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Perfusion imaging in Pediatric Acute Arterial Ischemic Stroke

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Stanford Stroke Center / Stanford Children's Health

ASN Conference, January 2021



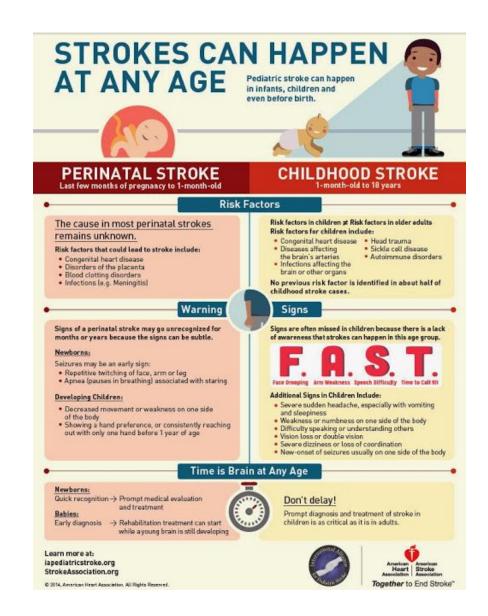
Disclosures

- Financial: None
- Intravenous alteplase and mechanical thrombectomy in children is not FDA-approved and considered investigational/compassionate use only



Background

- Childhood incidence: 2-13/100,000/year, 50% ischemic
- 5000 new cases in the US/year
- Hospitalizations for pediatric arterial ischemic stroke on the rise....
 - Better quality/access to diagnostic imaging
 - Increased survival of children with cardiac, metabolic disease





Background

- Cerebrovascular disease is among the top ten causes of death in young people
 - 65% of children with lasting motor deficits
 - 1/3rd develop epilepsy
 - Lasting deficits in cognition, language, executive function
 - Incidence of LVO in children is not known, but studies suggest that children with large artery territory infarction have poor long-term outcomes
- High cost of care
 - \$42,338: Median cost of care 1 year post-stroke
 - \$135,161: Average adjusted 5-year cost of childhood stroke





Background

- Cerebrovascular disease is among the top ten causes of death in young people
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 - \$42,338: Median cost of care 1 year post-stroke
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An intervention that could reduce or eliminate disability in children with stroke would have a major, lasting impact on individual and society



3.5.2. Time Windows	COR	LO	E		3.7.2. 0 to 6 Hours From Onset COR LOE	
1. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 8 to determine patient eligibility.		A			1. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset. I A	
2. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minut 10% of dose given as bolus over 1 minute) is also recommen patients who can be treated within 3 and 4.5 hours of ischen symptom onset or patient last known well or at baseline stat should review the criteria outlined in Table 8 to determine pa	nded for sele mic stroke te. Physiciar	ected ns	I	B-R	2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	B-R
3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on	lla	B-R	Ī		 2. Direct aspiration thrombectomy as first-pass mechanical thrombectomy is recommended as noninferior to stent retriever for patients who meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or M1; (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS ≥6; and (6) treatment initiation (groin puncture) within 6 hours of symptom onset. 	B-R
FLAIR. 1. In patients eligible for IV alteplase, benefit of therapy is time	e dependent,	and			3.7.3. 6 to 24 Hours From Onset COR LOE	
treatment should be initiated as quickly as possible.			I.	A	1. In selected patients with AIS within 6 to 16 hours of last known normal who have LV0 in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended. I A	
3.6. Other IV Fibrinolytics and Sonothrombolysis 1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg,	COR	LOE			2. In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.	
maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	Ш	B-R	5	20 10	X	T



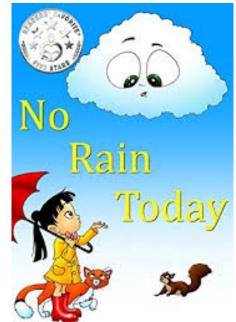


... no clear guidelines for children

AHA/ASA Scientific Statement

Management of Stroke in Neonates and Children A Scientific Statement From the American Heart Association/American Stroke Association

"In the absence of pediatric clinical trial data to guide treatment decisions, hyperacute therapies for childhood AIS remain controversial..."



Perfusion imaging identifies adult patients with salvageable tissue who will benefit from reperfusion

- DEFUSE 3: Thrombectomy 6-16 hours from last known well in patients with Target Mismatch on PWI: 28% increase in functional independence, 20% aRR in death or disability
- DAWN: Thrombectomy 6-24 hours from last known well in patients with clinical-core mismatch: 35.5% absolute increase in functional independence
- 2019 AHA guidelines: in acute stroke patients with LVO presenting 6-24 hours from last known well, <u>obtaining perfusion imaging (CTP or MRP) is recommended</u>; thrombectomy is recommended if they meet DAWN or DEFUSE 3 eligibility criteria.

3.7. Mechanical Thrombectomy (Continued)	COR	LOE
7. In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.	I	A
8. In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.	lla	B-R

EDITORIAL

Image-Guided Intravenous Alteplase for Stroke — Shattering a Time Window

Randolph S. Marshall, M.D.

 Penumbral imaging is now being used to triage patients presenting in extended time windows for IV thrombolysis

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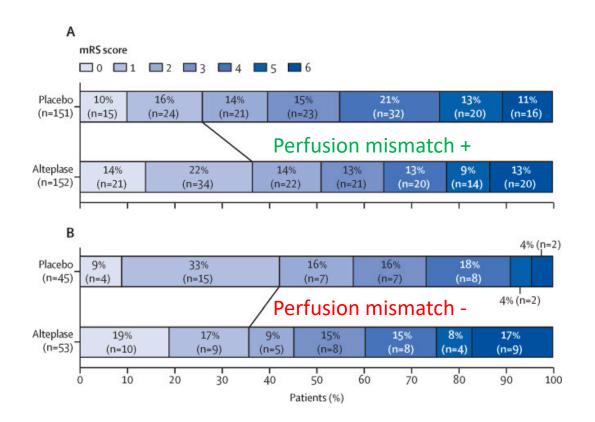
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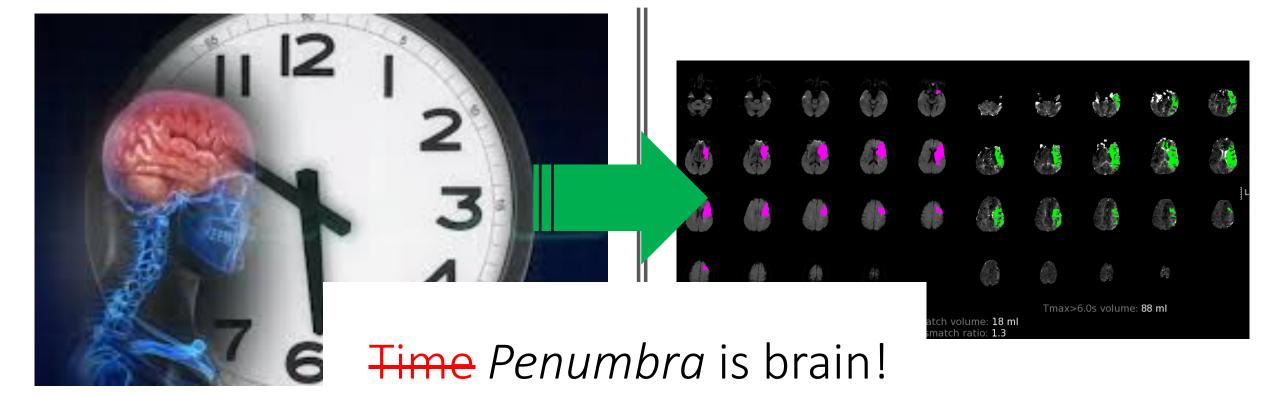
Children's Health

- EXTEND, ECASS4-EXTEND, EPITHET meta-analysis: Patients with mismatch benefit from IV thrombolysis in late time windows; patients without mismatch do worse
- TIMELESS IV tenecteplace 4.5-24 hours + Mismatch on perfusion imaging → ongoing trial



Campbell et al Lancet 2019 Ma et al NEJM 2019 Marshall et al NEJM 2019





Extended time window for acute stroke treatment is a major opportunity for children

ARTICLES

Delayed Recognition of Initial Stroke in Children: Need for Increased Awareness

CONTRIBUTORS: Jayasri Srinivasan, MBBS, FRACP,^{a,b} Steven P. Miller, MDCM, MAS, FRCPC,^{b,c} Thanh G. Phan, MBBS, FRACP,^d and Mark T. Mackay, MBBS, FRACP^a

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KEY WORDS

stroke, cerebrovascular disease, cerebral vascular accident

ABBREVIATIONS

WHAT'S KNOWN ON THIS SUBJECT: Pediatric AIS, like AIS in adults, is associated with high morbidity and mortality rates. Unlike that in adults, however, pediatric stroke often is unrecognized, for a variety of reasons.

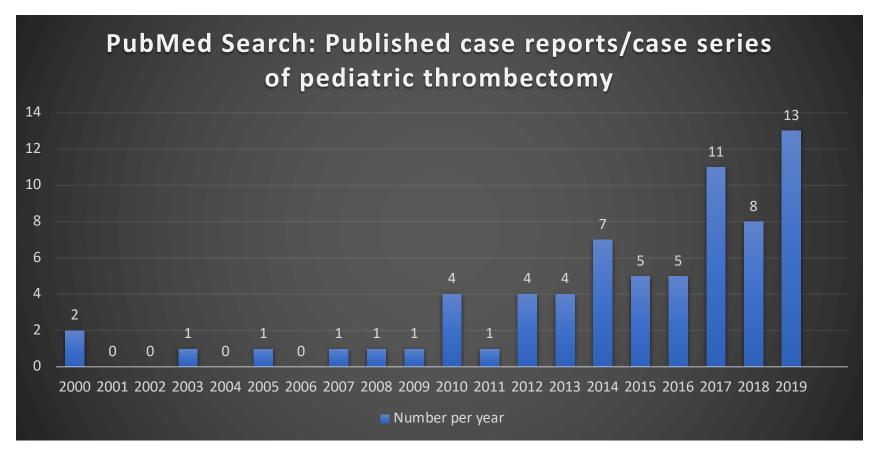
WHAT THIS STUDY ADDS: This study quantifies the time to diagnosis of pediatric stroke and aims to highlight the factors that perpetuate delay, namely, the lack of awareness of physicians regarding pediatric stroke. This is in contrast to many previous studies.

Delay to Diagnosis in Acute Pediatric Arterial Ischemic Stroke

Mubeen F. Rafay, MBBS; Ann-Marie Pontigon, BSc; Jackie Chiang, MD; Margaret Adams, BScN; D. Anna Jarvis, MD; Frank Silver, MD; Daune MacGregor, MD; Gabrielle A. deVeber, MD

- 12.7 hours: median in-hospital delay from presentation to diagnosis
- 22.7 hours: median time from symptom onset to diagnosis

Thrombectomy is increasingly being performed in children in extended time windows—and beyond



- 2019 meta-analysis: 113 MT cases published between 2000-2019
- Mean LKW to recanalization:
 14.3 hours (SD 8.0-20.6)
- Median LKW to recanalization: 7 hours (range 3.1 hours-6 days)

Are we selecting the right children for thrombectomy?

JAMA Neurology | Original Investigation

Feasibility, Safety, and Outcome of Endovascular Recanalization in Childhood Stroke The Save ChildS Study

- Sporns, et al: 73 children, 27 US and European centers 2000-2018
- Post-procedural complications: 1 patient with sICH and death, 3 patients developed malignant infarction requiring hemicraniectomy

Clinical Neurology

CASE REPORT

Endovascular thrombectomy in pediatric patients with large vessel occlusion

- Shoirah, et al: 19 patients with MT, 17 with outcome data 2008-2017
- 1 patient with ASPECTS 4, malignant infarction requiring hemicraniectomy

Feasibility, Safety, and Outcome of Recanalization Treatment in Childhood Stroke

Sandra Bigi, MD, MSc, 1* Andrea Dulcey, MD, 1* Jan Gralla, MD, MSc, 2

- Bigi, et al: 16 children recanalized 11 MT, 5 IVT 2000-2015
- 5 patients (all with partial recanalization) developed malignant infarction requiring hemicraniectomy; 1 died from herniation, all 5 poor outcome

Survey of practice patterns and preparedness for endovascular therapy in acute pediatric stroke

Jenny L. Wilson¹ · Catherine Amlie-Lefond² · Todd Abruzzo³ · Darren B. Orbach⁴ · Michael J. Rivkin⁵ Gabrielle A. deVeber⁶ · Paola Pergami⁷

Age minimum (years)*	
1	1 (3.6)
2	6 (21.4)
4	1 (3.6)
No age minimum or uncertain	19 (67.9)
Time window (anterior circulation)*	
< 6 h	3 (10.7)
< 8 h	2 (7.1)
<16 h	1 (3.6)
<24 h	16 (57.1)
No established time window	6 (21.4)
Time window (posterior circulation)*	
<12 h	3 (10.7)
<24 h	10 (35.7)

NIHSS minimum [†]	
NIHSS minimum 4	2 (7.4)
NIHSS minimum 6	9 (33.3)
No minimum, but deficits must be significant	5 (18.5)
Depends on clinical scenario	9 (33.3)
Uncertain	2 (7.4)
Imaging preference within 6 h*	
CT/CTA	2 (7.1)
CT/CTA/CT perfusion	3 (10.7)
MRI/MRA	7 (25.0)
MRI/MRA/MR perfusion	10 (35.7)
Case-dependent	6 (21.4)
Imaging preference after 6 h*	
CT/CTA	1 (3.6)
CT/CTA/CT perfusion	6 (21.4)
MRI/MRA	3 (10.7)
MRI/MRA/MR perfusion	11 (39.3)
Case-dependent	7 (25.0)

46.4% preferred perfusion studies ≤6 hours; 60.7% >6 hours



Children are not little adults!

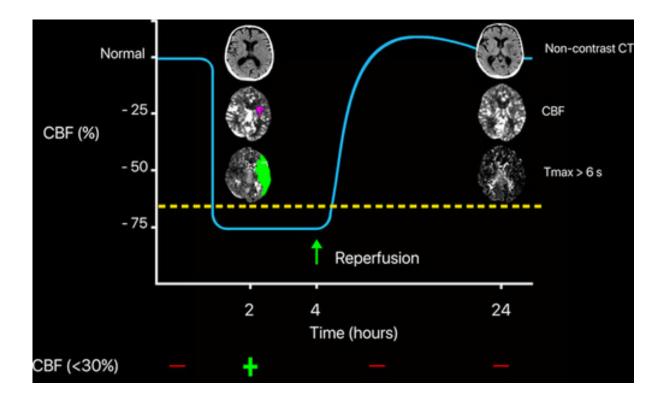
- No intervention is without risk
 - TIPSTERS study: 0/29 children receiving IV tPA experienced sICH
 - Save ChildS study: Thrombectomy complications included vasospasm, cardiac arrest in a congenital heart patient, 1 patient with sICH and death, 3 patients with malignant infarction and hemicraniectomy
 - No prospective safety data on hyperacute reperfusion therapies in children





DEFUSE 3 CT Perfusion parameters

- Dynamic acquisition of sequential slices during IV administration of contrast provides quantitative assessment of brain perfusion
- Severely reduced relative Cerebral Blood Flow (CBF) predicts irreversible infarcted tissue even before hypodensity appears on noncontrast CT
- Volume of rCBF < 30% corresponds with DWI lesion on MRI
- Tmax >6 seconds on CTP correlates with the same threshold on MR Perfusion



Albers et al Ann Neurol 2016 Cereda el at Cereb Blood Flow Metab 2016 Campbell et al Stroke 2011 Campbell et al Stroke 2012 Oct;43(10):2648-53



CT perfusion is feasible in children*

- Advantages, short (20-40 seconds), typically does not require anesthesia or specialized equipment—just a post-processing software
- Drawbacks of CT perfusion: limited spatial coverage with thick cuts, radiation exposure
- Wintermark, et al: CTP in an ER setting identified pathology with no false negatives (brain ischemia, n=2; head trauma n=9; brain infection n=2; Sickle cell disease n=1) and 1 "false positive" (hyperperfusion in the setting of migraine)
- Changes not detected on NCCT, and diagnoses were confirmed by subsequent MRI (unable to be obtained in the acute phase)
- Threshold of rCBF < 30% to estimate ischemic core has been extensively validated in adults, but not in children

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ACR-ASNR-SPR practice parameter

- "It may be reasonable to use CT brain perfusion in individual patients under 18 years of age for the same indications listed for adults, but the increased risk to the pediatric patient associated with radiation exposure obligates the practitioner to apply a higher threshold to any decision to use this technique and to strongly consider MRI as an alternative."
- *Our approach—<u>consider</u> CT perfusion in an older child eligible for thrombectomy with confirmed LVO and questionable ASPECTS who cannot get MRI

TABLE 1. Perfusion-CT Protocols Dedicated to the 4 Age Categories

	0-6 mo	6–12 mo	1–10 y	10–18 y
Acquisition parameters, kVp (mAs)	80 (60)	80 (60)	80 (80)	80 (100)
Duration of the CT acquisition (s)	20	30	35	40
CT image sampling interval (s)	0.5	1	1	1
Total number of images	40	30	35	40
Amount of contrast material for the bolus (mL/kg)	1	1	1	1
Injection rate*	1	1.2	1.5	2
Delay between beginning of intravenous administration of contrast material and data acquisition* (s)	3	4	5	5
Maximum absorbed dose to the brain (mGy)	84	126	196	280
Effective dose (mSv)	2.96	2.02	1.57	1.68
Effective dose ratio between perfusion data acquisition and conventional noncontrast and contrast-enhanced cerebral CT (%)	56	63	46	26

*This time delay was reduced by 1 to 2 seconds in case of central venous catheter.

Table 3

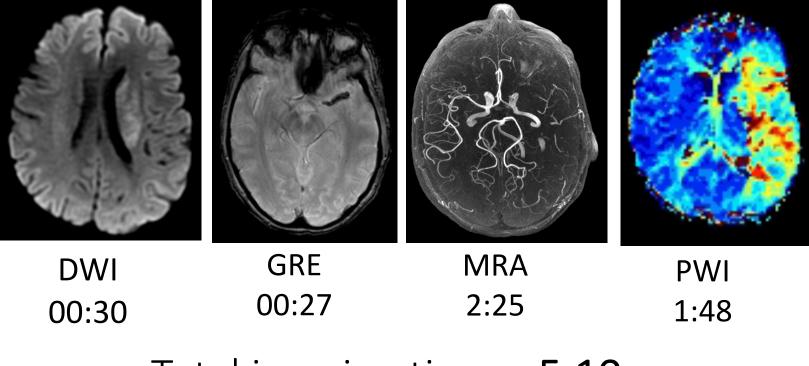
Shows the Dose Length Products for the different parts of the stroke protocol Abbreviations: Native-CT=Native computed tomography scan, CTA=CT-Angiography, CT-DSA=CT-digital subtraction angiography, mGy.cm=miligray per centimeter, DLP=Dose Length Product.

	DLP native CT (mGy.cm) mean (min.–max.)	DLP CT Perfusion (mGy.cm) mean (minmax.)	DLP extrakran. CTA (mGy.cm) mean (min.–max.)	Total DLP (mGy.cm) mean (min.–max.)
Age dependent CT-sti	roke protocol			
5-10a(n=1)	459	1341	31	1831
11 - 15a(n = 6)	625 (486-719)	1844 (1607-1882)	171 (89–292)	2613 (2295-2836)
>15a (n=3)	629 (495–773)	2321 (3056–3371)	238 (198–277)	3189 (3144–3375)



MRI is preferred over CT in children

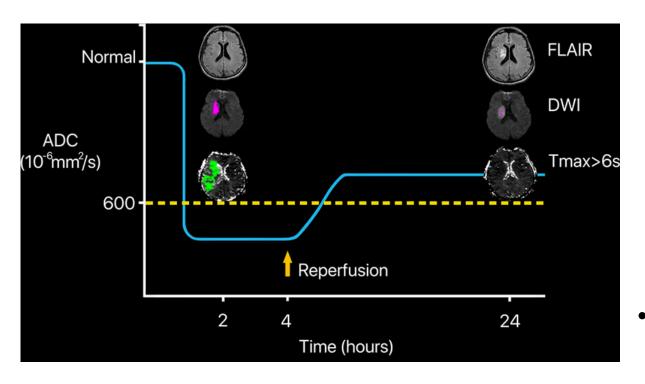
- Pros: Superior sensitivity for acute ischemia; lack of ionizing radiation
- Cons: Less available; longer scan, may require sedation; contraindications

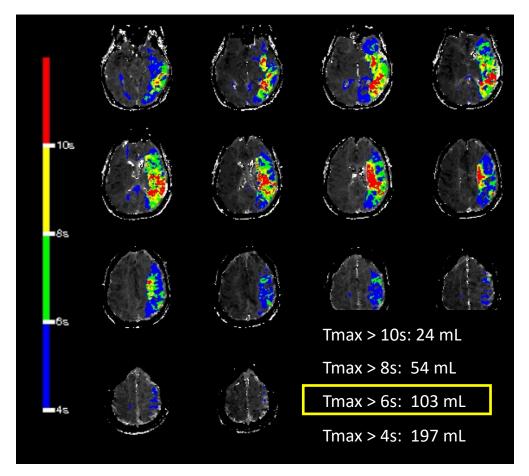


Total imaging time = 5:10

DEFUSE 3 MR Perfusion parameters

 Core: ADC <620x10⁻³ mm/s occurs with severe, acute hypoperfusion and identifies irreversibly injured tissue in the setting of persistent occlusion





 Tmax > 6 seconds in adults defines critically hypoperfused tissue that is salvageable but will go on to infarct if not reperfused



MR perfusion is feasible in children

- Brain tumor data: 83 children prospectively underwent MR DSC perfusion
 - Wide age range (6 months-16 years, mean 8.15 ± 4.7 years)
 - IV placement (arm 76%, hand 17%, foot 7%)
 - IV Gauge (18ga 11%, 20ga 51%, 22ga 29% varied)
 - Standard gadolinium dose (0.1mmol/kg) via power injector; flow rates: 1-5mL
 - Sedation in 33/83 (40%), all under 6 years
- No access site or systemic complications
- High-quality CBV and signal intensity-time curves achieved in 100%
- Quantitative values equal or superior to those reported for adults; no significant difference among the high flow-rate group



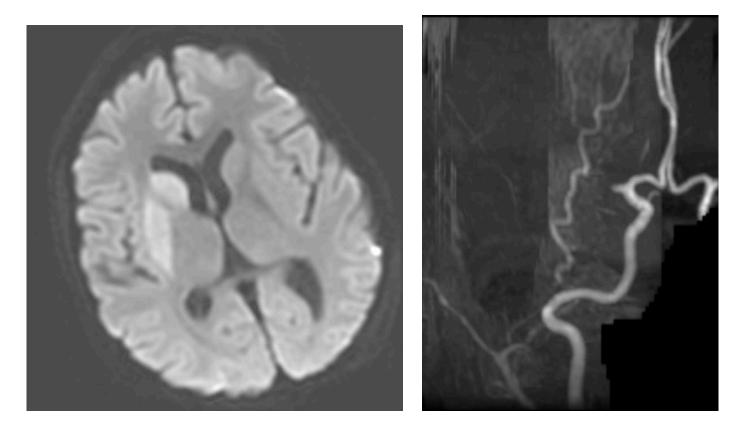
What about MR perfusion in pediatric stroke?

- Visser, et al: 29 children presenting acutely with ischemic stroke who underwent RAPID perfusion imaging
 - 12 with large vessel occlusion, 3 with penumbra detected by Tmax > 6 seconds
 - Mean ADC increased as time-to-imaging increased, similar to adult values
 - Movement, poor bolus timing or incorrectly selected AIF may confound accurate maps (notching and temporal dispersion)
- Lee, et al JNIS 2019: 5 children with acute LVO and RAPID perfusion
 - MR Perfusion in 4/5; 5/5 with interpretable, good quality images
 - Tmax > 4 seconds may better approximate penumbra than Tmax > 6 seconds

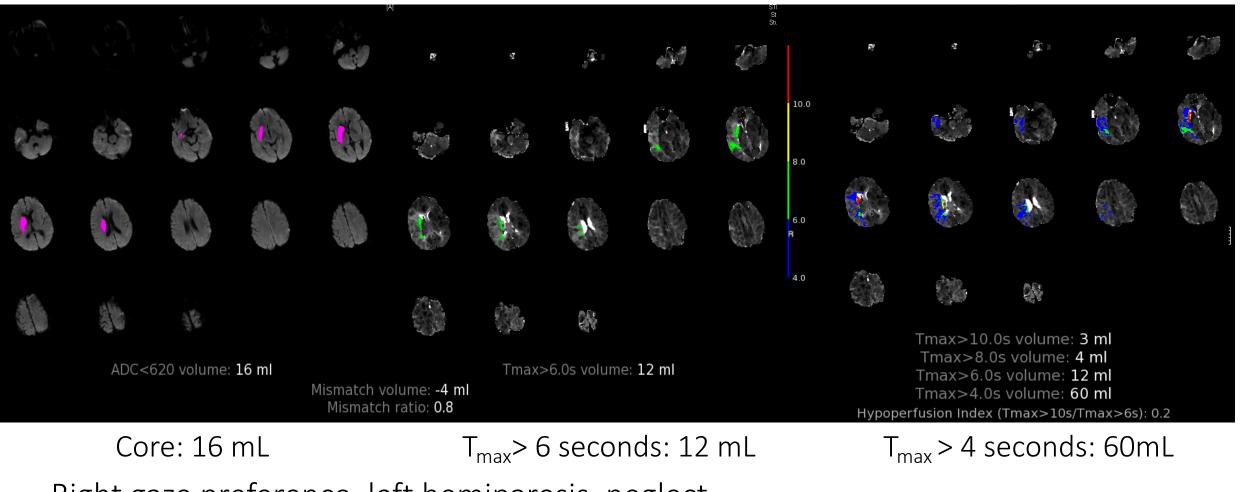


Case

• 10-year-old girl with dilated cardiomyopathy several months status post heart transplant presented with right gaze preference, left sided hemiparesis, neglect: NIHSS 13 with right M1 occlusion



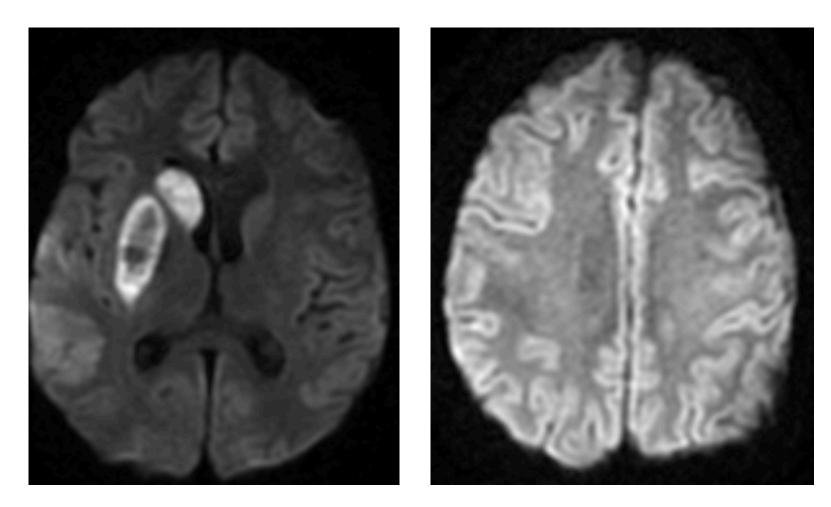




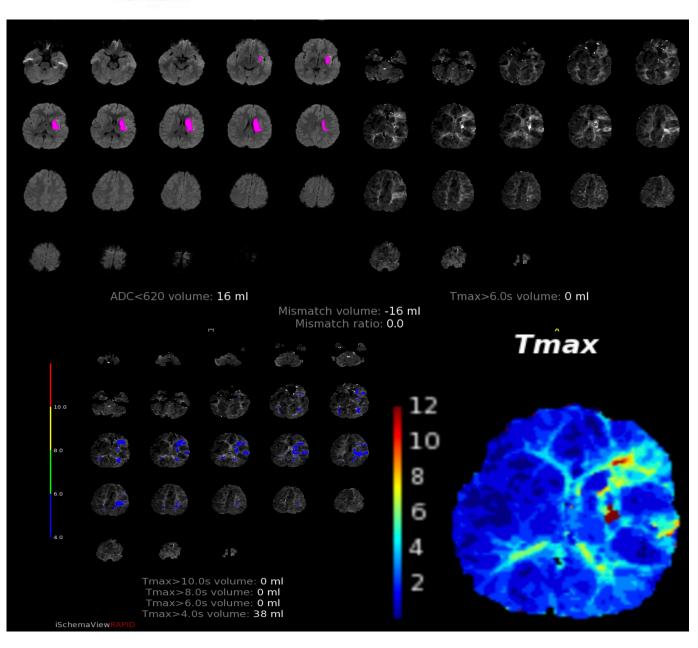
Right gaze preference, left hemiparesis, neglect To cath lab \rightarrow TICI 3 reperfusion



TTE revealed mobile thrombus, started on anticoagulation Mild left hand weakness at 12 months, PSOM 0.5







11-year-old previously healthy girl found down with aphasia and rightsided weakness, NIHSS 11

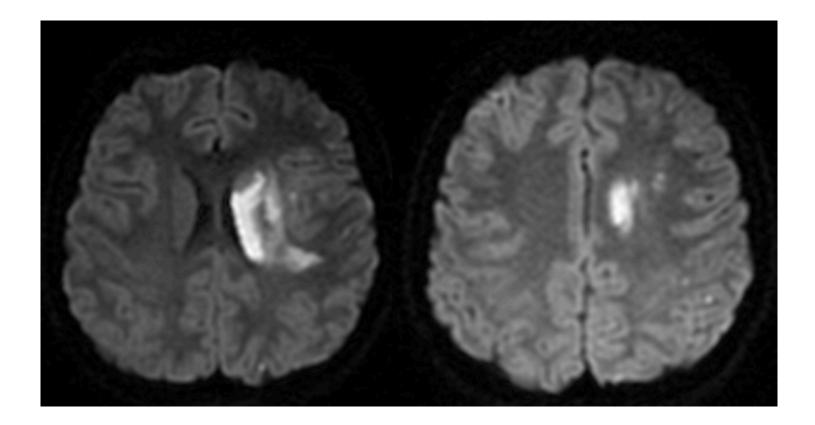
MRI performed 5 hours after last known well: proximal M2 cutoff

Tmax > 6 sec : 0 mL Tmax > 4 sec : 38 mL corresponding with aphasia on exam

Underwent thrombectomy with TICI 2b reperfusion



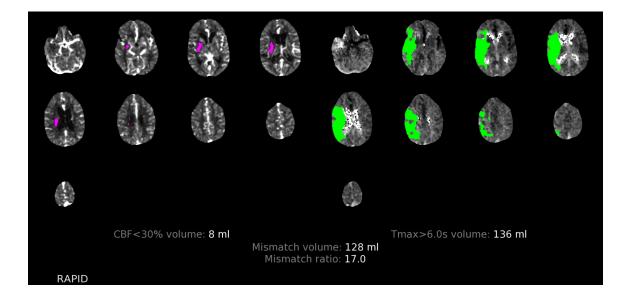
Aphasia resolved post-procedure Extensive workup negative—cryptogenic stroke NIHSS 1 at discharge, 0 at 1 year





MR Perfusion imaging in children

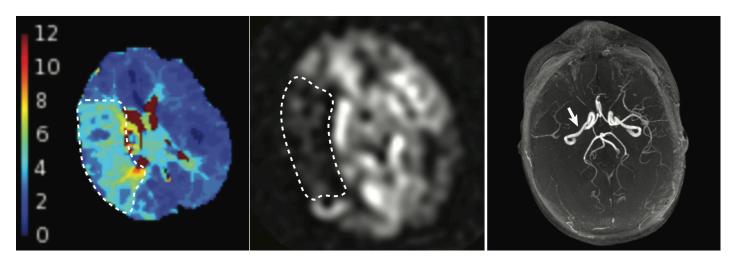
- Perfusion is becoming widely available and easily integrated with existing imaging systems—now recommended in 2019 AHA guidelines
- Automated threshold calculations: Core, penumbra, mismatch volume and mismatch ratios result instantaneously
- Water content, metabolically active brain regions change over infancy and childhood
 - Different ADC thresholds for different ages?
- Children have excellent collaterals:
 - Longer time window?
 - Lower Tmax threshold?
 - Neither? Or both?





What about ASL Perfusion?

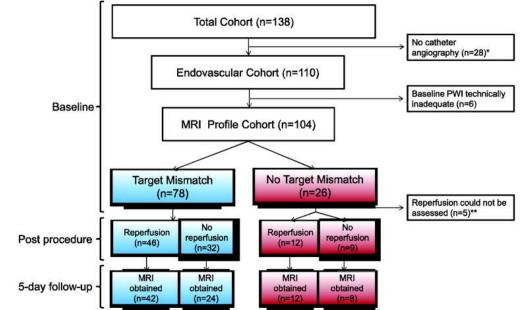
- Quantitative measure of CBF by using radiofrequency pulse(s) to magnetically label arterial blood water→ endogenous tracer
- Pros: Repeatable, avoids contrast (versus DSC perfusion)
- Limitations: Longer acquisition time, high signal-to noise ratio, measures only CBF; in some cases, may be over-sensitive to mild perfusion deficits and arterial delays that do not reach PWI Tmax>6 seconds
- Requires further investigation





Small core/high ASPECTS + LVO?

- Up to 60% of acute stroke missed on CT
- ASPECTS scoring is imperfect with only moderate inter-rater reliability
- Pediatric brains are fuller, sulci less distinct; pediatric neuroradiologists may not be as versed in scoring ASPECTS
- 24% of DEFUSE2 patients had LVO and underwent thrombectomy, but did not have target mismatch





Small core + High NIHSS?

- Children present differently than adults, and NIHSS may be unreliable
- Fluctuating symptoms commonly described in pediatric stroke
- Non-arteriopathic strokes typically present abruptly, but can progress, stutter or recur (?temporary improvement with collateral recruitment or perfusion-related changes)
- 28% of non-arteriopathic and 50% of cardioembolic strokes presented non-abruptly

Mode of Onset	Abrupt	Total Nonabrupt	Progressing	Stuttering	Recurring	Unclear But Not Abrupt
Stroke etiology						
Cardioembolic, n=8	4	4	2	0	2	0
Cryptogenic, n=10	9	1	1	0	0	0
Total nonarteriopathy, n=18	13 (72%)	5 (28%)	3	0	2	0
Total Arteriopathy, n=38	12 (32%)	26 (68%)	7	9	7	3
TCA/PVA, n=30	7	23	6	8	6	3
Dissection, n=8	5	3	1	1	1	0

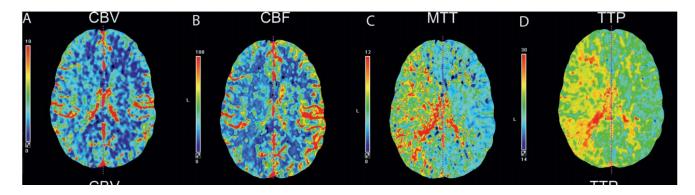
TABLE 2. Mode of Onset in Subtypes of Stroke Etiolog	gies
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• 16-year-old boy presented with left-sided weakness and dysarthria

CT perfusion #1

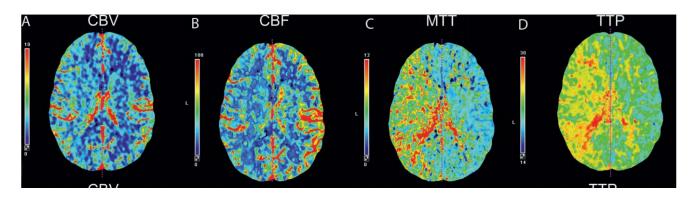
- CT normal, weakness improved, thus IV tPA was deferred
- 3 days after symptom onset, NIHSS worsened to 11 → transferred to tertiary center
- CTP at ~72 hours with persistent penumbra; angiogram confirmed R ICA occlusion with partial collateral flow to the R MCA
- Intervention deferred and patient was medically managed

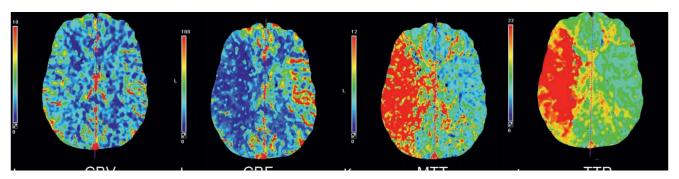




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CT perfusion #1



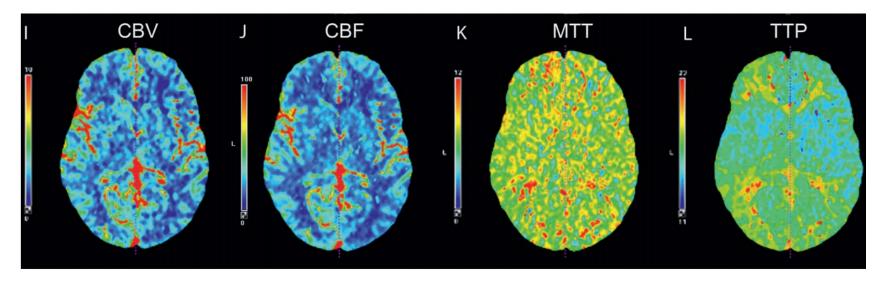


CT perfusion #2

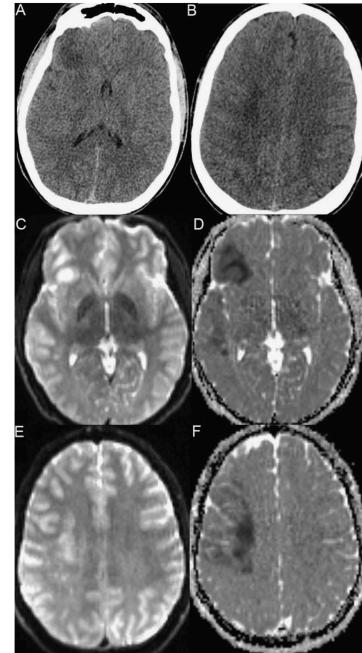
• Next day, NIHSS worsened to 15



- Taken for thrombectomy with successful reperfusion
- Post-procedure, perfusion deficit resolved



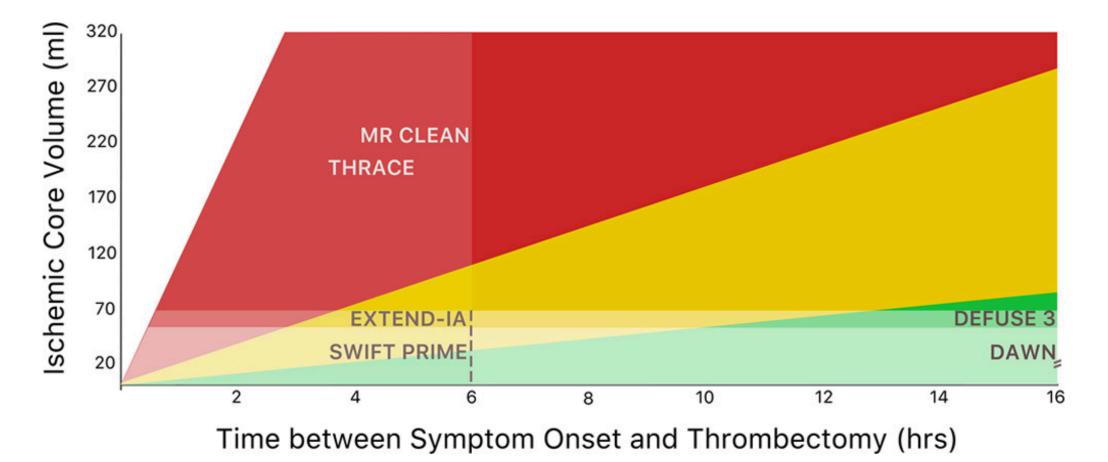
- At 3-month follow-up, mRS 1, NIHSS 1
- At 1 year, mild difficulty with left hand dexterity





Core growth highly variable in adults

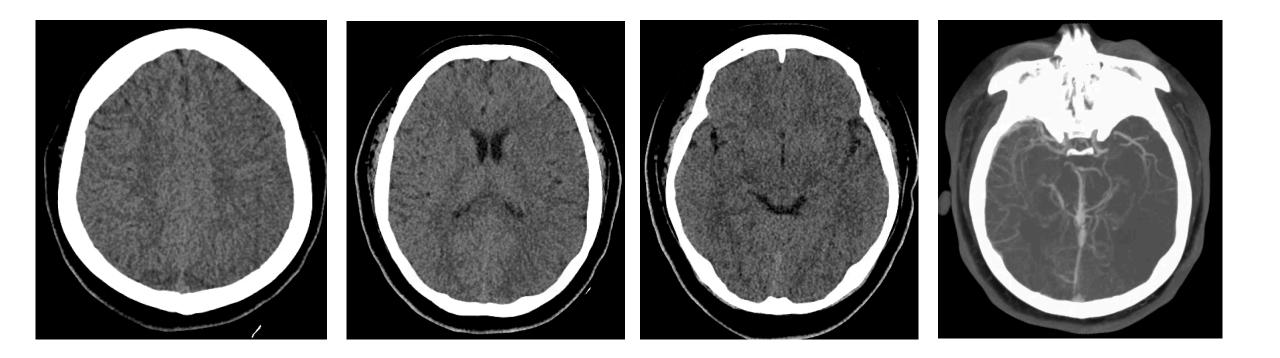
• Some complete their stroke within hours, and some grow over days--it can take 3 days for "slow-growers" to complete their infarcts



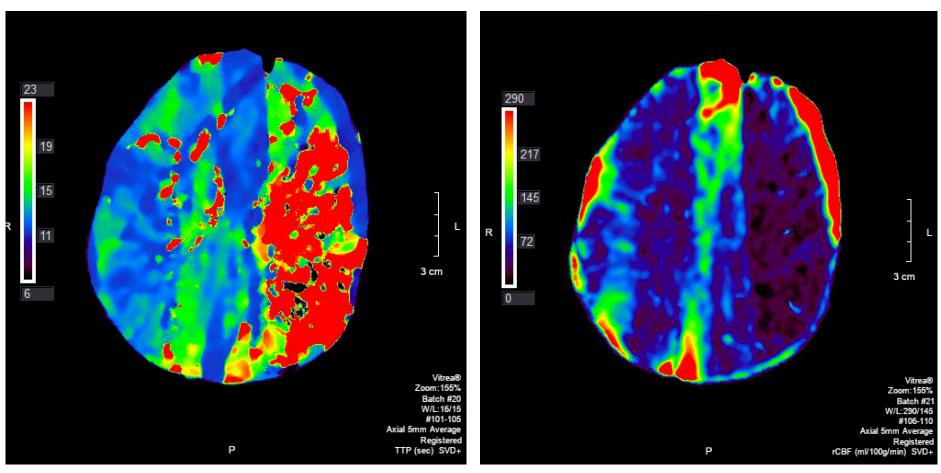


Core growth also varies in children

- 15-year-old boy collapsed at home with right-sided weakness and aphasia
- Taken to a local community hospital 2 hours after last known well
- IV alteplase given; transfer call initiated for possible thrombectomy



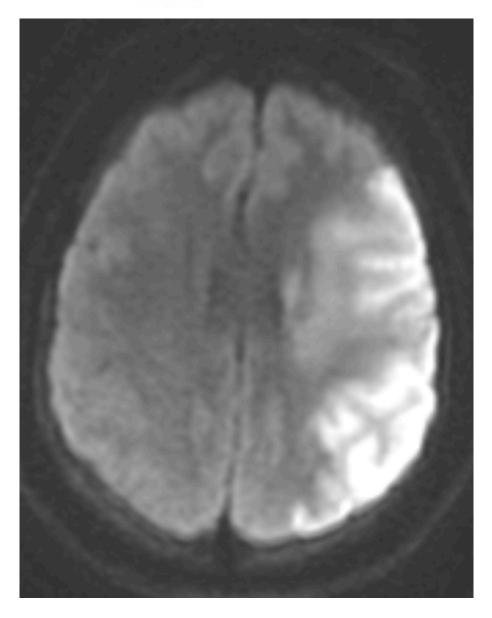




Time to Peak tissue residue

Cerebral Blood Flow

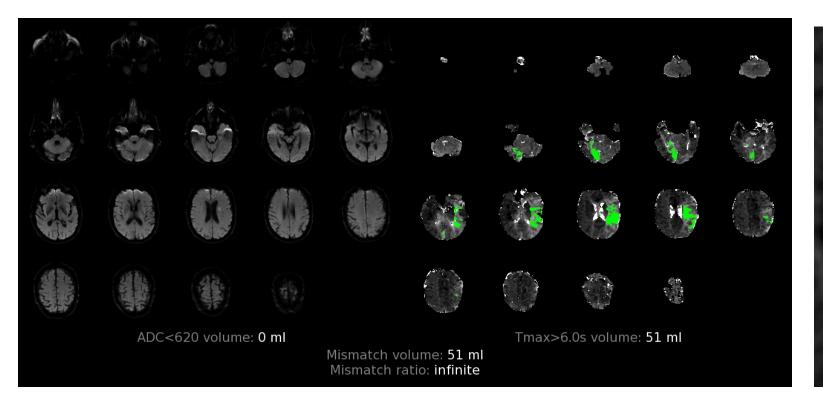


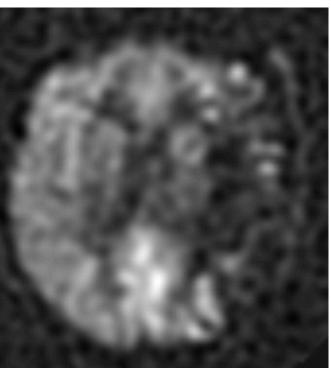


- Transferred direct to Stanford MRI, NIHSS 22
- MRI 3.5 hours after last known well with DWI lesion involving the entire left MCA territory, corresponding with TTP lesion seen on CTP
- Underwent hemicraniectomy
- Discharged to rehab facility with mRS 4: expressive/receptive aphasia, right-sided hemiparesis

Perfusion maps can provide information on collateral status

76-year-old man with atrial fibrillation presented with aphasia and right arm plegia Symptoms improved en route to ED—only facial droop and dysarthria on arrival CT noncontrast negative, CTA with left M1 occlusion—transfer requested



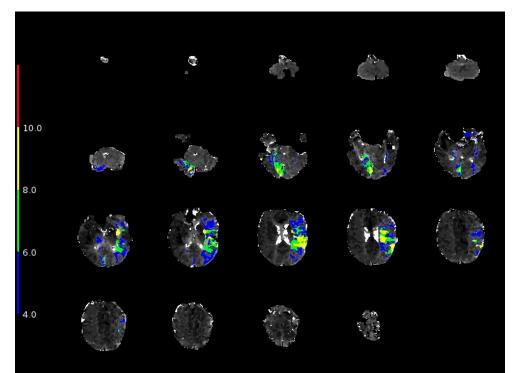




RAPID

Not for primary diagnosis.

Hypoperfusion Intensity Ratio: lower is better

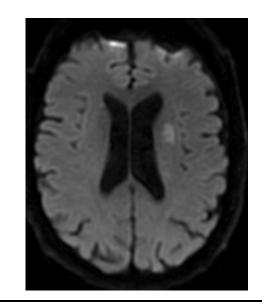


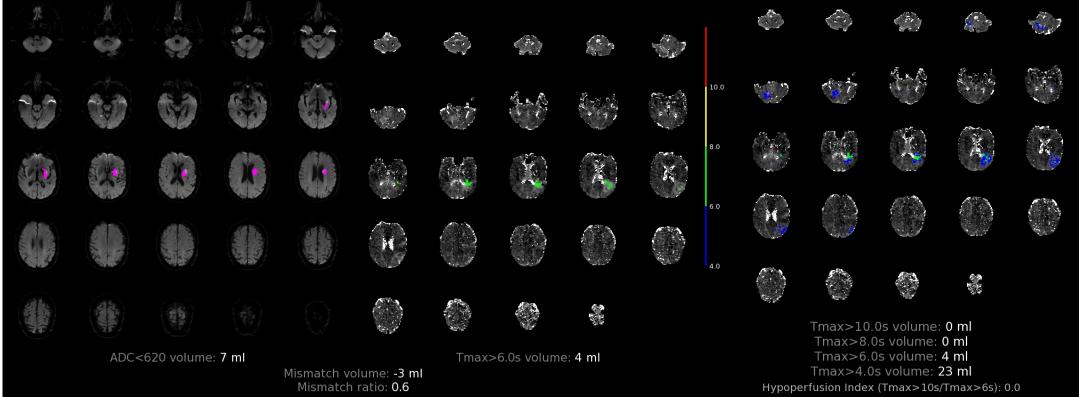
Tmax>10.0s volume: 0 ml Tmax>8.0s volume: 16 ml Tmax>6.0s volume: 51 ml Tmax>4.0s volume: 120 ml Hypoperfusion Index (Tmax>10s/Tmax>6s): 0.0 • HIR = $\frac{\text{Tmax} > 10 \text{ s}}{\text{Tmax} > 4 \text{ s}}$

- On arrival, NIHSS had improved to 1 (facial droop)
- Given low NIHSS and excellent collateral status, patient was admitted to ICU for close monitoring and medical management

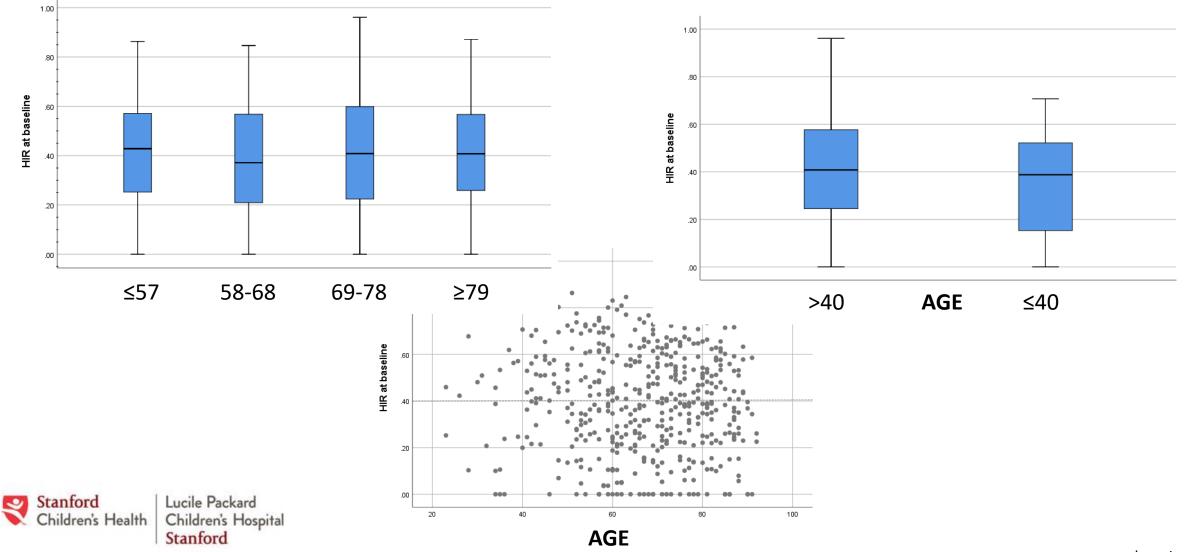


Final infarct burden



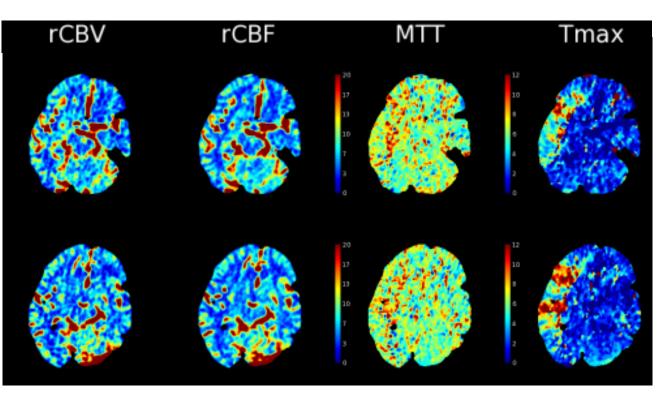


HIR did not vary by age in DEFUSE3 + DEFUSE2 + CRISP adult cohort



Perfusion may help distinguish between a chronic/ subacute process and an acute embolic occlusion

- Bigi, et al: Focal Cerebral Arteriopathy (FCA) 3/16 (18.8%)
- SaveChildS: FCA 8%, bilateral cerebral arteriopathy 1%, Aortic/cervical arteriopathy 10%
- Cobb, et al: vascular risk factors (26.5%), infectious risk factors (8.8%)
- Bhatia et al: Arteriopathy (9.3%)

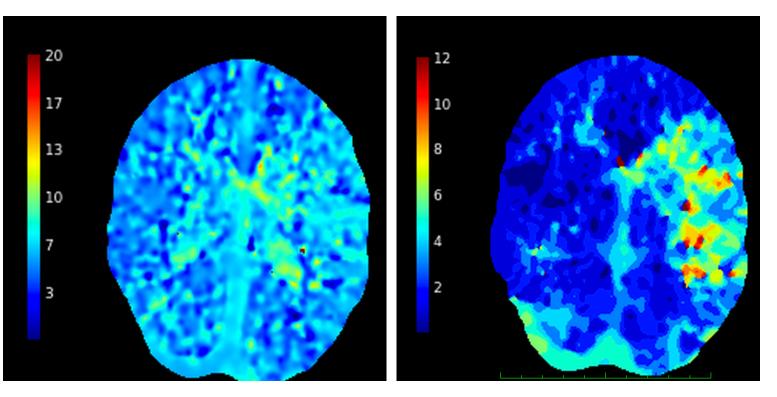


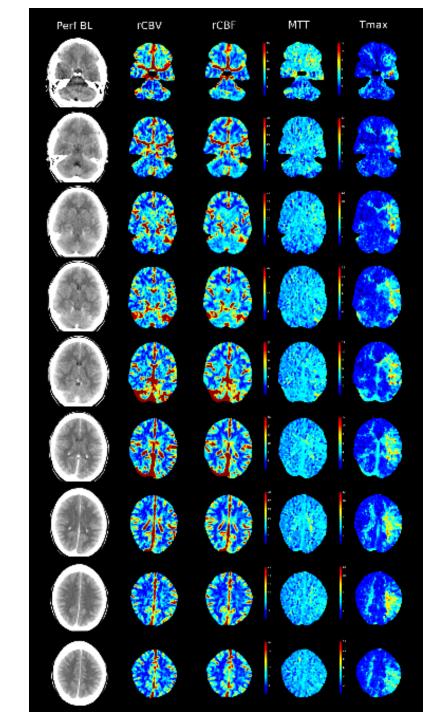
Chronic R ICA occlusion: Relatively preserved mean transit time + delayed Tmax



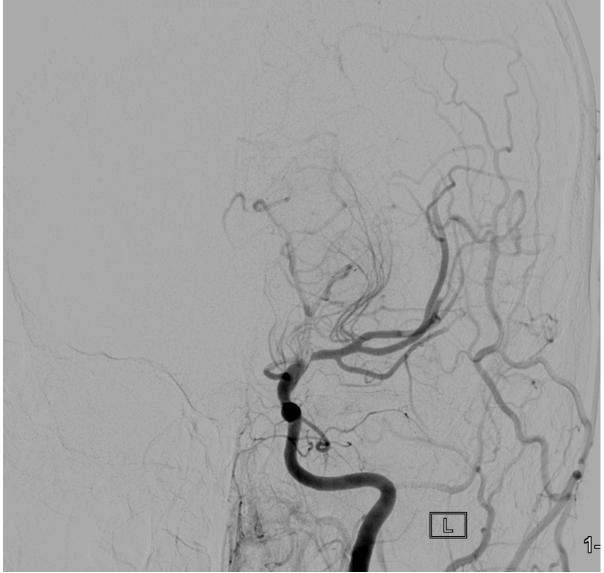


- SaveChildS case
- Child with stepwise worsening
- Taken for thrombectomy 24 hours after symptom onset
- MTT and CBV relatively preserved







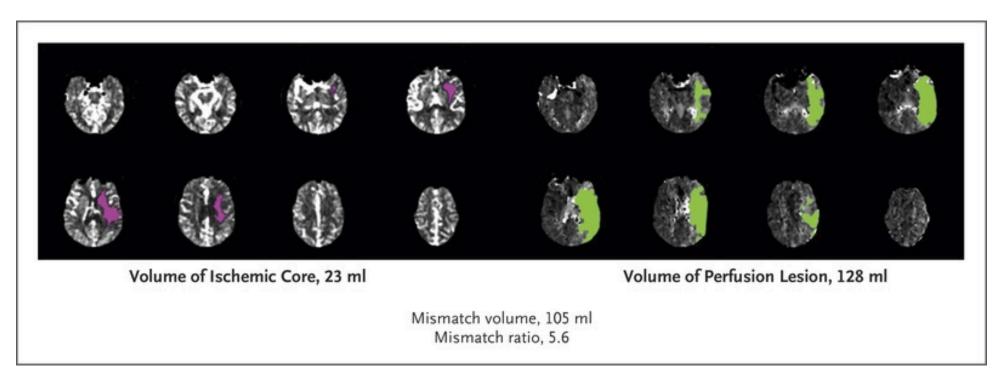


• Etiology: arteriopathy



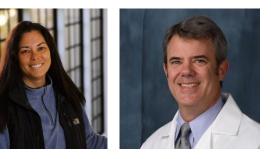
More research on PWI in pediatric LVO is needed!

- What thresholds best define core and penumbra in children?
- Is PWI helpful, or does it just add time?
- Are there other imaging biomarkers that inform acute management?





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