The role of CT perfusion in patients selection for acute treatment

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Reperfusion therapies

- intravenous thrombolysis

- endovascular treatment:
  - intra-arterial thrombolysis
  - thromboaspiration
  - mechanical thrombectomy

- are the current available reperfusion therapies for acute ischemic stroke (AIS) patients

- reverse stroke symptoms and improve clinical outcome
is very rigid at this time
Patient selection

- only 15-20% of AIS patients are eligible for IV thrombolysis

- many AIS patients treated with reperfusion therapies (25-50%) do not achieve a good clinical outcome
it is at present believed that prognosis depends on imaging-to-recanalization time

< 60-90 min = favorable outcome?
The goals of neuroimaging

- to extend the therapeutic window
- to improve patient selection so as to identify patients who will benefit from reperfusion therapy
- to not delay reperfusion therapies
• is the method of choice for the selection of AIS patients for IV thrombolysis:

- is rapid, easily feasible and widely available

- detects stroke mimics (hematomas, tumors, seizures)

- implies a low radiation exposure and is not associated with iodinated contrast administration

- recognizes early ischemic changes (infarct core) by using ASPECTS (Alberta Stroke Program Early CT Score) that is a strong predictor of prognosis (ASPECTS > 7 = good outcome)

Muir KW et al. Lancet Neurol 2006; 5: 755-758
Merino JG, Warach S. Nat Rev Neurol 2010; 6; 560–571
Barber PA et al. Lancet 2000; 355; 1670-1674
Effect of Baseline CT Scan Appearance and Time to Recanalization on Clinical Outcomes in Endovascular Thrombectomy of Acute Ischemic Strokes

Mayank Goyal, MD; Bijoy K. Menon, MD, DM; Shelagh B. Coutts, MD; Michael D. Hill, MD, MSc; Andrew M. Demchuk, MD; for the Penumbra Pivotal Stroke Trial Investigators, Calgary Stroke Program, and the Seaman MR Research Center

Stroke 2011; 42: 93-97

Alberta Stroke Program Early Computed Tomography Score to Select Patients for Endovascular Treatment

Interventional Management of Stroke (IMS)-III Trial

Michael D. Hill, MD, FRCPC; Andrew M. Demchuk, MD, FRCPC; Mayank Goyal, MD, FRCPC; Tudor G. Jovin, MD, Lydia D. Foster, MSc; Thomas A. Tomsick, MD; Rüdiger von Kummer, MD; Sharon D. Yeatts, PhD; Yuko Y. Palesch, PhD; Joseph P. Broderick, MD; for the IMS3 Investigators

Stroke 2014; 45: 444-449

• is a promising tool for the selection of AIS patients for endovascular treatment due to the association between ASPECTS and clinical outcome
Limitations of NCCT

- not always AIS patients with ASPECTS > 7 achieve good outcome

- interobserver agreement for ASPECTS is moderate

References:
Demchuk AM et al. Stroke 2005; 36: 2110-2115
Dzialowski I et al. Stroke 2006; 37: 973-978
Wardlaw et al. Radiology 2005; 235: 444-453
Wardlaw et al. Stroke 2007; 38: 1250-1256
Limitations of NCCT

- NCCT does not identify the occlusion site that can affect treatment decision making = in large vessel occlusions, interventional procedures are superior than IV thrombolysis in achieving high recanalization rate and good outcome

- ASPECTS ignores the penumbra that is considered the target of reperfusion therapies

References:

Moustafa RR, Baron JC. Br J Pharmacol 2008; 153: S44-S54
Heiss W-D. Cerebrovasc Dis 2011; 32: 307-320
Ischemic penumbra

- is a region of critically hypoperfused, still viable and potentially salvageable tissue at risk for infarction if circulation is not restored

- without reperfusion, the infarct core expands into the penumbra over time ("time is brain")
to overcome the constraints of NCCT, a multimodal CT protocol has been proposed:

• is fast (acquisition time = 10 min + post-processing)

• is available in many centers
• demonstrates occlusion site

• indicates the thrombotic load (Clot Burden Score) → good association with outcome
  (CBS > 6 = good outcome)

Srinivasan A et al. Radiographics 2006; 26: S75-S95

CTA

- is able to assess collateral circulation
- shows the recanalization after treatment

Rha JH, Saver JL. Stroke 2007; 38:967-973
Jovin TG et al. Stroke 2011; 42: 2206-2211

Lima FO et al. Stroke 2010; 41: 2316-2322
• can identify:

1) total hypoperfusion (core + penumbra) = CBF or MTT lesion extent

2) infarct core = CBV lesion size

3) ischemic penumbra = CBF or MTT lesion volume - CBV lesion volume = mismatch CBF or MTT - CBV

CTP mismatch assessment

• visual inspection (qualitative)
  Muir KV et al. JNNP 2006; 77: 334-339

• CTP ASPECTS (semiquantitative)
  Lin K et al. AJNR 2008; 29: 931-936
  Sillanpaa N et al. Neuroradiology 2012; 54: 663-672
  Psychogios MN et al. Stroke 2013; 44: 2188-2193
  Lum C et al. Stroke 2014; 45: 2683-2688

• threshold-based volumetric analysis after tissue segmentation of grey matter/white matter (quantitative):
  penumbral maps (pixel)/target mismatch (ml)
  Wintermark M et al. Stroke 2006; 37: 979-985
  Murphy BD et al. Stroke 2006; 37: 1171-1177
  Murphy BD et al Radiology 2008; 247: 818-825
  Kidwell CS et al. Stroke 2013; 44: 73-79
CTP mismatch reproducibility

- good interobserver agreement for CTP visual assessment and ASPECTS


Finlayson O et al. Stroke 2013; 44: 234-236
CTP mismatch reliability

- In recanalized patients
  \[ \text{final infarct volume} = \text{CBV lesion size} \]
  (penumbra is salvaged)

- In persistent occluded patients
  \[ \text{final infarct volume} = \text{CBF or MTT lesion size} \]
  (penumbra transforms into infarction)

Wintermark M et al., Radiology 2009; 251: 619-626
**CTP mismatch prognostic value**

- **large CTP mismatch** = large penumbra + small core  \[\rightarrow\]  favorable prognosis

- **small CTP mismatch** = small penumbra + large core  \[\rightarrow\]  unfavorable prognosis

CTP post-treatment reperfusion

- CTP can measure reperfusion = the percentage reduction of baseline MTT lesion at 24 hours > 75%
- reperfusion is different from recanalization = sometimes are not associated
- reperfusion is a stronger predictor of good outcome than recanalization

Multimodal CT protocol safety

Dose Exposure of Patients Undergoing Comprehensive Stroke Imaging by Multidetector-Row CT: Comparison of 320-Detector Row and 64-Detector Row CT Scanners

BACKGROUND AND PURPOSE: Recently introduced 320-detector row CT enables whole brain perfusion imaging compared to a limited scanning area in 64-detector row CT. Our aim was to evaluate patient radiation exposure in comprehensive stroke imaging by using multidetector row CT consisting of standard CT of the head, CTA of cerebral and cervical vessels, and CTP.

MATERIAL AND METHODS: Organ doses were measured by using UF-TLDs located at several organ sites in an Allerton-Rando phantom. Effective doses were derived from these measurements. Stroke protocols including noncontrast head CT, CTA of cerebral and cervical vessels, and CTP were performed on 320- and 64-detector row scanners.

RESULTS: Measured effective doses for the different scanning protocols ranged between 1.61 and 4.56 mSv, resulting in an effective dose for complete stroke imaging of 7.52 (6.4 mSv (m/CT) for 64-detector row CT and 10.56 (10.6 mSv (m/CT) for 320-detector row CT. The highest organ doses within the area of the primary beam were measured in the skin (0.1 mGy) and cerebral hemispheres (0.91 mGy). Use of an eye-protection device resulted in a 54% decrease of the lens dose measured for the combo protocol for whole-brain perfusion with the 320-detector row CT scanner.

CONCLUSIONS: Phantom measurements indicate that comprehensive stroke imaging with multidetector row CT may result in effective radiation doses from 7.52 mSv (64-detector row CT) to 10.6 mSv (320-detector row CT). The technique of 320-detector row CT offers additional information on the time course of vascular enhancement and whole-brain perfusion. Physicians should weigh the potential of the new technique against the higher radiation dose that is needed. Critical doses that would cause organ damage were not reached.

Am J Neuroradiol 2010; 31: 1003-1009

Functional Contrast-Enhanced CT for Evaluation of Acute Ischemic Stroke Does Not Increase the Risk of Contrast-Induced Nephropathy

BACKGROUND AND PURPOSE: Concerns have recently grown regarding the safety of iodinated contrast agents used for CTA and CTP imaging. We tested whether the incidence of AN, defined by a >25% increase in the post-contrast serum creatinine level, was higher among patients with ischemic stroke who underwent a functional contrast-enhanced CT protocol compared with those who had no iodinated contrast administration.

MATERIALS AND METHODS: The contrast-exposed group consisted of 575 patients with acute ischemic stroke who underwent CTA (n = 313), CTA/CTP (n = 224), or CTA/CTP followed by conventional angiography (n = 386) within 24 hours of stroke onset and were consecutively enrolled in a prospective cohort study. The nonexposed group consisted of 2,483 patients with ischemic stroke, consecutively admitted to the same institution, who did not receive iodinated contrast material. Patients were stratified by baseline eGFR. In the primary analysis, the Fisher exact test was used to compare the incidence of AN between the contrast-exposed and the nonexposed patients at 24, 48, and 72 hours and on a cumulative basis. A secondary analysis compared the incidence of AN in patients who underwent conventional angiography following CTA/CTP versus patients who underwent CTA/CTP only.

RESULTS: The incidence of AN was 5% in the exposed and 16% in the nonexposed group (P = .003). Patients who underwent conventional angiography after contrast CT were at no greater risk of AN than patients who underwent CTA/CTP alone (28 patients, 5%; and 2 patients, 5%, respectively, P = .7).

CONCLUSIONS: Administration of a contrast-enhanced CT protocol involving CTA/CTP and conventional angiography in selected patients does not appear to increase the incidence of CIN.

Am J Neuroradiol 2010; 31: 817-821

- radiation dose (7.52 mSv) is lower than critical values when recommended parameters (80 KV, 100 mAs) are used

- contrast administration is without risks
Multimodal CT protocol delay

**BACKGROUND AND PURPOSE:** Patients with acute ischemic stroke require immediate medical treatment, and a CT is required before ICA. We adopted our protocols to include multimodal CT: unenhanced CT, CTA, and PCT. The purpose of this study was to determine whether multimodal CT imaging delays initiation of IV tPA beyond 60 minutes from hospital arrival.

**MATERIALS AND METHODS:** All patients admitted during 3 years through the ED with a stroke alert and time from symptom onset to hospital arrival <3.5 hours were included. We examined 2 subgroups: multimodal CT versus unenhanced CT; to determine whether multimodal CT delayed ICA administration. Logistic regression was used to identify variables that predicted ICA within 60 minutes.

**RESULTS:** There were 123 patients in the analysis, including 108 patients who were examined with multimodal CT. The median time from arrival to ICA was 56 minutes and was shorter for patients examined with multimodal CT (62 versus 78 minutes, P < .05). After adjustment, variables that were associated with ICA administration within 60 minutes included prehospital stroke alert (OR 3.47, P = .03), time to CT ICA = 0.84, P = .01), and onset-to-arrival time (OR 1.02, P = .04). There was no statistically significant difference in the odds of receiving timely ICA for multimodal versus unenhanced CT (OR 3.99, P = .27).

**CONCLUSIONS:** In our single-center experience, the use of multimodal imaging in patients with acute stroke did not delay IV tPA beyond 60 minutes. Further study is needed to assess the feasibility of the routine use of multimodal imaging in the acute setting.

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**Advanced modality imaging evaluation in acute ischemic stroke may lead to delayed endovascular reperfusion therapy without improvement in clinical outcomes**

Kevin N Sheth,1 John B Terry,2,3 Raul G Nogueira,4,5 Anat Horev,6 Thanh N Nguyen,7 Albert K Fong,8 Dheeraj Gandhi,9 Shyam Prabhakaran,10 Dolores Wisco,11 Brenda A Glenn,4,5 Ashish H Tayal,12 Bryan Ludwig,2,3 Muhammad Shazam Hussain,11 Tudor G Jovin,6 Paul F Clemmons,13 Carolyn Cronin,1 David S Liebeskind,8 Melissa Tian,12 Rishi Gupta4,5

*Am J Neuroradiol 2011; 32: 864-868*

*J NeuroIntervent Surg 2013; 5: i62–i65*

**if multimodal CT protocol delay therapeutic intervention is still debated**
• there was a shift from a temporal concept (“time is brain“) to a physiological model (“penumbra is brain“)

• it is not important how much time has elapsed from symptom onset, but how much penumbra is still present
Encouraging first results

• after IV thrombolysis within 6 hours from onset, good outcomes were achieved more frequently in patients with than in those without CTP mismatch

• after endovascular treatment within 8 hours from onset and beyond, patients with CTP mismatch were more likely to have good outcomes than those without

Stroke 2011; 42: 2206-2211

The failure of clinical trials

Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion–diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study


Lancet Neurol 2009; 8: 141-150

A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

Chelsea S. Kidwell, M.D., Reza Jahan, M.D., Jeffrey Gornbein, Dr.P.H., Jeffry R. Alger, Ph.D., Yal Ninov, Ph.D., Zahra Ajani, M.D., Lei Feng, M.D., Ph.D., Brett C. Meyer, M.D., Scott Olson, M.D., Lee H. Schwamm, M.D., Albert J. Yoo, M.D., Randolph S. Marshall, M.D., Philip M. Meyers, M.D., Dileep R. Yavagal, M.D., Max Wintermark, M.D., Judy Guzy, R.N., Sidney Starkman, M.D., and Jeffrey L. Saver, M.D., for the MR RESCUE Investigators

N Engl J Med 2013; 368: 914-923

• after IV thrombolysis within 9 hours from onset, outcomes were comparable between patients with and without CTP mismatch

• after endovascular treatment within 8 hours from onset, patients with and without CTP mismatch had equivalent outcomes

these surprising findings have some potential explanations
Lack of standardization

- different commercial software programs provide different CTP absolute values

- the definitions of CTP mismatch are extremely variable in the different studies

Kudo K et al. Radiology 2010; 254: 200-209

Dani KA et al. Ann Neurol 2011; 70: 384-401
Imprecision of CBV in defining core

- not always CBV lesion size corresponds to final infarct volume

- hyperemia often occurring in penumbra region can mask infarct core = underestimation of CBV lesion

- too short acquisition time leading to bolus truncation = overestimation of CBV lesion (a two-phase acquisition protocol is needed)


Inaccuracy of MTT in defining ischemia

- MTT lesion includes hypoperfused regions of benign oligoemia = overestimates penumbra extent

Kamalian S A et al., Am J Neuroradiol 2012; 33: 545-549
Core as determinant of outcome

Jovin TG et al. Stroke 2003; 34: 2426-2435

• prognosis could be dependent on infarct core (CBV) volume and not on penumbra (CTP mismatch) extent
The new CTP mismatch

- the old CTP mismatch concept has recently been replaced by a new one:

1) total hypoperfusion (core + penumbra) = Tmax lesion extent

2) infarct core = CBF lesion size

3) ischemic penumbra = Tmax lesion volume - CBF lesion volume = mismatch Tmax - CBF
Visualization of the new CTP mismatch

- infarct core is rapidly visible at visual assessment only after setting of CBF maps with appropriate absolute threshold values

- these thresholds still remain to be definitively identified for many software programs
The old CTP mismatch strikes back

- very recent studies have demonstrated that MTT - CBV mismatch:
  - remains a determinant of functional outcome
  - is effective for the selection of patients for endovascular treatment
  - is useful to evaluate the amount of salvaged penumbra after endovascular therapy
What can we do?

Which type of CTP mismatch we have to use in clinical practice?

- we could visually assess both the old and new mismatches simultaneously by applying the absolute threshold values to CTP maps which are currently available for obtaining complementary information to better identify infarct core and ischemic penumbra.
Waiting for PROVE-IT findings

**Precise and Rapid assessment of collaterals using multi-phase CTA in the triage of patients with acute ischemic stroke for IA Therapy (PRove-IT)**

Bijoy K. Menon, MD

Calgary Stroke Program, Department of Clinical Neurosciences, University of Calgary; Department of Radiology, University of Calgary; Department of Community Health Sciences, University of Calgary; Hotchkiss Brain Institute;

*a multicenter study that aims at:*

- verifying the prognostic value of collaterals measured by a multi-phase CTA technique

- finally establishing CTP core and penumbra absolute values
CTP increases diagnostic accuracy and confidence compared to NCCT independently on the definition of infarct core and ischemic penumbra.

better detection territorial ischemic regions of hypoperfusion = improvement of patient selection
Our protocol (onset)

• NCCT = detection and quantification of early ischemic changes (ASPECTS)

• CTA = identification of occlusion site + evaluation of clot burden + collaterals

• CTP = assessment of ischemic lesion size + presumed infarct core and ischemic penumbra extent
Our protocol (24 hours)

- **NCCT** = assessment of final infarct volume + detection of hemorrhagic transformation

- **CTA** = evaluation of recanalization status

- **CTP** = demonstration of reperfusion grade
THANK YOU FOR YOUR ATTENTION