

Regional Tau Burden Associated With Nitric Oxide-mediated Neurovascular Dysfunction in Mild Cognitive Impairment

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Question: Can multimodal clinical imaging resolve a tau-linked, NO-mediated neurovascular-coupling deficit at the vessel-territory scale?

Background & hypothesis

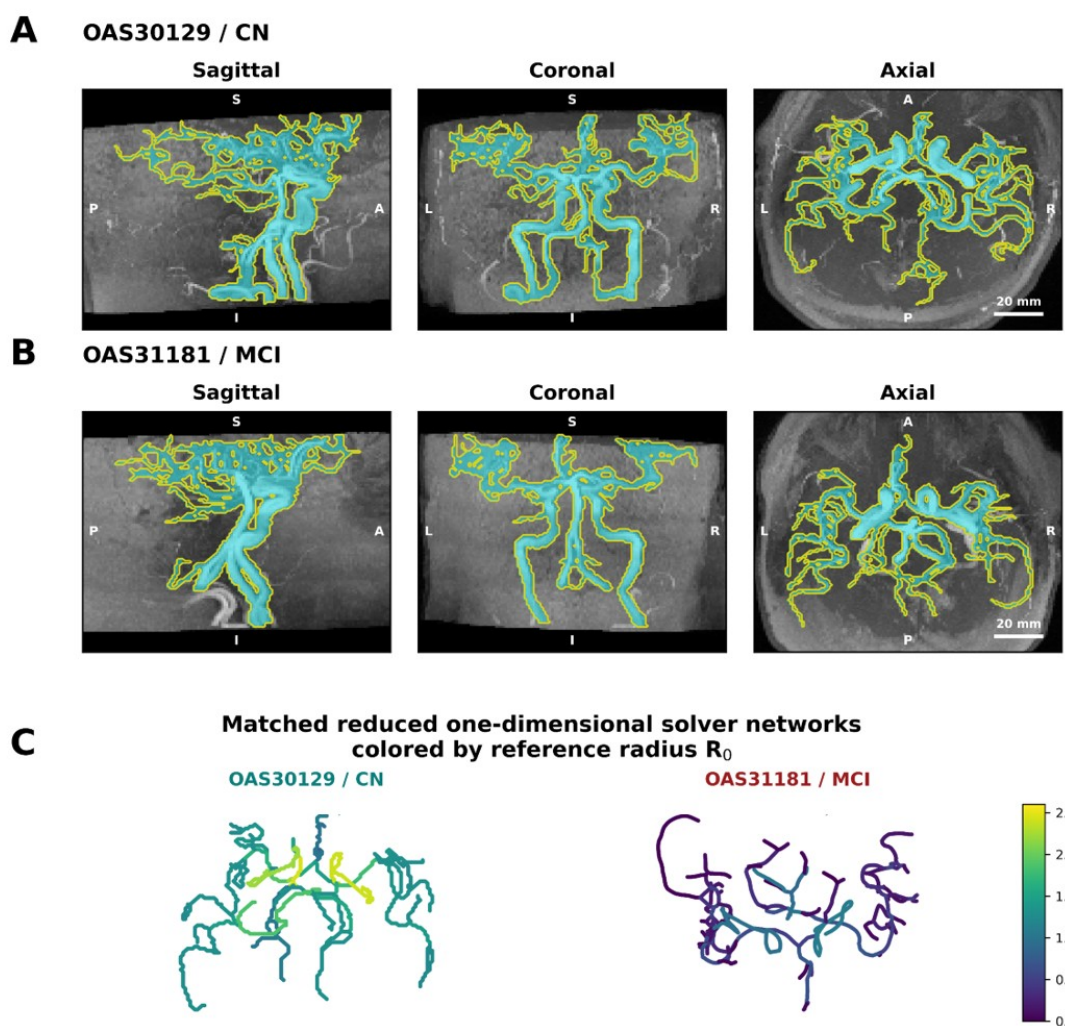
- Vascular dysfunction and hypoperfusion are increasingly recognized as early contributors to Alzheimer disease pathobiology.
- Tau may impair neurovascular coupling by reducing nitric oxide (NO) signaling during activity-driven vasodilation.
- We hypothesized that higher regional tau burden is associated with lower modeled NO-mediated neurogenic vascular responsiveness (η NO).

Objective

Build a subject-specific image-to-hemodynamics workflow that maps TOF-MRA geometry, ASL perfusion demand, and AV-1451 tau PET into a mechanistic autoregulation model.

Cohort & imaging streams

- Six OASIS-3 participants: 3 cognitively normal (CN) and 3 mild cognitive impairment (MCI).
- TOF-MRA: subject-specific arterial centerlines and radii.
- ASL: terminal tissue-perfusion territories integrated to volumetric-flow demand.
- AV-1451 PET: vessel-territory tau SUVR, anchored to SUVR floor 1.32.



TOF-MRA lumen reconstructions and matched reduced solver networks: representative CN (OAS30129) versus MCI (OAS31181).

Quality control

- All modalities were resampled to subject T1 space before sampling.
- ASL and vessel masks showed strong spatial agreement; 98.4% of vascular sampling points fell inside masks.
- Every solved network reached a regulated steady state under the four-mechanism model.

Tau → NO coupling

$$\tau_{\text{vess}} = \text{clip}[(\text{SUVR}_{\text{term}} - 1.32) / (S_1 - 1.32), 0, 1]$$

$$I(\tau) = \tau_{\text{vess}}^2 / (0.5^2 + \tau_{\text{vess}}^2)$$

$$g_{\eta} = \text{clip}(1 - \alpha_{\eta} \cdot I(\tau), 0, 1)$$

$$J_{\text{NO}} = 1000 \cdot (\eta_{\text{NVC}} \cdot g_{\eta}) \cdot S_{\text{vess}}$$

Rising tau raises $I(\tau)$, lowering the NO-gain g_{η} and NO output J_{NO} — the modeled η NO deficit.

where

- $S_0 = 1.32$ SUVR positivity floor; $S_1 = \text{SUVR}$ at full impairment
- $I(\tau)$: Hill-type impairment fraction (half-max at $\tau_{\text{vess}} = 0.5$)
- g_{η} : tau-gain on NO production; α_{η} sets tau-sensitivity
- η_{NVC} : baseline NVC amplitude; S_{vess} : synaptic drive

PET SUVR → vessel-wise τ_{vess} → impairment fraction $I(\tau)$ → attenuated NO production.

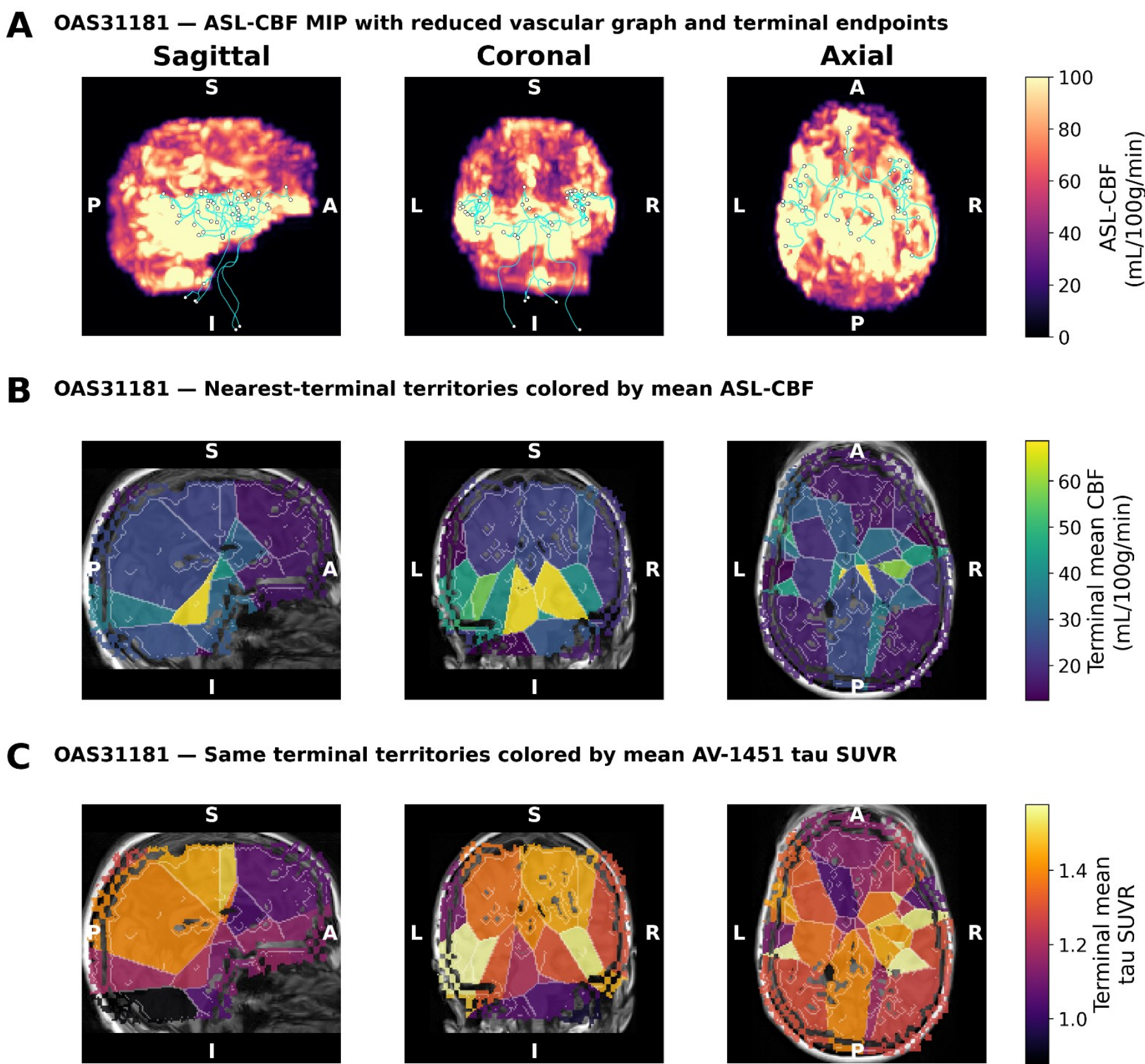
Conclusion

This pilot establishes a clinically grounded image-to-model workflow linking regional tau burden to modeled NO-mediated neurovascular responsiveness. In six OASIS-3 subjects, MCI reconstructions showed a near-threefold reduction in neurogenic regulatory share, motivating validation of η NO as a pathway-specific vascular biomarker that complements AT(N) measures.

Limitations: n = 6 pilot; descriptive, cross-sectional; η NO is model-derived and requires independent validation.

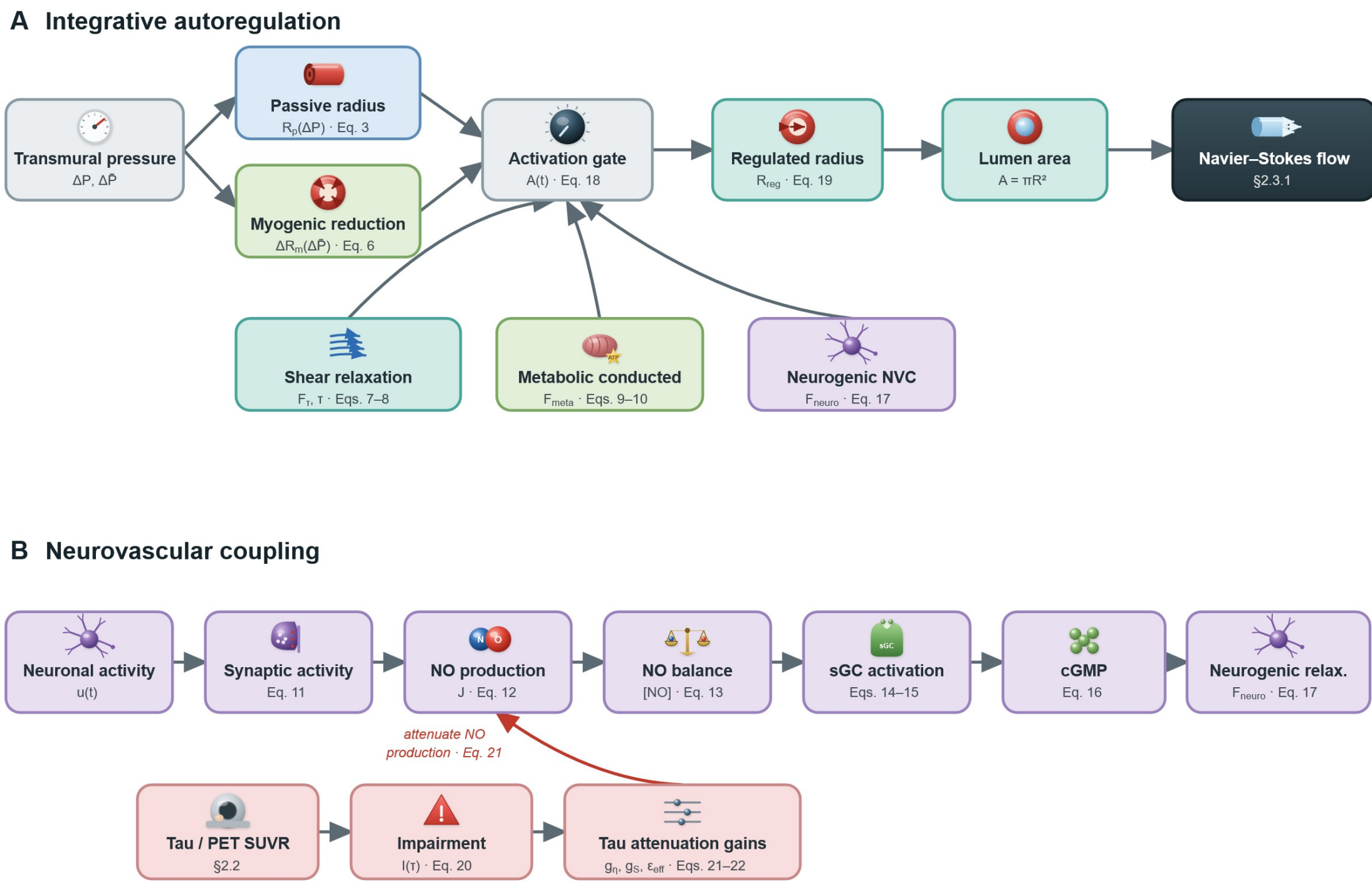
Selected refs: Park 2020 Nat Neurosci; Chen 2023 JAD; Hoiland 2022 J Physiol; Krolak 2025 Cell; LaMontagne 2019 OASIS-3.

Image-derived terminal territories



OAS31181 example: ASL-CBF, nearest-terminal territories, and matched AV-1451 tau SUVR sampled in a common T1 coordinate frame.

Autoregulation model



Four regulatory channels modulate vessel radius: myogenic, endothelial shear-NO, metabolic conducted, and tau-attenuated neurogenic NO-sGC-cGMP signaling.

Model implementation

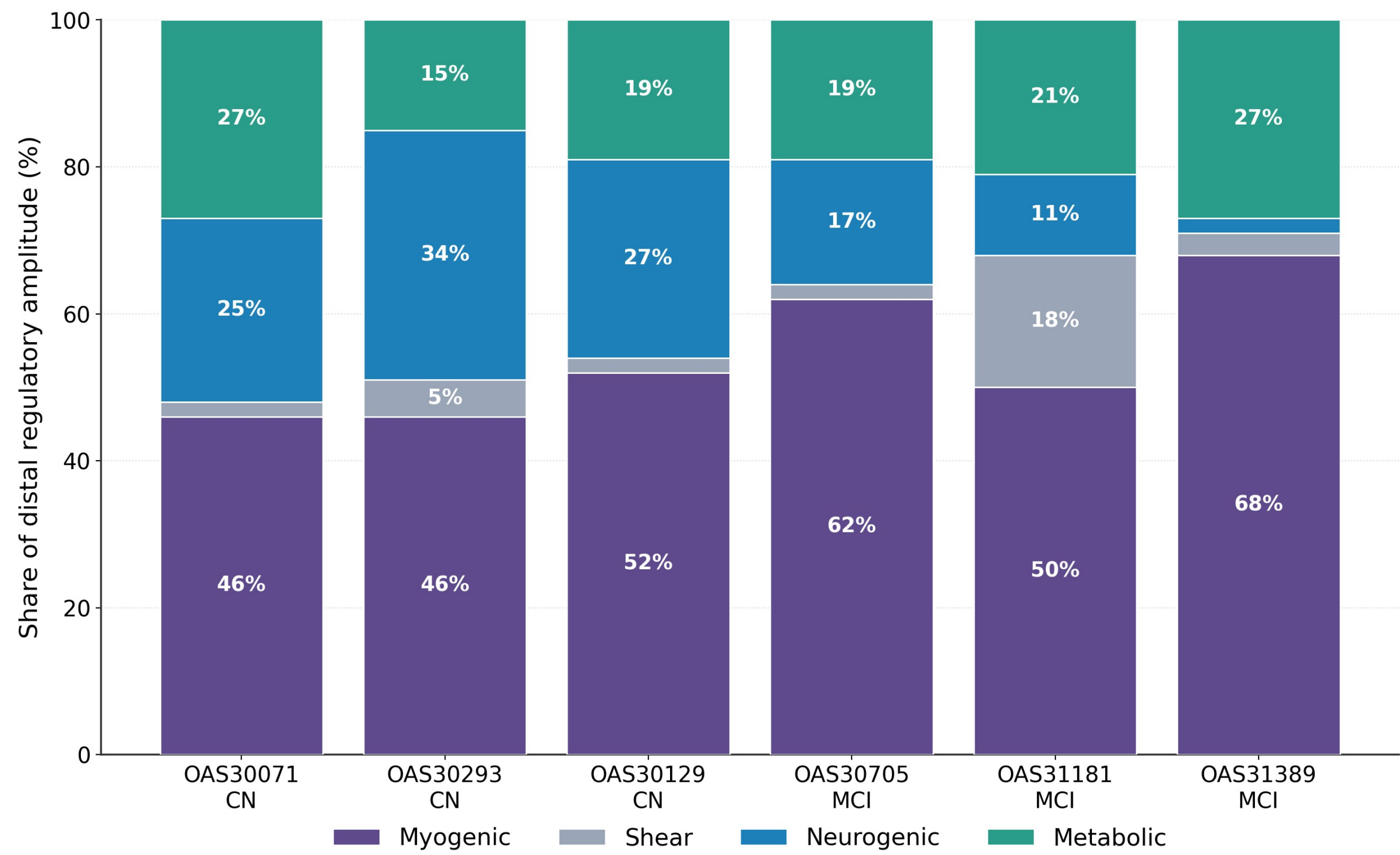
- 1-D autoregulated flow solve in FEniCSx/DOLFINx on TOF-MRA centerline meshes.
- Terminal flows calibrated from ASL-derived territories rather than assuming uniform outlet demand.
- Tau enters only through the neurogenic arm by attenuating NO production and downstream responsiveness.
- Outputs: radius, flow, WSS, Reynolds number, hydraulic resistance, compliance, and mechanism-specific share.

Core readout

η NO = modeled NO-mediated neurogenic vascular responsiveness

A lower η NO means activity-linked vasodilation contributes less to the distal regulatory reserve.

Primary results

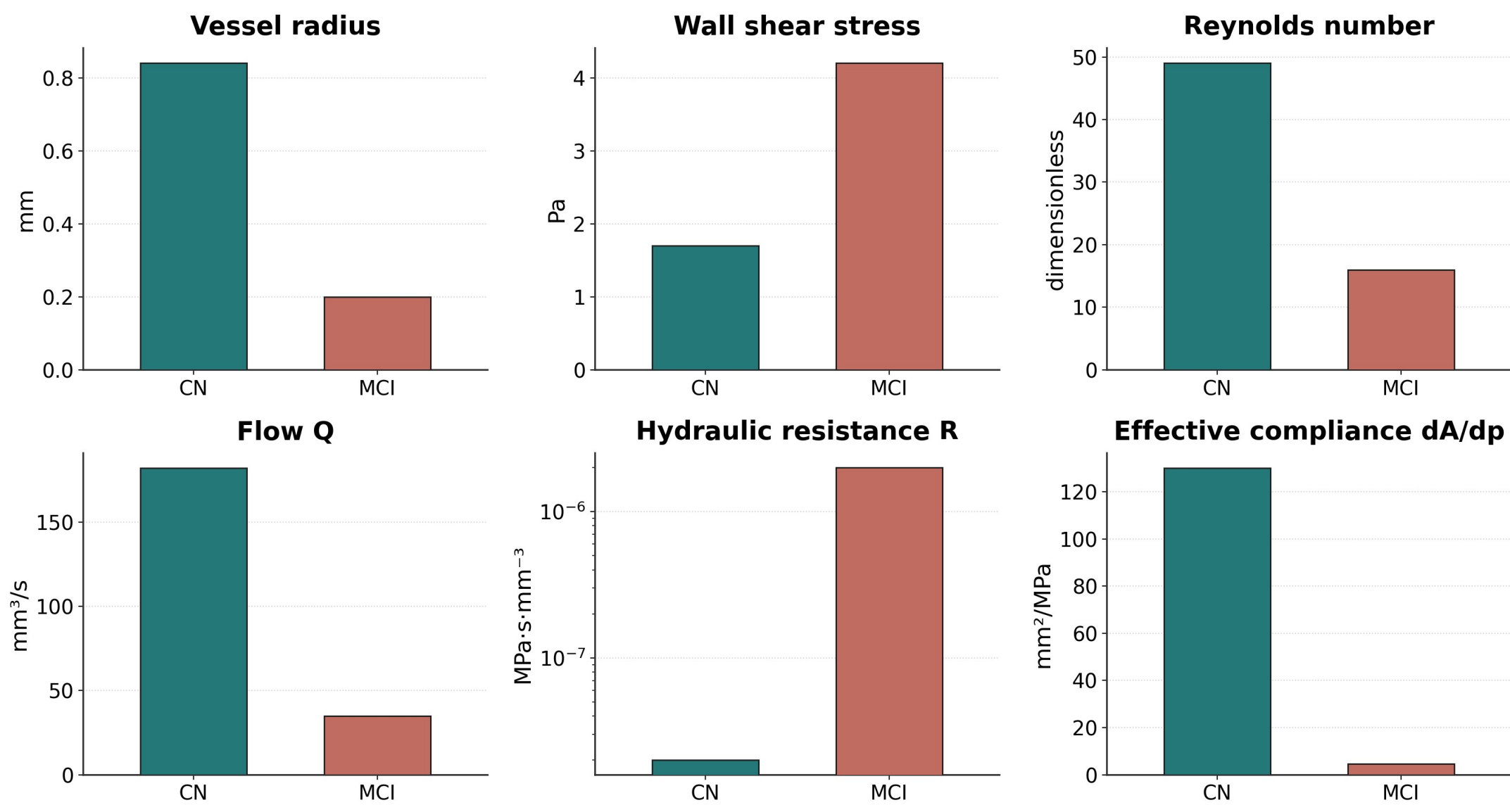


Mechanistic decomposition: neurogenic NO-sGC-cGMP share falls in MCI while myogenic share rises.

Key signal

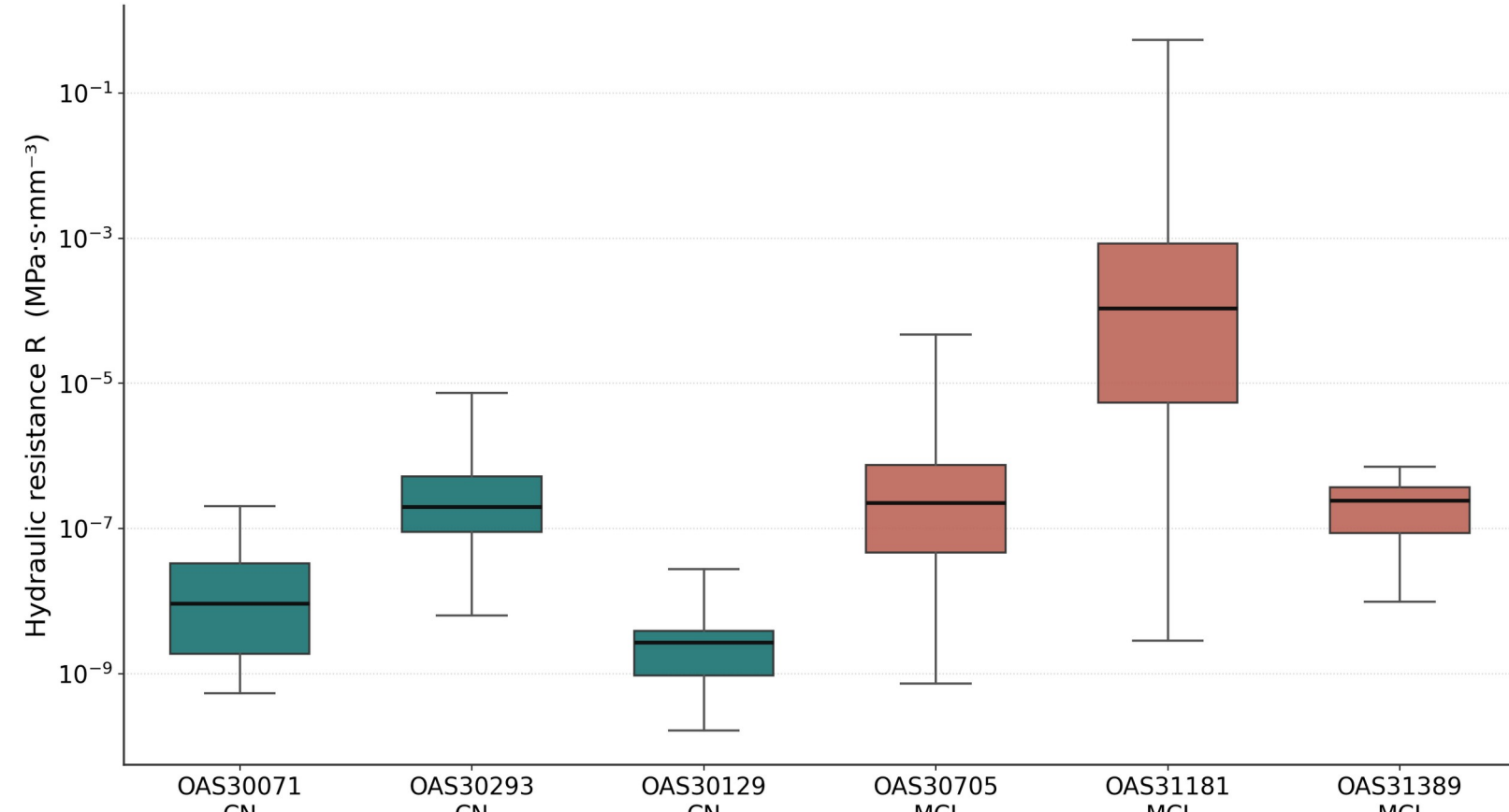
- Neurogenic share: $28.7 \pm 4.7\%$ in CN vs $10.0 \pm 7.6\%$ in MCI.
- Subject-level ranges did not overlap: CN 25–34%; MCI 2–17%.
- Myogenic share increased from $48.0 \pm 3.5\%$ in CN to $60.0 \pm 9.2\%$ in MCI.

CN-versus-MCI group means (per-subject medians)



Group summaries: CN reconstructions showed wider radius, higher flow, higher Reynolds number, lower resistance, and higher compliance; WSS was higher in MCI due to caliber effects.

Per-vessel hydraulic resistance $R = 8 \mu\text{L}/\pi r^4$



Per-vessel hydraulic resistance spans orders of magnitude because $R = 8 \mu\text{L}/\pi r^4$, amplifying small-radius distal segments.

Interpretation

Functional decomposition separated CN and MCI even where caliber or flow overlapped, supporting η NO as a candidate tau-linked vascular signature.

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