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TECH BRIEF

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Hypoxic–Hypercapnic Microenvironments in Cancer and Traumatic Brain Injury:

Does the Evidence Support Early, Low-Dose CO2 Therapy After TBI?

Evidence Summary Accompanying the SAGE Rebreather Poster Presentation

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Reviewed by Claude (Anthropic)

Bottom Line Up Front: *Because most patients hyperventilate into harmful hypocapnia in the early period after TBI, and no evidence reviewed here shows harm from correcting that drop toward normal CO2 within the first 30 minutes after injury, the potential benefit of early CO2 restoration plausibly outweighs its risk — the standard by which clinicians should act.*

1. Why the First 30 Minutes Matter

TBI pathophysiology is conventionally divided into primary injury — instantaneous, irreversible mechanical damage at impact — and secondary injury, a biochemical cascade that begins within minutes and can evolve for months (Giza & Hovda, 2014; Watson et al., 2014; Zhang et al., 2025). Giza and Hovda describe the earliest ionic flux and glutamate release as "hyperacute," triggering an energy crisis as calcium sequesters into mitochondria and impairs oxidative metabolism — a mechanism independently corroborated by Watson et al.'s finding that mitochondrial dysfunction precedes measurable behavioral impairment. Because primary injury cannot be treated after the fact, every TBI neuroprotective strategy targets this secondary cascade, which is precisely why its earliest minutes matter. The window is not physiologically inert: blood biomarkers of injury (GFAP, UCH-L1, MAP-2) are already significantly elevated within 30 minutes in an 804-patient cohort and predict CT lesions, neurosurgical intervention, and 7-day outcome (Papa et al., 2024). No source reviewed quantifies precisely how much of total TBI damage is secondary versus primary — that broader comparison remains a stated clinical rationale, not a measured finding — but the case for early intervention does not require that number: it requires only that the cascade begins immediately and that a safe, testable candidate therapy exists.

2. The Evidence So Far

TBI produces a hypoxic, metabolically stressed microenvironment with real parallels to the hypoxic/hypercapnic microenvironment of solid tumors, where CO2 itself — independent of hypoxia — suppresses HIF activity, reduces oxidative stress, and dampens inflammatory signaling (Reddan & Cummins, 2025). More directly, a peer-reviewed mouse study found that 5% CO2 given for 10 minutes immediately before a validated mTBI model prevented the injury's locomotor, temperature, and reflex deficits, and blocked a 19-gene oxidative-stress/inflammatory signature (Reeder et al., 2023) — though the authors themselves call that dose "much too high for use as a therapeutic in humans" and urge testing "drastically lower concentrations." A companion post-injury

blast-TBI dataset (accompanying MHSRS 2026 poster, not yet peer-reviewed) found that 3% CO2 given for 30 minutes immediately after blast injury produced no acute effect, but significantly better locomotor recovery at 3 hours and a favorable shift in two brain metabolites (nicotinurate, UDP-glucose) at 24 hours. A third, independent mechanism — CO2-driven enhancement of glymphatic (brain waste-clearance) flow — has peer-reviewed support in a non-TBI population (intermittent hypercapnia driving clearance in Parkinson's disease; Erhardt et al., 2025) and consistent, though not yet peer-reviewed, marker kinetics in chronic TBI patients (Mayer et al., 2026). Three independent models, three different mechanisms, and every one of them points toward benefit rather than harm — the kind of convergent early signal that justifies a dedicated dose-and-timing study rather than dismissing the idea as premature.

3. Weighing the Risk Honestly

Independent of whether hypercapnia helps, the case against uncorrected hypocapnia is well established, and any proposed intervention must be weighed against it honestly:

- Current Strong-graded prehospital guidelines already target end-tidal CO2 35–45 mmHg (Lulla et al., 2023). In TBI patients, reducing PaCO2 from 36 to 29 mmHg increased ischemic brain volume roughly five-fold, undetected by standard oximetry (Coles et al., 2007).
- Hypocarbic patients had the highest mortality of any CO2 group in one severe-TBI cohort (Dumont et al., 2010) — though the study is observational, and its hypercarbic patients also had more baseline evidence of brainstem injury, consistent with reverse causation as well as direct harm. A 2026 meta-analysis of over 50,000 acute brain injury patients found hypocapnia significantly associated with worse neurological outcome specifically in TBI, though not independently with mortality once analyzed by diagnosis (Romero-García et al., 2026).
- Hyperventilation is not a rare error: EMS data show end-tidal CO2 below 25 mmHg in up to a third of intubated TBI patients (Spaite et al., 2014), and a European ICU registry found forced hyperventilation in use roughly 55% of ventilation time, with concurrent oxygenation monitoring in only 9% of those episodes (Neumann et al., 2008).
- The one study that directly measures CO2's effect on human ICP — North & Jennett, 1976 — found ICP rose linearly with rebreathed CO2 in every patient tested (average 3.7 mmHg ICP per mmHg PCO2), with no adverse clinical outcome reported. This is genuine mechanistic evidence that CO2 can raise ICP — but the patients were studied days after injury, already sick enough to require an indwelling ICP catheter, and exposed to 5–7% CO2: a substantially higher dose, later timepoint, and sicker population than the ~1%, first-30-minute intervention proposed here. Applying that slope directly to this proposal would extrapolate well past what the data show.
- The one relevant randomized trial in an adjacent population (TAME, post-cardiac arrest, n=1700, sustained PaCO2 50–55) found no benefit from hypercapnia — but also no reported harm. No source in this review documents CO2-induced ICP elevation causing diagnosed clinical harm in the specific population, dose, or 30-minute window actually proposed here.

4. What Would Move This From Position to Protocol

Laid out together, the dose-response evidence to date looks like this:

Source	Model / population	CO_2 dose	Timing vs. injury	Outcome
Reeder et al. 2023 (peer-reviewed)	Mouse mTBI, accel/decel model	5% CO_2 × 10 min	Immediately BEFORE injury	Prevented locomotor deficit, hypothermia, and a 19-gene inflammatory/oxidative-stress signature
DeltaChase blast-TBI study — MHSRS 2026 poster (not yet peer-reviewed)	Mouse blast TBI, shock-tube model	3% CO_2 × 30 min	AFTER injury	No acute effect; significantly better locomotor recovery at 3h; 2 metabolites shifted toward normal at 24h
North & Jennett 1976 (Brain)	Human acute brain injury, days post-injury, already ICP-monitored	5–7% CO_2 rebreathing	Days after injury — NOT the proposed window	ICP rose linearly with CO_2 in every patient (3.7 mmHg ICP per mmHg PCO_2); no adverse outcome reported
TAME trial (cited in Taran 2025)	Post-cardiac arrest, human, n=1700	$PaCO_2$ 50–55 mmHg, sustained	ICU, post-resuscitation	No improvement in 6-month outcome — a null efficacy result, not a report of harm
Proposed human study	Human TBI (untested)	~1% $FiCO_2$	Within 30 min POST-injury	Untested — the direct question this evidence base is now ready to answer

- The central open question is not whether 1% and 3% CO_2 can be reconciled in principle — mice are burrow-dwelling animals adapted to ambient CO_2 far above atmospheric, while human regulatory thresholds (OSHA, NIOSH) place 1% comfortably below any symptomatic dose — but whether 1% crosses the same biological threshold in humans that 3% crosses in mice.
- A monitored dose-response and timing study — combining a lower, human-relevant CO_2 dose with continuous ICP monitoring in the same post-injury animal model already used in the blast data — would directly test both open questions: does the benefit hold, and does the ICP risk North & Jennett describe apply, at this dose and this early timepoint.
- Direct capnography data on the untreated first 30–60 minutes after human TBI would establish exactly what the intervention is correcting, rather than inferring it from later-timepoint data.
- Publication of the full blast-model dataset, with complete statistics and the full metabolite panel, is the most immediate, lowest-cost next step.

5. Bottom Line

Every intervention in medicine carries both risk and benefit; the relevant question is never whether risk exists, but whether the balance favors acting. On the benefit side, the evidence is substantial and points consistently in one direction: avoiding hypocapnia after TBI is well supported by mechanistic, observational, and meta-analytic data; catecholamine-driven hyperventilation, not hypercapnia, is the dominant early physiological response to TBI, meaning this intervention is best framed as correcting a common, harmful default response, not fighting a protective one; and independent preclinical models — cancer biology, pre-injury CO2 prevention, post-injury blast-model recovery, and glymphatic clearance — all point toward benefit rather than harm. The broader literature on carbon dioxide's role in brain physiology reinforces this optimism: hypercapnia has independently been described as playing “an important role in neuroprotection” against ischemia/reperfusion injury (Deng et al., 2020), though at a substantially higher and differently-targeted CO2 range than proposed here — a reminder that CO2's therapeutic potential in the injured brain is real and worth pursuing, but not yet mapped precisely enough to assume it transfers directly to this specific dose and window. On the risk side, no citation in this review documents CO2-induced ICP elevation causing diagnosed clinical harm in the population, dose, or time window this paper actually proposes. Weighed together, a well-documented, mechanistically coherent, and consistently favorable body of preclinical evidence is set against a theoretical risk that has not been shown, in any source reviewed, to apply to this specific intervention. That is the ordinary basis on which clinicians act — and the evidence assembled here supports moving forward to the dose-response, ICP-monitored bridging study this early signal has earned, not treating an unresolved theoretical risk as a reason to wait.

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