Imaging-based patient selection for Intra-arterial stroke therapy

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Chapter 14

General Discussion
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Part I. Brain parenchymal imaging: Infarct volume, clinical-core mismatch and methods of infarct detection

The impact of infarct volume on outcomes after IAT and its utility for patient selection

The direct goal of reperfusion therapy is to halt the progression of infarct growth (Chapter 2). However, it is axiomatic that at some point, infarcts become too large for a reasonable chance at a meaningful clinical outcome. Therefore, the purpose of infarct imaging in LVO patients is to exclude those patients with infarcts that are too large to reasonably benefit from IAT. In order to quantify the relationship between infarct volume and outcome and to identify appropriate thresholds for treatment selection, it is best to examine final infarct volume (FIV) data. This is because baseline or pre-treatment infarct volumes continue to evolve, such that their relationship to long-term outcomes will also depend on the effectiveness of the revascularization strategy in question.

In an investigation of 107 anterior circulation LVO patients who underwent IAT (Chapter 3), FIV was the single best predictor of 90-day functional independence (mRS 0-2; c-statistic=0.86) and mortality (c-statistic=0.77). In multivariate analysis, only FIV and age were independent predictors of these endpoints. As expected, greater reperfusion produced smaller final infarcts. These findings support the critical role of infarct volume in shaping clinical outcome, and were confirmed by another study of IAT patients presenting with proximal MCA occlusions. Our study further explored infarct volume thresholds that would be useful for IAT selection, and found that FIV greater than 90-100 ml was highly specific (≥90%) for a poor outcome (90-day mRS 3-6). Less than 5% of patients with FIV >100 ml were independent at 90 days. It follows that if an LVO patient presents with a baseline infarct larger than this threshold, the chance of a good outcome will be very low, even with early reperfusion, because the infarct will only grow or at best remain stable.

This idea was supported by a proof-of-concept study of anterior circulation LVO patients imaged with MRI before IAT (Chapter 4). Reference standard DWI was used to determine pre-treatment infarct volume in 34 patients. Among six patients with large DWI lesions (>70 ml), all had a poor outcome (90-day mRS 3-6), with 3 deaths, despite successful reperfusion (mTICI 2-3) in half. Only the patients with smaller baseline infarcts demonstrated a clinical benefit from early reperfusion, supporting the utility of pre-treatment infarct volume for excluding patients in whom revascularization is unlikely to improve outcomes.
Infarct volume thresholds: Shifting lines in the sand?

As IAT devices continue to improve, reperfusion will be faster, more complete and achieved in a higher proportion of patients. These improvements will reduce intra-procedural infarct growth, and thereby, allow neurointerventionists to treat larger infarcts. This has been demonstrated in follow-up studies to our proof-of-concept investigation (Chapter 4). In one study, among 19 patients with baseline DWI lesion volume >70 ml, complete reperfusion was associated with an increased rate of good outcome (43% vs. 8%, P=0.12). This was further confirmed in a larger population of IAT patients, wherein good outcome (90-day mRS 0-2) was achieved in 36% of patients with pre-treatment DWI lesion volume >70 ml who underwent substantial reperfusion (mTICI 2b-3) versus 9% of those who did not (P=0.01). The most likely explanation for the difference between these subsequent studies and ours is that our study was performed before the availability of stent retrievers, resulting in a lower rate of complete reperfusion and longer time to reperfusion. Assuming the best case scenario of zero intra-procedural infarct growth, baseline infarct volume thresholds for treatment exclusion can be taken directly from FIV data. Indeed, in the study by Olivot and colleagues, the largest pre-treatment DWI lesion volume associated with a good outcome was 121 ml for patients who achieved complete reperfusion. This agrees strongly with our FIV data, where a volume >120 ml had 100% specificity for a poor outcome.

Additional factors will influence what infarct volume threshold is used for patient selection. Numerous studies have shown that in IAT patients, age is a major determinant of outcome in addition to infarct volume. In a post hoc analysis of the DEFUSE 2 study, which acquired MRI prior to IAT, only age and pre-treatment DWI lesion volume were independent predictors of outcome (90-day mRS 0-3) among the baseline variables studied (Chapter 5). Moreover, patient age has been shown to modify the relationship between infarct volume and outcome. Among 214 anterior circulation LVO patients treated with IAT, the optimal FIV threshold for predicting a good outcome decreased with increasing age (49 ml for age <70 years, 33 ml for 70-79 years and 15 ml for ≥80 years). The same investigators analyzed the impact of age on the maximal admission infarct volume compatible with good outcome after IAT (MALCOM), which they defined as the volume over which there was <10% probability of 90-day mRS 0-2. They found that among octogenarians this value was 15 ml versus 40 ml in younger patients. The reduced tolerance to infarct volume in older patients is likely related to a combination of increased comorbidities and stroke-related complications and reduced neuronal plasticity and social support among very elderly patients.

Infarct volume thresholds will also depend on the clinical endpoint of interest. Clearly, thresholds will be higher when favorable outcomes are defined less stringently, which might be necessary when studying more severe stroke populations. Moreover, thresholds will vary based on whether they are used for clinical trials versus practice. In
the former, the optimal infarct volume threshold should maximize both sensitivity and specificity to best discriminate outcomes and increase statistical power. In our FIV analysis (Chapter 3), this threshold was 50 ml. Supporting this idea, SWIFT PRIME initially excluded patients with admission infarct volume >50 ml, and demonstrated the largest absolute effect size among the recent phase III RCTs. On the other hand, for clinical practice, the goal is to maximize good outcomes. Hypothetically, if one neglects treatment risk, this could be achieved by treating all LVO patients, but this comes at the expense of treating (and potentially harming) nonresponders and clearly would not be cost effective. A more reasonable approach is to use a baseline infarct volume threshold that would exclude an acceptably low number of patients who might benefit from IAT, such as a population with a number needed to treat (NNT) of greater than 10. This is similar to the MALCOM concept, described above.

Can the ischemic penumbra be defined clinically?

In addition to excluding patients with large infarcts, it is necessary to identify LVO patients for whom there is a meaningful amount of tissue to save with reperfusion. The challenges to using perfusion imaging to define the ischemic penumbra were reviewed in Chapters 1 and 2. Alternatively, for LVO patients, a clinically meaningful penumbra can be inferred when there is a significant neurological deficit in the presence of a small baseline infarct (i.e., core-clinical mismatch). In order to establish an NIHSS threshold as a marker of a significant penumbra, a logical approach would be to exclude patients considered “too good to treat”, namely those with an excellent prognosis. Therefore, a study was undertaken in part to identify an NIHSS score below which all patients achieved a good outcome (Chapter 6). Of 54 anterior circulation stroke patients studied, all 17 (31%) patients with NIHSS <8 had good outcomes (90-day mRS 0-2), supporting a NIHSS threshold of ≥8 for patient selection. In support of this threshold, a previous study showed that AIS patients with NIHSS ≥8 had a significantly increased rate of neurological worsening. Furthermore, a study of MCA M1 occlusions with baseline DWI volume ≤25 ml found that baseline NIHSS ≥8 was the only independent predictor of >20% infarct growth. On the other hand, there was no significant association between perfusion imaging mismatch and infarct growth. Finally, SWIFT PRIME and REVASCAT, two positive RCTs of IAT, utilized a core-clinical mismatch for patient selection. In the former, the clinical penumbra was defined as NIHSS ≥8 and <30, while in the latter it was NIHSS ≥6.

Utility of NCCT ASPECTS for IAT selection

The major advantages of NCCT for AIS imaging are speed and widespread availability, as well as the high specificity for detecting hyperacute infarction. The primary limitations are the reduced sensitivity for assessing infarction compared to DWI and the inability to quantitatively measure infarct volume. In order to establish the utility of NCCT ASPECTS for IAT selection, a post hoc analysis of the pooled PICS-Pivotal dataset of IAT patients
treated with aspiration thrombectomy was performed (Chapter 7). It sought to determine whether baseline NCCT ASPECTS predicted outcome after IAT as well as the clinical response to endovascular reperfusion. Based on previous work, ASPECTS was trichotomized as 0-4, 5-7 and 8-10, with lower scores indicating larger infarcts. The primary finding was the dismal outcomes after IAT in the ASPECTS 0-4 group (n=40 patients), which demonstrated 5% rate of functional independence (90-day mRS 0-2), 55% mortality and 17.5% rate of symptomatic intracranial hemorrhage (sICH). A significant benefit of early reperfusion was seen in the 8-10 group, with a comparable signal of benefit in the 5-7 group. No benefit of reperfusion was seen in the 0-4 group. The utility of excluding LVO patients with baseline NCCT ASPECTS 0-4 from IAT was examined in a prespecified subgroup analysis of the MR CLEAN trial (Chapter 8). Among the 496 patients (of the 500 total trial patients) included in the study, there was no modification of IAT effect by trichotomized ASPECTS or by ordinal ASPECTS. In addition, there were no safety concerns with treating larger infarcts. Therefore, the analysis provided no justification for using NCCT ASPECTS for IAT selection. This is particularly relevant for the ASPECTS 5-7 patients, who have been excluded from treatment in many centers as a result of a post hoc analysis of PROACT II which demonstrated no benefit of IAT in patients with ASPECTS ≤7. In MR CLEAN, however, these patients had a strong suggestion of treatment benefit. Further data are needed to better estimate IAT effect in the ASPECTS 0-4 group, as there were only 30 (6%) such patients in the trial, likely resulting in an underpowered test for treatment interaction. Closer inspection of the data revealed that the potential treatment benefit in this group would likely be modest. Moreover, it confirmed the very poor prognosis in these patients (3% rate of 90-day mRS 0-2 and 40% mortality). Therefore, even if a significant relative treatment benefit were established for ASPECTS 0-4 patients, the absolute benefit would be constrained by the poor outcomes, leading to a high NNT and rendering treatment cost ineffective in these patients. Importantly, there was substantial interobserver agreement for ASPECTS grading among the MR CLEAN readers, which is consistent with the results of a previous study examining reliability of ASPECTS grading in LVO patients undergoing IAT. These results suggest that with appropriate training, ASPECTS grading can be performed in a consistent manner across different medical centers. However, a major challenge remains in the very early time window. A study by Bal and colleagues found that interobserver reliability for NCCT ASPECTS was poor in the first 90 minutes (intraclass coefficient [ICC]=0.48). This is because ionic and vasogenic edema typically develop in the 3-6 hour window, and therefore, ischemic hypodensity is often too subtle and difficult to detect at early time points.

**Improving infarct detection on CT: Collateral-based methods**

In an effort to improve the sensitivity of CT for acute infarct detection, numerous contrast based methods, including CTP, CTA source imaging (CTA-SI), and CTA collateral
grading, have been used to define the ischemic core. All of these methods rely on the pial collaterals for delivery of contrast to the ischemic bed. CTP is the most widely used of these techniques but it is also the most complex, and this complexity may itself be the source of the poor reliability and image noise described in Chapters 1 and 2.21 The other approaches are more straightforward and rely on fewer assumptions, but there has been relatively little investigation into their utility for infarct imaging. On CTA-SI, the region of tissue hypoattenuation in the ischemic brain reflects decreased capillary-level contrast filling, and has been proposed as the region of irreversible tissue injury. A study by Camargo and colleagues demonstrated that this approach was 100% specific for final infarction, with greater sensitivity than NCCT (70% vs. 48%).22 Another study found a very strong correlation (r=0.92) between lesion volumes on CTA-SI and DWI performed within six hours of onset and approximately one hour apart.23 However, with the advent of faster multidetector CT scanners and associated fast CTA protocols optimized for early arterial phase imaging, substantial overestimation of the DWI lesion by CTA-SI was noted in clinical practice. To investigate this relationship, lesion volumes on fast protocol CTA-SI and concurrent DWI were measured and compared in 48 consecutive AIS patients (Chapter 9).24 In pairwise comparison, CTA-SI lesion volumes significantly overestimated the DWI lesion volume, with greater than 25 ml difference observed in 29% of cases. The protocol dependence of the CTA-SI lesion volume was confirmed in a subsequent study of 100 anterior circulation stroke patients (Chapter 10).25 Shorter time from contrast injection to brain imaging was a predictor of substantial (≥20%) overestimation of the DWI lesion by CTA-SI, owing to insufficient time for the contrast to traverse the pial collaterals into the ischemic region. Notably, in 44% of cases, lesion volume on fast protocol CTA-SI was determined to be >100 ml when the corresponding DWI lesion volume was <100 ml, which would lead to inappropriate exclusion of many patients from treatment. In an exploratory analysis, a duration between contrast injection and imaging of at least 40 seconds produced the best agreement between CTA-SI and DWI lesion volumes. This finding must be validated, and subsequently CTA-SI protocols must be standardized before CTA-SI is used for infarct volume determination in the clinical setting.

CTA collateral grading entails a qualitative comparison of the number and regional extent of the distal cortical vessels between the ischemic and normal hemispheres. Unfortunately, there are numerous grading schemes, none of which have been correlated with the extent of tissue infarction.26 Therefore, a study was performed to identify a CTA collateral signature that would be highly specific for a large baseline infarct on DWI (Chapter 11).27 Based on clinical observation, a “malignant profile” was defined as absent collaterals in >50% of an M2 territory, which was felt to correspond to a tissue volume of 70-100 ml. Among 197 patients with intracranial ICA and/or MCA M1 occlusions, the malignant profile was >95% specific (and 55% sensitive) for a concurrent DWI lesion volume >100 ml, and 96% of these patients had poor outcomes (90-day mRS >2). There was excellent interobserver agreement for determining the
malignant collateral profile (kappa=0.83). Based on these results, this imaging approach holds great promise for improving the sensitivity of CT for detecting large infarcts when combined with NCCT ASPECTS 0-4. The importance of CTA collateral grading was recently confirmed by a subgroup analysis of MR CLEAN, which found a significant treatment modification by CTA collateral grade.\textsuperscript{38} In support of the malignant profile, MR CLEAN patients with absent collaterals in greater than 50\% of the MCA territory demonstrated a point estimate for IAT effect that approximated unity, suggesting that these patients are unlikely to benefit from IAT.

Part II. Thrombus imaging and its impact on the success of IAT

Recent advances in thrombectomy devices have resulted in marked improvements in the rates of substantial reperfusion (mTICI 2b-3). Nevertheless, in the recent trials of IAT, reperfusion was not achieved in up to 30-40\% of patients. In order to further improve revascularization rates, increased attention is being paid to thrombus characterization and understanding device-thrombus interaction. Thrombus imaging is currently in its early stages, but will play an increasingly important role in IAT research and practice.

The impact of CBS on outcomes after IAT

Current imaging techniques can provide estimates of thrombus burden. CBS is a semiquantitative measure that is easy to calculate on CTA images. Lower CBS (i.e., higher thrombus burden) has been associated with lower odds of functional independence, larger final infarct size and higher rate of parenchymal hematoma.\textsuperscript{29} An exploratory, post hoc analysis of the MR CLEAN trial was performed to evaluate the effect of CBS on outcomes and treatment effect of IAT (Chapter 12, unpublished). In 499 of 500 trial patients, higher CBS was associated with a higher likelihood of revascularization, smaller final infarct volume and better long-term functional outcome. CBS did not modify IAT effect for any of the endpoints. Therefore, CBS was a prognostic biomarker but not a therapeutic biomarker in the MR CLEAN dataset. However, it has been reported (personal communication, Dr. Andrew Demchuk) that a significant interaction between CBS and IAT was found in an analysis of the ESCAPE trial. Patients with CBS 0-4 had greater IAT effect than those with higher scores.

Hyperdense thrombus length versus outcome in the THERAPY trial

An alternative measure of thrombus burden is hyperdense thrombus length on thin-section (<2.5 mm) NCCT. This imaging finding was used as a selection criterion in the THERAPY trial, which was a randomized trial of bridging IAT versus IV rt-PA alone. To include subjects that would preferentially benefit from IAT, enrollment was restricted to patients with thrombus length ≥8 mm based on a previous study demonstrating that such patients were unlikely to respond to IV rt-PA.\textsuperscript{30} THERAPY was halted early after the
presentation of multiple RCTs demonstrating the efficacy of IAT. 108 patients of the planned 692 patients were enrolled. A post hoc analysis was performed to evaluate whether greater thrombus length was associated with larger IAT effect (Chapter 13, unpublished). In adjusted analysis, longer thrombi were associated with worse functional outcomes on the ordinal mRS scale, larger final infarcts, higher rates of sICH and serious adverse events, and increased mortality. Although there was no association between mTICI 2b-3 reperfusion and thrombus length in the IAT arm, the time to endovascular reperfusion was significantly longer in patients with longer thrombi. There was a significant modification of treatment effect, such that the benefit of IAT was greater with increasing thrombus length, supporting the study aim. This finding is consistent with the unpublished results of the ESCAPE analysis mentioned previously.

Recommendations for future research

The utility of pre-treatment infarct imaging has been recognized by the American Heart Association (AHA)/American Stroke Association (ASA) guidelines, which included NCCT ASPECTS ≥6 as a criterion for its Class I, Level A recommendation regarding IAT.31 However, numerous questions remain concerning the role of imaging to further improve the clinical response to IAT.

Does IAT benefit patients with large baseline infarcts?

Despite a strong biological rationale and supportive evidence from clinical imaging studies, there is uncertainty regarding whether patients with larger infarcts should be excluded from IAT, given the paucity of RCT evidence.31 For this reason, an RCT of IAT versus best medical management is needed for patients with large infarcts (NCCT ASPECTS 0-4 or DWI lesion volume ≥70-100 ml). Randomization should be stratified by patient age, as young patients have the greatest likelihood to benefit in such a trial. The primary endpoint should be improvement in ordinal mRS (Rankin shift) to ensure that beneficial shifts are not missed, particularly at the higher end of the mRS scale.

Is CT or MRI a better method for selecting patients for IAT?

DWI is the most accurate method for detecting hyperacute infarction,32,33 an advantage which may translate to improved patient selection for IAT, as recent studies have suggested. A post hoc analysis of DEFUSE 2 evaluated 74 patients who underwent both NCCT and DWI before IAT, and found that DWI ASPECTS predicted 90-day mRS 0-2 better than NCCT ASPECTS (c-statistic: 0.71 vs. 0.55, P=0.03).34 DWI ASPECTS had excellent inter-rater agreement whereas NCCT did not (ICC: 0.87 vs. 0.58). In another study, two patient cohorts were compared based on different imaging selection approaches for IAT.35 One group consisted of patients selected based on NCCT and CTA, and the other group were patients selected after the addition of hyperacute MRI, in whom NCCT, CTA and DWI were performed. The DWI group (both treated and non-
treated patients) had significantly higher rate of 30-day mRS 0-2 (23.6% vs. 9.1%), significantly lower mortality (25% vs. 48.5%) and nonsignificantly lower rate of PH2 hemorrhage (3.9% vs. 10.2%). These better outcomes were achieved despite substantially fewer patients being treated in the DWI group (51.7% vs. 96.6%). These results suggest that DWI excludes patients for whom IAT causes harm, namely those with large baseline infarcts. Therefore, MRI may improve the safety and cost-effectiveness of IAT.

Based on these studies, an RCT comparing CT- versus MRI-based selection for IAT is indicated. In such a trial, the entire population of treated and untreated patients in each arm must be compared. Moreover, imaging paradigms must be optimized before a trial is undertaken. Specifically, in-hospital stroke workflow and access to MRI must be streamlined. This includes early stroke alert activation for clearing the MRI scanner, rapid assessment of MRI safety, and presence of an in-house MRI technologist around-the-clock. Time delays related to MRI are due to these process issues rather than actual imaging time, which is often under 5-10 minutes depending on the sequences obtained.36, 37 Also, further work should identify CT approaches that will increase the sensitivity of infarct detection while preserving high specificity (>90%). One such approach might be to exclude patients who have either NCCT ASPECTS score of 0-4 or a malignant collateral profile on CTA.

How can we improve the relationship between infarct volume and outcome?

Future studies should evaluate whether age-adjusted infarct volume thresholds lead to better patient selection for IAT. In addition, adjustment of infarct volume thresholds based on health status and comorbidities should be explored. The THRIVE (Totaled Health Risks in Vascular Events) score incorporates age, NIHSS and the presence of hypertension, diabetes and atrial fibrillation, and has been demonstrated to be a strong prognostic marker in patients treated with mechanical thrombectomy.38 Finally, studies should investigate whether tissue eloquence improves the prognostic performance of infarct volume.

Can perfusion imaging improve IAT selection for M2 occlusions?

There is uncertainty regarding the efficacy of IAT for MCA M2 occlusions.31 One complicating factor is the variability of M2 anatomy, specifically whether an M2 branch is dominant (i.e., supplies the majority of the MCA territory) or not. Perfusion imaging is a sensitive measure of altered hemodynamics and can easily answer this question, allowing studies to investigate treatment effect by variations in M2 anatomy. Furthermore, because the M2 territory is smaller, there is a reasonable chance of identifying an imaging match between the infarct and the hypoperfused region. Such patients can be confidently excluded from treatment.
Can thrombus imaging improve angiographic outcomes?

There is strong evidence that larger thrombus burden is a negative prognostic marker for IAT. Therefore, new devices and techniques should be developed to specifically target these difficult to treat lesions. Moreover, the impact of thrombus density on angiographic outcomes should be investigated and compared to thrombus burden in the data from the recent RCTs of IAT. Finally, new imaging techniques to better characterize thrombus composition are needed.
References

General discussion
