Imaging-based patient selection for intra-arterial stroke therapy

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Chapter 1

General Introduction
Introduction

Acute ischemic stroke, large vessel occlusion and intra-arterial therapy

Stroke is a major cause of death and disability worldwide. Approximately 90% are of the ischemic subtype (i.e., arterial blockage by thrombus), and of these up to 40% are secondary to occlusion of the major arteries supplying the brain (e.g., internal carotid artery [ICA] and proximal middle cerebral artery [MCA]). These large vessel occlusions (LVO) account for the preponderance of stroke-related morbidity, mortality and health care costs.1,3

During an acute ischemic stroke (AIS), arterial blockage leads to impaired energy metabolism and electrical failure in the ischemic brain which will manifest clinically as neurological deficits. Without removal of the thrombus and tissue reperfusion, the affected brain will progressively die over the next few hours leading to a growing volume of infarction or irreversible tissue injury. Timely reperfusion is the only proven treatment for AIS.

There are two reperfusion therapies demonstrated to be safe and effective for AIS: intravenous thrombolysis using recombinant tissue plasminogen activator (IV rt-PA), and intra-arterial therapy (IAT). Guideline recommendations mandate IV rt-PA treatment for eligible patients within 4.5 hours of stroke onset. However, for treatment of LVO, it has been known for some time that IV rt-PA is much less effective than IAT at opening the blockage, with rates of recanalization ranging from <10 to 30% depending on the level of occlusion. As a result, combined rates of death and dependence at 90 days among LVO patients treated with IV rt-PA alone are 60-70%. IAT is considered the primary treatment for LVO, and is delivered via catheters inserted into the peripheral arteries and navigated to the major brain arteries under x-ray fluoroscopic guidance. Mechanical devices are then introduced to ensnare and remove the thrombus. There has been a rapid evolution in the field of mechanical thrombectomy, with the newest generation devices, including stent retrievers and large bore aspiration catheters, achieving rates of substantial (>50% territory [mTICI 2b/3]) reperfusion in 70-80% of LVOs. In five recent randomized trials, IAT using these devices (primarily stent retrievers) produced dramatically improved outcomes over medical therapy alone, which included IV rt-PA in the vast majority of cases. In a subsequent individual patient meta-analysis of these trials, the number needed to treat (NNT) to reduce disability by one point on the modified Rankin Scale (mRS) for one patient was 2.6. Based on these data, IAT is now standard of care for LVO patients within 6 hours of onset. Nevertheless, further work must be done to improve the clinical response to thrombectomy, as 90-day rates of combined death and disability in the trials ranged between 40-67%.
Chapter 1

Brain parenchymal imaging

The core-penumbra model

The guiding principle of reperfusion therapy for AIS is to salvage threatened yet viable brain tissue. This region is termed the ‘ischemic penumbra’. Based on physiological studies in animals, there are two primary determinants of neuronal progression to cell death: the degree of ischemia or cerebral blood flow (CBF) reduction, and the duration of ischemia.\textsuperscript{18} With lower CBF (i.e., more severe), the duration of ischemia that the tissue can withstand before dying is shorter. The degree of CBF impairment is determined in turn by the strength of the pial collateral circulation, which is a network of tiny bypass vessels over the brain surface that can deliver blood in varying degrees from the periphery of the ischemic zone to the center. Because of this spatial arrangement, CBF is lower centrally, adjacent to the site of occlusion. Consequently, the deepest region is typically the first to die, and for this reason the area of infarction is termed the ‘ischemic core’. As time progresses, the infarct will grow in a centrifugal pattern into the penumbra. The pial collateral vessels are variable in number and size between individuals.\textsuperscript{19} Therefore, CBF in the affected brain can vary widely between stroke patients. This fact, along with the interdependence of CBF and time for determining neuronal viability, means that time from stroke onset alone cannot be used to reliably estimate infarct size. This has been demonstrated in acute MRI studies,\textsuperscript{20} and highlights the critical role of imaging to identify brain tissue that is dead (ischemic core) versus salvageable (ischemic penumbra).\textsuperscript{21}

Identifying the ischemic core

The purpose of infarct imaging is to identify large infarcts that are not likely to benefit, and may be harmed, from IAT. The ideal imaging method is fast, widely available and highly accurate for determining irreversible tissue injury. Unfortunately, there are tradeoffs between the currently available approaches. However, there are two essential criteria that must be met for clinical use. First, the imaging definition of infarction must have high specificity (>90%) in order to avoid the inappropriate exclusion of patients that are falsely deemed to have large infarcts. Second, the imaging criterion must have acceptable interobserver reliability, so that the imaging selection can be applied uniformly across medical centers.

Noncontrast CT (NCCT)

NCCT is the predominant stroke imaging tool because it is the fastest and most widely available modality. The physical principle behind CT scanning is that different tissues attenuate X-rays to varying degrees based on their electron density. Differences in X-ray attenuation are depicted on CT images using a gray scale, which depicts a measure of attenuation called the Hounsfield unit (HU). By convention, pure water is assigned an
HU value of zero. Less dense regions such as air (-1000 HU) appear darker on CT. Cortical bone has a density of approximately 1000 HU. During the first 3-6 hours from stroke onset (hyperacute window), the water content in severely ischemic tissue will increase progressively due to ionic and vasogenic edema. This produces tissue hypoattenuation (i.e., tissue becomes darker on CT), such that a 1% increase in tissue water corresponds to a 2-3 HU decrease in tissue density. This imaging finding is very specific (>90%) for irreversible parenchymal injury. Because gray matter is more vulnerable to ischemia and is 10-15 HU higher in density than white matter, infarct-related hypoattenuation is best appreciated in gray matter structures, manifesting as defects in the basal ganglia or loss of gray-white matter differentiation in the cortical and insular ribbons. The major limitation of NCCT for infarct detection is reduced sensitivity (20-75%) to subtle changes in brain water content. This impairs accurate delineation of infarct borders, particularly within the white matter, and thus prevents infarct volume determination in the hyperacute window. For this reason, a semiquantitative approach called ASPECTS (Alberta Stroke Program Early CT Score) has been adopted. Ten ASPECTS regions within the anterior circulation are evaluated (caudate, lentiform nucleus, posterior limb of the internal capsule, insula, and six cortical regions), with one point deducted for each region involved by ischemic hypoattenuation. The advantage of this approach is that 9 of the 10 regions contain gray matter, so that gray-white matter distinction can be inspected. Importantly, the interobserver agreement for ASPECTS grading of LVO patients has been demonstrated to be good.

MRI diffusion weighted imaging (DWI)

DWI is designed to measure the diffusion of water molecules, which is restricted when severe ischemia results in cellular energy failure and cytotoxic edema. It is the most accurate method to identify hyperacute infarction. The sensitivity and specificity of DWI for detecting infarction in the first 6 hours is above 90%. However, its primary drawback is limited availability for emergent stroke imaging. Although DWI can be acquired in 2 minutes using ultrafast echo planar imaging, screening to ensure MRI safety can be time consuming if in-hospital stroke workflow has not been optimized. One issue that has raised doubts regarding the clinical utility of DWI is potential reversal of diffusion restriction after early reperfusion. However, recent studies have demonstrated that this phenomenon is unlikely to be clinically significant. A post hoc analysis of DEFUSE 2 that examined 60 patients with baseline DWI lesions larger than 10 ml found that 32% had early (within 12 hours after IAT) DWI reversal of greater than 10 ml volume. In approximately half of these patients, there was no sustained reversal on final infarct imaging at 5 days. Most importantly, the median volume of permanent DWI reversal was only 3 ml, and only 3% of the study cohort had a final infarct volume smaller than the baseline DWI infarct volume. Early diffusion reversal was not an independent predictor of clinical outcome.
Given the high contrast-to-noise ratio (CNR) of DWI lesions, infarct boundaries are typically well-defined, and therefore, infarct volumes can be quantified easily. Moreover, the interrater agreement for DWI lesion volume measurement is excellent.\textsuperscript{31}

**CT perfusion (CTP)**

In order to improve the accuracy of CT for infarct detection, many investigators have examined the role of CTP for assessing tissue viability. CTP is a dynamic contrast imaging method which seeks to measure perfusion impairment within the ischemic tissue. A bolus of contrast (approximately 35-50 ml at 7 ml/sec) is injected via a large bore (18-20 gauge) intravenous line placed in the antecubital fossa. A few seconds after contrast injection, rapid and repeated cine imaging of a fixed brain volume is performed to image the first pass transit of contrast through the ischemic bed. This cine imaging should be carried out for at least 60-75 seconds to prevent truncation of the contrast concentration-time curve, which will lead to underestimation of cerebral blood volume (CBV). There are numerous methods to derive tissue-level perfusion parameters, which are broadly classified as deconvolution and non-deconvolution based. Deconvolution corrects for bolus delay and dispersion up to the level of a user-defined or automatically selected arterial input function, which is often placed at the proximal arteries. Using one of these methods, the raw CTP images are processed by dedicated software to produce visual maps of CBV, cerebral blood flow (CBF) and mean transit time (MTT) or time to maximum intensity of the tissue residue function (TMax).

Previous work has established thresholds for both CBV and CBF to define the ischemic core.\textsuperscript{32,33} However, this approach has been shown to have poor specificity for determining infarction, which raises significant concern regarding its use for treatment decision making. In 35 LVO patients in the MR CLEAN trial, a pairwise comparison of predicted infarct volume on baseline CTP and final infarct volume on NCCT within the first week demonstrated that a median 62\% (IQR 49-80\%) of the predicted infarct volume was not infarcted on the follow up imaging.\textsuperscript{34} Similar findings have been reported by other studies.\textsuperscript{35}

There are several challenges to using perfusion imaging for determining infarction. Based on physiologic studies, collateral flow is only one determinant of neuronal viability. Duration of ischemia (and probably tissue susceptibility or preconditioning) must also be considered. These data cannot be known with a sufficiently high degree of precision. Moreover, CTP provides a snapshot in time, and it is likely that CBF fluctuates from moment to moment. Another major challenge is the lack of standardization in CTP technique and post-processing which limits the generalizability of derived thresholds.\textsuperscript{36} Finally, there are numerous studies which show too much variability (or noise) within perfusion measurements to allow the reliable use of thresholds.\textsuperscript{37,38} Practically, this leads to low CNR, indistinct lesion borders and thus significant variability in infarct volume measurements.\textsuperscript{39}
Identifying the ischemic penumbra

The goal of identifying at-risk tissue is to determine whether there is a sufficient volume of tissue to salvage with reperfusion. For LVO and consideration of IAT, there are two primary approaches to this question.

Perfusion imaging mismatch

The penumbra must be distinguished not only from the ischemic core but also the outer region of benign oligemia, where CBF reduction is mild enough that the tissue can survive indefinitely without reperfusion. This boundary has been defined using various time measures and thresholds including relative MTT of at least 145% and Tmax delay of at least six seconds compared to the normal hemisphere. The latter definition was used in the recent IAT trials, although the exact mismatch criteria differed between trials. A post hoc subgroup analysis of MR CLEAN revealed that the CTP imaging mismatch utilized in EXTEND-IA did not modify treatment effect for both ordinal and dichotomized mRS endpoints. Beyond this finding, the aforementioned error inherent in perfusion measurement raises doubts regarding the clinical appropriateness of this technique.

Clinical-core mismatch

In the setting of LVO, the region of impaired CBF is typically large. Therefore, a substantial perfusion mismatch is virtually always present when there is occlusion of the intracranial ICA or MCA M1 segment and the infarct is not extensive enough to preclude treatment. This has been demonstrated in numerous studies. In place of a perfusion imaging mismatch, it has been proposed that a significant neurological deficit is a more discriminative approach to identify LVO patients who will do poorly absent successful reperfusion. The utility of a ‘clinical penumbra’ is supported by data from the PROACT II trial of intra-arterial thrombolysis. In this trial of proximal MCA occlusions, only patients with baseline NIHSS 11-20 demonstrated a significant benefit of IAT, with a signal of benefit among the smaller number of patients with NIHSS >20. The rate of good outcomes was equivalent in the treatment and control arms among patients with milder deficits (NIHSS 4-10). Among the positive RCTs of IAT, a clinical-core mismatch was utilized in REVASCAT and in the majority of patients enrolled in SWIFT PRIME.

Thrombus imaging

Imaging-based patient selection for stroke therapy has focused almost exclusively on the status of the brain parenchyma. However, treatment benefit assumes early and effective revascularization, and the direct target of reperfusion therapies is the thrombus. As such, thrombus attributes likely play an important role in the effectiveness of various revascularization strategies.
Primary thrombus characteristics include location, burden and composition. The most proximal vessel segment containing thrombus defines thrombus location, and is straightforward to determine on CT angiography (CTA). More proximal location is a proxy for greater thrombus burden,\textsuperscript{44,45} owing to the greater likelihood of larger thrombi to lodge more proximally within the vasculature. However, occlusion location may impact the success of revascularization beyond this association. Specifically, the worse collaterals seen with ICA terminus occlusions may impede reperfusion by decreasing blood pressure distal to the thrombus and potentially increasing thrombus impaction.

Direct measures of thrombus burden including length and volume may be obtained using various imaging approaches. On NCCT, visualization of the hyperdense thrombus is critically dependent on slice thickness. Numerous studies have shown that a slice thickness of 2.5 mm or less is necessary for adequate thrombus visualization.\textsuperscript{46-48} With thicker sections, partial volume effects from adjacent brain and cerebrospinal fluid may obscure the thrombus. Thrombus length has also been determined by measuring the contrast gap on CTA. However, it is necessary to use delayed images in the late venous phase to allow adequate time for the contrast to traverse the pial collaterals and reach the distal thrombus face, particularly when the collaterals are weak.\textsuperscript{49} Otherwise, thrombus length may be grossly overestimated. A semiquantitative method for determining thrombus burden on CTA is the clot burden score (CBS).\textsuperscript{50} In this scoring system, two points are deducted for lack of contrast opacification in each of the supraclinoid ICA, proximal MCA M1 segment and distal MCA M1 segment, and one point is deducted for lack of contrast in each of the M2 branches, the A1 segment and the infraclinoid ICA. A CBS of ten indicates no occlusion. Finally, blooming artifact on susceptibility-weighted MRI has been used to measure thrombus length.\textsuperscript{51,52}

Histologic examination of thrombi demonstrate varying proportions of fibrin, red blood cells, platelets and white blood cells, with calcification and endothelialization less common.\textsuperscript{45,53-55} Currently, imaging of thrombus composition is rudimentary. The hyperdense vessel sign on NCCT and blooming artifact within the vessels on susceptibility-weighted MRI have been associated with greater red blood cell content.\textsuperscript{53} However, more precise determination of thrombus composition is not possible. Nevertheless, studies have revealed that lower density thrombi are resistant to both intravenous and intra-arterial thrombolysis.\textsuperscript{56-58} The impact of thrombus attenuation on mechanical thrombectomy has been studied with mixed results.\textsuperscript{57,59,60}
Aims

This thesis is structured around two primary aims regarding the utility of imaging for improving outcomes of intra-arterial stroke therapy.
1. Can brain parenchymal imaging, specifically infarct volume, predict the clinical response to intra-arterial therapy, and if so, what are the optimal approaches to infarct imaging?
2. Can thrombus imaging provide insights into the angiographic and clinical response to intra-arterial therapy?

The first section begins with a comprehensive review of the literature concerning imaging selection for acute stroke reperfusion therapies (Chapter 2). This is followed by studies that seek to establish the prognostic role of infarct volume after IAT (Chapter 3), and to examine the utility of pre-treatment infarct volume on baseline MRI DWI for predicting the response to endovascular reperfusion (Chapter 4). Chapter 5 will examine the interaction of age and baseline infarct volume in predicting outcome after IAT. Chapter 6 is an investigation into the use of the NIH stroke scale for defining a clinical penumbra, and whether a clinical-core mismatch is appropriate. Chapters 7 and 8 explore whether infarct size on baseline NCCT using ASPECTS can predict outcome after IAT, and whether NCCT ASPECTS modifies intra-arterial treatment effect using data from the MR CLEAN randomized trial. CT-based methods for collateral imaging will be investigated as a means to improve hyperacute infarct detection over NCCT alone (Chapters 9-11).

The second section begins with an investigation into the previously described clot burden score, which is a semiquantitative method for determining thrombus burden on CTA, and its impact on outcomes in the MR CLEAN trial (Chapter 12). Chapter 13 is a post hoc analysis of the THERAPY randomized trial that seeks to determine whether hyperdense thrombus length on thin-section NCCT may be a prognostic and therapeutic biomarker for IAT.

The thesis concludes with a general discussion of the results, their implications and directions for future research.
Chapter 1

References


