Acute Stroke Treatment
Collaterals in Acute Ischemic Stroke

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Objectives
- role of collaterals in acute ischemic stroke
- collateral therapeutic strategies

framework for flow

framework & basis for flow
- stroke 2013
- dynamic aspect of cerebral ischemia, artificial separation of phases in ischemic stroke
- continuum of flow or homeostasis of brain perfusion
- serial imaging may capture evolution of injury and impact of reperfusion
- imaging core infrastructure now exists to measure angiographic and tissue biomarkers of ischemia
stroke 2013

- prevention
  - recognition of numerous vascular risk factors from hypertension to glucose intolerance to dyslipidemia
  - embolic source and microvascular disease
  - novel anticoagulants, devices, and other therapies
- optimal medical therapy
- paradoxical omission of hypoperfusion and ischemia

remainder of lecture on flow
bias regarding collaterals

time is not brain!

- across population of stroke cases studied from onset to chronic phase, not in a given patient during early phases
- time of symptom onset ≠ time of vascular occlusion
- collaterals prone to failure over time

Early DWI

- 307 stroke patients (mean age 69 ± 17 years, 51% female) from 2004-2012 had DWI with TLKW < 4.5 hours (mean 147 ± 62 min)
- DWI lesion volume (median 3.76 cm³) varied extensively (TLKW: DWI < 1 hour [n=98] 5.40 cm³ [0.9-28.9], 1-2 hours [n=126] 3.12 cm³ [0-263], 2.5-3 hours [n=39] 2.11 cm³ [0-103], 3.5-4.5 hours [n=98] 6.16 cm³ [0-227])
- Negligible correlation (r=0.175, p=0.002) noted for DWI lesion volume and TLKW-DWI time duration
- DWI-negative findings < 4.5 hours occurred in 8.5%
- Malignant strokes (>70 cc) were noted in 7.5%
- Older age was associated with DWI-negative strokes (mean 77 vs. 68 years, p=0.013)
- TLKW-DWI time duration was unrelated to DWI-negative strokes, yet malignant strokes were more common later (p=0.009)
- Majority of malignant strokes on DWI had TLKW during daytime

flow determines time

- If collaterals compensate for arterial occlusion or stenosis, symptoms may be negligible or absent
- Pace of collateral recruitment may influence the timeline of symptom progression
- Poor collaterals may predispose to impaired reperfusion
  - no reflow
  - reperfusion injury or hemorrhagic transformation

continuum and homeostasis of flow

balance of antegrade flow and collateral perfusion
cerebral arteriogenesis
- process of collateralization
- pressure drop
- reverse flow
- increased shear stress
- cytokine release
- hypertension
- vascular remodeling

imaging infrastructure
- serial imaging routinely used in clinical practice
- saga of imaging in stroke trials...
- secondary to clinical outcomes
- exploratory or ancillary
- impact of funding source, cost, implications
- systematic, prospective versus retrospective
- imaging insurance on understanding pathophysiology
- ongoing, large-scale imaging core lab activities

prehospital neuroprotection

neuroprotection
- early ischemia in FAST-MAG
- neuroprotection via collaterals
- combined neuroprotection and revascularization

FAST-MAG
- Los Angeles and Orange Counties
- Ethnically diverse population 13.3 million
- 59 receiving hospitals
- 353 rescue ambulances
- 3300 paramedics
- >400 emergency physicians
- >100 neurologists, neurosurgeons

Chain Cell Forwarding System
- English-Line First On-Call Investigator
- Spanish-Line First On-Call Investigator
- English-Line Second On-Call Investigator
- Spanish-Line Second On-Call Investigator
- English-Line Third On-Call Investigator
- Spanish-Line Third On-Call Investigator

Voice-Over-Internet Phone (VOIP) System
- Direct Call to VOIP System in English Line (Blue) and Spanish Line (Red)
FAST-MAG (n=1470)

- currently enrolled n=1584 (6/18/12)
- age 69 (range 39-95)
- female 42%
- index event diagnosis
  - cerebral ischemia 71.9%
  - intracerebral hemorrhage 24.4%
  - stroke mimic 3.7%
- stroke severity
  - LAMS (prehospital) 4.0 (range 1-5)
  - NIHSS (hospital arrival, after Rx start) 11.4 (range 0-40)

FAST-MAG times (n=1470)

- stroke onset to study drug (median) 46 mins
- paramedic arrival on scene to drug (mean) 25 mins
- paramedic arrival on scene to ED (mean) 35 mins
- treated within 1 hour of onset 73%
- treated 1-2 hr after onset 24%

FAST-MAG imaging

- Initial ASPECTS median 9 (IQR 8-10) to 7 (IQR 4-9) at 24 hrs

penumbral neuroprotection

thrombolysis
extending thrombolysis
- intravenous thrombolysis – early and late
- baseline imaging patterns predict response
- revascularization – recanalization and reperfusion
- serial imaging of thrombolysis
- hyperperfusion and hemorrhage

early and late – time matters?

Key Results of the DEFUSE Study
- **Target Mismatch** pattern (49%)
  - Benefit substantially from early reperfusion
- **Match** pattern (15%)
  - No benefit from early reperfusion
- **Small DWI / PWI lesions** (28%)
  - Associated with favorable outcomes
- **Malignant MRI** pattern (8%)
  - Predicts severe ICH following reperfusion

ASPECTS

Bayesian PWI – collateral perfusion

ASL & DSC MRI
definitive reperfusion

recanalization & reperfusion

HASTIER

defining definitive reperfusion
- reperfusion of downstream tissue
- angiographic measures of TICI and collaterals
- endovascular therapies
- serial imaging of reperfusion injury
- definitive reperfusion with good clinical outcome

TICI

Grade 0: No Thrombus: The adequate flow beyond the point of occlusion.
Grade 1: Partial Thrombus (Minor Thrombus): The contrast medium passes beyond the area of obstruction but fails to opacify the entire contrast-filled blood pool in the region of the occlusion or aggregate clot.
Grade 2: Partial Thrombus: The contrast medium passes beyond the occlusion and opacifies the arterial bed distal to the occlusion. However, the rate of entry of contrast into the normal bed is slower than the rate of clearance from the distal bed and appears to have a slower entry and clearance than comparable areas not perfused by the previously occluded vessel, i.e., the opacified contrast lying in the arterial bed proximal to the occlusion.
Grade 2a: One or more minor branches are not or minimally reperfused.
Grade 2b: Complete filling of all the occluded vessels is visualized, but the filling is slower than normal.
Grade 3: Complete Thrombus: Adequate flow into the bed distal to the occlusion, as well as into the occluded and occluded branches of the vessel proximal to the lesion is seen as fast as from an unoccluded vessel of the same caliber or of the opposite internal carotid artery.
TREVO 2 vs. SWIFT: Differences

Baseline Definition
sICH “Roll number” – In
mRS Efficacy
Phase None 2
MR RESCUE
Recanalization
Successful
Revascularization TICI
regardless of treatment assignment
infarct growth, compared with nonpenumbral pattern,
Improved outcomes, smaller infarct volumes, attenuation
deterioration.

TICI 2a, 2b, or 3 at completion of procedure
Any or NIHSS ≥ 4, associated with death
≥ 2/3 brain/cranium hemorrhage, or intraventricular hemorrhage associated with ≥ 1 TICI 2a, 3
Any or NIHSS ≥ 4, associated with death
≥ 2/3 brain/cranium hemorrhage, or intraventricular hemorrhage associated with ≥ 1 TICI 2a, 3

Favorable Clinical Response
All point improvement in NIHSS at day 30 or NIHSS of ≤ 2 at day 30

Reperfusion
(PSW criteria)** in patients with a major vessel occlusion (TICI 0 or 1) on baseline imaging
Reperfusion (DSA criteria)** TICI 2b or 3 at completion of procedure

Note:
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TREVO 2 vs. SWIFT: Comparisons

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TREVO 2 (n=88)</th>
<th>SWIFT (n=90)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mRS 0-3 at 90d</td>
<td>49.4%</td>
<td>52.9%</td>
<td>0.220</td>
</tr>
<tr>
<td>Recanalization*</td>
<td>96.5% (83/85)</td>
<td>86.4% (76/88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 6s)</td>
<td>68.5% (54/80)</td>
<td>60.0% (32/53)</td>
<td>0.186</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 10s)</td>
<td>65.3% (52/80)</td>
<td>52.9% (31/59)</td>
<td>0.085</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 15s)</td>
<td>62.3% (52/83)</td>
<td>56.4% (31/55)</td>
<td>0.489</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 20s)</td>
<td>59.3% (51/85)</td>
<td>51.1% (29/57)</td>
<td>0.211</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 30s)</td>
<td>56.4% (47/83)</td>
<td>48.9% (27/55)</td>
<td>0.166</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 60s)</td>
<td>53.4% (46/87)</td>
<td>46.2% (25/54)</td>
<td>0.308</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 180s)</td>
<td>49.4% (43/87)</td>
<td>42.5% (23/55)</td>
<td>0.729</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 360s)</td>
<td>46.2% (40/87)</td>
<td>39.5% (22/56)</td>
<td>0.213</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 720s)</td>
<td>43.4% (37/86)</td>
<td>37.9% (21/56)</td>
<td>0.308</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 1440s)</td>
<td>40.4% (34/85)</td>
<td>34.1% (20/59)</td>
<td>0.321</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 2400s)</td>
<td>37.3% (31/84)</td>
<td>30.2% (17/56)</td>
<td>0.566</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 3600s)</td>
<td>34.3% (28/82)</td>
<td>27.3% (15/55)</td>
<td>0.308</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 4800s)</td>
<td>31.3% (25/80)</td>
<td>23.3% (13/56)</td>
<td>0.489</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 6000s)</td>
<td>28.3% (22/78)</td>
<td>16.2% (9/56)</td>
<td>0.166</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 7200s)</td>
<td>25.3% (19/76)</td>
<td>9.1% (5/55)</td>
<td>0.003</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 8400s)</td>
<td>22.3% (16/73)</td>
<td>6.1% (4/65)</td>
<td>0.068</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 9600s)</td>
<td>19.3% (13/68)</td>
<td>4.6% (3/66)</td>
<td>0.020</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 10800s)</td>
<td>16.3% (12/74)</td>
<td>2.1% (2/95)</td>
<td>0.400</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 12000s)</td>
<td>13.3% (10/76)</td>
<td>0.5% (1/196)</td>
<td>0.001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 13200s)</td>
<td>10.3% (8/78)</td>
<td>0.1% (1/975)</td>
<td>0.001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 14400s)</td>
<td>7.3% (6/83)</td>
<td>0.2% (1/537)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 15600s)</td>
<td>4.3% (3/71)</td>
<td>0.2% (1/537)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 16800s)</td>
<td>1.3% (1/75)</td>
<td>0.1% (1/537)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 18000s)</td>
<td>0.3% (1/33)</td>
<td>0.1% (1/537)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 19200s)</td>
<td>0.3% (1/33)</td>
<td>0.1% (1/537)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 20400s)</td>
<td>0.3% (1/33)</td>
<td>0.1% (1/537)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 21600s)</td>
<td>0.3% (1/33)</td>
<td>0.1% (1/537)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 22800s)</td>
<td>0.3% (1/33)</td>
<td>0.1% (1/537)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MSA 2.0: MRIs (PWI ≥ 24000s)</td>
<td>0.3% (1/33)</td>
<td>0.1% (1/537)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Note:
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MR RESCUE

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IMS III

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Collateral grade was strongly associated with:
- recanalization (AOL)
- reperfusion
- discharge location
- disability or good clinical outcome at Day 90

Collateral grade was unrelated to:
- hemorrhage within 30 hours of IV tPA initiation
- death within 90 days

Collaterals, SICH and outcome
- Partial or worse collaterals were associated with symptomatic hemorrhage ($p=0.075$).
- Better collaterals were linked with TICI 2b/3 reperfusion ($p=0.019$), better median NIHSS at Day 7/discharge ($p<0.001$) and better Day 90 mRS ($p<0.001$).
- Better collaterals were noted in patients with successful revascularization without symptomatic hemorrhage, mean 2.3 (95% CI 2.1-2.5) vs. 1.9 (95% CI 1.7-2.2), $p=0.021$.

ASPECTS of collaterals
- Collaterals were strongly related to ASPECTS at baseline ($p<0.001$):
  - 0-1 - median 5 (3-10)
  - 2 - 9 (5-10)
  - 3 - 9 (7-10)
  - 4 - 9 (8-10)

impact of collaterals
- smaller strokes
  - baseline DWI lesion volume ($b=0.025$, $p=0.001$)
- more reperfusion
  - higher TICI reperfusion rates ($b=0.191$, $p=0.045$)
- less hemorrhage
  - lower hemorrhagic transformation rates ($b=-0.229$, $p=0.015$)
- better clinical outcomes
  - mRS at discharge inversely correlated with collateral grade ($b=-0.317$, $p=0.001$)

TREVO2 imaging details
- 166/177 cases in TREVO2 were anterior circulation occlusions.
- Baseline ASPECTS was ≤7 in 83/166 (50%) cases.
- Baseline ASPECTS scores ≤7 was unrelated to age, gender, or any other clinical parameter other than NIHSS score (median 17 (17-23) vs. 17 (15-20) for ASPECTS ≤ 7, $p=0.010$) and clot location (more ICA than M2 occlusions, $p=0.044$).
- Univariate imaging predictors of good clinical outcome at day 90 included baseline ASPECTS ($OR\ 1.89, p=0.001$), baseline ASPECTS ≥ 8 ($OR\ 2.54, p=0.006$), collateral grade ($OR\ 1.68, p=0.008$), post procedure TICI ($OR\ 2.11, p=0.001$), 24-hour ASPECTS ($OR\ 1.47, p=0.001$) and 24-hour ASPECTS ≥ 8 ($OR\ 4.38, p=0.001$).
- Time to TICI 2a or greater was not predictive.
- Multivariate analyses showed that 24-hour ASPECTS (OR 1.70, $p=0.003$) and post procedure TICI (OR 2.49, $p=0.003$) best predicted good outcome.

TREVO2 – perfusion angiography
flow from prehospital to reperfusion

Serial ASPECTS as a Novel Endpoint
ASPECTS change from 8 at baseline to 3 at 24 hrs

collaterals & hemorrhage in AIS

definitive reperfusion
- qualified by clinical outcome at day 90, not arbitrarily defined as effective
  - optimal degree of TICI reperfusion unestablished (2a or 2b?)
  - SICH ignores other forms of hemorrhage
  - reperfusion injury unexplored
  - vessel-specific definitions (ICA, M1, M2)

conclusions & collaterals

conclusions
- framework for flow exists
- homeostasis of flow, balanced by collaterals
- hemodynamics as future of ischemic stroke