Intracranial Collateral Circulation

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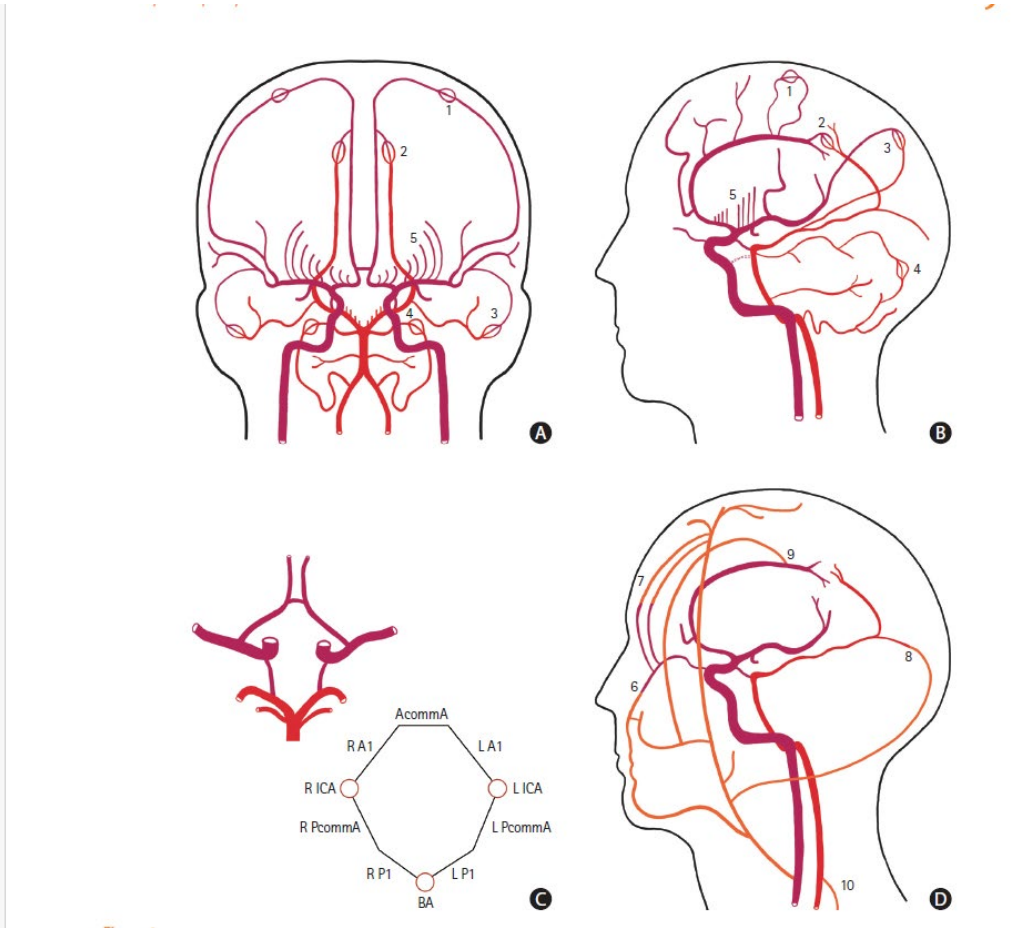
- No disclosures

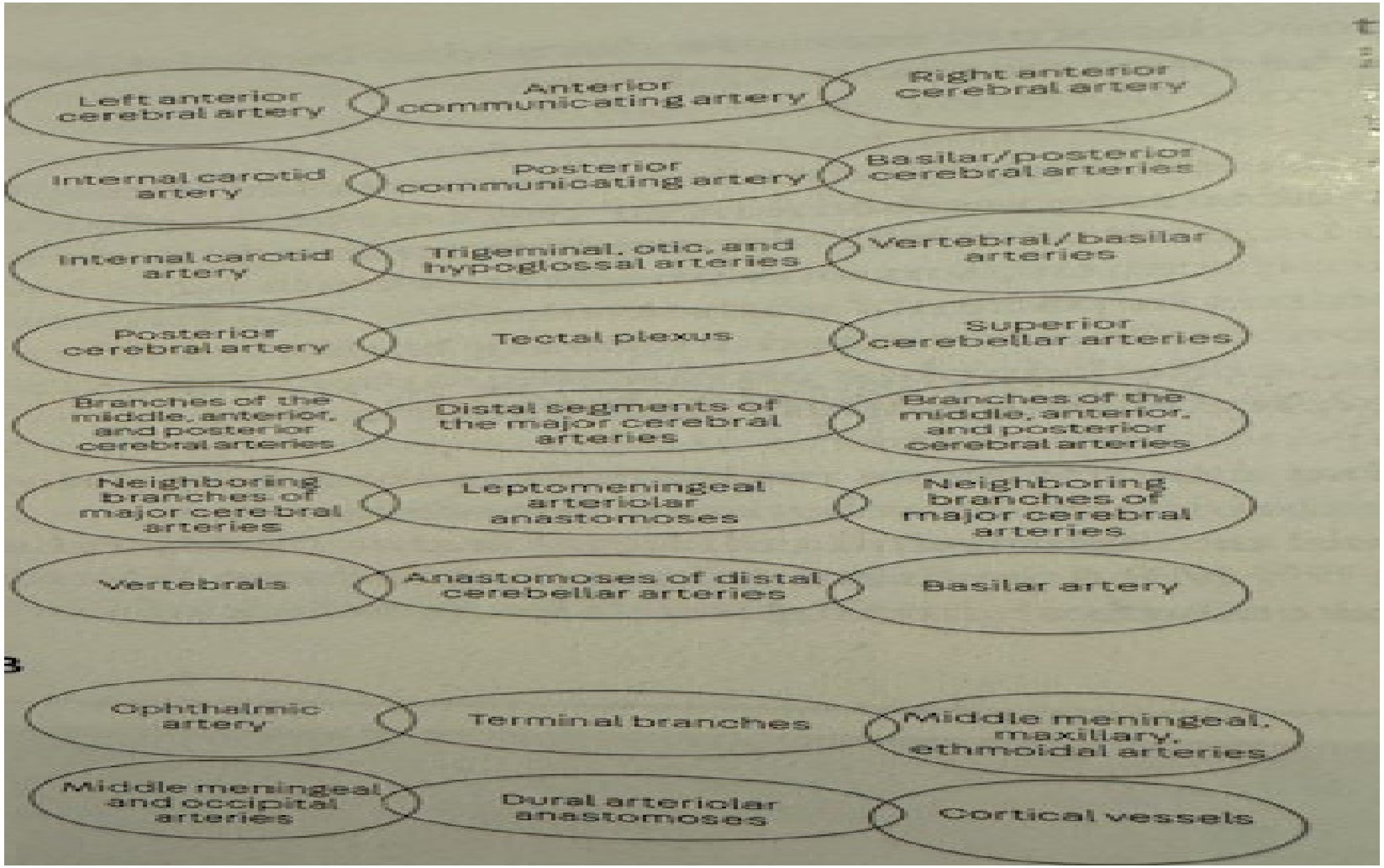
Classification of the collateral circulation

Structural classification	Functional classification
• Circle of Willis	• Primary
• Microvascular intracranial collaterals	• Secondary
– Leptomeningeal (pial) collaterals	• Tertiary
– Subcortical collaterals	
• Extracranial sources of collateral circulation	

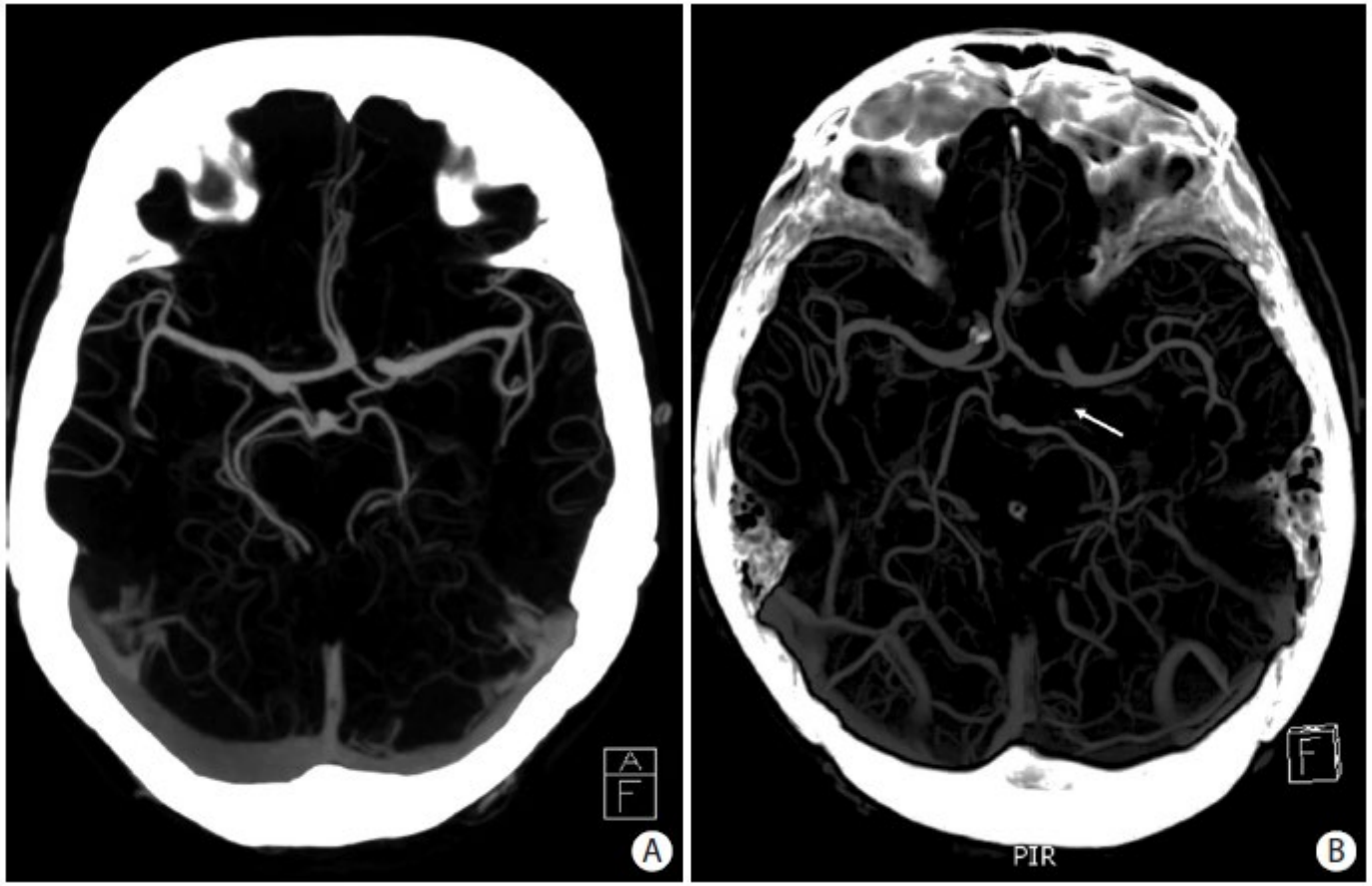
Schematic representation of the collateral circulation of the brain.



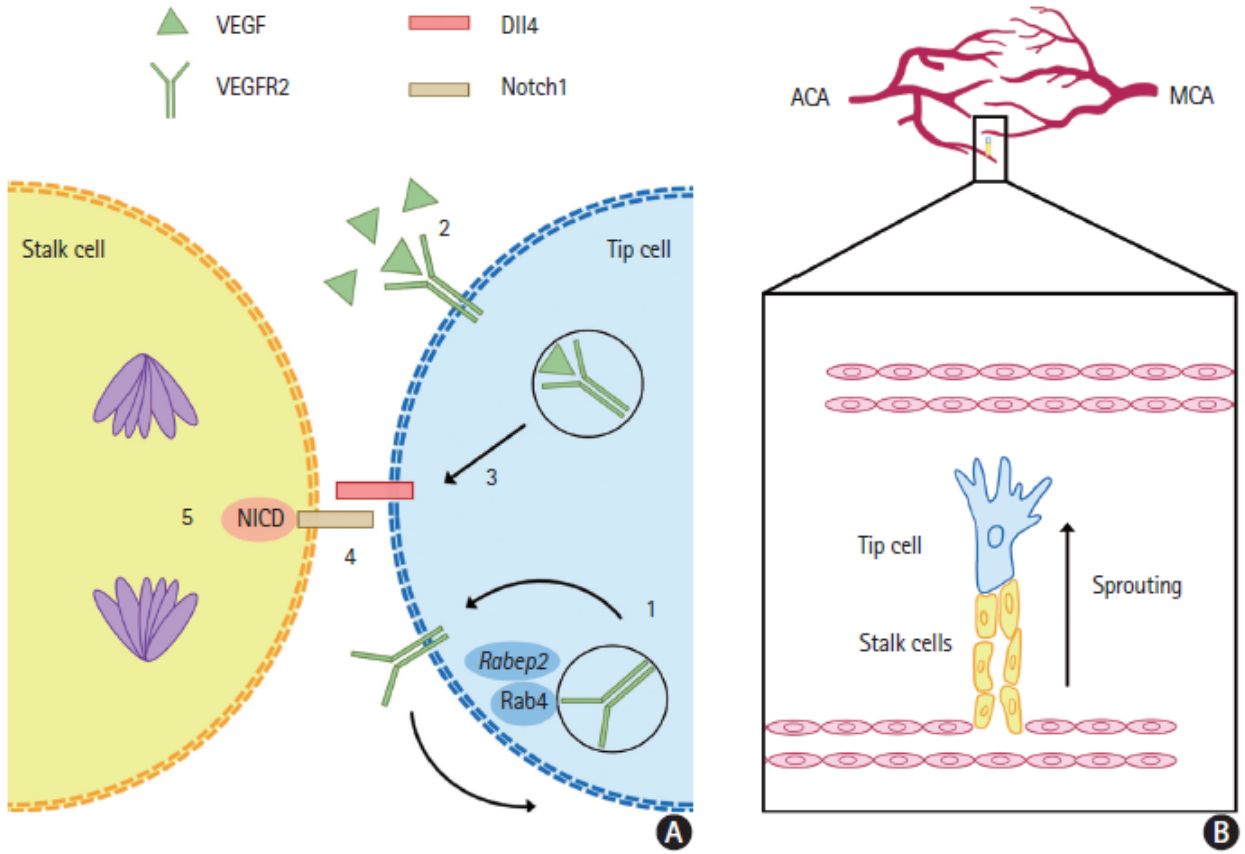
Connections



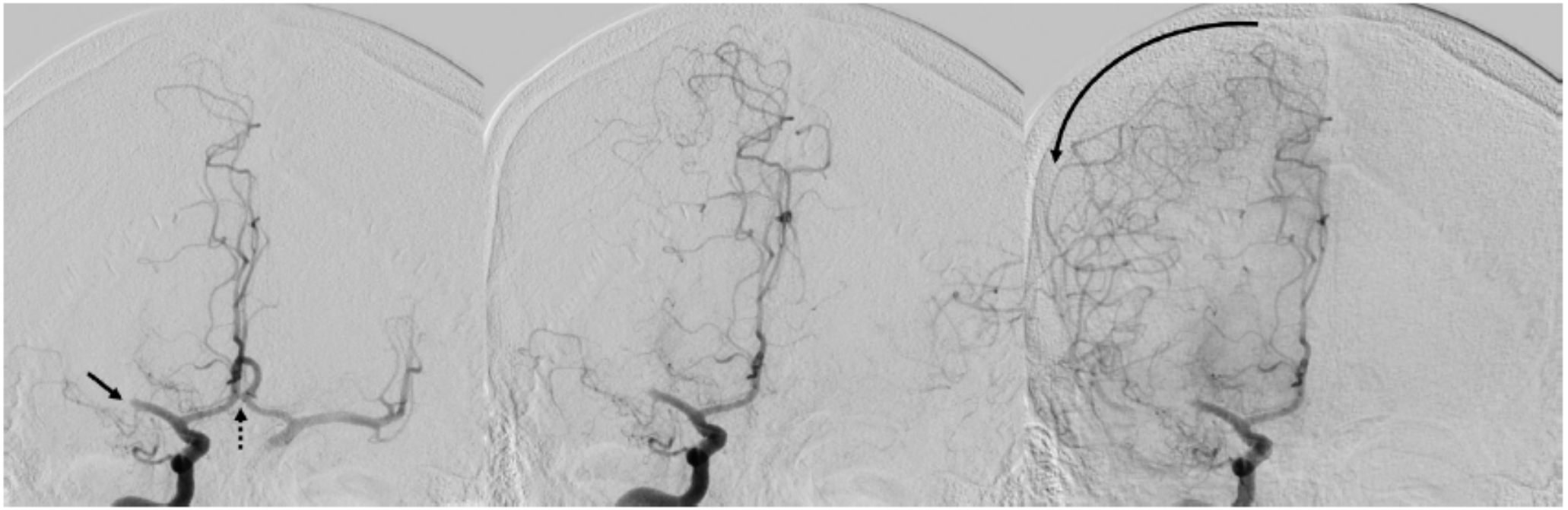
CoW



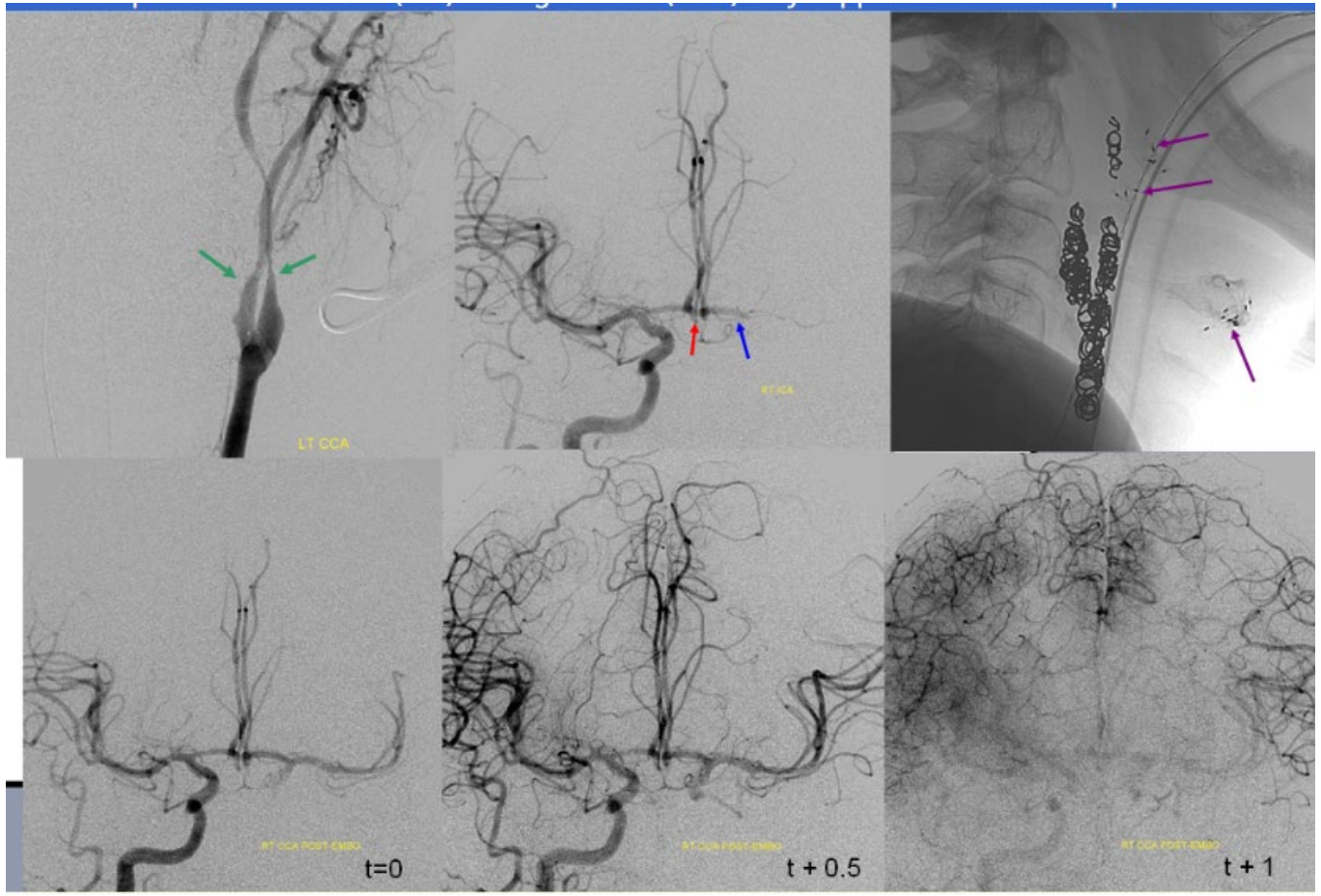
Collaterogenesis occurs during the embryonic period.



Right M 1 occlusion & collaterals



Left Carotid occlusion



Tertiary collaterals

- Angiogenesis- new blood vessels arise from pre-existent ones. Ischemia and Hypoxia

- Arteriogenesis- shear stress on the endothelium, which is generated by pressure gradients. Moya Moya like spectrum.

Evaluation of the collateral circulation

- **Structural studies**

- *Methods based on CT*- Single-phase CT angiography (sCTA), Multiphase CTA (mCTA)

- *Methods based on MR*- Time-of-flight MR angiography (TOF-MRA) is a T1-based sequence, Contrast-enhanced MR angiography (CE-MRA) and fluid-attenuated inversion recovery (FLAIR) sequence

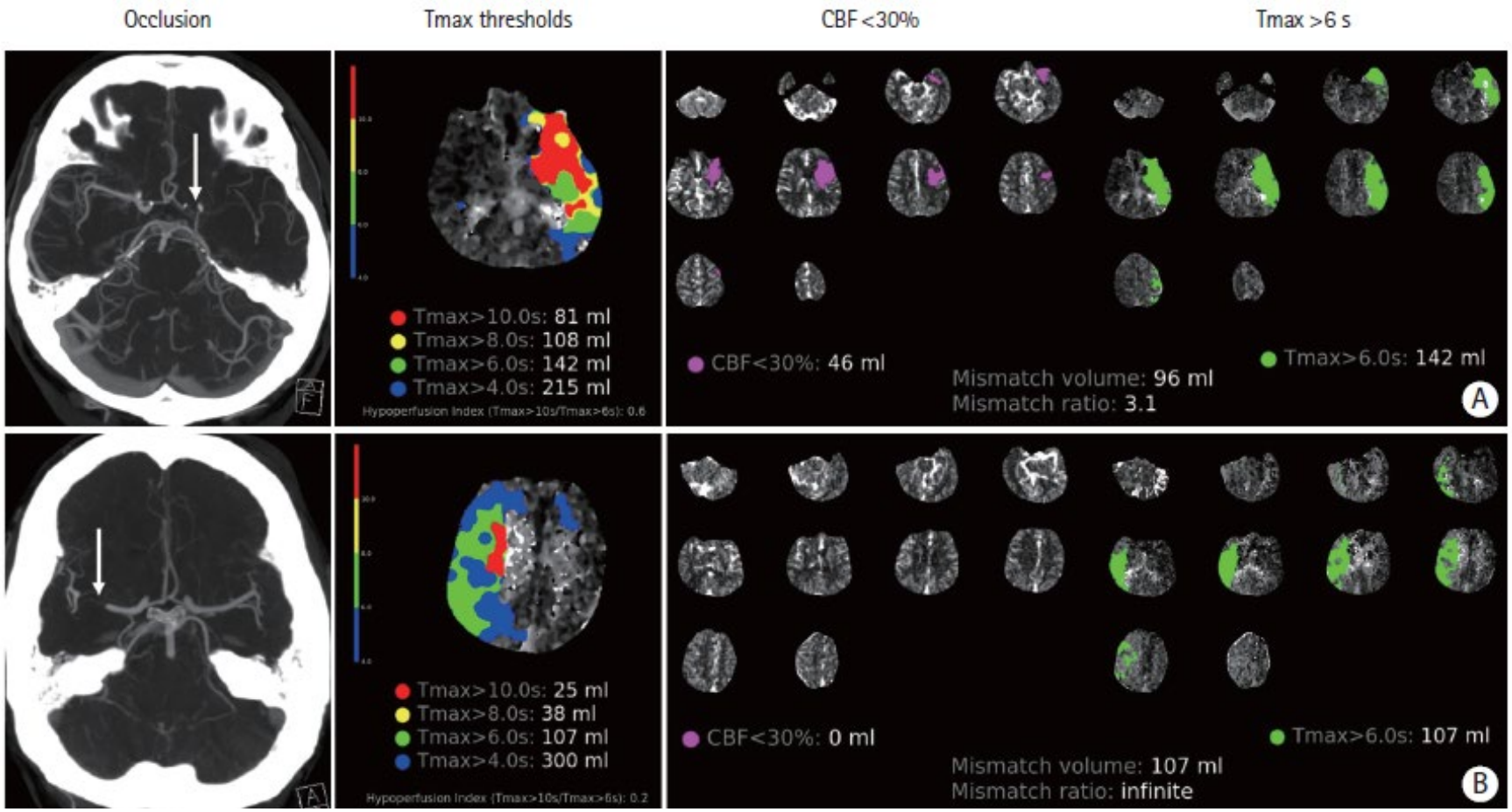
- *Transcranial Doppler*

- *Digital subtraction angiography*

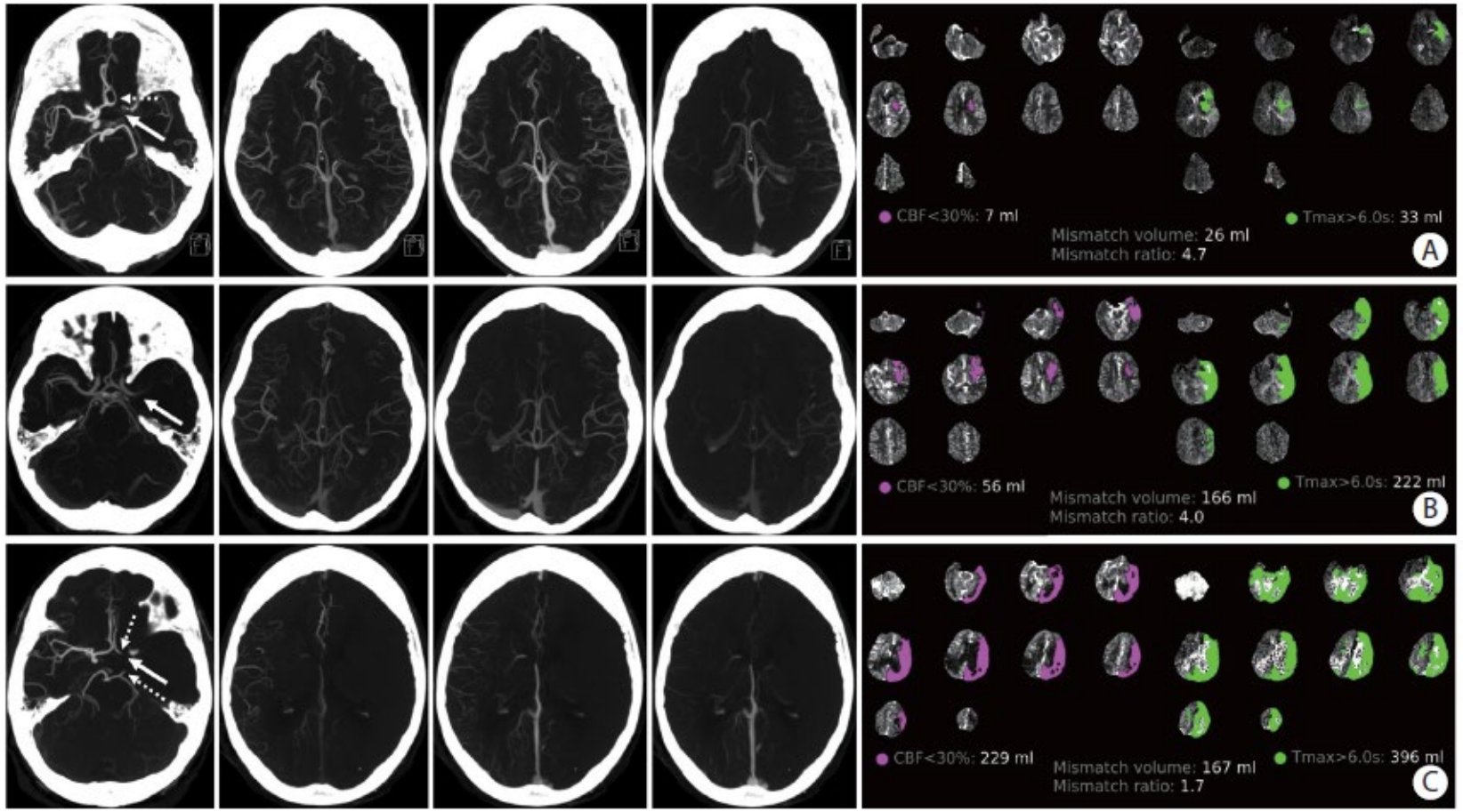
Functional studies

- *CT perfusion*
- *MR perfusion*
- *Positron emission tomography CT and single-photon emission CT*
- Arterial spin labeling (ASL)
- Retinal vessel metrics

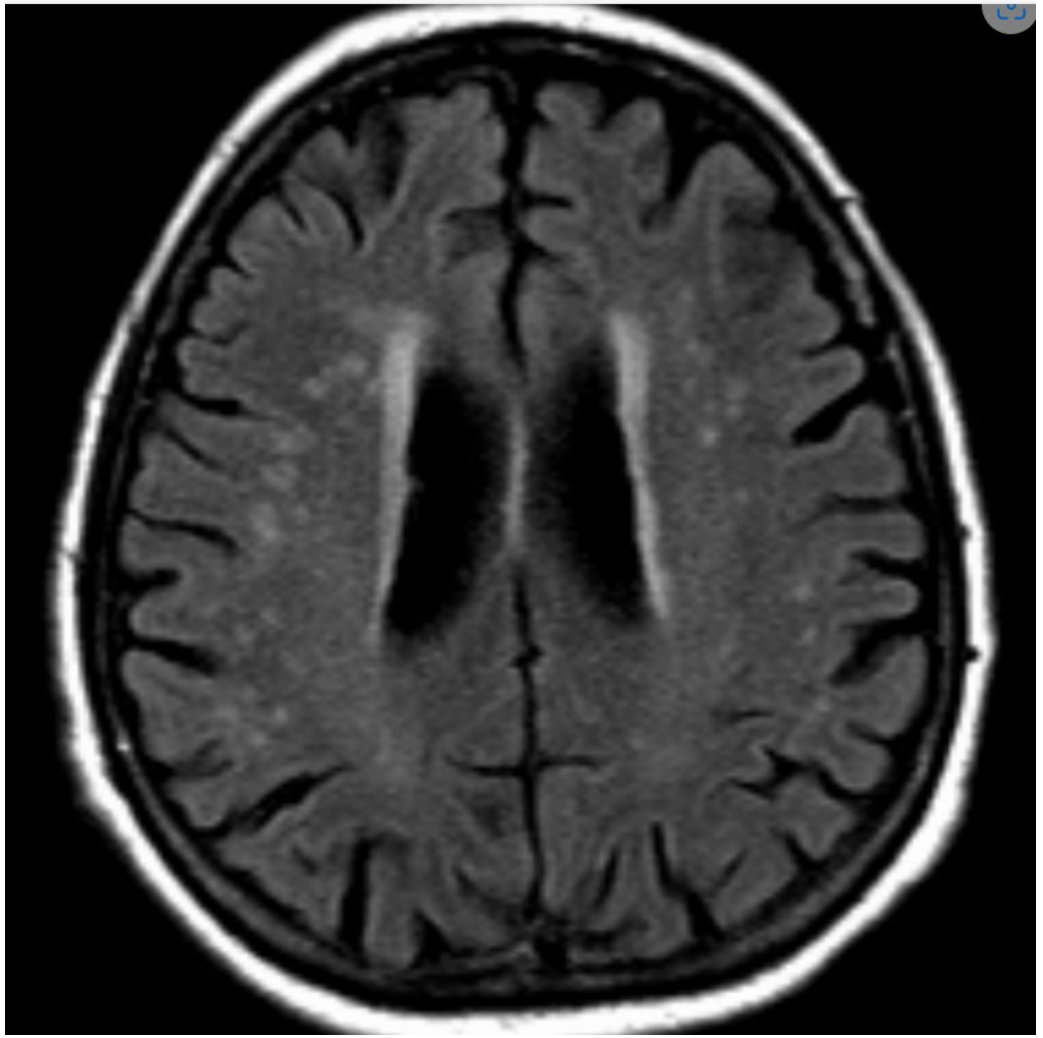
Fast vs slow progressor



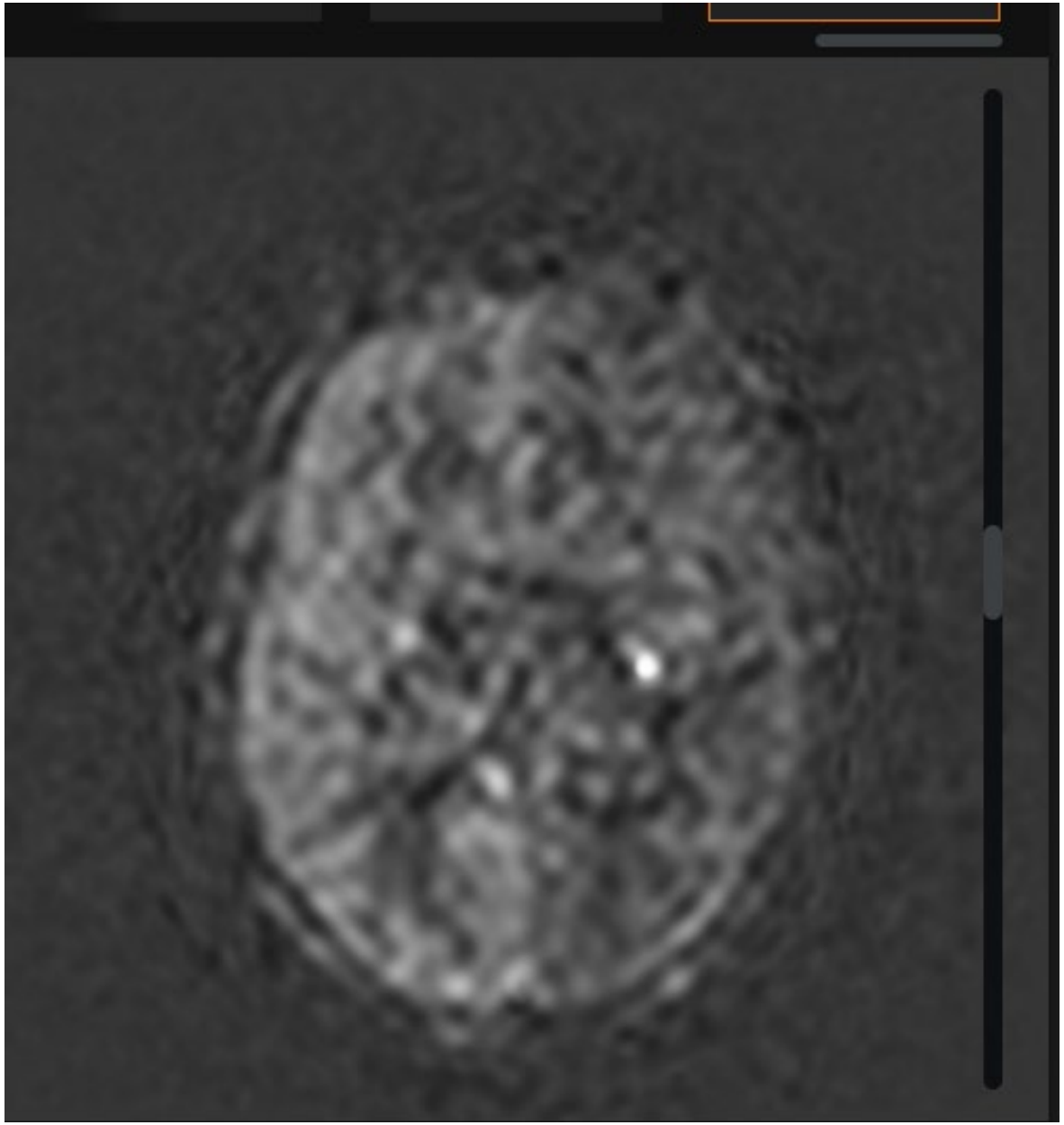
Good, moderate and bad collaterals



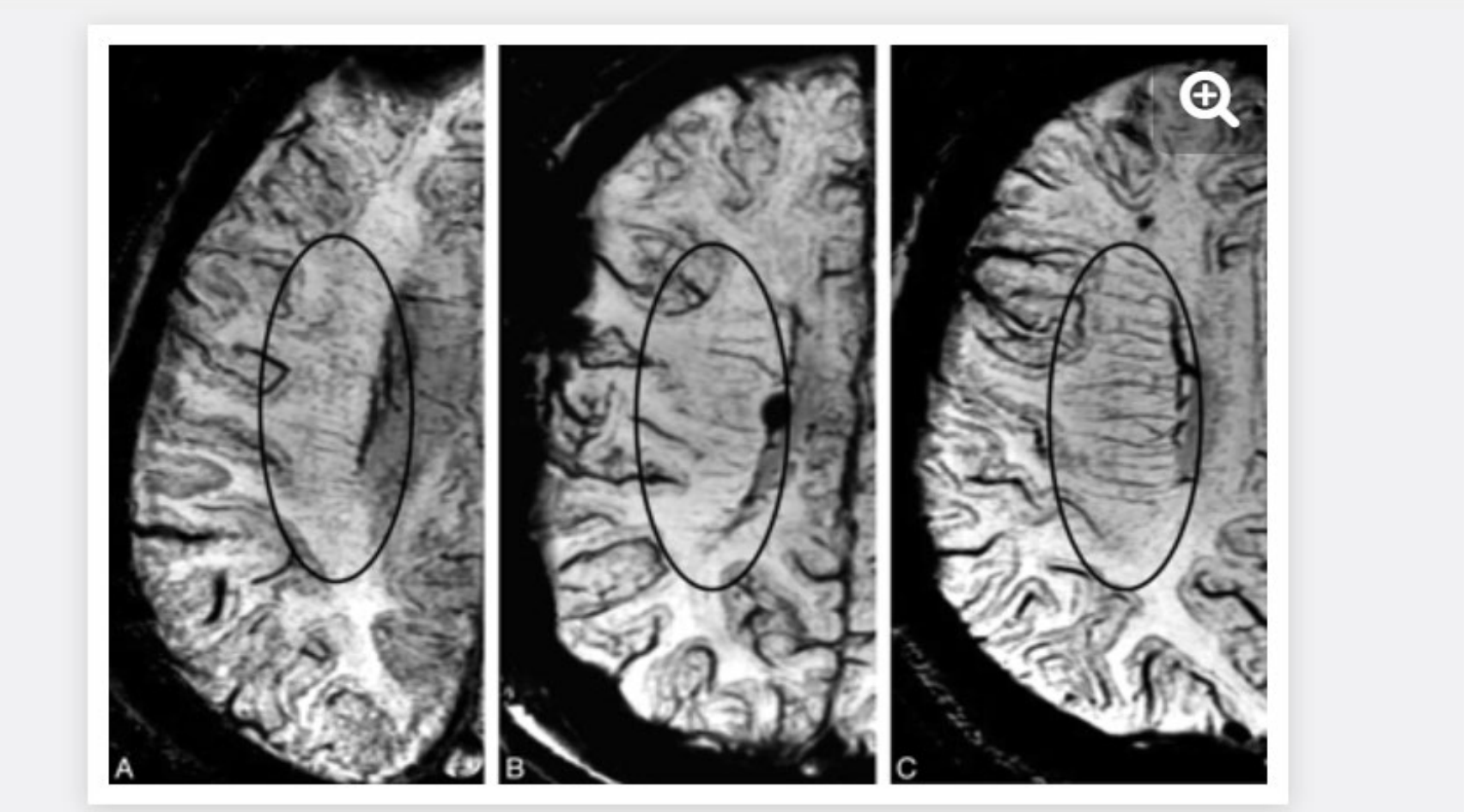
Distal collateral pathways



ASL



Brush Sign



Clinical applications

- **The collateral status might provide insights into the etiology of LVOs**
- **The collateral circulation is a prognostic factor for both clinical and imaging outcomes in ischemic stroke**
- **The collateral circulation has become an important factor to consider when selecting or excluding patients from acute reperfusion therapies**
- **The collateral circulation is an important factor to consider when determining the optimal blood pressure level in the peri-EVT period**
- **The collateral circulation is an important factor to consider when evaluating experimental neuroprotective agents**

Collaterals and Etiology

- A recent meta-analysis in patients with acute stroke receiving reperfusion therapies found that large artery atherosclerosis etiology was associated with a significantly increased rate of pre-treatment good collaterals

(risk ratio [RR] 1.24; 95% CI 1.04–1.50; *P*=0.020) when compared to cardioembolic etiology.

Prognosis

Study	Patients (n)	Collateral scale (method)	Main findings
Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke trials (HERMES) collaboration[75]	1,764 (871 EVT, 893 control)	Tan et al.[76] (sCTA, mCTA, or CE-MRA)	Analyses suggested benefit with EVT across all strata of collateral circulation status; however, patients with poor collaterals were less likely to benefit from EVT than those with better collaterals (not statistically significant).
Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial[77]	130 (65 EVT, 65 control)	Tan et al.[76]	No significant association with good clinical outcome*, sICH, or death. Good collaterals were associated with significantly smaller ischemic core volume and less ischemic core growth.
Diffusion-Weighted Imaging or Computed Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) trial[92]	161 (91 EVT, 70 control)	Tan et al.[76] (CTA) ASITN/SIR[78] (DSA)	Significant association between collateral status and infarct core at 24 h, ASPECTS at 24 h, successful revascularization (eTICI ≥2b), good functional outcome*, and death.
Gerber et al.[79]	93	Tan et al.[76]	Good collaterals were significantly associated with good clinical outcome* (OR 9.69; 95% CI 2.28–59.27; *P*=0.001).
Sedation versus Intubation for Endovascular Stroke TreAtment (SIESTA) trial[80]	104	Tan et al.[76]	Good collaterals were significantly associated with smaller final infarct volume, improvement in the mean NIHSS at 24 h, and in-house mortality. No significant association was found with functional outcome or 3-month mortality.
Sallustio et al.[81]	135	Tan et al.[76] (CTA) Christoforidis et al.[82] (DSA)	Significant association between good collaterals and good functional outcome* (OR 2.13; 95% CI 1.44 to 3.15; *P*<0.001), lower mortality rate, lower rate of sICH, higher ASPECTS at 24 h, and higher NIHSS improvement at 24 h.
Park et al.[83]	119	Regional colateral scoring system[84]	Good collaterals were an independent predictor of good functional outcome* (OR 5.14; 95% CI 1.62–16.26; *P*=0.005).
Renú et al.[85]	339 (257 EVT, 82 no EVT)	Tan et al.[76]	The benefit of EVT (reduction in infarct growth, functional outcome, and mortality) was significantly higher in patients with poor collaterals.
Weiss et al.[86]	84	Tan et al.[76] (sCTA) Miteff et al.[87] (sCTA) Maas et al.[88] (sCTA)	Good collaterals in the Miteff and Maas scores were significantly associated with good functional outcome*.
Al-Dasuqi et al.[89]	283	Miteff et al.[87] (sCTA)	Collateral grade was significantly associated with final infarct volume but not with functional outcome.
Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT) study[90]	361 (285 EVT, 76 medical management)	mCTA[40]	Collateral status was significantly associated with early infarct growth rate which in turn was significantly associated with functional outcome.
Endovascular Treatment in Ischemic Stroke (ETIS) Registry[91]	2,020	ASITN/SIR (DSA)	Good collaterals were associated with successful reperfusion (OR 1.77; 95% CI 1.32–2.39; *P*<0.001), excellent reperfusion (OR 1.71; 95% CI 1.41–2.09; *P*<0.001), and good functional outcome* (OR 1.5; 95% CI 1.19–1.88; *P*<0.001), but not with sICH or mortality at 3 months.

EVT, endovascular thrombectomy; sCTA, single-phase computed tomography angiography; mCTA, multiphase computed tomography angiography; CE-MRA, contrast-enhanced magnetic resonance angiography; sICH, symptomatic intracranial hemorrhage; CTA, computed tomography angiography; ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology scale; DSA, digital subtraction angiography; ASPECTS, Alberta Stroke

Exclude or not

- The latest American Heart Association/American Stroke Association guidelines suggest that it may be reasonable to incorporate collateral flow status into clinical decision-making in some candidates to determine eligibility for mechanical thrombectomy with a IIb level of evidence. No specific criteria are suggested.

Patients with low ASPECTS

- In a retrospective analysis of 100 patients with LVO and ASPECTS ≤5 who were treated with EVT, a good

collateral status and younger age (<73 years) were associated with better functional outcomes

Late time window

- A pooled analysis of late window EVT studies compared patients selected using collateral status plus perfusion imaging (current standard criteria) with those selected using collateral status only.
- They found no significant difference in functional outcomes at 3 months, but sICH was twice more frequent in the collateral only group with no significant difference in mortality at 3 months.

late window EVT with CT and CTA

- Randomization of Endovascular Treatment in Acute Ischemic Stroke in the Extended Time Window (RESILIENTExt, NCT04256096; Brazil) and
- Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands for Late Arrivals (MR CLEAN-LATE, ISRCTN19922220; Netherlands).

BP

- Patients with better collaterals might have better tolerance to BP fluctuations and it has been shown that poor baseline collaterals can aggravate the deleterious effects of higher BP levels or higher BP variability on clinical outcomes

Therapeutic strategies

- Extracranial-intracranial indirect bypass surgery
- Remote ischemic conditioning
- Sphenopalatine ganglion stimulation
- NO donors
- Other vasodilator agents

Extracranial-intracranial indirect bypass surgery

- The EDAS Revascularization for Symptomatic Intracranial Atherosclerotic Steno-occlusive (ERSIAS) trial was a phase-II single-arm trial in patients with symptomatic ICAD (>70% stenosis in the intracranial ICA or M1 segment) and failure to best medical therapy. It compared EDAS plus intensive medical therapy versus intensive medical therapy alone.

- They found a reduction of any stroke or death in the first 30 days or any stroke in the territory of the affected vessel thereafter.

RIC

- RIC is a simple, low-cost, and safe treatment, so the demonstration of its benefit could easily lead to widespread implementation
- In the case of ischemic stroke, clinical studies have not revealed a clear benefit to recommend its use.
- There is low-quality evidence suggesting that postconditioning might have a beneficial effect on clinical and neuroimaging outcome

SPG stimulation

- A parasympathetic ganglion located in the pterygopalatine fossa, could be beneficial in ischemic stroke: vasodilation with the subsequent increase in blood flow through collateral pathways, stabilization of the blood brain barrier, neuroprotection via central cholinergic and adrenergic pathways, and enhancement of neuroplasticity.

- (ImpACT) trials failed to show a significant benefit in the intention to treat population. However, they did demonstrate a significant benefit as an improvement beyond expectation in the mRS in the subgroup of patients with a confirmed cortical infarct, highlighting the importance of adequate patient selection

NO Donors

- Prehospital transdermal glyceryl trinitrate in patients with presumed acute stroke (Multicenter Randomized trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch [MR ASAP]) trial failed to demonstrate a clinical benefit of this treatment when applied within 3 hours of symptom onset in the prehospital setting.

Other vasodilator agents

- There is an ongoing phase 1 multicenter clinical trial for treatment of LVO in patients undergoing endovascular thrombectomy (Safety Study of PP-007 in Subjects With Acute Ischemic Stroke [HEMERA-1]).

- Rapamycin- NO release as a mechanism of collateral enhancement by rapamycin.

- TM5441 is a selective inhibitor of plasminogen activator inhibitor- 1. It has a vasodilator effect that is mediated through NO release.

CONCLUSION

COLLATERAL CLOCK/ TISSUE CLOCK

STROKE THERANOSTICS

QUESTIONS ?

THANK YOU