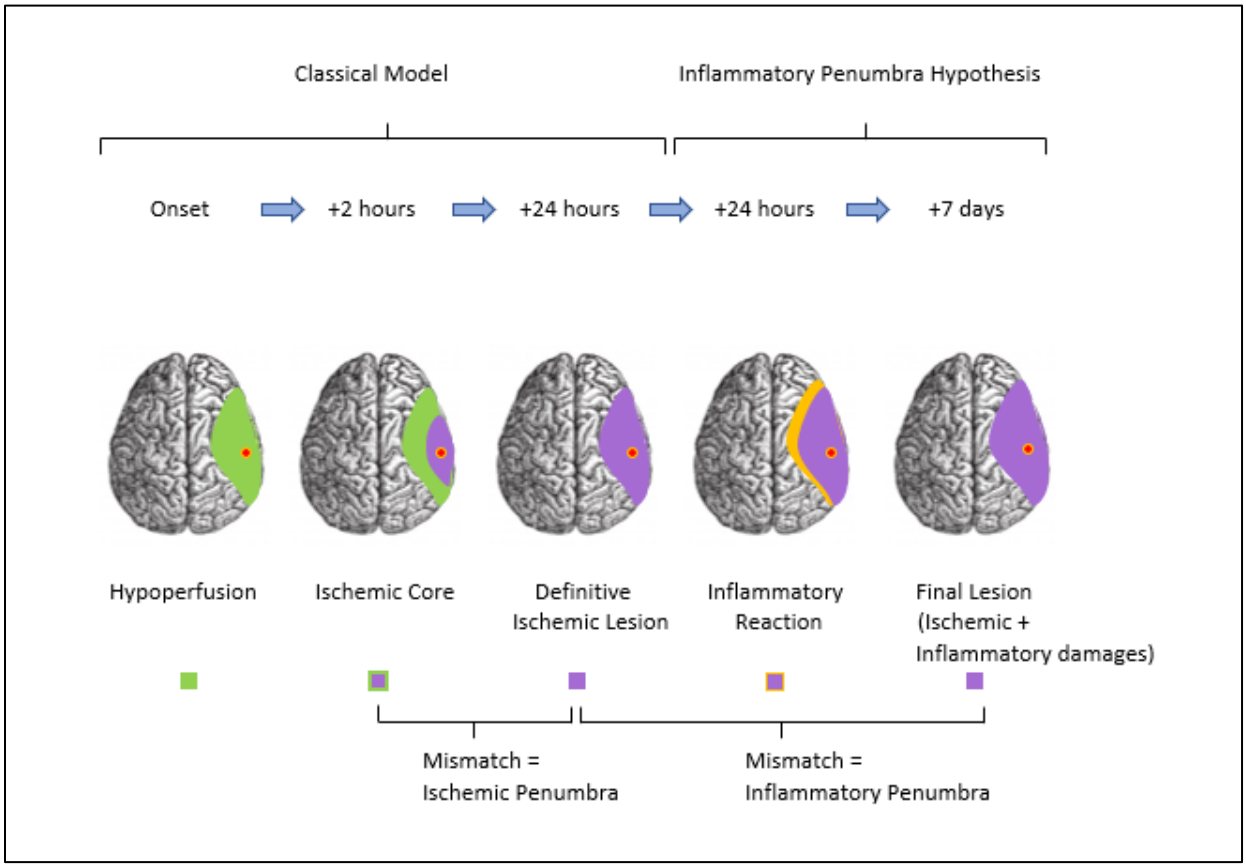

Figure 1.13. Inflammatory penumbra after ischemic stroke. Re-illustrated - Adopted from Krishnan et al. [82]

1.12. Limitations of CTP parameters and novel CTP indices:

For most commercially available and validated automated softwares, CBF < 30% is accepted as a decent threshold for core and a Tmax > 6 seconds as penumbra. [81, 83, 84-87] However, there are other proposed CBF thresholds, including CBF < 20% in very early window for identifying core more accurately than < 30% (which is presumed to overestimate core (ghost core) early after stroke onset). [90] To add, early established infarct on NCCT with recanalization can be missed by estimation of core using CBF due to inherent nature of software design. [83] This limits

the reliance on existing thresholds for estimating core and thus infarct growth. Similarly, an alternative to Tmax, Delay Time > 3 seconds, has been proposed to be a better estimate of penumbra and is based on a modified deconvolution technique with delay and dispersion correction. These variations have led to contrasting results for estimation of CTP metrics especially core between different softwares using different thresholds. [87] Figure 1.14. shows a comparison of CTP maps as analyzed by two commercially available automated softwares commonly used for stroke perfusion imaging.

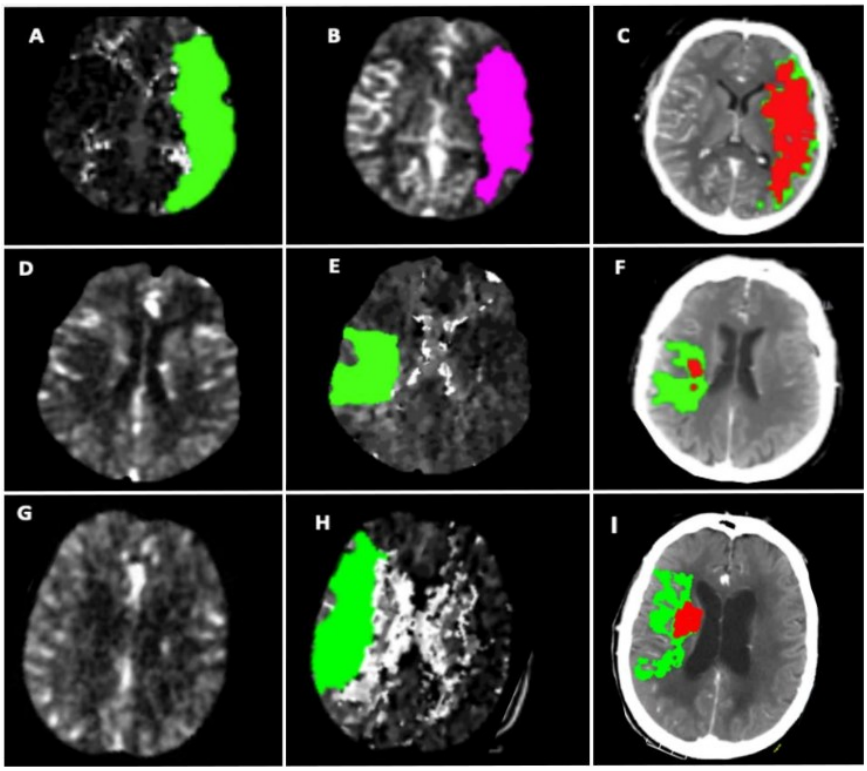

Figure 1.14. CT perfusion software comparison; for RAPID [Core (purple), Penumbra (green)] and AutoMIStar [Core (red), Penumbra (green)]. **Patient 1 (A-C):** Left M1 occlusion in a 35 year old male; ***RAPID:*** Core = 179 mL (A), Penumbra = 221 mL (B); ***AutoMIStar:*** Core = 98 mL, Penumbra = 160 mL (C). **Patient 2 (D-F):** Right M2 occlusion in a 45 year old male; ***RAPID:***

Core = 0 mL (D), Penumbra = 36 mL (E); ***AutoMIStar:*** Core = 1 mL, Penumbra = 28 mL (F). **Patient 3 (G-I):** Right M1 occlusion in an 83 year old female; ***RAPID:*** Core = 0 mL (G), Penumbra = 101 mL (H); ***AutoMIStar:*** Core = 7 mL, Penumbra = 43 mL (I).

A novel metric known as hypoperfusion index (HI) or hypoperfusion intensity ratio (HIR) has been proposed to be a robust marker of infarct growth in LVO and does not rely on CBF. It is calculated as ratio of Tmax > 10 to Tmax > 6 seconds and marked as a value on an 11-point scale from 0 to 1.0 (figure 1.15). [88, 91-94] It has been proposed that HI is a marker of potential stroke evolution (when tested in small population cohorts) and is associated with stroke outcomes in anterior circulation LVO. [91-94]

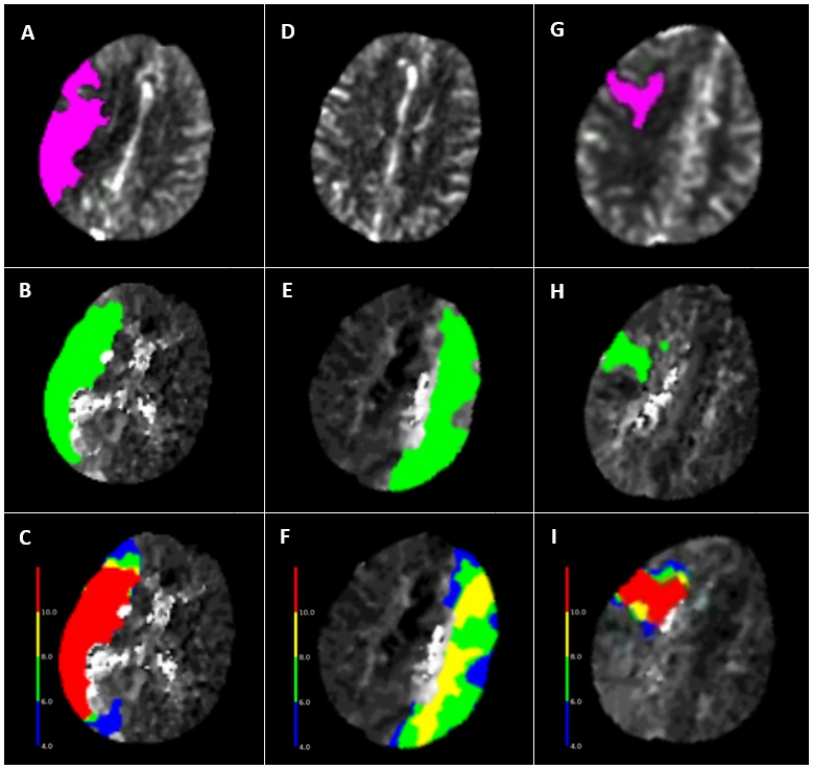

Figure 1.15. Automated CT perfusion maps and hypoperfusion index; RAPID: *A, B and C* - Patient 1: 72 year old male with right M1 occlusion at 1.6 hours from onset of symptoms and

NIHSS 21. Core 78 mL (A), penumbra 111 mL (B), mismatch 33 mL, mismatch ratio 1.4, HI 0.7 (C). No thrombolysis. Thrombectomy done. 90 day mRS 6. ***D, E and F*** - Patient 2: 74 year old female with left M1 occlusion at 12.4 hours from onset of symtpoms and NIHSS 6. Core 0 (D) mL, penumbra 148 mL (E), mismatch 148 mL, mismatch ratio > 1.8, HI 0 (F). Thrombectomy done. 90 day mRS 0. ***G, H and I*** - Patient 3: 79 year old female with right M2 occlusion at 2 hours from onset of symtpoms and NIHSS 7. Core 9 mL (G), penumbra 14 mL (H), mismatch 5 mL, mismatch ratio 1.5, HI 0.8 (I). Thrombolysis done. No thrombectomy. 90 day mRS 4. Purple represents core in top row scans, green represents penumbra in middle row scans. Colored coded bar on left side of bottom row scans represents Tmax values in seconds.

1.13. Validation of CTP:

While CTP is a sophisticated imaging technique, the accuracy of the flow values obtained has not been fully validated in all possible situations with ischemic stroke. [83, 87] However its utility is quickly growing in clinical practice. Validation studies of perfusion imaging by several clinical investigators have demonstrated that CTP can give information similar to that provided by MRI. [83, 89] Although optimal imaging acquisition and analysis techniques remain debatable, RAPID (Rapid processing of perfusion and diffusion; iSchemaView, California, USA) CTP software has been extensively studied and validated across multiple studies and randomized trials. [27, 38-40, 86, 87] It is reliable, fast and convenient for estimation of perfusion parameters and is widely utilized in acute stroke care. [83, 84, 86, 87, 89]

1.14. Imaging and collateral failure:

There has been substantial literature studying collaterals after stroke onset. Early collateral failure leads to early infarct growth. [55] However, the estimation of collaterals by available and conventionally used ways provides only an anatomical estimation, whether be it on CTA, digital subtraction/ conventional angiography or MR angiography (figure 1.16. and 1.17.). [55] This makes the estimation of collaterals quite subjective and prone to disqualifying the contribution of microcirculation (which is not visualized) towards stroke size and infarct growth. One of the dynamic ways to study collaterals and presumably their potential failure is by estimating stroke evolution on CT or MR perfusion imaging. [89] Furthermore, CTP is a marker of composite measure of both macro- and micro-circulation. Few of the scoring criteria used for grading of collaterals are shown in figure 1.16. [55]

	Modality	Grading system	Comments
Kucinski et al[25]	Cerebral angiography	1 (good): ≥3 MCA branches (retrograde filling) 2 (poor): <3 MCA branches	Small series; scoring system not validated
Higashida et al[59]	Cerebral angiography	0: no collateral vessels filled 1: slow collateral filling to periphery 2: rapid collateral filling to periphery 3: collaterals with slow but complete flow in ischaemic bed 4: rapid and complete flow in entire ischaemic territory	Scoring system not validated
Miteff et al[9]	CT angiography	1 (good): entire MCA distal to occlusion reconstituted with contrast 2 (moderate): some branches of MCA reconstituted in Sylvian fissure 3 (poor): distal superficial branches reconstituted	Large thrombolysis series; excellent outcome in patients with good collaterals
Maas et al[60]	CT angiography	1: absent 2: less than contralateral side 3: equal to contralateral side 4: greater than contralateral side 5: exuberant	Large series from two centres; scoring system not validated
Tan et al[61]	CT angiography	0: absent 1: <50% collateral MCA filling 2: >51–99% 3: 100%	Small series; clot volume also calculated; scoring system not validated
Lee et al[62]	MRI, magnetic resonance angiography	Distal hyperintense vessels on FLAIR MRI 1: absent 2: subtle 3: prominent	Small series; all patients had proximal MCA occlusion; prominent hyperintense vessels predicted good outcome; scoring system not validated
Silvestrini et al[63]	Transcranial doppler	Collateral supply inferred by direction of flow in ophthalmic artery, anterior cerebral artery, and posterior cerebral artery Good: ≥2 vessels insonated Poor: ≤1 vessel insonated	Carotid dissection case series; good collateral flow associated with good prognosis; no validation study

MCA=middle cerebral artery. FLAIR=fluid-attenuated inversion recovery.

Figure 1.16. Collateral scores. Adopted from Shuaib et al. [55]

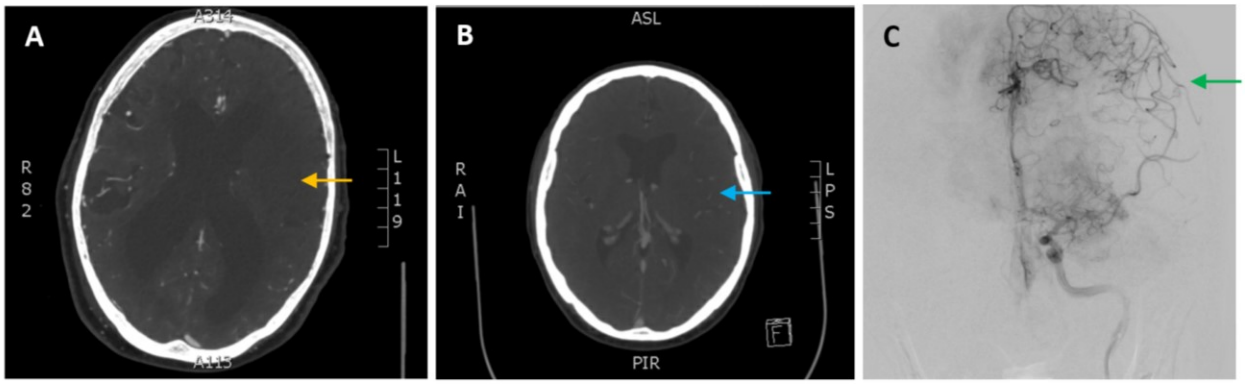

Figure 1.17. Collateral imaging; in left Middle Cerebral Artery M1 occlusion AIS. **A:** CT Angiography with poor collaterals (yellow arrow). **B:** CT Angiography with good collaterals (blue arrow). **C:** Collaterals as visualized on conventional angiography (green arrow).

1.15. Rate of core progression:

Stroke evolution is variable among patients and affects both success of reperfusion strategy as well as functional outcome. [38-40, 79, 80, 91] While there are many ways to predict infarct growth, one of the most commonly used methods to estimate rate of core progression is a comparison of ratio of core volume to time from onset of stroke on index imaging; also known as early infarct growth rate (EIGR). EIGR is a relatively sensitive and specific marker of early core growth but ignores the total area of affected hypoperfused territory. [91] One of the recent secondary analysis of a prospective, multicenter cohort study of imaging selection, SELECT (Optimizing Patient Selection for Endovascular Treatment in Acute Ischemic Stroke) showed that EIGR is an independent predictor of good collateral scores and good functional outcomes in LVO AIS (aOR, 0.73 (95% CI, 0.61-0.89), p=0.001). Despite similar Alberta Stroke Program Early CT Score (ASPECTS) (6-10), slow progressors have higher chances of good outcomes as compared to fast progressors (62.2 % versus 36.5%, aOR, 3.42, CI, 1.66-7.02), but the effect of reperfusion is time sensitive and declines by a factor of 14% with each 5 mL/hour rise in EIGR (p<0.001). Slow

progressors have 3 times greater odds of achieving functional independence with EVT as compared to fast progressors, whose chances of good outcome rapidly decline with time without achieving recanalization. [91] Give the profound impact of rate of core progression, early characterization of slow and fast progressors is therefore crucial as it may affect both the transport and treatment decisions in patients with AIS. Randomized trials comparing slow and fast progressors, especially those with a direct comparison of both small and larger core volumes, will eventually help to ascertain the best strategy to minimize core growth and thus improve patient outcomes.

1.16. Research objectives:

While HI has been evaluated in LVO patients mostly up to 6-8 hours of stroke onset to study core growth, its evaluation within first 24 hours is limited. Furthermore, a direct comparison of HI in MeVO and LVO has not been done to date, neither has it been compared directly in early and late windows. To add further, the mechanism behind infarct growth and cerebral microcirculatory failure is also poorly understood.

The objectives of this research project were to evaluate markers of early infarct growth in patients with AIS. This comprised observing CTP markers of EIGR including HI as a marker of infarct growth by estimating total area of hypoperfused territory in both LVO and MeVO patients, out to maximum treatment window of 24 hours in both early and late windows, and the evaluation of factors including small vessel disease that might contribute to EIGR in AIS patients. We explored approaches to differentiate stroke progression in different patient cohorts and tried to explain how these can be used for clinical decision making for reperfusion, understanding mechanism of infarct growth and evaluation of patients with AIS.

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Chapter 2

How to define fast and slow progressors in acute ischemic stroke

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*This chapter is a descriptive analysis and review of limitations described in literature to differentiate fast and slow progressors and has been expanded with preliminary analysis of a cohort for clarity. It is being submitted for publication as a brief communication.

2.1. Abstract

The variable rate of infarct progression in patients with acute-ischemic-stroke is assessed by various methods, some of which exclude a substantial proportion due to time-or-core-constrained thresholds. We evaluated 106 stroke patients with any-type-occlusion to compare these methods and assess performance of hypoperfusion-index (HI) to describe fast- and slow-progressors. 7(12.5%) were classified as fast-progressors and 23(46%), 25(50%), 12(24%) and 33(66%) as slow-progressors using different core-and-time criteria. In comparison, HI categorized 100%(n=106) of the cohort with optimal cut-off 0.5; [slow-progressors (HI≤0.5) and fast-progressors (HI>0.5)], sensitivity-100%, specificity-91% and AUC-0.94, having better outcomes (median 90-day-mRS; 2 versus 5) for HI≤0.5. Estimation of progressors by HI seem to be more comprehensive but needs external validation.

2.2. Introduction:

The rate of infarct core progression after arterial occlusion in acute ischemic stroke (AIS) is a variable and dynamic process. [1, 2] Whether a patient with acute ischemic stroke will progress quickly to their final volume of infarct or will gradually transform is difficult to ascertain. [2] Various methods in literature have been described to designate patients as fast, slow or intermediate progressors. [2-4]

The conventional core and time thresholds use core > 70 mL within 6 hours of stroke onset for fast and < 30 mL between 6-24 hours for slow progressors. [1, 2] Alternatively, using core to time ratio also called early infarct growth rate (EIGR), slow progressors are defined as those with EIGR of < 1, intermediate as ~ 2.5 and fast as > 20 (mL/ hour) or alternatively ~ 1 as slow and ~ 10 (mL/ hour) as fast progressors. [3, 4]

The core and time threshold-based definitions exclude a substantial proportion of stroke patients due to inherent nature of description. A relatively recent method to estimate infarct growth is by measuring hypoperfusion index (HI), which is a combination of degree of hypoperfusion marked on an 11-point scale (0-1, 0.1 each), and is correlated with collaterals, patient eligibility for thrombectomy and functional outcomes. [5-8] We evaluated 106 stroke patients with any-type occlusion in internal carotid artery (ICA)/ middle cerebral artery (MCA) territory to compare different ways to define fast and slow progressors and assessed performance of HI to differentiate between fast and slow rate of core progression in AIS.

2.3. Material and methods:

The medical records and imaging of 106 prospectively recruited patients with anterior circulation acute ischemic stroke were analyzed after approved by the Health Ethics Committee of

the University of Alberta. CT Perfusion (CTP) head was acquired within 24 hours of symptom onset and post-processed by FDA-approved RAPID (Rapid processing of perfusion and diffusion; iSchemaView, California, USA) software for estimation of core and mismatch. The perfusion deficit volume was defined using Tmax > 6 seconds. Core was diagnosed if the relative cerebral blood flow (CBF) was <30% of that in normal tissue. Mismatch was defined as tissue within the Tmax > 6 seconds deficit, which was not the ischemic core (CBF >30%). [9] Mismatch ratio was calculated as ratio of total perfusion deficit volume to core volume. Hypoperfusion index was defined as ratio of Tmax > 10 seconds to Tmax > 6 seconds. [6]

For purpose of analysis, using core and time thresholds, we defined fast progressors as patients with ischemic core >70 mL in the early tier after stroke onset (0–6 hours) using cut-off extrapolated from stroke trials of CTP in patients with large vessel occlusion (LVO). [1, 2]

For slow progressors, we evaluated following definitions based on criteria used by CTP stroke trials; DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3), EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) and TIMELESS (Thrombolysis in imaging eligible late window patients (4.5-24 hours) to evaluate the efficacy and safety of tenecteplase). [1, 10-13]

Definition "A": In patients with LVO, slow progressors were defined as patients with ischemic core ≤30 mL in the late tier after stroke onset (6–24 hours). [1]

Definition "B": In patients with LVO, slow progressors were defined as patients with ischemic core ≤50 mL in the late tier after stroke onset (6–24 hours). [11]

Definition "C": In patients with or without LVO (any occlusion type), slow progressors were defined as patients with ischemic core <70 mL, mismatch ratio > 1.2, mismatch > 10 mL, in the late tier after stroke onset (6-9 hours). [12]

Definition "D": In patients with ICA, M1, M2 occlusions, slow progressors were defined as patients with ischemic core ≤70 mL, mismatch ≥ 15 mL and ratio ≥1.8 in the late tier after stroke onset (6-24 hours). [10, 11, 13]

For purpose of analysis and discussion, group of patients at 0-6 hours was called "early tier" and 6-24 hours as "late tier". LVOs were defined as ICA/ M1 occlusions. [10, 11] Outcomes were analyzed on modified Rankin Scale (mRS).

Due to non-normality of data assessed on Shapiro-Wilk test, quantitative data was summarized as median (IQR-interquartile range), unless otherwise specified. Wilcoxon rank sum test and x^2 or Fischer exact tests were used for comparison as appropriate. The rate of core progression was determined using core to time ratio, that was dichotomized by > or ≤ 0.1 mL/min as fast and slow. [3, 4, 5] HI and rate of core progression were compared, and the best fitting model (cut-off) was determined using receiver operating characteristic (ROC). Data analysis was conducted using STATA 16.0 (Stata Corp LLC Texas, USA). A p value < 0.05 was considered significant.

2.4. Results:

After exclusion of stroke mimics, non-perfusion deficit strokes, those with imaging artifacts and non-ICA/ MCA occlusions, 106 patients were analyzed, whose baseline characteristics are shown in table 2.1.

Table 2.1. Baseline characteristics

Characteristics	**Value**
Age, median (IQR) (years)	74 (28-97)
Gender (Male), n (%)	68 (64.1)
Comorbidities	
Hypertension, n (%)	68 (64.1)
Diabetes Mellitus, n (%)	23 (21.7)
Coronary Artery Disease, n (%)	22 (20.7)
Previous Stroke, n (%)	8 (7.5)
Previous transient ischemic attack, n (%)	10 (9.4)
Current Smoking, n (%)	22 (20.7)
Atrial Fibrillation, n (%)	26 (24.5)
Hyperlipidemia, n (%)	36 (33.9)
Pre-stroke modified Rankin Scale, median (IQR)*	0 (0-3)
NIHSS score, median (IQR)†	14.6 (1-30)
Symptom onset to imaging, median (IQR) (minutes)	286.5 (29-1151)
ASPECTS‡	
<5, n (%)	6 (5.6)
5-7, n (%)	13 (12.2)
8-10, n (%)	87 (82.1)
Occluded vessel	
T occlusion, n (%)§	3 (2.8)
ICA occlusion, n (%)	18 (16.9)
M1, n (%)| |	57 (53.7)
M2, n (%)#	18 (16.9)
Distal to M2, n (%)	10 (9.4)
Treatment	
IV Thrombolysis only, n (%)	52 (49)
Endovascular Thrombectomy with or without thrombolysis, n (%)	53 (50)

Characteristics	**Value**
Full Recanalization (TICI 3), n (%)**	48 (45.2)
Hemorrhagic transformation	
Symptomatic, n (%)	2 (1.8)
Asymptomatic, n (%)	32 (30.1)

*Scores on the modified Rankin scale for the assessment of global disability range from 0 (no symptoms) to 6 (death).

†Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficit.

‡The Alberta Stroke Program Early CT Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller infarct core on NCCT.

§Acute occlusion of the terminal bifurcation of the ICA, 'carotid T

| |M1 segment of MCA is identified as the arterial trunk from its origin at ICA to first bifurcation or trifurcation into major branches.

#M2 segment of the MCA was defined as the vertical segment lying within the mesial margin of the sylvian fissure as identified on the coronal CT angiogram

**Thrombolysis In Cerebral Infarction (TICI) 3 defined as complete perfusion based on angiographic appearances.

The median (IQR) core volume was 9 (0-37) mL, mismatch was 81 (40-113) mL, mismatch ratio was 3.2 (2.2-9.7) and HI was 0.4 (0.2-0.6). Ischemic core was ≤10 mL in 57 (53.7%), ≤30 mL in 76 (71.69%), ≤50 mL in 89 (83.96%) and ≤70 mL in 93 (87.73%) patients. Mismatch was >15 mL in 93 (87.7%). Mismatch ratio was > 1.2 in 99 (93.4%) and > 1.8 in 90 (84.9%) patients.

56 (52.8%) were in < 6 hours early tier. 78 (73.5%) were LVO. Patient distribution across the cohort is shown in figure 2.1.

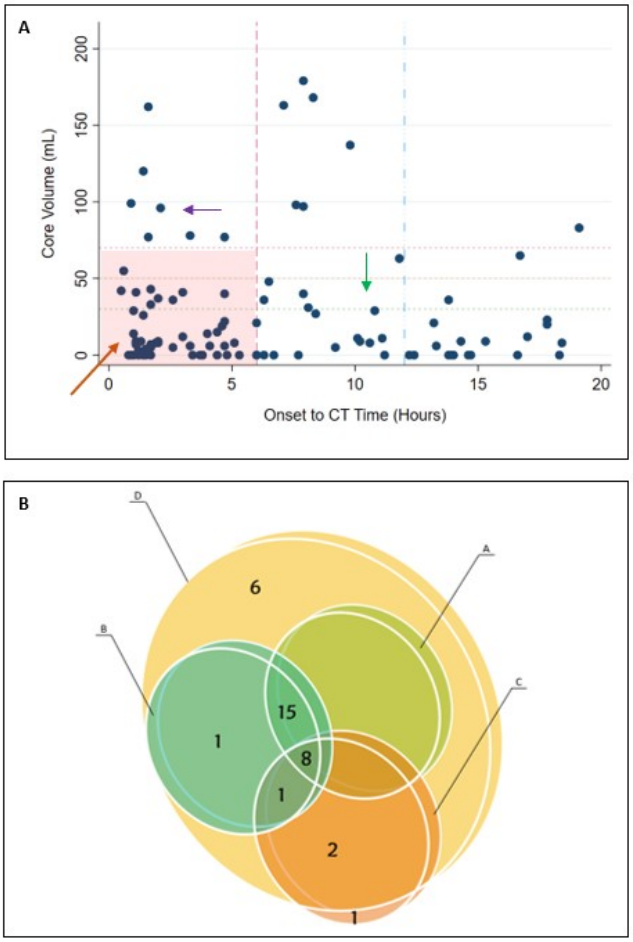

Figure 2.1. Patient distribution and definition overlap. A: Distribution of patient cohort. Onset to CT Time in hours (x-axis) plotted agianst core volume in mL on CTP (y-axis). Vertical red dash line shows 6 hours mark. Vertical blue dash and dot line shows 12 hours mark. Horizontal dotted lines represent core volumes at 30-, 50- and 70-mL marks. Patients towards top left marked by purple arrow are fast progressing. Patients towards bottom right marked by green arrow are slow progressing. Patients towards bottom left marked by orange arrow represent early presenting unclassified patients who do not meet criteria for either (core-and-time threshold). **B: Inclusion,**

exclusion and overlap distribution using different definition criteria A-D for slow progressors. Each circle shows the number of patients included by each definition (A-D) and their overlap. Note that Defintion D includes all patients from other defintions except 1.

By using different criteria, the number of patients who could be classified as slow progressors by each definition was different, as shown in figure 2.1. and 2.2. 7 (12.5%) were fast progressors in the early tier and 23 (46%), 25 (50%), 12 (24%) and 33 (66%) were slow progressors in the late tier according to criteria A, B, C and D respectively. Criteria "D" was most inclusive as it incorporated nearly all patients from other definitions, covered all core thresholds and included non-LVO (M2) occlusions as well (figure 2.1. and 2.2.).

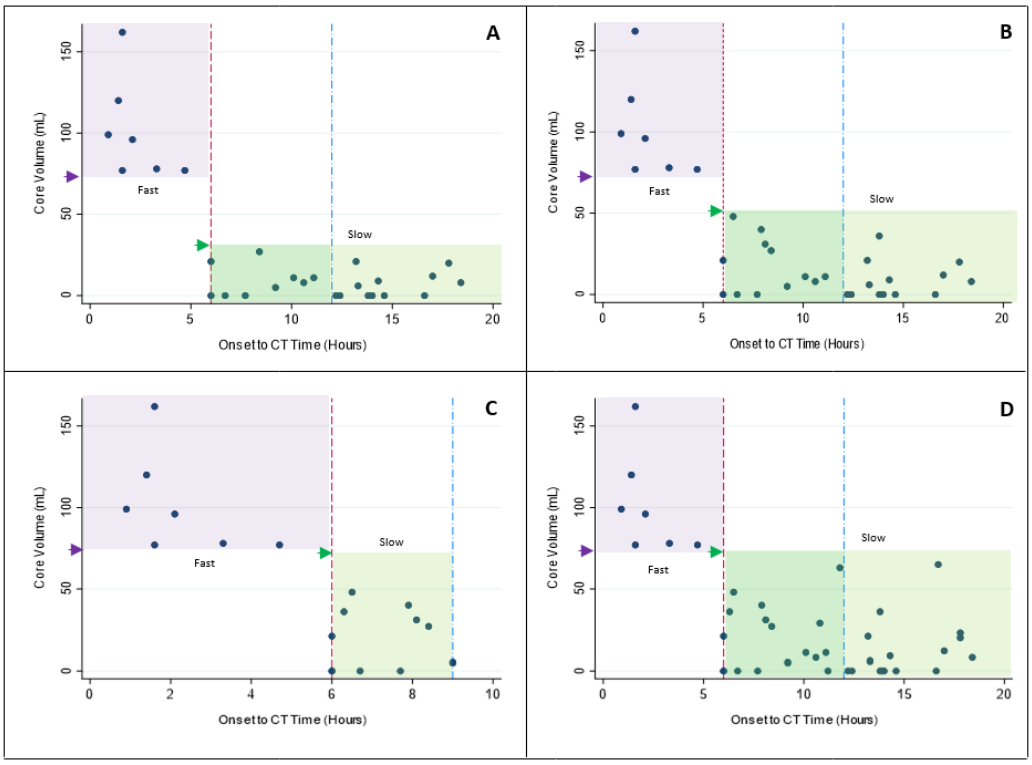

Figure 2.2. Distribution of cohort using different definitions. Onset to CT Time in hours (x-axis) plotted agianst core volume in mL on CTP (y-axis). Vertical red dash line shows 6 hours

mark. Vertical blue dash and dot line shows 12 hours mark for A, B, D and 9 hours mark for C. Small arrow heads point towards respective core volume cut-off used for each definition (lower limit for fast (dark purple) and upper for slow (bright green) progressor group). Highlighted box areas represent progressor types (purple=fast, green=slow). **A:** Definition "A". **B:** Definition "B". **C:** Definition "C". **D:** Definition "D".

HI for overall cohort was ≤ 0.5 in 77 (72.6%). HI was significantly different between fast and slow groups across all definitions (table 2.2.). For the overall cohort, the median (IQR) rate of core progression was 0.02 (0-0.06) in ≤ 0.1 (n=75, 70.7%) and 0.28 (0.04-0.66) in > 0.1 (n=29, 27.3%) mL/ min core-to-time ratio groups, ($p < 0.001$). HI cut-off ≤ 0.5 (good) and > 0.5 (poor) differentiated slow from fast rate of infarct progression, having sensitivity of 100%, specificity of 90.9% and AUC of 0.94 (figure 2.3.).

Table 2.2. Percentage of patient distribution between fast and slow progressor type and characteristics in each definition

Category	All	Fast	Slow	p value
Definition A				
Total	30 (28.3)	7 (23.3)	23 (76.6)	-
Age, median (IQR) (years)	71.5 (49-95)	72 (63-83)	71 (61-80)	0.52
Gender (Male), n (%)	23 (76.6)	4 (57.1)	19 (82.6)	0.16
Symptom onset to imaging, median (IQR) (minutes)	583.5 (58-1106)	98 (58-287)	737 (353-1106)	0.001*
Core, median (IQR) (mL)	11 (0-162)	96 (77-162)	8 (0-48)	0.001*
Mismatch, median (IQR) (mL)	111 (32-232)	108 (34-161)	113 (32-232)	0.25
Mismatch ratio, median (IQR)	6.3 (2.5-12.4)	2.4 (1.5-2.5)	8.8 (6.3-15)	< 0.001*
HI, median (IQR)	0.4 (0.2-0.6)	0.7 (0.6-0.7)	0.3 (0.2-0.5)	< 0.001*
Rate of core progression, median (IQR) (mL/ min)	0.01 (0-0.12)	0.80 (0.38-1.65)	0.008 (0-0.01)	< 0.001*
Definition B				
Total	32 (30.1)	7 (21.8)	25 (78.1)	-
Age, median (IQR) (years)	72 (49-95)	72 (63-83)	72 (62-80)	0.56
Gender (Male), n (%)	24 (75)	4 (57.1)	20 (80)	0.21
Symptom onset to imaging, median (IQR) (minutes)	583.5 (58-1106)	98 (58-287)	737 (353-1106)	0.001*
Core, median (IQR) (mL)	11.5 (0-162)	96 (77-162)	8 (0-48)	0.001*
Mismatch, median (IQR) (mL)	109.5 (32-232)	108 (34-161)	112 (32-232)	0.38

Category	All	Fast	Slow	p value
Mismatch ratio, median (IQR)	5.9 (2.4-12.4)	2.4 (1.5-2.5)	7.2 (5.8-14.0)	< 0.001*
HI, median (IQR)	0.4 (0.2-0.6)	0.7 (0.6-0.7)	0.3 (0.2-0.5)	< 0.001*
Rate of core progression, median (IQR) (mL/ min)	0.01 (0-0.10)	0.80 (0.38-1.65)	0.01 (0-0.02)	< 0.001*
Definition C				
Total	19 (17.9)	7 (36.8)	12 (63.1)	-
Age, median (IQR) (years)	72 (36-88)	72 (63-83)	72.5 (62-79)	0.69
Gender (Male), n (%)	11 (57.8)	4 (57.1)	7 (58.3)	0.96
Symptom onset to imaging, median (IQR) (minutes)	361 (58-540)	98 (58-287)	400 (360-540)	0.001*
Core, median (IQR) (mL)	36 (0-162)	96 (77-162	13 (0-48)	0.001*
Mismatch, median (IQR) (mL)	89 (13-232)	108 (34-161)	70.5 (13-232)	0.52
Mismatch ratio, median (IQR)	2.4 (1.8-5.8)	2.4 (1.5-2.5)	5.8 (2.2-7.1)	0.03*
HI, median (IQR)	0.5 (0.3-0.7)	0.7 (0.6-0.7)	0.3 (0.1-0.5)	0.001*
Rate of core progression, median (IQR) (mL/ min)	0.08 (0-0.73)	0.80 (0.38-1.65)	0.03 (0-0.07)	< 0.001*
Definition D				
Total	40 (37.7)	7 (17.5)	33 (82.5)	-
Age, median (IQR) (years)	71.5 (28-95)	72 (63-83)	71 (61-78)	0.38
Gender (Male), n (%)	29 (78.7)	4 (57.1)	25 (75.7)	0.31
Symptom onset to imaging, median (IQR) (minutes)	644 (58-1106)	98 (58-287)	711 (353-1106)	0.001*
Core, median (IQR) (mL)	16 (0-162)	96 (77-162)	9 (0-65)	0.001*

Category	All	Fast	Slow	p value
Mismatch, median (IQR) (mL)	105 (15-232)	108 (34-161)	104 (15-232)	0.95
Mismatch ratio, median (IQR)	3.6 (2.3-8.8)	2.4 (1.5-2.5)	6.3 (2.9-12.4)	0.003*
HI, median (IQR)	0.4 (0.2-0.5)	0.7 (0.6-0.7)	0.4 (0.2-0.5)	< 0.001*
Rate of core progression, median (IQR) (mL/ min)	0.01 (0-0.08)	0.80 (0.38-1.65)	0.01 (0-0.04)	< 0.001*

*represents significant p; HI=hypoperfusion index

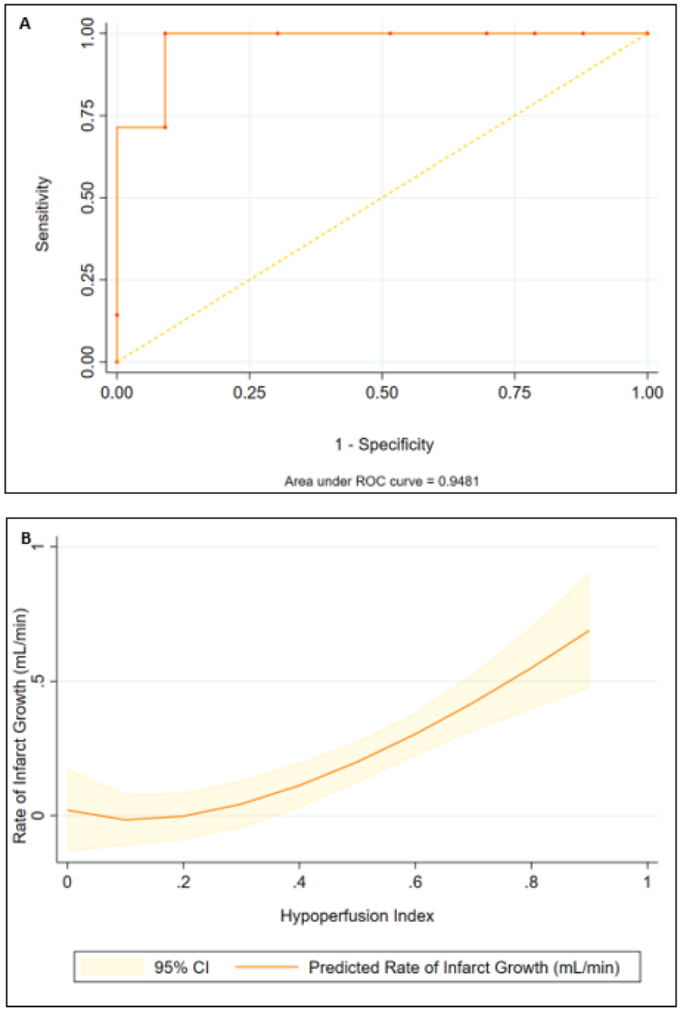

Figure 2.3. Hypoperfusion index and infarct growth rate. A: ROC for predicting fast versus slow rate of core progression using HI cut-off 0.5. Fast = > 0.5, Slow = ≤ 0.5. **B:** HI (y-axis) versus Infarct Growth Rate (mL/ min) (x-axis).

Patients with HI ≤ 0.5 had better outcomes as compared to those with HI > 0.5, having median (IQR) 90-day mRS of 2 (1-5) and 5 (3-6) for poor and good HI groups respectively, (p=0.02) (figure 2.4. and 2.5.).

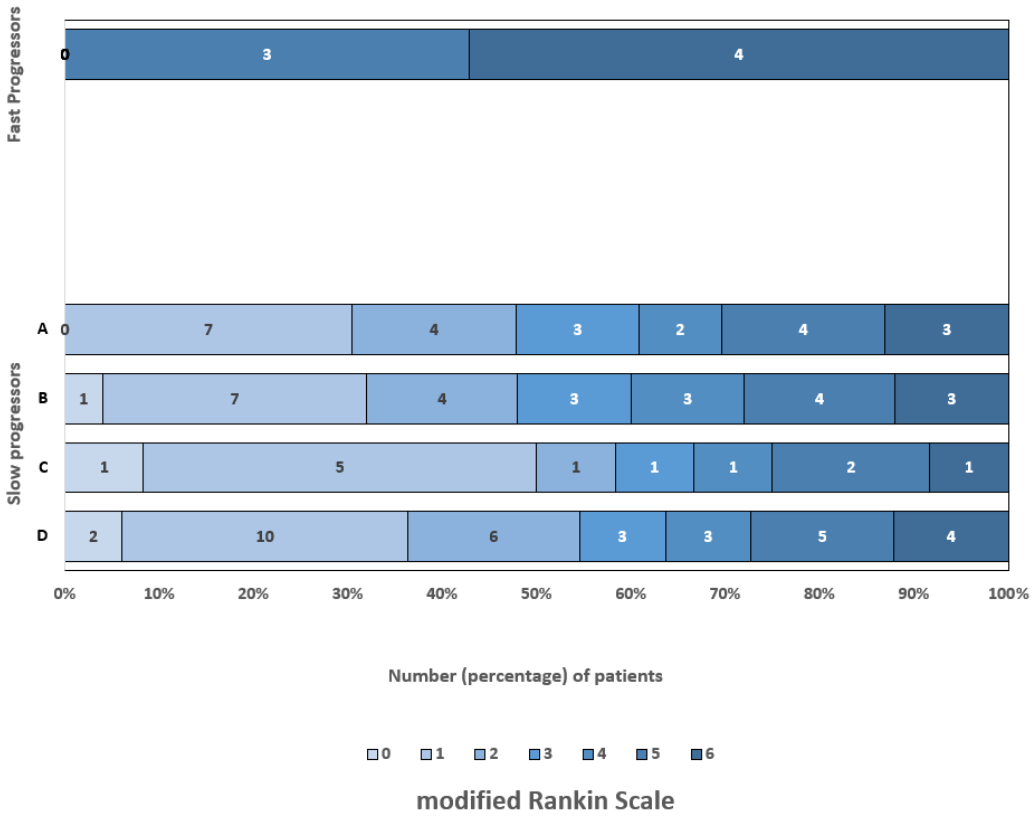

Figure 2.4. Patient outcomes (90-day mRS) in slow progressors (by different definitions) and fast progressors.

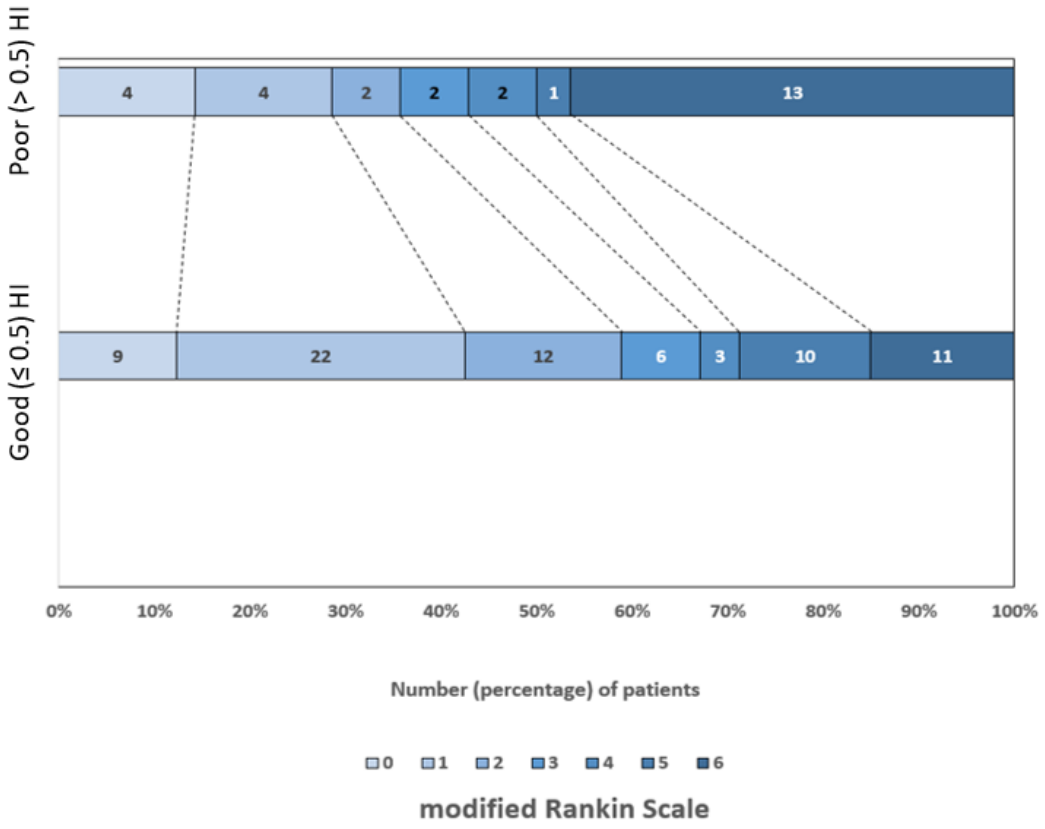

Figure 2.5. Patient outcomes in good and poor hypoperfusion index groups.

2.5. Discussion:

Our study indicated that ~13% patients in early tier were fast progressors whereas 24-66% were slow progressors in late tier using different time and core constrained definitions. Definition D was most comprehensive by being inclusive of M2 occlusions and classified most number of patients. 31% were classifiable as slow progressors in the overall cohort by definition D as compared to 11-23 % by others. In comparison, HI categorized 100% (n=106) of the cohort with optimal cut-off 0.5 with good sensitivity and specificity to differentiate between slow and fast rate of core progression. Using HI, ~73% were classified as having slow rate of core progression (HI≤0.5) and had better outcomes.

Slow progressors are associated with reduced level of disability than fast progressors. [4] We have shown that by using <70 mL core criteria and including M2 occlusions for slow progressors, we can identify more patients who can potentially benefit from reperfusion than anticipated by earlier definitions. [14-16] Furthermore, we have shown that estimation of progressors by HI seem to be more comprehensive and affects functional outcomes in all type occlusions. This however needs external validation. Nonetheless, description of fast and slow infarct progression in various stroke sub-populations can help guide transfer and treatment decisions but should be interpreted carefully due to limitations of CTP. [17, 18] While our findings are likely to be applicable to the clinical experience of similar high-volume comprehensive stroke centers, the observed proportions and relevance of fast and slow progressors, and transfer strategies may vary depending upon unique regional geography. Future trials of HI can help validate its utility in patients with stroke.

2.6. Conclusions:

HI ≤0.5 differentiates slow from fast rate of infarct progression in AIS with any-type occlusion and can affect clinical outcomes. Estimation of progressors by HI seem to be more comprehensive but needs external validation.

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Chapter 3

Relationship of hypoperfusion index to core progression in medium and large vessel ischemic stroke

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*A version of this chapter has been submitted for publication. The chapter has been expanded and supplementary data and methods have been included in the main manuscript for clarity.

3.1. Abstract

3.1.1. Objectives: The rate of infarct progression in patients with acute ischemic stroke is variable and affects outcome from reperfusion therapy. We evaluated hypoperfusion index (HI) to estimate the initial rate of infarct progression in stroke patients with medium-vessel-occlusion (MeVO) compared to large-vessel-occlusion (LVO), both in early and late windows.

3.1.2. Methods: Infarct progression was assessed in 106 acute stroke patients. Fast progressors had core >70mL within 6-hours of stroke onset. Slow progressors had core ≤70mL, mismatch ≥15mL and mismatch-to-core-ratio ≥1.8 within 6-24 hours. The relationship between HI and infarct core progression was examined in MeVO and LVO patients.

3.1.3. Results: In the 106 acute strokes 6.6% were fast progressors, 27.4% were slow progressors, and 66% were indeterminate. An HI>0.5 was associated with fast progression and able to distinguish fast from slow progressors (AUC=0.94). In MeVO patients (n=26) HI>0.5 had a core progression of 0.30ml/min compared to 0.03ml/min with HI≤0.5 ($p<0.001$). In LVO patients (n=80) HI>0.5 had a core progression of 0.26mL/min compared to 0.02mL/min with HI≤0.5 ($p<0.001$). In the indeterminate group (n=70), those with an HI>0.5 had progression rate of 0.21 mL/min compared to 0.03 mL/min with HI≤0.5 ($p<0.001$).

3.1.4. Conclusions: HI can differentiate fast from slow core progression in MeVO and LVO patients within the first 24-hours of stroke. Consideration of core progression rate at time of stroke evaluation may have implications in the selection of MeVO and LVO stroke patients for reperfusion therapy that warrant further study.

3.2. Introduction:

When cerebral artery occlusion occurs, the supplied brain region becomes ischemic. Without restored blood flow the ischemic brain shifts over time to permanent infarction (core). The rate at which infarct progression occurs varies among patients with acute ischemic stroke. [1, 2] In some, core progression is fast over a few hours, whereas in others it is slower over many hours or even days. The rate of core progression is important, as it provides an indication of time remaining to salvage ischemic brain tissue by reperfusion therapy. [1-7] Accurate assessment of core progression may be useful clinically to aid in decisions of acute stroke transport, reperfusion therapy, and potentially neuroprotection strategy. [1, 2, 8-12] Indeed, the rate of core progression is an important determinant regarding benefit of reperfusion therapy. [8, 9, 12]

The initial rate of core progression depends on several factors, including collaterals and their ability to maintain adequate oxygenation and nutrient supply to the brain during arterial occlusion. [1, 2, 13, 14] However, predicting collateral failure remains a challenge. [13-15] Core progression can be estimated by core size on Computed Tomography (CT) Perfusion relative to the time from stroke onset. Patients who develop a large core within the first few hours of stroke onset are fast progressors, whereas those with a small core and large mismatch in the late window are slow progressors. [1, 2, 16-19] However in many stroke patients, a clear designation as a fast or slow progressors is difficult to ascribe. [1, 2, 8-11, 18-20] While repeat perfusion imaging can assess core growth over time, this often is not feasible and can introduce unnecessary delays. [8, 20] Furthermore, a progression rate that considers only core to time ratio fails to consider remaining tissue at risk. The hypoperfusion index (HI) is a CT perfusion-based measure that provides an indication of shift of ischemic brain tissue to infarction. HI is calculated as the ratio of time-to-peak concentration at

> 10 seconds to time-to-peak concentration at > 6 seconds. [21] Thus HI provides an expected degree of evolution of core based on severity of delay in blood flow to the brain. [21]

Using time definition of progression, there remains a subset of patients where the rate of core progression is indeterminate, and which HI may be able to classify. Additional evidence is needed to assess the role of HI in ischemic stroke and the relationship to core progression. Most studies to date have assessed HI in patients with large vessel occlusion (LVO) within the first 6-8 hours of stroke onset, whereas treatment windows for acute stroke interventions have been extended up to 24 hours. [21] Moreover, a significant proportion of strokes have medium vessel occlusions (MeVO); a group increasingly being considered for possible endovascular therapy. [22] In this study we provide evidence regarding the performance of HI to assess initial rate of core progression in MeVO compared to LVO patients within the first 24 hours of stroke, and a comparison between early and late windows.

3.3. Materials and methods:

The study was approved by the Health Ethics Committee of the University of Alberta. Patients admitted to the University of Alberta hospital with suspected stroke who had CT Perfusion between March and November of 2019 were enrolled. Written informed consent was taken from all study participants. The medical records and imaging of 106 prospectively recruited patients with acute ischemic stroke were analyzed.

3.3.1. Images post-processing and automated analysis: After non-contrast CT head and CT Angiography head and neck, CT Perfusion head was acquired and post-processed by FDA-approved RAPID (Rapid processing of perfusion and diffusion; iSchemaView, California, USA) software for estimation of core and mismatch. RAPID used a delay-insensitive algorithm. The

perfusion deficit volume was defined using time-to-peak concentration > 6 seconds. Core was diagnosed if the relative Cerebral Blood Flow was <30% of that in normal tissue. Mismatch was defined as tissue within the time-to-peak concentration > 6 seconds deficit, which was not the ischemic core (Cerebral Blood Flow >30%). [23] Mismatch ratio was calculated by dividing total perfusion deficit volume by core volume. Hypoperfusion index was defined as time-to-peak concentration > 10 seconds divided by time-to-peak concentration > 6 seconds. [21]

3.3.2. Eligibility: All patients were older than 18 years and had CT Perfusion performed within 24 hours of symptom onset and had pre-stroke modified Rankin Scale (mRS) of 2 or less. We excluded patients with stroke mimics, perfusion maps of inadequate quality due to technical artifacts, negative perfusion maps, and posterior circulation strokes. We included patients with LVO (ICA (Internal Carotid Artery) and M1), and MeVO (M2 middle cerebral artery).

3.3.3. Patient groups: Based on prior reports, fast progressors were defined as strokes with LVO/MeVO occlusions and core >70 mL, within 6 hours of onset. Patients with LVO/MeVO and core ≤70 mL, mismatch ≥ 15 mL and ratio ≥1.8 in 6-24 hours were defined as slow progressors. [4-6, 22-25] These criteria are based on thresholds used in Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES), Tenecteplase in Stroke Patients Between 4.5 and 24 Hours (TIMELESS), Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3) and DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN). [3-5, 7, 16] National Institutes of Health Stroke Scale (NIHSS) was determined by stroke neurologist on admission and 24-48 hours. Alberta Stroke Program Early CT Score (ASPECTS) was reported on non-contrast CT as ≤ 7 or higher (scores range from 0-10, with higher scores indicating a smaller infarct core). LVO/MeVO were assessed on CT Angiography and recanalization on conventional angiography

using Thrombolysis in Cerebral Infarction (TICI) by certified radiologist (see supplementary methods). [4-6, 22-24]

3.3.4. Statistical analysis: Quantitative data were summarized as median (IQR-interquartile range) and qualitative as proportions. We used nonparametric tests unless otherwise specified due to non-normality of data assessed by Shapiro-Wilk test. Characteristics of fast, slow and indeterminate groups were compared by ANOVA, Kruskal-Wallis Rank, Pearson Chi-square or Fischer exact as appropriate. Receiver operating characteristic analysis was used to assess the ability of HI to differentiate fast and slow progressors in classified group and to define the optimal cut-off. Characteristics of dichotomized HI groups and LVO versus MeVO groups were compared using Mann-Whitney test for medians (IQR) and Pearson Chi-square or Fischer exact test for proportions.

In a secondary analysis, the performance of cut-off was assessed in the entire cohort whether LVO or MeVO (including patients not classified by our standard (< 6 or 6-24 hours) time-based definition i.e., indeterminate group). Core progression was determined using core to time ratio, that was dichotomized by > or ≤ 0.1 mL/min. We defined "high rate of core progression" as patients with initial rate of core progression > 0.1 mL/min no matter the time from stroke onset and "low rate of core progression" as ≤ 0.1 mL/ min. This was derived from previous publications estimating core progression as core to time ratio, to separate fast from slow rate of core evolution. [21, 26] We used this alternative definition to allow the inclusion of all patients in the analysis by circumventing the restrictions related to the time window when CT Perfusion is performed (before or after 6 hours). Time restrictions defined in literature make it impossible to define fast progressors after 6 hours or slow progressors before 6 hours. [1, 2] The benefit of using HI is that it can be applied to all patient groups at any point in time unlike clock-based approach. [21, 26] We

assessed core progression in the overall cohort, in MeVO and LVO groups, and early and late tiers. We also assessed this HI cut-off in indeterminate group separately. Statistical tests were 2-sided and were considered significant with $p \leq 0.05$. Data analysis was conducted using STATA 16.0 (Stata Corp LLC Texas, USA).

3.3.5. Data availability: The anonymized data supporting the findings of the study are available from the corresponding author upon reasonable request.

3.4. Results

3.4.1. Baseline characteristics: Among 352 patients undergoing CT Perfusion during the study period, 258 had a confirmed diagnosis of stroke. Perfusion deficits were evident in 137. We excluded 24 cases due to imaging artifacts and 7 due to non-ICA/M1/M2 strokes (figure 3.1.).

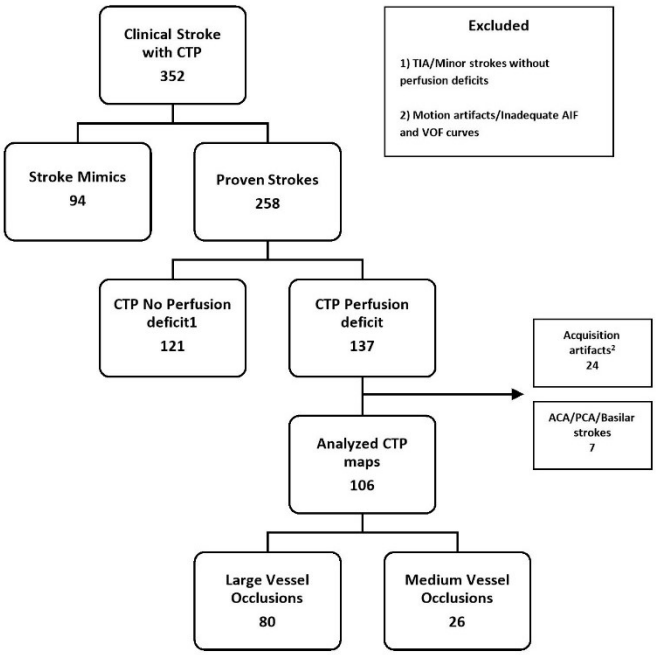

Figure 3.1. Flow diagram for patient screening and inclusion. CTP=Computed Tomography

Perfusion, ACA=Anterior Cerebral Artery, PCA=Posterior Cerebral Artery, TIA=Transient Ischemic Attack, AIF=Arterial Input Function, VOF=Venous Output Function.

For the overall cohort, the median (IQR) CT Perfusion core volume was 9mL (0-37), mismatch volume 81mL (40-113), mismatch ratio 3.2 (2.2-9.7), HI 0.4 (0.2-0.6) and baseline NIHSS was 14 (10-20). There were 60 patients (56.6%) within the first 6 hours of stroke onset, and 46 (44.4%) in the 6-24 hour cohort.

Fast progression was present in 6.6% (7/106) of patients, slow progression in 27.4% (29/106), and 66% (70/106) were indeterminate (table 3.1.). There were no significant differences in age, sex and medical comorbidities between fast and slow groups (table 3.1.). Baseline median (IQR) NIHSS was higher in fast progressors, 21 (20-23); compared to slow progressors, 14 (10-18), (p=0.02). Median (IQR) NIHSS at 24-48 hours was also higher in fast progressors, 21 (20-23); compared to slow progressors, 6 (2-15), (p=0.04). Median (IQR) core was larger in the fast progressors at 96 mL (77-120) versus 9mL (0-27) in the slow progressors, ($p < 0.001$). Fast progressors had lower median (IQR) mismatch ratio, 2.4 (1.5-2.5); compared to slow progressors, 6.3 (2.5-13.1), (p=0.004). ASPECTS was not significantly different between fast and slow progressors, (p=0.99).

Table 3.1. Comparison of baseline patient characteristics between Fast, Slow and Indeterminate progressors in patient group classified by our standard (< 6 or 6-24 hours) time and core-based (≤ or > 70 mL) definition and Hypoperfusion Index groups in overall cohort

Variables	**Progressor type n=106**				**Hypoperfusion Index n=106**		
	Fast n=7	***Slow n=29***	***Indete-rminate n=70***	***p-value***	***HI >0.5 n=29***	***HI ≤0.5 n=77***	***p-value***
Age, median (IQR) (years)	72.0 (63.0-83.0)	65.0 (61.0-76.0)	75.0 (65.0-86.0)	0.08	75.0 (62.0-83.0)	73.0 (62.0-85.0)	0.94
Sex (Male), n (%)	4 (57.1)	23 (79.3)	41 (58.8)	0.13	20 (68.9)	48 (62.3)	0.65
Hypertension, n (%)	4 (57.1)	18 (62.0)	46 (65.7)	0.87	18 (62.0)	50 (64.9)	0.82
Diabetes Mellitus, n (%)	1 (14.2)	6 (20.6)	16 (22.8)	0.86	6 (20.6)	17 (22.0)	1.00
Coronary Artery Disease, n (%)	2 (28.5)	7 (24.1)	13 (18.5)	0.71	6 (20.6)	16 (20.7)	1.00
Previous Stroke, n (%)	2 (28.5)	4 (13.7)	2 (2.8)	0.01	4 (13.7)	4 (5.1)	0.21
Previous Transient Ischemic Attack, n (%)	1 (14.2)	2 (6.8)	7 (10)	0.80	3 (10.3)	7 (9.0)	1.00
Current Smoking, n (%)	2 (28.5)	8 (27.5)	12 (17.1)	0.44	6 (20.6)	16 (20.7)	1.00
Atrial Fibrillation, n (%)	3 (42.8)	8 (27.5)	15 (21.4)	0.41	9 (31.0)	17 (22.0)	0.44

Variables	**Progressor type n=106**				**Hypoperfusion Index n=106**		
	Fast n=7	***Slow n=29***	***Indeterminate n=70***	***p-value***	***HI >0.5 n=29***	***HI ≤0.5 n=77***	***p-value***
Hyperlipidemia, n (%)	3 (42.8)	8 (27.5)	25 (35.7)	0.64	11 (37.9)	25 (32.4)	0.64
NIHSS score, median (IQR) at admission	21.0 (20.0-23.0)	14.0 (10.0-18.0)	13.5 (10.0-19.0)	0.03	18.0 (12.0-21.0)	14.0 (10.0-18.0)	0.02
NIHSS score, median (IQR) at 24-48hrs	21.0 (20.0-23.0)	6.0 (2.0-15.0)	6.0 (2.0-15.0)	0.15	8.0 (3.0-23.0)	6.0 (2.0-15.0)	0.16
ASPECTS ≤ 7, n (%)	1 (14.2)	7 (24.1)	11 (15.7)	0.59	10 (34.4)	9 (11.6)	0.01
CTP core, median (IQR) (mL)	96.0 (77.0-120.0)	9.0 (0-27.0)	8.0 (0-36.0)	< 0.001	77.0 (15.0-99.0)	7.0 (0.0-20.0)	< 0.001
CTP mismatch, median (IQR) (mL)	108.0 (76.0-113.0)	104.0 (57.0-125.0)	67.0 (28.0-108.0)	0.02	76.0 (40.0-110.0)	84.0 (42.0-120.0)	0.32
CTP mismatch ratio, median (IQR)	2.4 (1.5-2.5)	6.3 (2.5-13.1)	3.2 (2.2-9.0)	0.03	2.2 (1.5-2.6)	6.4 (2.8-12.5)	< 0.001
Occluded vessel							
ICA, n (%)	3 (42.8)	7 (24.1)	13 (18.5)	0.30	5 (17.2)	18 (23.3)	1.00
Carotid T, n (%)	1 (14.2)	0 (0)	1 (1.4)	0.22	1 (3.4)	1 (1.2)	1.00
M1, n (%)	4 (57.1)	20 (68.9)	33 (47.1)	0.13	16 (55.1)	41 (53.2)	1.00

Variables	**Progressor type n=106**				**Hypoperfusion Index n=106**		
	Fast n=7	***Slow n=29***	***Indete-rminate n=70***	***p-value***	***HI >0.5 n=29***	***HI ≤0.5 n=77***	***p-value***
M2, n (%)	0 (0)	2 (6.8)	24 (34.2)	0.005	8 (27.5)	18 (23.3)	0.8
Treatment							
IVT only, n (%)	0 (0)	5 (17.2)	23 (32.8)	0.07	5 (17.2)	23 (29.8)	0.22
EVT only, n (%)	1 (14.2)	15 (51.7)	16 (22.8)	0.01	5 (17.2)	27 (35.0)	0.09
IVT + EVT, n (%)	2 (28.5)	4 (13.7)	15 (21.4)	0.57	3 (10.3)	18 (23.3)	0.17
Recanalization (TICI 2b/3), n (%)	2 (28.5)	17 (58.6)	29 (41.4)	0.07	6 (20.6)	42 (54.5)	0.06
Hemorrhagic Transformation, n (%)	3 (42.8)	8 (27.5)	23 (32.8)	0.51	8 (27.5)	26 (33.7)	0.53
Symptom onset to imaging, median (IQR) (minutes)	98.0 (58.0-201.0)	711.0 (542.0-859.0)	228.5 (98.5-362.5)	< 0.001	287.0 (98.0-617.0)	309.0 (117.0-542.0)	0.99
Hypoperfusion Index							
≤ 0.5, n (%)	0 (0)	26 (89.6)	51 (72.8)	< 0.001	-	-	-
> 0.5, n (%)	7 (100.0)	3 (10.3)	19 (27.1)	< 0.001	-	-	-
Rate of core progression (ratio	0.80 (0.38-1.70)	0.01 (0-0.05)	0.05 (0-0.17)	<0.001	0.28 (0.11-0.76)	0.02 (0-0.06)	<0.001

Variables	Progressor type n=106				Hypoperfusion Index n=106		
of core to time), mL/ min							

*CTP=Computed Tomography Perfusion; ICA=Internal Carotid Artery; NIHSS=National Institutes of Health Stroke Scale; ASPECTS=Alberta Stroke Program Early CT Score; IQR=Interquartile range; TICI=Thrombolysis In Cerebral Infarction; IVT=Intravenous thrombolysis; EVT=Endovascular Thrombectomy; HI=Hypoperfusion Index.

3.4.2. Hypoperfusion index threshold to distinguish fast from slow progressors and rate of core progression: In fast progressors the median HI was 0.6 (IQR 0.5-0.7); in slow progressors the median HI was 0.2 (IQR 0.1-0.4), ($p<0.001$). An HI of 0.5 differentiated fast from slow progressors with sensitivity of 100% and specificity 89% and area under curve (AUC) of 0.94 (figure 3.2.). In all patients studied the median core progression for HI $\leq$ 0.5 was 0.02 (IQR 0-0.06) mL/min compared to 0.28 (IQR 0.11-0.76) mL/min for HI > 0.5 ($p<0.001$). For stroke patients within 6 hours of onset, the median core progression for HI $\leq$ 0.5 was 0.04 (IQR 0-0.09) mL/min compared to 0.66 (0.30-1.44) mL/min for HI > 0.5, ($p<0.001$) (AUC 0.77). For strokes at 6-24 hours of onset, the median core progression for HI $\leq$ 0.5 was 0.01 (IQR 0-0.03) mL/min compared to 0.17 (IQR 0.01-0.21) mL/min for HI > 0.5, ($p<0.001$) (AUC 0.87).

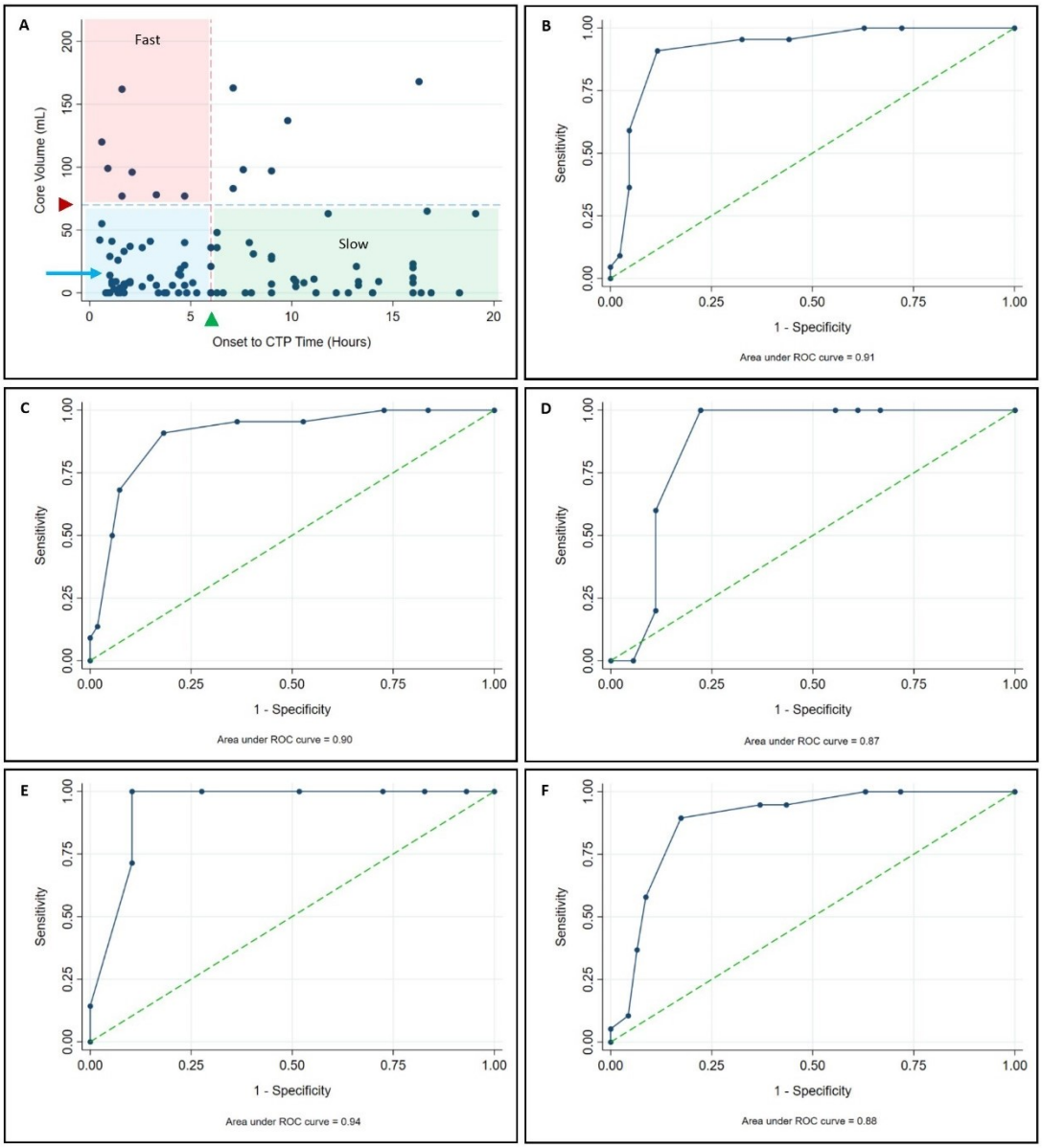

Figure 3.2. Relationship of core volume to time and hypoperfusion index in patients with acute stroke. A: Distribution of cohort by time versus core volume. Onset to CT time in hours (x-axis) plotted against core volume by CT Perfusion (y-axis). Highlighted blue box area represents group of patients physicians may be especially interested in to differentiate fast from slow initial rate of core progression. **B:** Optimal HI cut-off (0.5) to distinguish high and low rate of core progression in entire cohort. **C:** Optimal HI cut-off (0.5) to distinguish core progression in LVO

group. **D:** Optimal HI cut-off (0.5) to distinguish core progression in MeVO group. **E:** Optimal HI cut-off (0.5) to distinguish fast from slow progressors in patient group classified by our standard (< 6 or 6-24 hours) time and core-based (≤ or > 70 mL) definition (see methods). **F:** Optimal HI cut-off (0.5) to distinguish core progression in indeterminate group. *CT=Computed Tomography; CTP=Computed Tomography Perfusion; HI=Hypoperfusion Index; MeVO=Medium Vessel Occlusion; LVO=Large Vessel Occlusion.

3.4.3. Medium versus Large vessel occlusion group: There were 26 patients with MeVO and 80 patients with LVO. Characteristics were comparable between the MeVO and LVO groups (supplementary e-table 3.1.). Within the MeVO and LVO groups, baseline variables were not significantly different between HI ≤ 0.5 and HI > 0.5 groups (supplementary e-table 3.2.). In MeVO patients the median core progression for HI ≤ 0.5 group was 0.03 (IQR 0-0.07) mL/min compared to 0.30 (IQR 0.06-0.31) mL/min for patients with HI > 0.5, ($p<0.001$). In LVO patients with HI ≤ 0.5 the median core progression was 0.02 (IQR 0-0.06) mL/min compared to 0.26 (IQR 0.17-0.80) mL/min for patients with HI > 0.5, ($p<0.001$) (figure 3.3.). For the MeVO and LVO groups, HI of 0.5 differentiated high (> 0.1 mL/min) from low (≤ 0.1 mL/min) core progression with AUC 0.87 and 0.90 respectively (figure 3.2.). Median onset to imaging time in LVO (361.5, IQR 156-617 minutes) was longer as compared to MeVO (140.5, IQR 94-363 minutes), however this was not statistically significant (supplementary e-table 3.1.).

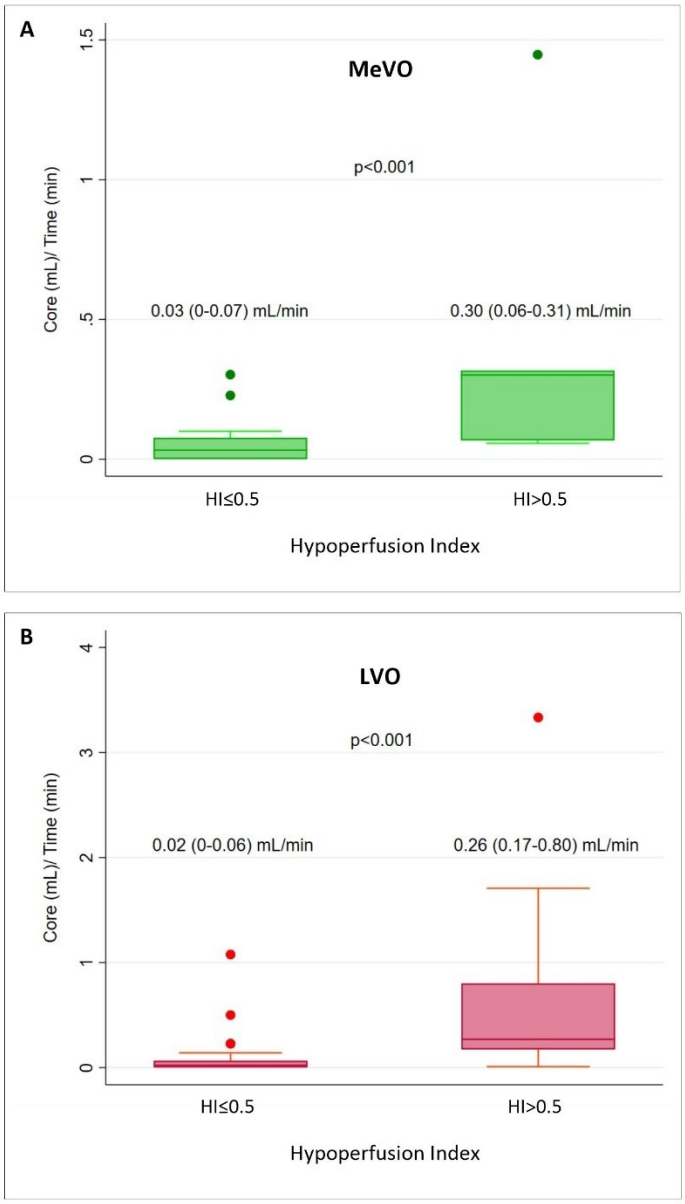

Figure 3.3. Comparison of Initial Rate of Core Progression between ≤ and > 0.5 Hypoperfusion Index groups. A: in stroke patients with Medium Vessel Occlusion (MeVO) and **B:** in stroke patients with Large Vessel Occlusion (LVO).

3.4.4. Ability of hypoperfusion index to identify rate of core progression in indeterminate group: There were 70 patients not meeting time and core-based criteria for fast or slow progressors (see methods). Among these patients, 67.1% (47/70) had low (≤ 0.1 mL/min) rate of core progression and 51 (72.8%) had ≤ 0.5 HI. In the indeterminate group, those with an HI > 0.5 had faster median progression rate of 0.21 (IQR 0.06-0.38) mL/min) compared to 0.03 (IQR 0-0.07) mL/min in those with HI ≤ 0.5, ($p<0.001$). When analyzed by time, in the < 6 hours group, those with an HI > 0.5 had faster median progression rate of 0.31 (IQR 0.06-1.44) mL/min) compared to 0.04 (IQR 0-0.09) mL/min in those with HI ≤ 0.5, ($p=0.001$). For 6-24 hours group, those with an HI > 0.5 had median progression rate of 0.18 (IQR 0.11-0.22) mL/min) as compared to 0 (IQR 0-0.01) mL/min in those with HI ≤ 0.5, ($p=0.001$) (supplementary e-table 3.3.).

In MeVO patients in this cohort (n=24), those with an HI $\underline{\leq}$ 0.5 had a median core progression of 0.01 (IQR 0-0.07) mL/min compared to those with an HI > 0.5 where the median core progression was 0.30 (IQR 0.06-0.31) mL/min, ($p=0.03$). In LVO patients (n=46), those with an HI $\underline{\leq}$ 0.5 had a median core progression of 0.03 (IQR 0-0.07) compared to those with an HI > 0.5 where the median core progression was 0.20 (IQR 0.17-0.38) mL/min, ($p=0.001$). The HI was able to assess progression rate in 24 additional (24/26 = 92.3%) MeVO patients and 46 additional (46/80 = 57.5%) LVO patients (AUC 0.88) compared to time- (< 6 or 6-24 hours) and core- (≤ or > 70 mL) constrained definition for fast and slow progression described in the methods.

3.5. Discussion:

HI was associated with rate of core progression in both MeVO and LVO patients. An HI >0.5 was able to distinguish fast from slow progressors, both in early and late windows. In MeVO patients an HI > 0.5 had a core progression of 0.30 mL/min compared to 0.26 mL/min in LVO.

Furthermore, HI was able to estimate rate of core progression in patients with otherwise indeterminate progression due to time constraint definitions. This ability of HI to estimate core progression rates may have implications for the selection of patients for reperfusion therapy as discussed below.

Our study is supported by prior studies evaluating HI in acute ischemic stroke. [19, 27, 28] In stroke patients with LVO, Olivot et al. found an HI > 0.4 to be associated with collateral failure on perfusion imaging and conventional angiography (AUC 0.73). [19] Guenego et al., found a similar result in LVO strokes with an HI > 0.4 being associated with worse collaterals (sensitivity 79%, specificity 56%, AUC 0.70). [28] In 28 patients with LVO undergoing thrombectomy, an HI of 0.5 was related to core progression. [21] In our study, an HI > 0.5 was associated with an increased rate of core progression in patients with LVO. Furthermore, an HI > 0.5 also was associated with increased core progression rate in patients with MeVO. Given patients with MeVO account for large percentage (35-40%) of acute ischemic strokes, this is an important group of patients to consider. Which MeVO patients benefit from thrombectomy remains unclear. [29, 30] The rate of core progression estimated by HI may be a useful criterion to consider in the selection of MeVO patients for recanalization therapy. [25, 29-32] Given MeVO strokes tend to be smaller compared to LVO, a rapid rate of core progression may have greater implications regarding timing of reperfusion by thrombectomy. MeVO may shift to a completed stroke faster than a LVO despite having similar progression rates. [6, 7, 17] This will be of interest to examine in thrombectomy treatment trials of MeVO. Potentially a very rapid progressor with a high HI and long transfer may benefit more from thrombolysis, whereas a slow progressor with low HI and long transit may benefit from transfer for endovascular therapy. [9-11]

HI may also be of value in the assessment of LVO but low NIHSS, a group where the treatment strategy is yet unclear. Several ongoing trials are evaluating endovascular therapy for the treatment of LVO with low NIHSS. [33-36] Potentially patients with high HI may derive greater benefit from reperfusion, which may guide triage pathways, as they are more likely to experience core progression and infarct growth without treatment. [21] HI may have a role in the decisions of late window thrombolysis prior to transport for thrombectomy. Thrombolysis beyond 4.5 hours of stroke onset might be considered in some patients being transported for endovascular thrombectomy. [6] Whether patients with high HI derive greater benefit from such late window thrombolysis will be of interest to explore, as they may be more likely to experience infarct progression during transport. Further studies are needed to determine the role of HI to select patients for reperfusion therapy and potentially guide decisions regarding transport.

The HI adds to the ability to assess core progression. Progression rate determined by time, leaves a large number of patients in an indeterminate category where rate of infarct progression is challenging to accurately assess. Within the first 6 hours of stroke onset, only fast progressors can be reliably identified. [1, 2] Moreover, a small core at later time-period may be a slow progressor or completed small stroke. [2, 8, 11, 17] By assessing time-to-peak concentration parameters (tissue likely to become infarcted), HI is able to provide an assessment of core progression rate in the indeterminate category in a manner that is less reliant on time from stroke onset. [21, 28]

Our study does have limitations. First, posterior circulation strokes were not included in the study, thus further evaluation in this patient group is needed. Second patients were recruited from a single tertiary referral center for stroke; thus a selection bias may exist toward patients being transferred for intervention. Brain imaging was performed slightly longer from stroke onset in LVO as compared to MeVO, though this was not significant. This trend was most likely related

to interfacility transport of LVO patients for thrombectomy. Third, we made the assumption that core growth starts at symptom onset and proceeds in a linear fashion over time. While consistent with prior studies, core growth is likely a dynamic process that is influenced by a range of factors such as blood pressure, recanalization, collateral failure, and tolerance of brain ischemia. [15, 37-39] Fourth, HI relies on CT perfusion that is not available at all centers where stroke patients present. This limits its use to centers where CT Perfusion can be performed, which may expand over time as data supporting the role of CT Perfusion in the management of stroke patients emerges. Automated processing of perfusion scans as performed by software programs such as RAPID are reducing barriers to widespread implementation of CT Perfusion. [37] Finally, serial imaging over time is another method to assess core progression which we did not perform. However, serial imaging in often not available in clinical practice, and HI assessment of core progression from a single imaging time point is thus an advantage. Further multicenter imaging studies monitoring infarct growth over time will be of value to further understand the dynamics of core growth in patients and how best to model it.

3.6. Conclusions:

HI was able to estimate the initial rate of core progression in acute ischemic stroke in patients with both MeVO and LVO up to 24 hours of onset. Patients with a HI > 0.5 have a fast rate of infarct progression. Further evaluation of HI is needed to determine whether it could aid in the selection and management of stroke patients treated with reperfusion therapy.

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3.8 Supplementary materials

3.8.1. Supplementary methods

3.8.1.1. Image Acquisition: CT Perfusion head was conducted with the toggling table technique, allowing an extended 96 mm coverage of the brain. All scans were performed using a Virtual 128-slice CT scanner (Acquisition 128 x 0.6 mm) equipped with a 38.4-mm wide detector (Somatom Definition AS, Siemens Medical Systems, Germany). The imaging parameters were as follows: 1) 70 kVp, 200 mAs, and 32×1.2 mm detector collimation, 2) Slice spacing 5.0 mm, 3) number of images 418, 4) 4D range 96 mm 1.50 s, craniocaudal and a scan duration of 60 s. Scan delay of 9 s was applied as standard after injecting 40 mL (flow rate 5 mL/s) of iodinated contrast agent (350 mgl/mL Iomeprol 350, Bracco Imaging, Ravensburg, Germany if eGFR (estimated Glomerular Filtration Rate) ≥ 30 mL/min/1.73 m^2 or 320 mgl/mL Iodixanol 320, GE Healthcare Inc. if eGFR < 30 mL/min/1.73 m^2). CT Perfusion source maps were generated based on standard parameters including Cerebral Blood Flow, Cerebral Blood Volume, Mean Transit Time and time-to-peak concentration/ Tmax. [4] An imaging workstation was available on the CT viewing area. The source images were uploaded automatically to Picture Archiving and Communication System (PACS*)* on the workstation immediately through a Digital Imaging and Communications in Medicine (DICOM) mode after the completion of the CT studies to generate final maps.

3.8.1.2. Vessel identification and recanalization: On CT Angiography, terminal bifurcation of the internal carotid artery was identified as ‘carotid T”. M1 segment of middle cerebral artery was identified as the arterial trunk from its origin at internal carotid artery, that courses laterally parallel to the sphenoid ridge to first bifurcation or trifurcation into major branches. M2 was identified as vertical arterial segment after bifurcation or trifurcation, within the mesial margin of the sylvian

fissure that terminates at the circular sulcus of insula. TICI grades were defined as follows: 2b - antegrade reperfusion of more than half of the previously occluded target artery, 3 - complete antegrade reperfusion of the previously occluded target artery. [4-6, 22-24]

Supplementary e-table 3.1. Patient characteristics in acute ischemic strokes with Medium and Large vessel occlusion.

Variables	MeVO n=26	LVO n=80	p-value
Age, median (IQR) (years)	74.5 (57.0-86.0)	73.5 (62.5-83.0)	0.73
Sex (Male), n (%)	18 (69.2)	50 (62.5)	0.64
Hypertension, n (%)	20 (76.9)	48 (60.0)	0.15
Diabetes Mellitus, n (%)	6 (23.0)	17 (21.2)	0.99
Coronary Artery Disease, n (%)	5 (19.2)	17 (21.2)	0.99
Previous Stroke, n (%)	2 (7.6)	6 (7.5)	0.99
Previous Transient Ischemic Attack, n (%)	2 (7.6)	8 (10.0)	0.99
Current Smoking, n (%)	4 (15.3)	18 (22.5)	0.58
Atrial Fibrillation, n (%)	4 (15.3)	22 (27.5)	0.29
Hyperlipidemia, n (%)	12 (46.1)	24 (30.0)	0.15
NIHSS score, median (IQR) at presentation	10.0 (5.0-14.0)	17.0 (11.0-21.0)	<0.001
NIHSS score, median (IQR) at 24-48hrs	3.0 (1.0-5.0)	10.0 (3.0-20.0)	<0.001
ASPECTS ≤ 7, n (%)	0 (0)	19 (23.75)	0.003
CTP core, median (IQR) (mL)	7.5 (0.0-22.0)	10.0 (0.0-45.0)	0.05
CTP mismatch, median (IQR) (mL)	29.0 (12.0-55.0)	98.5 (56.5-121.5)	<0.001
CTP mismatch ratio, median (IQR)	2.3 (2.2-3.2)	4.3 (2.2-12.3)	0.05
Treatment			
IVT only, n (%)	15 (57.6)	13 (16.2)	<0.001
EVT only, n (%)	1 (3.8)	31 (38.7)	<0.001
IVT + EVT, n (%)	2 (7.6)	19 (23.7)	0.09

Variables	**MeVO n=26**	**LVO n=80**	**p-value**
Hemorrhagic Transformation, n (%)	5 (19.2)	29 (36.2)	0.11
Symptom onset to imaging, median (IQR) (minutes)	140.5 (94.0-363.0)	361.5 (156.0-617.0)	0.06
Progressor type by (< 6 or 6-24 hours) definition			
Fast, n (%)	0 (0)	7 (8.7)	0.99
Slow, n (%)	2 (7.6)	27 (33.7)	0.99
Hypoperfusion Index			
≤ 0.5, n (%)	18 (69.2)	59 (73.7)	0.80
> 0.5, n (%)	8 (30.7)	21 (26.2)	0.80

CTP=Computed Tomography Perfusion; NIHSS=National Institutes of Health Stroke Scale; ASPECTS=Alberta Stroke Program Early CT Score; IQR=Interquartile range; MeVO=Medium Vessel Occlusion; LVO=Large Vessel Occlusion; IVT=Intravenous thrombolysis; EVT=Endovascular Thrombectomy.

Supplementary e-table 3.2. Comparison of patient characteristics between ≤ 0.5 and > 0.5 Hypoperfusion Index groups in medium and large vessel occlusion stroke patients.

Variables	MeVO (n=26)			LVO (n=80)		
	HI >0.5 n=8	***HI ≤0.5 n=18***	***p-value***	***HI >0.5 n=21***	***HI ≤0.5 n=59***	***p-value***
Age, median (IQR) (years)	62.0 (55.0-73.0)	80.5 (66.0-87.0)	0.11	79.0 (66.0-85.0)	71.0 (61.0-80.0)	0.19
Sex (Male), n (%)	7 (87.5)	11 (61.1)	0.36	13 (61.9)	37 (62.7)	0.99
Hypertension, n (%)	5 (62.5)	15 (83.3)	0.33	13 (61.9)	35 (59.3)	0.99
Diabetes Mellitus, n (%)	1 (12.5)	5 (27.7)	0.62	5 (23.8)	12 (20.3)	0.76
Coronary Artery Disease, n (%)	0 (0)	5 (27.7)	0.28	6 (28.5)	11 (18.6)	0.36
Previous Stroke, n (%)	1 (12.5)	1 (5.5)	0.52	3 (14.2)	3 (5.0)	0.18
Previous Transient Ischemic Attack, n (%)	0 (0)	2 (11.1)	0.99	3 (14.2)	5 (8.4)	0.42
Current Smoking, n (%)	0 (0)	4 (22.2)	0.27	6 (28.5)	12 (20.3)	0.54
Atrial Fibrillation, n (%)	2 (25.0)	2 (11.1)	0.56	7 (33.3)	15 (25.4)	0.57
Hyperlipidemia, n (%)	2 (25.0)	10 (55.5)	0.21	9 (42.8)	15 (25.4)	0.16
NIHSS score, median (IQR) at admission	10.0 (7.5-11.5)	11.0 (5.0-14.0)	0.63	20.0 (17.0-23.0)	16.0 (10.0-19.0)	0.001
NIHSS score, median (IQR) at 24-48hrs	2.0 (1.0-4.5)	3.5 (2.0-6.0)	0.35	20.0 (6.0-24.0)	7.5 (3.0-16.0)	0.01
ASPECTS ≤ 7, n (%)	0 (0)	0 (0)	-	10 (47.6)	9 (15.2)	0.006
CTP core, median (IQR) (mL)	11.5 (0.0-35.0)	7.0 (0.0-12.0)	0.29	96.0 (63.0-137.0)	6.0 (0.0-21.0)	<0.001

Variables	**MeVO (n=26)**			**LVO (n=80)**		
	HI >0.5 n=8	***HI ≤0.5 n=18***	***p-value***	***HI >0.5 n=21***	***HI ≤0.5 n=59***	***p-value***
CTP mismatch, median (IQR) (mL)	25.5 (9.0-68.5)	29.0 (15.0-54.0)	0.69	90.0 (56.0-111.0)	100.0 (57.0-125.0)	0.48
CTP mismatch ratio, median (IQR)	2.2 (2.0-2.3)	2.8 (2.2-5.1)	0.22	2.0 (1.4-2.6)	7.3 (4.0-15.0)	<0.001
Treatment						
IVT only, n (%)	3 (37.5)	12 (66.6)	0.21	2 (9.5)	11 (18.6)	0.49
EVT only, n (%)	0 (0)	1 (5.5)	0.99	5 (23.8)	26 (44.0)	0.12
IVT + EVT, n (%)	1 (12.5)	1 (5.5)	0.52	2 (9.5)	17 (28.8)	0.13
Recanalization (TICI 2b/3), n (%)	1 (12.5)	1 (5.5)	0.52	3 (14.2)	31 (52.5)	0.002
Hemorrhagic Transformation, n (%)	2 (25.0)	3 (16.6)	0.62	6 (28.5)	23 (38.9)	0.39
Symptom onset to imaging, median (IQR) (minutes)	194.0 (112.0-999.0)	137.5 (86.0-293.0)	0.34	428.0 (96.0-616.0)	361.0 (199.0-677.0)	0.57

CTP=Computed Tomography Perfusion; NIHSS=National Institutes of Health Stroke Scale; ASPECTS=Alberta Stroke Program Early CT Score; IQR=Interquartile range; TICI=Thrombolysis In Cerebral Infarction; MeVO=Medium Vessel Occlusion; LVO=Large Vessel Occlusion; IVT=Intravenous thrombolysis; EVT=Endovascular Thrombectomy.

Supplementary e-table 3.3. Comparison of patient characteristics between low and high Hypoperfusion Index groups in indeterminate category in < 6 and 6-24 hour tiers

Variables	**Indeterminate n=70**					
	< 6 hours n=53			***6-24 hours n=17***		
	HI >0.5 n=8	***HI ≤0.5 n=45***	***p-value***	***HI >0.5 n=11***	***HI ≤0.5 n=6***	***p-value***
Age, median (IQR) (years)	72.5 (56-83.5)	76 (67-87)	0.47	78 (55-85)	63 (57-85)	0.80
Sex (Male), n (%)	6 (75)	24 (53.3)	0.25	8 (72.7)	3 (50)	0.34
Hypertension, n (%)	5 (62.5)	31 (68.8)	0.72	6 (54.5)	4 (66.6)	0.62
Diabetes Mellitus, n (%)	2 (25)	10 (22.2)	0.86	2 (18.1)	2 (33.3)	0.48
Coronary Artery Disease, n (%)	2 (25)	9 (20)	0.74	2 (18.1)	0 (0)	0.26
Previous Stroke, n (%)	0 (0)	1 (2.2)	0.67	1 (9)	0 (0)	0.44
Previous Transient Ischemic Attack, n (%)	1 (12.5)	4 (8.8)	0.74	1 (9)	1 (16.6)	0.64
Current Smoking, n (%)	1 (12.5)	10 (22.2)	0.53	1 (9)	0 (0)	0.44
Atrial Fibrillation, n (%)	1 (12.5)	12 (26.6)	0.39	2 (18.1)	0 (0)	0.26
Hyperlipidemia, n (%)	2 (25)	19 (42.2)	0.35	4 (36.3)	0 (0)	0.09
NIHSS score, median (IQR) at admission	16.5 (10-21.5)	14 (10-18)	0.35	15 (12-26)	7 (3-12)	0.07

Variables	**Indeterminate n=70**					
	< 6 hours n=53			***6-24 hours n=17***		
	HI >0.5 n=8	***HI ≤0.5 n=45***	***p-value***	***HI >0.5 n=11***	***HI ≤0.5 n=6***	***p-value***
NIHSS score, median (IQR) at 24-48hrs	3 (1.5-12.5)	5.5 (2-15)	0.46	15 (5-26)	6.5 (1-10)	0.31
ASPECTS ≤ 7, n (%)	2 (25)	2 (4.4)	0.04	7 (63.6)	0 (0)	0.01
CTP core, median (IQR) (mL)	39 (24-48.5)	6 (0-14)	<0.001	97 (9-163)	0 (0-7)	0.01
CTP mismatch, median (IQR) (mL)	68.5 (25.5-114.5)	78 (46-122)	0.49	42 (9-90)	19.5 (12-49)	0.29
CTP mismatch ratio, median (IQR)	2.2 (1.6-3.2)	7.1 (3.1-12.8)	0.004	1.7 (1.2-2.3)	2.3 (0-8)	0.71
Occluded vessel						
ICA, n (%)	0 (0)	7 (15.5)	0.23	2 (18.1)	4 (66.6)	0.04
Carotid T, n (%)	0 (0)	1 (2.2)	0.67	0 (0)	0 (0)	-
M1, n (%)	3 (37.5)	23 (51.1)	0.47	7 (63.6)	0 (0)	0.01
M2, n (%)	5 (62.5)	15 (33.3)	0.11	2 (18.1)	2 (33.3)	0.48
Treatment						
IVT only, n (%)	3 (37.5)	16 (35.5)	0.91	2 (18.1)	2 (33.3)	0.48
EVT only, n (%)	2 (25)	11 (24.4)	0.97	1 (9)	2 (33.3)	0.21
IVT + EVT, n (%)	0 (0)	15 (33.3)	0.05	0 (0)	0 (0)	-
Recanalization (TICI 2b/3), n (%)	1 (12.5)	18 (40)	0.13	0 (0)	1 (16.6)	0.16

Variables	**Indeterminate n=70**					
	< 6 hours n=53			***6-24 hours n=17***		
	HI >0.5 n=8	***HI ≤0.5 n=45***	***p-value***	***HI >0.5 n=11***	***HI ≤0.5 n=6***	***p-value***
Hemorrhagic Transformation, n (%)	1 (12.5)	17 (37.7)	0.18	3 (27.2)	2 (33.3)	0.79
Symptom onset to imaging, median (IQR) (minutes)	104 (38-123)	158 (86-283)	0.08	604.5 (457-984)	511 (400-541)	0.10
Rate of core progression (ratio of core to time), mL/ min	0.31 (0.06-1.44)	0.04 (0-0.09)	0.001	0.18 (0.11-0.22)	0 (0-0.01)	0.001

CTP=Computed Tomography Perfusion; ICA=Internal Carotid Artery; NIHSS=National Institutes of Health Stroke Scale; ASPECTS=Alberta Stroke Program Early CT Score; IQR=Interquartile range; TICI=Thrombolysis In Cerebral Infarction; IVT=Intravenous thrombolysis; EVT=Endovascular Thrombectomy.

Chapter 4

Advanced small vessel disease is associated with hypoperfusion index in large vessel occlusion acute ischemic stroke

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*A version of this chapter is being submitted for publication. The chapter has been expanded for clarity.

4.1 Abstract

4.1.1. Background and Purpose: The mechanism of cerebral small vessel disease (SVD) associated with worse outcome in patients with large vessel occlusion (LVO) acute ischemic stroke (AIS) remains poorly understood. Higher hypoperfusion index (HI) as assessed on computed tomography perfusion (CTP) is associated with early infarct growth. In this study we explore the relationship between small vessel disease and HI. We hypothesized patients with severe SVD are more likely to have a higher HI with LVO AIS.

4.1.2. Methods: HI was evaluated using CTP, and SVD was graded by: 1) deep-white-matter-hypodensities (DWMH) and peri-ventricular-white-matter-hypodensities (PVWMH) using the Fazekas scale, 2) lacunes and 3) enlarged-peri-vascular-spaces (EPVS) on non-contrast-CT in 139 LVO AIS patients. HI ≥ 0.5 was indicative of fast progressors. Severe SVD was defined as Fazekas 2-3 for DWMH and PVWMH. Multivariate regression model with adjustment of confounding variables was used to assess odds of advanced SVD and HI ≥ 0.5, with $p \leq 0.05$ considered significant.

4.1.3. Results: Amongst 139 LVOs, HI was ≥ 0.5 in 43.8% (61/139). Median (IQR) HI was higher in those with lacunes [0.5 (0.3-0.6) versus 0.4 (0.2-0.5), p=0.05], EPVS [0.5 (0.4-0.7) versus 0.4 (0.2-0.6), p=0.09], DWMH (Fazekas 2-3) [0.5 (0.4-0.7) versus 0.4 (0.2-0.6), p=0.006] and PVWMH (Fazekas 2-3) [0.5 (0.4-0.7) versus 0.4 (0.2-0.6), p=0.001], indicating HI ≥ 0.5 with more severe SVD. On multivariate regression, lacunes and PVWMH (Fazekas 2-3) were significantly higher in those with ≥ 0.5 HI. EPVS and DWMH (Fazekas 2-3) demonstrated a trend towards ≥ 0.5 HI [(OR=2.5, p=0.11) and (OR=2.3, p=0.12) respectively].

4.1.4. Conclusions: Advanced SVD is associated with higher HI, thus higher chances of early infarct growth in patients with LVO AIS. This can potentially support the hypothesis that increased burden of SVD is an imaging biomarker for impaired circulatory reserve. Future studies should explore how HI relates to SVD and can better predict micro-circulatory failure and patient outcomes.

4.2. Introduction:

There is significant patient variability in early infarct growth rate (EIGR) and progression in acute ischemic stroke (AIS) with large vessel occlusion (LVO). [1] For example, in patients with occlusion of M1 segment of the middle cerebral artery, the rate of infarct growth can range from ~1 to 10 ml/hour. [2] This variability in infarct growth is in part related to the presence and persistence of collaterals which maintain adequate cerebral perfusion in the setting of an acute arterial occlusion. [1, 3, 4] While the importance of collaterals in determining infarct growth is well established, other factors that contribute to this variability, in particular the severity of cerebral small vessel disease (SVD) are less well understood. [3-6]

Small vessel disease refers to a group of diffuse pathologies with overlapping mechanisms and risk factors that affect perforating cerebral arterioles, capillaries, and venules.[7] Markers of the presence and severity of SVD can be visualized on Computed Tomography (CT) and Magnetic Resonance (MR) imaging. [7, 8] Studies have shown that the presence of SVD is associated with impairment in the brains ability to tolerate ischemia in the setting of stroke, resulting in more tissue damage for a given ischemic insult, independent of stroke size and subtype. [7-9] Additionally, SVD may be associated with poor recruitment of collaterals although this relationship is not consistent across studies. [3, 9] These findings in part may explain why clinically patients with advanced SVD have worse outcomes and are less like to recover even after successful thrombectomy. [10] One possible mechanism SVD may be contributing to poor outcomes is reducing the capacity of tissue to tolerate ischemia by increasing microvascular resistance during progressive infarction. [11] The presence of SVD may impact stroke outcomes by affecting the rate of early infarct growth and may be a factor determining the rate of infarct progression. [3, 8]

While dynamics of collateral failure can be easily studied by visualizing vascular-conduits on conventional, or CT Angiography (CTA), it is challenging to estimate contribution of microvascular circulation in infarct growth. [4-6, 12] Moreover, both former mentioned modalities are qualitative and highly prone to interobserver variability. [4, 6, 13] CT perfusion (CTP) can accurately study both macro- and microvascular circulation using hypoperfusion index (HI) without user dependence. [13] At present, the most established imaging marker of infarct progression is the hypoperfusion index. [2, 14, 15] In the setting of an acute ischemic stroke, HI on perfusion CT and MR provides an estimate of how fast penumbral brain tissue will shift to infarcted core based on the severity of delay in blood flow to the brain. It is calculated as the ratio of time-to-peak concentration at > 10 seconds (Tmax > 10) to time-to-peak at > 6 seconds (Tmax > 6). [2, 5, 14, 15] HI provides an expected degree of evolution of core based on severity of delay in blood flow to the brain (macro- and microvascular) and thus can predict early infarct growth as a composite measure. HI has been proposed as a mean to classify acute stroke patients as fast or slow progressors using a cut point of 0.5 (i.e., patients with ≥ 0.5 HI are fast progressors). [2, 5, 14, 15] Faster infarct progression as indexed by higher HI values is associated with clinical factors such as poor collateral score and time from stroke onset. [16] In this study, we aimed to determine whether the speed of early infarct growth and rate of infarct progression in ischemic stroke as indexed by HI is additionally impacted by the presence of SVD. We hypothesized LVO AIS patients with severe SVD are more likely to have a higher HI.

4.3. Materials and methods:

The study was approved by the Health Ethics Committee of the University of Alberta. Patients admitted to the University of Alberta hospital with suspected stroke who had CTP between

March and November of 2019 were enrolled in the study. The medical records and imaging of prospectively enrolled patients with AIS were reviewed.

4.3.1. Images post-processing and automated analysis: Non-contrast Computed Tomography (NCCT) was performed on a Siemens CT machine, followed by CTA and CTP as part of clinical protocol for acute stroke patients. CTP was post-processed by FDA-approved RAPID (Rapid processing of perfusion and diffusion; iSchemaView, California, USA) software for estimation of core and mismatch. RAPID used a delay-insensitive algorithm. The perfusion deficit volume was defined using Tmax > 6 seconds. Core was diagnosed if the relative CBF was <30% of that in normal tissue. Mismatch was defined as tissue within the Tmax > 6 seconds deficit, which was not the ischemic core (i-e-, CBF >30%). Mismatch ratio was automatically calculated in each software by dividing total perfusion deficit volume by core volume. [17, 18] Hypoperfusion index was defined as Tmax > 10 seconds / Tmax > 6 seconds. [2, 5, 14, 15]

4.3.2. Eligibility: All patients were older than 18 years and had CTP performed within 24 hours of symptom onset with pre-stroke modified Rankin Scale (mRS), (scores range from 0-6, with higher scores indicating greater disability/ death-6) of 1 or less. For wake-up strokes, the time when the patient was last known to be well was considered a surrogate of onset time. We excluded patients with stroke mimics, perfusion maps of inadequate quality due to technical or other artifacts, negative perfusion maps, Transient Ischemic Attack (TIA), posterior circulation strokes and perfusion deficits not compatible with the stroke syndrome. We included patients with large vessel occlusion (LVO) i.e., (ICA (Internal Carotid Artery) and M1 occlusion. [2, 5]

4.3.3. Patient groups and small vessel disease parameters: For the purpose of analysis and discussion, groups of patients were referred to have HI of < 0.5 or ≥ 0.5. This was based on earlier literature on HI. [2, 5, 14, 15] SVD was graded on NCCT on following parameters: 1) Lacunes, 2)

enlarged peri-vascular spaces (EPVS), 3) deep white matter hypodensities (DWMH) graded as either none/ mild (Fazekas Grade 0-1) or moderate/severe (Fazekas Grade 2-3) and 4) peri-ventricular white matter hypodensities (PVWMH) graded as either none/ mild (Fazekas Grade 0-1) or moderate/severe (Fazekas Grade 2-3). Lacunes were defined as "3 to 15 mm cerebrospinal fluid-filled cavities in the basal ganglia or white matter". [19] EPVS were defined as "when PVS was greater than 5 mm; but atypical morphology consisting of irregular shape was also used rather than a precise size criteria to classify EPVS". [20] DWMH were graded as: 0 = absent, 1 = punctate foci, 2 = beginning confluence, 3 = large confluent areas. [21] PVWMH were graded as: 0 = absent, 1 = "caps" or pencil-thin lining, 2 = smooth "halo", 3 = irregular periventricular signal extending into the deep white matter. [21] For purpose of this study, those with DMWH (Fazekas 2-3) and PVWMH (Fazekas 2-3) were called "severe SVD". We used NCCT to delineate parameters for SVD as used by previous reports due to clinical feasibility. [22] SVD was graded on NCCT by two independent/ unique raters (certified neurologists) using Cohen's kappa. Both were blinded to the data set, with the following kappa statistics: Lacunes: Kappa=0.86 (good), $p<0.001$, agreement=94.87%, EPVS: Kappa=1.0 (almost perfect), $p<0.001$, agreement=100%, DWMH: Kappa=1.0 (almost perfect), $p<0.001$, agreement=100%, PVWMH: Kappa=0.89 (good), $p=0.007$, agreement=97.44%. [23] To estimate SVD as a single composite measure, we used SVD score (modified version) to grade all SVD categories in a scale ranging from 0 to 3 (0=no disease; 3= severe disease). This included scoring 1 point each for presence of ≥ 1 lacunae, moderate-to-severe EPVS, Fazekas 3 PVWMH and Fazekas 2-3 DWMH. [3] Collaterals were graded by two independent raters using criteria by Tan et al as 0: absent, 1: $\leq$50% collateral middle cerebral filling, 2: >50-99%, 3: 100% and with 78% agreement. [4]

National Institutes of Health Stroke Scale (NIHSS) was determined by stroke neurologist on admission. Alberta Stroke Program Early CT Score (ASPECTS) was reported on NCCT as ≤ 7 or higher (scores range from 0-10, with higher scores indicating a smaller infarct core). LVO was assessed on CTA and recanalization on conventional angiography using Thrombolysis In Cerebral Infarction (TICI) by certified radiologist. Hemorrhagic transformation was determined by radiologist on 24-48 hours NCCT post-stroke. Time of onset was either witnessed time of index event or last known well, which is in line with previous reports. [1]

4.3.4. Vessel identification and recanalization: On CTA, terminal bifurcation of the ICA was identified as 'carotid T". M1 segment of middle cerebral artery was identified as the arterial trunk from its origin at ICA, that courses laterally parallel to the sphenoid ridge to first bifurcation or trifurcation into major branches. M2 was identified as vertical arterial segment after bifurcation or trifurcation, within the mesial margin of the sylvian fissure that terminates at the circular sulcus of insula. TICI grades were defined as follows: 2b - antegrade reperfusion of more than half of the previously occluded target artery, 3 - complete antegrade reperfusion of the previously occluded target artery. [2, 5]

4.3.5. Statistical Analysis: Quantitative data were summarized as median (IQR-interquartile range) and qualitative as proportions. We used nonparametric tests unless otherwise specified due to non-normality of data assessed by Shapiro-Wilk test. Characteristics of patients were compared using Student t-test or Mann-Whitney test for means and medians (IQR) and Pearson x^2 or Fischer exact test for proportions respectively, as appropriate. SVD parameters were compared between dichotomous HI (< or ≥ 0.5) categories using Pearson x^2 or Fischer exact test. Multivariate logistic regression model was used to ascertain factors predictive of dichotomous HI (< or ≥ 0.5) and was adjusted for potential confounders - age, gender, hypertension, diabetes mellitus, coronary artery

disease, previous history or stroke or TIA, atrial fibrillation, NIHSS and onset to CTP Time. We also tested dose-dependent trends in burden of DWMH and PVWMH on Fazekas across 1-3. Statistical tests were 2-sided and were considered significant at $\alpha \leq 0.05$ level. Data analysis was conducted using STATA 16.0 (Stata Corp LLC Texas, USA).

4.3.6. Data availability: The anonymized data supporting the findings of the study are available from the corresponding author upon reasonable request.

4.4. Results:

During a period of 6 months, 520 patients with acute stroke syndromes and advanced brain imaging were admitted to the University of Alberta Hospital. The diagnosis of AIS was confirmed in 391 patients on subsequent imaging (NCCT or Magnetic Resonance Imaging (MRI) - Diffusion Weighted sequence. After screening, we included 139 LVO patients with AIS in the final analysis. The screening process for the final cohort of 139 patients is shown in figure 4.1.

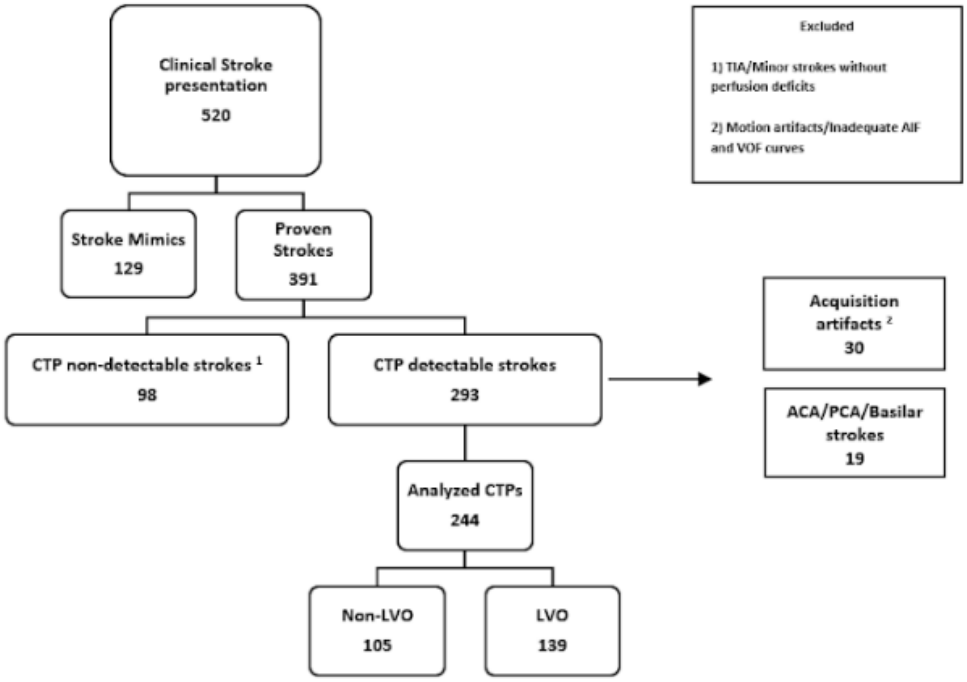

Figure 4.1. Flow diagram for patient screening and inclusion. CTP=Computed Tomography Perfusion, ACA=Anterior Cerebral Artery, PCA=Posterior Cerebral Artery, TIA=Transient Ischemic Attack, AIF=Arterial Input Function, VOF=Venous Output Function.

The median (IQR) age was 71 (61-80), 54.67% (76/139) were males. At presentation, median (IQR) NIHSS was 17 (12-21), ASPECTS was 9 (7-10) and HI was 0.4 (0.2-0.6). Median (IQR) symptom onset to imaging was 5.1 (1.9-11.2) hours. Intravenous alteplase was delivered in 40% and 62% underwent thrombectomy. Overall, 61.1% had SVD; 55.3% had lacunes, 14.3% had EPVS, 46.7% had DWMH and 56.1% had PVWMH. 21.5% had severe SVD (i-e-., DMWH-Fazekas 2-3 or PVMWH-Fazekas 2-3). Comparison of baseline characteristics between SVD categories is shown in table 4.1. Amongst DWMH, 74 (53.2%) had Fazekas 0, 37 (26.5%) had Fazekas 1, 14 (10%) had Fazekas 2 and 14 (10%) had Fazekas 3. Amongst PVWMH, 61 (43.8%)

had Fazekas 0, 48 (34.5%) had Fazekas 1, 13 (9.3%) had Fazekas 2 and 17 (12.2%) had Fazekas 3. For SVD score, 58 (41.7%) scored 0, 52 (37.4%) scored 1, 16 (11.5%) scored 2 and 13 (9.3%) scored 3.

Table 4.1. Baseline patient characteristics according to small vessel disease score

Variables	Overall	SVD score		
	n=139	***0-1 (n=110)***	***2-3 (n=29)***	***p value***
Age, median (IQR) (years)	71 (61-80)	67 (60-77)	84 (75-88)	<0.001*
Sex (Male), n (%)	76 (54.67)	66 (60)	10 (34.4)	0.02*
Hypertension, n (%)	88 (63.3)	65 (59)	23 (79.3)	0.05
Diabetes Mellitus, n (%)	29 (20.8)	26 (23.6)	3 (10.3)	0.13
Coronary artery disease, n (%)	20 (14.3)	15 (13.6)	5 (17.2)	0.56
Previous Stroke, n (%)	15 (10.7)	12 (10.9)	3 (10.3)	0.99
Previous Transient Ischemic Attack, n (%)	23 (16.5)	18 (16.3)	5 (17.2)	0.99
Current Smoking, n (%)	36 (25.8)	29 (26.3)	7 (24.1)	0.28
Atrial Fibrillation, n (%)	38 (27.3)	24 (21.8)	14 (48.2)	0.009*
Hyperlipidemia, n (%)	53 (38.1)	42 (38.1)	11 (37.9)	0.99
NIHSS score, median (IQR) at presentation	17 (12-21)	16 (11-21)	18 (14-21)	0.12
ASPECTS ≤7, n (%)	44 (31.6)	75 (68.1)	19 (65.5)	0.82
CTP core, median (IQR) (mL)	9 (0-40)	9 (0-36)	19 (6-63)	0.09
CTP mismatch, median (IQR) (mL)	10.4 (3.8-100)	100 (71-128)	90 (72-124)	0.63

Variables	Overall	SVD score		
	n=139	***0-1 (n=110)***	***2-3 (n=29)***	***p value***
CTP mismatch ratio, median (IQR)	0.4 (0.2-0.6)	12.2 (3.8-100)	7.7 (2.7-21.7)	0.10
IV Thrombolysis, n (%)	56 (40.2)	47 (42.7)	9 (31)	0.44
Endovascular Thrombectomy, n (%)	86 (61.8)	70 (63.6)	16 (55.1)	0.52
Hemorrhagic Transformation, n (%)	47 (33.8)	43 (39)	4 (13.7)	0.01*
Symptom onset to imaging, median (IQR) (hours)	5.1 (1.9-11.2)	4.9 (1.9-11.5)	5.4 (2.0-8.4)	0.83
TICI3, n (%)	55 (39.5)	42 (38.1)	13 (44.8)	0.65
ICA, n (%)	27 (19.4)	22 (20)	5 (17.2)	0.99
Carotid T, n (%)	5 (3.5)	3 (2.7)	2 (6.8)	0.27
M1, n (%)	131 (94.2)	103 (93.6)	28 (96.5)	0.99
Tan et al score	2 (1-3)	2 (1-3)	1 (1-2)	0.03*

CTP=Computed Tomography Perfusion; ICA=Internal Carotid Artery; NIHSS=National Institutes of Health Stroke Scale; ASPECTS=Alberta Stroke Program Early CT Score; IQR=Interquartile range; TICI=Thrombolysis In Cerebral Infarction; IV=Intravenous; EPVS=enlarged peri-vascular space; DWMH=deep white matter hypodensity; PVWMH=peri-ventricular white matter

hypodensity; SVD=small vessel disease; HI= Hypoperfusion Index; Tan et al [4]. *statistically significant

The HI was ≥ 0.5 in 43.8% (61/139). Figure 2 compares patients with ≥ 0.5 versus < 0.5 HI to SVD categories. Patients with ≥ 0.5 HI were more likely to have lacunes, EPVS, DMWH-Fazekas 2-3 and PVMWH-Fazekas 2-3 ($p<0.05$). Median (IQR) HI was higher in those with lacunes [0.5 (0.3-0.6) versus 0.4 (0.2-0.5), $p=0.05$], EPVS [0.5 (0.4-0.7) versus 0.4 (0.2-0.6), $p=0.09$], DWMH (Fazekas 2-3) [0.5 (0.4-0.7) versus 0.4 (0.2-0.6), $p=0.006$] and PVWMH (Fazekas 2-3) [0.5 (0.4-0.7) versus 0.4 (0.2-0.6), $p=0.001$], indicating those with higher HI (i.e., ≥ 0.5) have significantly more severe SVD.

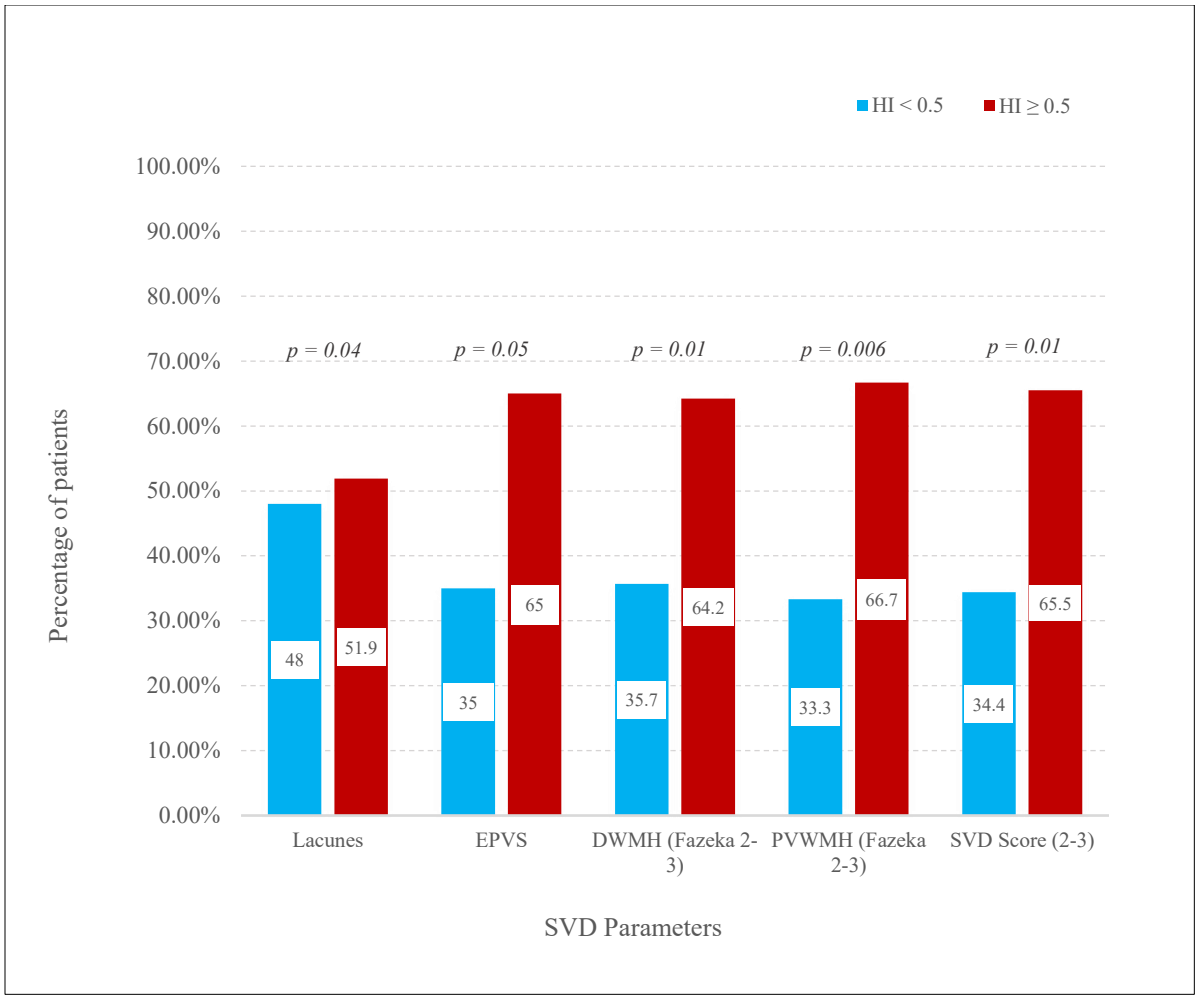

Figure 4.2. Hypoperfusion index versus small vessel disease categories: Proportion and percentage of HI (Hypoperfusion Index) groups (< 0.5 or ≥ 0.5) in different SVD (small vessel disease) categories i.e., lacunes, EPVS (enlarged peri-vascular space), DMWH (deep white matter hypodensity) and PVWMH (peri-ventricular white matter hypodensity).

After adjusting for covariates, those with SVD continued to have more likelihood of having ≥ 0.5 HI as compared to those without SVD (table 4.2.). Among SVD categories, ≥ 0.5 HI was associated with lacunes (aOR=2.3, 95% CI, 1.1-5.49) and PVWMH-Fazekas 2-3 (aOR=3.4, 95% CI, 1.1-10.2). Although not statistically significant, there was still a trend towards ≥ 0.5 HI with EPVS (aOR=2.6, 95% CI, 0.8-8.3) and DWMH-Fazekas 2-3 (aOR=2.3, 95% CI, 0.7-7.2) (table

4.2.). Moreover, there was a dose-dependent relationship between WMH burden and ≥ 0.5 HI. The adjusted odds of having ≥ 0.5 HI were 0.8, 2.2, 1.6 and 1.0, 1.6, 3.7, across DWMH and PVWMH Fazekas scores from 1-3 respectively (table 4.3.). Figure 4.3. shows an example of a patient with no SVD and HI as compared to one with severe SVD and HI.

Table 4.2. Odds of higher (≥ 0.5) Hypoperfusion Index; crude and adjusted in different small vessel disease categories

Variables	Prevalence of ≥ 0.5 HI, n (%)	Crude			Adjusted†		
		OR	***CI***	***P value***	***OR***	***CI***	***P value***
Lacunes	40 (65.5)	2.11	1.05-4.20	0.03*	2.35	1.10-5.49	0.04*
EPVS	13 (65)	2.74	1.02-7.38	0.04*	2.60	0.81-8.35	0.10
DWMH (Fazekas 2-3)‡	18 (64.2)	2.84	1.20-6.74	0.01*	2.39	0.78-7.26	0.12
PVWMH (Fazekas 2-3)‡	20 (66.6)	3.31	1.41-7.77	0.006*	3.41	1.13-10.27	0.02*
SVD Score (2-3)§	19 (65.5)	3.07	1.30-7.24	0.01*	2.26	0.80-6.31	0.11

EPVS=enlarged peri-vascular space; DWMH=deep white matter hypodensity; PVWMH=peri-ventricular white matter hypodensity; HI= hypoperfusion index; OR=odds ratio; CI=confidence interval; SVD=small vessel disease. *statistically significant

†Adjusted for age, gender, National Institutes of Health Stroke Scale, onset to imaging time, hypertension, coronary artery disease, diabetes mellitus, previous stroke or transient ischemic attack, atrial fibrillation

‡(Fazekas 0-1) is reference §(SVD score 0-1) is reference

Table 4.3. Odds of higher (≥ 0.5) Hypoperfusion Index; crude and adjusted with severity of white matter hypodensities and small vessel disease score

Variables	Prevalence of ≥ 0.5 HI, n (%)	Crude			Adjusted†		
		OR	***CI***	***P value***	***OR***	***CI***	***P value***
DWMH							
Fazekas 0	25 (33.7)	Ref			Ref		
Fazekas 1	18 (48.6)	1.29	0.61-2.76	0.49	0.87	0.35-2.15	0.77
Fazekas 2	10 (71.4)	3.62	1.07-12.20	0.03*	2.22	0.56-8.67	0.25
Fazekas 3	8 (57.1)	1.81	0.59-5.53	0.29	1.66	0.40-6.86	0.48
PVWMH							
Fazekas 0	19 (31.1)	Ref			Ref		
Fazekas 1	22 (45.8)	1.12	0.55-2.27	0.73	1.07	0.45-2.53	0.86
Fazekas 2	8 (61.5)	2.20	0.68-7.11	0.18	1.63	0.42-6.23	0.47
Fazekas 3	12 (70.5)	3.5	1.18-10.78	0.02*	3.78	0.96-14.87	0.05*

Variables	**Prevalence of ≥ 0.5 HI, n (%)**	**Crude**			**Adjusted†**		
		OR	***CI***	***P value***	***OR***	***CI***	***P value***
SVD Score							
0	19 (32.7)	Ref			Ref		
1	23 (44.2)	1.02	0.51-2.04	0.94	1.42	0.62-3.28	0.40
2	9 (56.2)	1.75	0.61-5.01	0.29	1.17	0.34-3.93	0.79
3	10 (76.9)	4.90	1.28-18.68	0.02*	3.56	0.80-15.78	0.09

DWMH=deep white matter hypodensity; PVWMH=peri-ventricular white matter hypodensity; HI= hypoperfusion index; OR=odds ratio; CI=confidence interval; Ref=reference; SVD=small vessel disease. *statistically significant

†Adjusted for age, gender, National Institutes of Health Stroke Scale, onset to imaging time, hypertension, coronary artery disease, diabetes mellitus, previous stroke or transient ischemic attack, atrial fibrillation

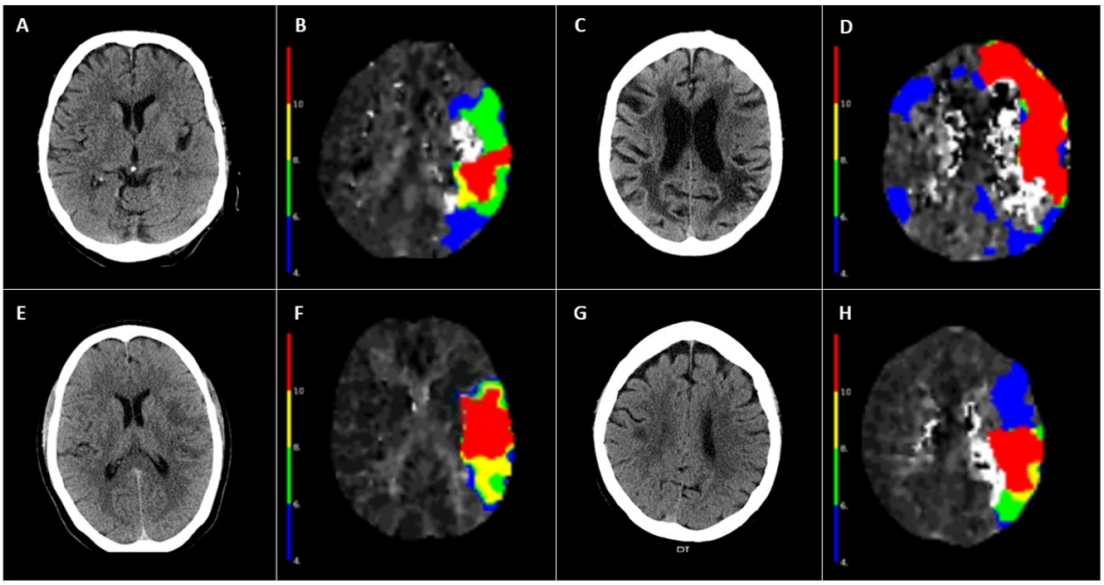

Figure 4.3. Example of patients with < 0.5 or ≥ 0.5 Hypoperfusion Index and severity of small vessel disease. Patient 1 with no SVD (score 0) (A) having HI 0.2 (B) at 0.6 hours from stroke onset. Patient 2 with severe SVD (score 3) (C) having HI 0.7 (D) at 0.6 hours from stroke onset. Patient 3 with no SVD (score 0) (E) having HI 0.4 (F) at 11.2 hours from stroke onset. Patient 4 with severe SVD (score 3) (G) having HI 0.6 (H) at 11.0 hours from stroke onset. Color coded bar on left side of perfusion scans represents Tmax values in seconds.

Amongst those with SVD score 2-3, 19 (65.5%) had ≥ 0.5 HI (figure 4.2.). There was an incremental trend towards significance in odds of having a higher SVD score with ≥ 0.5 HI (table 4.3.). The crude odds for higher SVD score (2-3) were 3 times higher (CI, 1.30-7.24, p=0.02) and showed adjusted odds of 2.26 (CI, 0.80-6.31, p=0.11) with ≥ 0.5 HI (table 4.2.). There was a dose-dependent relationship between SVD score and ≥ 0.5 HI (table 4.3.).

4.5. Discussion:

Patients with more severe coexistent SVD with large vessel occlusion have ~3-5 folds increased odds to have higher (≥ 0.5) HI as compared to those with minimal or no SVD. Amongst SVD categories, higher ≥ 0.5 HI was associated with PVWMH and lacunes, and a trend towards higher HI was seen for those with DWMH and EPVS. These findings support our underlying hypothesis that increased burden of SVD is an imaging biomarker for impaired circulatory reserve. The lower reserve to withstand acute large vessel occlusion by limited recruitment of both macro- and microvascular circulation may lead to failure to salvage penumbral brain tissue. This may result in faster early infarct growth and earlier completion of stroke. [3, 16] The presence of significant SVD has previously been shown to affect stroke outcomes, despite adequate collaterals. [9, 10] One possible mechanism for poor recovery in such patients may relate to contribution by microvascular circulatory failure that can be readily assessed using HI. The role of HI in LVO AIS is well established and can be used as a substitute imaging marker on index scan to predict core growth. [15]

Previous studies have shown diverse relationship of SVD burden and core growth. [3, 9, 10, 24-26] In contrast to our study which used perfusion parameters, most studies have assessed collateral scoring and therefore undermine the effect of microcirculation on core growth. In one study, white matter changes were independently associated with reduce odds of robust collaterals interpreted on CTA (OR, 0.8 [95% CI, 0.73-0.98) in patients with proximal artery occlusion. [9]A recent study by Lin et al investigated 100 patients with different burden of various SVD parameters and found that poor collaterals are associated with white matter changes. [3]They however mentioned the limitation of their results due to estimation of collaterals on single phase CTA instead of multiphase, thus capturing blood flow only in arterial phase. [3] Contrarily, a study by Eker et al

showed similar odds of poor collaterals with or without SVD (OR=1.1, 95% CI, 0.8-1.5, p=0.51). [25]Another study on 102 patients with AIS revealed no relationship between SVD [either PVWM-changes (p=0.77, r=0.02) or DWM-changes (p=0.55, r=-0.05)] and stroke outcomes after thrombectomy. [27] Their study however used inconsistent imaging (NCCT or MRI) for SVD estimation and evaluated both LVO (47% M1, 35% ICA) and distal (9% M2/M3) anterior circulation occlusions, as well as posterior circulation (9%); thus, potentially diluting effect modifiers. In another research, Luijten and colleagues concluded that patients with SVD have poor outcomes without treatment modification effect of thrombectomy. [26] These contrasting results may be secondary to effects of microcirculation been overlooked during estimation of core growth. HI based estimation on the other hand provides a dynamic gradient by providing an expected degree of evolution of core based on severity of delay in blood flow to the brain for both macro- and microvascular circulation, as used in our study.

Our study demonstrated that SVD contributes to compromised macro- and microcirculation by anticipated early failure and transition to irreversible infarction predicted by HI. It is known that some patients even after having good macrovascular collaterals have faster early infarct growth and thus poor eventual outcomes. [9, 10] The plausible mechanism for this may be decreased resilience of microvascular circulation. [3] Thus, despite good collateral visualization on CTA, infarct growth continues. Risk factors for SVD like hypertension, diabetes and age can potentially lead to this reduced pliability of microvascular circulation by lowering their vasodilatory capacity and stiffening of vessel wall. [3, 29] Various animal and human studies support this hypothesis. A study by Cipolla et al showed that vasodilatory capability of vessels is impaired in presence of risk factors for SVD in a rat model. [29] A recent study by Li et al compared effects of angiotensin-converting enzyme inhibitor, hydralazine or a vehicle in hypertensive normotensive

Winstar rats and evaluated vascular perfusion and stroke outcomes. [30] They were able to show that possible mechanism of micro-circulatory failure is increased vessel tone. [30] El Amki et al showed that despite recanalization of macrovascular circulation, distal capillaries i.e., microcirculation remains stalled in 35% of core and 15% of penumbral tissue, with stagnant flow. [31] Similarly, human studies have shown that higher SVD burden relates to poor outcomes despite reperfusion, suggesting possible contribution of SVD to reduce vasodilatory capacity of microvascular circulation. [3, 26] Our study provides a better understanding of impending failure of circulatory reserve and reduction in tissue resilience by showing that HI is affected by burden of SVD.

Our study has certain strengths and limitations. First, it is one of the few studies exploring LVO AIS with burden of SVD, considering impending circulatory failure. Second, we included patients irrespective of thrombectomy decisions, thus reducing bias of not capturing those who were anecdotally not taken for thrombectomy and prevented sample dilution. Third, we graded SVD by two independent raters and applied kappa statistics to validate the reproducibility of results. Fourth, we graded SVD into respective categories with implied plan to explore potential mechanism of micro-circulatory failure. SVD parameters were graded on NCCT. While this might appear as a limitation, it can rather be perceived as a strength in certain aspects. NCCT is clinically more feasible and has been used by previous researchers to estimate SVD, having good agreement with MRI. The limitations include that the patients were recruited from a tertiary referral center for stroke; thus, a selection bias may exist. Also, posterior circulation strokes were not included in the study. As such, results cannot be generalized and need further evaluation. We assumed that core growth starts at symptom onset and proceeds in a linear fashion over time when interpreting HI. While consistent with prior studies, the initial rate of core growth is a dynamic process. [13, 32]

Detailed imaging studies monitoring infarct growth over time would be of value to understand the dynamics of core growth in patients with LVO AIS and how best to model it with SVD.

4.6. Conclusions:

Advanced SVD is associated with higher HI, thus higher chances of early infarct growth in patients with LVO AIS. This can potentially support the hypothesis that increased burden of SVD is an imaging biomarker for impaired circulatory reserve. Future studies should explore how HI relates to SVD and can better predict micro-circulatory failure and patient outcomes.

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Chapter 5

Summary discussion and conclusion

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*This chapter is a discussion on practical applications of hypoperfusion index and future directions in assessment of infarct growth.

5.1. Infarct growth and hypoperfusion index:

Infarct growth is one of the most significant factors affecting clinical outcomes in patients with acute ischemic stroke (AIS). [1-6] The estimation of infarct growth is a challenging task and various authors have suggested different methods to quantify degree of infarct evolution. [1, 4, 7] While conventional methods like non-contrast CT are able to quantify this by serial imaging techniques, dynamic studies like perfusion imaging have paved a new pathway to visualize and study stroke evolution. [4, 6] Perfusion imaging is one of the most sophisticated of imaging techniques that records dynamic blood flow to the brain and can predict infarct growth. [6]

Following results of stroke trials, a mismatch profile on CT perfusion (CTP) is used to select patients for reperfusion. [8-10] However, both thrombolysis and endovascular thrombectomy (EVT) trials, whether it be for early or late windows, only cover a handful of patients. [5, 8-11] A substantial knowledge gap exists for different patient groups who might benefit from reperfusion, especially those with medium vessel occlusion (MeVO), 50% of whom might have poor eventual outcomes without recanalization. [12] Therefore, absolute core, mismatch ratio and mismatch volume on CTP might be insufficient to categorize such patients and they can be studied using alternative methods like hypoperfusion index (HI), which combines degree of hypoperfusion and hence stroke evolution. [3, 13, 14] Reperfusion therapy can be made more effective by better use of CTP to select, triage and transport patients with acute ischemic stroke.

It is well known that one out of every three patients being transferred to comprehensive stroke center gets ineligible for treatment on arrival. [12, 14] The recently published results of RACECAT (Direct Transfer to Endovascular Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory) were unable to show superiority of direct transfer to EVT centers. [15] A better estimation of infarct growth by predicting core evolution in patients

with AIS might help better redirect patients towards an increased chance of recanalization and thus potential good outcomes. Furthermore, markers predictive of higher chances of core growth might explain additional factors beyond collaterals that may contribute to decreased tissue resilience and thus poor stroke outcomes.

Our results show that HI ≤0.5 differentiates slow from fast rate of infarct progression and can potentially affect clinical outcomes. Estimation of progressors by HI seem to be more comprehensive but needs external validation. We further showed that HI is able to estimate the initial rate of core progression in acute ischemic stroke in patients with both MeVO and large vessel occlusion (LVO) likewise up to 24 hours of onset. We also showed that advanced small vessel disease (SVD) is associated with higher HI, thus higher chances of early infarct growth in patients with LVO AIS. This can potentially support the hypothesis that increased burden of SVD is an imaging biomarker for impaired circulatory reserve and thus poor patient outcomes. Future studies should explore the relationship of HI and SVD to better understand predictors of micro-circulatory failure. Further evaluation of HI is needed to determine whether it can aid in the selection and management of stroke patients treated with reperfusion therapy.

5.2. Limitations:

There are certain limitations to the estimation of infarct growth by hypoperfusion index. While HI is based on CTP, availability of CTP at all centers especially peripheral sites might not be universal. However, this may expand over time as CTP becomes more widely accessible. [16] To add further, the estimation of core to time ratio and infarct growth based on HI is based on the assumption that infarct growth follows a linear relationship to time, which might not be always accurate. A real-time assessment of core growth by implementing serial imaging with final infarct

volume might be the best strategy to assess dynamics of infarct evolution. Also, infarct growth might be affected by other unknown parameters and thus sometimes hard to accurately assess. [18] In terms of contribution of SVD to infarct growth, the predilection of our cohort with elderly and those with hypertension to SVD itself may have introduced bias by promoting collateral failure. [19-20] This may affect the ability to adjust for age and comorbidities. While HI seems to be a promising tool, the lack of randomized clinical trials makes it difficult to directly translate clinical utility of HI in management of stroke in the real world. Thus, external validation of our results is required in larger and more diverse population cohorts.

5.3. Future directions and implications:

By estimation of infarct growth independent of cerebral blood flow (CBF), HI may be able to predict evolution of stroke. When compared to ratio of core to mismatch i.e., mismatch ratio, HI may be able to capture tissue dynamics which can provide additional information on infarct growth. As mismatch ratio primarily relies on CBF< 30% threshold to define core, sometimes it can erroneously be calculated as infinity due to lack of core, thus making estimation of core growth problematic. [21] HI on the other hand always lies between a value from 0-1 on an 11- point scale of 0.1 each and depends on relative degree of hypoperfusion in the tissue. To further explore the relationship between mismatch ratio and HI, we analyzed the correlation between the two in the LVO cohort (n=139). A moderate agreement was found between HI and mismatch ratio ($r = -0.4$), supporting the hypothesis that HI may provide additional value about infarct growth (figure 5.1.).

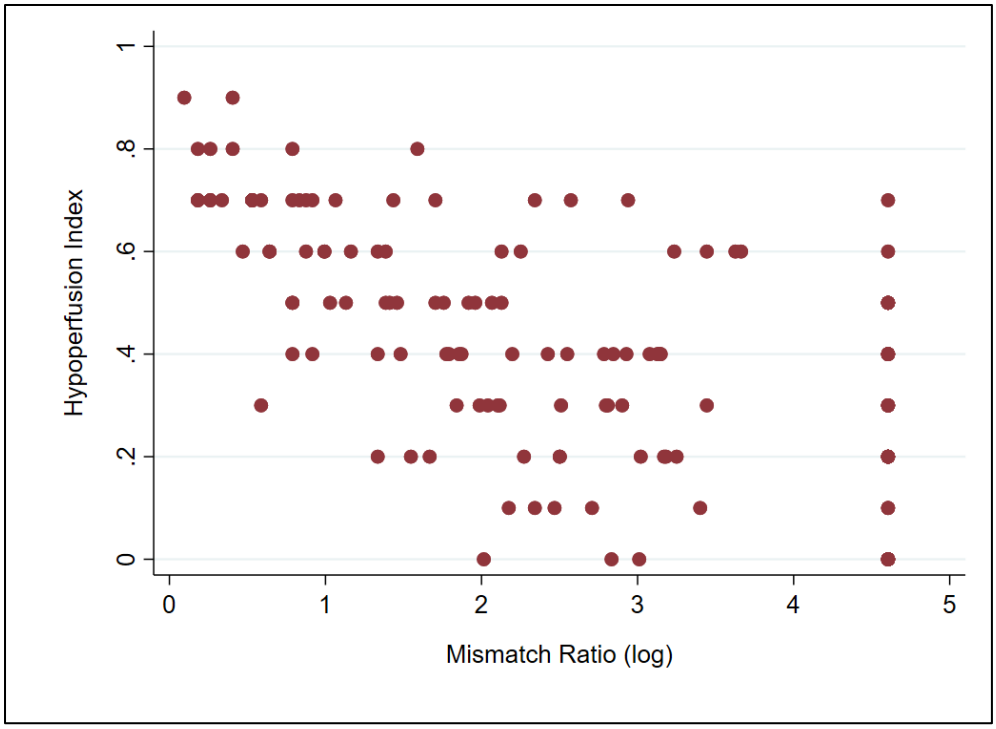

Figure 5.1. Relationship of hypoperfusion index and mismatc ratio; r = -0.4.

Association of HI to rate of infarct growth shows good sensitivity and specificity using receiver operating characteristic (ROC). ROC is a statistical method to illustrate the diagnostic ability of a binary classifier system as its discrimination threshold varies and thus compare predictors of outcome of interest. [22] In terms of imaging, it allows for appropriate comparison of a biomarker (HI) to identify dichotomous assessment of a disease state (fast or slow progressor) and to show the relevance that the new marker (HI) may improve upon existing ones. Application of ROC using an ideal imaging gold standard like serial scans will be the optimal way to study dynamics of infarct growth over time in future studies. Further investigations are therefore necessary to determine the accuracy, reliability, and reproducibility of clinical utility of novel CTP parameters like HI in evaluation of acute ischemic stroke.

The rate of infarct progression estimated by HI may be helpful to select MeVO patients for recanalization therapy. With a comparable rate of infarct progression to LVO, the implications of reperfusion in smaller MeVO strokes may be even greater due to earlier anticipated completion of stroke. Future trials of MeVO recanalization can help answer this knowledge gap. For LVO, a shorter transfer for potential recanalization with thrombolysis should be weighed against a longer transfer for thrombectomy between fast and slow progressors. Potentially patients with poor HI may derive greater benefit from early reperfusion as they are more likely to experience core progression and infarct growth without treatment.

To validate HI across different population cohorts, a direct comparison of HI to serial infarct growth in all type occlusions, posterior circulation strokes and in time windows beyond 24 hours should be explored. By validating its value to predict infarct growth, HI can be used to redefine the triage pathways that are most beneficial to the patients by having higher chances of potential early recanalization. This can also be tested in similar animal models of stroke. To add further, future randomized trials with selection of patients based on HI will be the most vigorous method to assess utility of HI in both evaluation of drip and ship versus mothership model, as well as patient selection for extended window thrombolysis and thrombectomy.

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Appendices

Appendix A. Ethics approval

EDMONTON ZONE
ADMINISTRATIVE APPROVAL FOR CLINICAL RESEARCH

All clinical research being conducted within the Edmonton Zone requires operational approval to access AHS areas and ethics approval by a recognized Alberta Research Ethics Board.
Other related documents may be required depending on the scope of the study.
Research in the Edmonton Zone cannot begin until Administrative Approval has been issued.

PROJECT: PRJ34092

Protocol Title: Genomics of Stroke and Neurological Disease

Principal Investigator:
Glen Jickling
Medicine & Dentistry
Medicine - Neurology

Funding Agency: CIHR (Canadian Institutes of Health Research)
Funding Type: Investigator-Initiated/Grant
Overhead Rate: 0%
Contract Finalized: Jan 06, 2020

Related Documents:	ID#	Status	Effective
Research Ethics:	Pro00066577	Approved	Sep 07, 2016
eClinician Access:	EC33003	Fully Executed	Sep 13, 2016
HSA Data Disclosure Agreement:	RA81915	Fully Executed	Jan 12, 2017

AHS Operational Approval: The following AHS areas have agreed to support your research. To gain access, you must have Edmonton Zone Administrative Approval.

33130: University of Alberta Hospital - Inpatient Neurology
33131: University of Alberta Hospital - Emergency Department
33132: University of Alberta Hospital - Stroke Clinic
33134: University of Alberta Hospital - Neural ICU
34816: University of Alberta Hospital - Laboratory Services

Edmonton Zone Administrative Approval

Approved: Oct 24, 2016
Approved By: Ron Welch
Director of Operations, NACTRC

Appendix B. Copyright agreement and disclosure

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