Supplementary Table 3. Candidate phenotypes, selection features, and operational considerations for POM across the ischemic stroke continuum

Stroke continuum stage and temporal window	Candidate phenotype or clinical scenario	Clinical, physiological, and imaging selection features	Candidate POM strategy and timing	Treatment target and monitoring	Exclusion, precaution, de-escalation, or stopping criteria	Current clinical status
I Pre-stroke: prevention and conditioning	Hemodynamic vulnerability or impaired cerebrovascular reserve	Symptomatic severe intracranial stenosis or chronic ICA/MCA occlusion; perfusion deficit; reduced cerebrovascular reserve/reactivity; poor collaterals[42–45,58]	Protocolized RIC added to standard secondary prevention; IH only within stable-phase research protocols	Improve cerebral perfusion, reserve, and tolerance to hypoperfusion; monitor blood pressure, symptoms, limb status, adherence, and perfusion/reactivity	No hemodynamic target; severe limb vascular disease, local injury, or RIC intolerance; stop IH for symptomatic hypoxemia, syncope, arrhythmia, or hemodynamic instability	Phenotype-enriched trial target; sustained reduction in recurrent stroke remains unproven
	Vascular or metabolic vulnerability	Hypertension, endothelial dysfunction, obesity, or metabolic dysfunction; clinically stable with adequate cardiopulmonary reserve[46–49,57]	RIC or mild IH as an investigational adjunct to standard risk-factor management	Improve blood pressure, endothelial function, and metabolic adaptation; monitor SpO_2, blood pressure, heart rate/rhythm, symptoms, and metabolic markers	Uncontrolled cardiovascular disease, active arrhythmia, severe pulmonary disease, or poor hypoxia tolerance; stop for chest pain, syncope, or symptomatic hypoxemia	Exploratory, indirect evidence; studies largely involve nonstroke populations and surrogate outcomes
II Pre-reperfusion/ peri-EVT	Anterior-circulation LVO with salvageable tissue	Planned EVT; relatively preserved ASPECTS; limited ischemic core; clinical-core or perfusion mismatch; residual collateral perfusion[28–30,38,97,98]	Early, time-limited, protocolized NBO added to standard EVT; see main Table 1 for dosing	Preserve penumbra and slow core growth; monitor SpO_2, PaO_2, NIHSS, core/mismatch, collaterals, reperfusion, and early infarct volume	No salvageable tissue, large core, or loss of target; de-escalate or stop for persistent hyperoxemia, pulmonary complications, or other oxygen-related adverse events	Candidate adjunct with randomized-trial signals; the optimal phenotype and workflow require validation
IIIa Early post-reperfusion: tissue reperfusion assessment	Residual hypoperfusion or suspected microvascular no-reflow	Persistent CTP/MR perfusion deficit after eTICI 2c–3; distal emboli; delayed inflow or venous outflow; continued infarct growth[33,34,61,63,70,71]	Candidate enrichment phenotype only for imaging- or physiology-guided oxygen-modulation trials	Improve tissue oxygen delivery and microvascular reperfusion and limit secondary infarct growth; monitor perfusion deficit, venous outflow, infarct evolution, NIHSS, and hemorrhagic transformation	Resolution of hypoperfusion, no salvageable tissue, marked hemorrhagic transformation, or reperfusion injury; stop and reassess for rising PaO_2 or neurological worsening	Phenotype-enriched research target; current evidence does not support routine prolonged NBO
IIIb Early post-reperfusion: oxygen de-escalation	Resolved tissue target or persistent hyperoxemia	Systemic hypoxemia corrected; no residual hypoperfusion or salvageable tissue; elevated PaO_2; no indication for continued high FiO_2[31,32]	Promptly reduce FiO_2 or flow and withdraw nonindicated therapeutic hyperoxia	Avoid sustained hyperoxemia and reperfusion-related injury; monitor SpO_2, PaO_2, FiO_2 exposure duration, pulmonary status, and neurological course	Rapidly de-escalate when the warning threshold is reached, the tissue target is lost, or pulmonary injury, seizure, or other oxygen-toxicity signals emerge	Observationally informed de-escalation; PaO_2 >120 mm Hg is a hypothesis-generating warning, not a validated ceiling
IV Subacute/chronic: rehabilitation	Trainable motor deficit with stable cardiopulmonary status	Stable subacute or chronic stroke; persistent gait, endurance, balance, or upper-limb deficits; able to complete intensive or task-specific training[35,80]	Time IH to intensive gait or task-specific training	Enhance motor plasticity and retention; monitor SpO_2, blood pressure, heart rate/rhythm, gait speed, endurance, symmetry, and training tolerance	Active arrhythmia, uncontrolled cardiovascular disease, severe pulmonary impairment, or hypoxia intolerance; stop for chest pain, syncope, or arrhythmia	Early investigational strategy with a randomized phase II functional signal
	Persistent disability considered for HBOT	Persistent motor, cognitive, or activities-of-daily-living impairment in the subacute/chronic phase; suspected perfusion or metabolic deficit; able to tolerate chamber exposure and the treatment course[24,37,81–83]	HBOT only within standardized trials and combined with usual rehabilitation	Explore effects on perfusion, plasticity, and neurovascular repair; monitor functional and cognitive outcomes, walking, perfusion imaging, and oxygen-related adverse events	Uncontrolled seizures, severe pulmonary disease, high barotrauma risk, or inability to complete treatment; stop for barotrauma, seizure, pulmonary toxicity, or other oxygen-related harm	Research use only; inconsistent randomized evidence does not support routine use

This table summarizes candidate phenotypes, selection features, monitoring targets, and de-escalation considerations for POM across the ischemic stroke continuum. The proposed strategies and thresholds are hypothesis-generating and should not be interpreted as validated treatment recommendations. RIC is included as a conditioning strategy with shared adaptive pathways rather than a direct oxygen-exposure intervention. Reference numbers correspond to the revised manuscript.

POM, precision oxygen modulation; ICA, internal carotid artery; MCA, middle cerebral artery; RIC, remote ischemic conditioning; IH, intermittent hypoxia; SpO_2, peripheral oxygen saturation; EVT, endovascular thrombectomy; LVO, large-vessel occlusion; ASPECTS, Alberta Stroke Program Early CT Score; NBO, normobaric oxygen; PaO_2, arterial oxygen tension; NIHSS, National Institutes of Health Stroke Scale; CTP, computed tomography perfusion; MR, magnetic resonance; eTICI, expanded Treatment in Cerebral Ischemia; FiO_2, fraction of inspired oxygen; HBOT, hyperbaric oxygen therapy.

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