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# Brain Shock—Toward Pathophysiologic Phenotyping in Traumatic Brain Injury

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**ABSTRACT:** Severe traumatic brain injury (TBI) is a heterogeneous pathophysiologic entity where multiple interacting mechanisms are operating. This viewpoint offers an emerging, clinically actionable understanding of the pathophysiologic heterogeneity and phenotypic diversity that comprise secondary brain injury based on multimodality neuromonitoring data. This pathophysiologic specification has direct implications for diagnostic, monitoring, and therapeutic planning. Cerebral shock can be helpfully subanalyzed into categories via an examination of the different types of brain tissue hypoxia and substrate failure: a) ischemic or flow dependent; b) flow-independent, which includes oxygen diffusion limitation, mitochondrial failure, and arteriovenous shunt; c) low extraction; and d) hypermetabolic. This approach could lead to an alternative treatment paradigm toward optimizing cerebral oxidative metabolism and energy crisis avoidance. Our bedside approach to TBI should respect the pathophysiologic diversity involved; operationalizing it in types of "brain shock" can be one such approach.

**KEY WORDS:** brain tissue hypoxia; intracranial pressure; neuromonitoring; shock; traumatic brain injury

Outcomes after severe traumatic brain injury (TBI) have not substantially changed over the last 30 years with mortality of 30–40% (1). This, despite almost 200 randomized controlled trials of various interventions for patients in the moderate to severe spectrum (2). A central problem is the current "one-size-fits-all" clinical approach (3–5). The assumption that patients within the traditional groupings (mild-moderate-severe) are homogeneous in terms of types of brain injuries, pathologies, and clinical trajectories, is erroneous (6–8). This viewpoint offers an emerging, clinically actionable classification of the pathophysiologic heterogeneity and phenotypic diversity that comprise secondary brain injury (SBI) based on multimodality neuromonitoring data. The goal is to also motivate terminology that suggests a pathophysiology-based differential diagnosis, such as "Brain Shock" (9). Shock is a life-threatening systemic form of acute circulatory failure associated with inadequate oxygen and energy-substrate delivery and utilization (10). The result is cellular dysoxia, a switch from aerobic to anaerobic metabolism, energy crisis, and if not reversed tissue necrosis. Shock results from a number of often combining mechanisms. This pathophysiologic specification has direct implications for diagnostic, monitoring, and therapeutic planning. Cerebral shock can be helpfully subanalyzed into categories via an examination of the different types of brain tissue hypoxia and substrate failure: a) ischemic or flow dependent; b) flow-independent, which includes oxygen diffusion limitation, uncoupling due to mitochondrial failure, and arteriovenous shunt; c) low extraction; and d) hypermetabolic. All types of hypoxias share a failing cerebral metabolic rate of oxygen consumption ($CMRO_2$) (11); they differ in their varied pathomechanisms and consequently on their management approaches (**Fig. 1**



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illustrates the mechanisms discussed; **Table 1** reviews pathophysiology, neuromonitoring signatures, and targeted management).

## FLOW-DEPENDENT

Ischemic hypoxia (low cerebral blood flow [CBF]) has long been thought as the predominant cause of SBI. This paradigm motivated management strategies directed at enhancing oxygen delivery by augmentation of cerebral perfusion pressure (CPP) and CBF, either via the increase of mean arterial pressure (MAP) or via reduction of intracranial pressure (ICP). However, clinical strategies using indiscriminate augmentation of CPP did not improve, and may be associated with worse, clinical outcomes (13, 17). On pathophysiologic grounds and based on the CBF pressure autoregulation curve, the most vulnerable time for ischemia occurs when the relationship between MAP and CBF is linear, or codependent, and below the lower inflection point of the autoregulatory curve (exceeding the upper inflection point risks hyperemia, breakthrough loss of vascular reactivity leading to vasodilation, luxury perfusion, and intracranial hypertension) (18). The ability to address ischemic hypoxia due to inadequate CBF, and prevent hyperemia, may be enhanced by using bedside techniques that assess

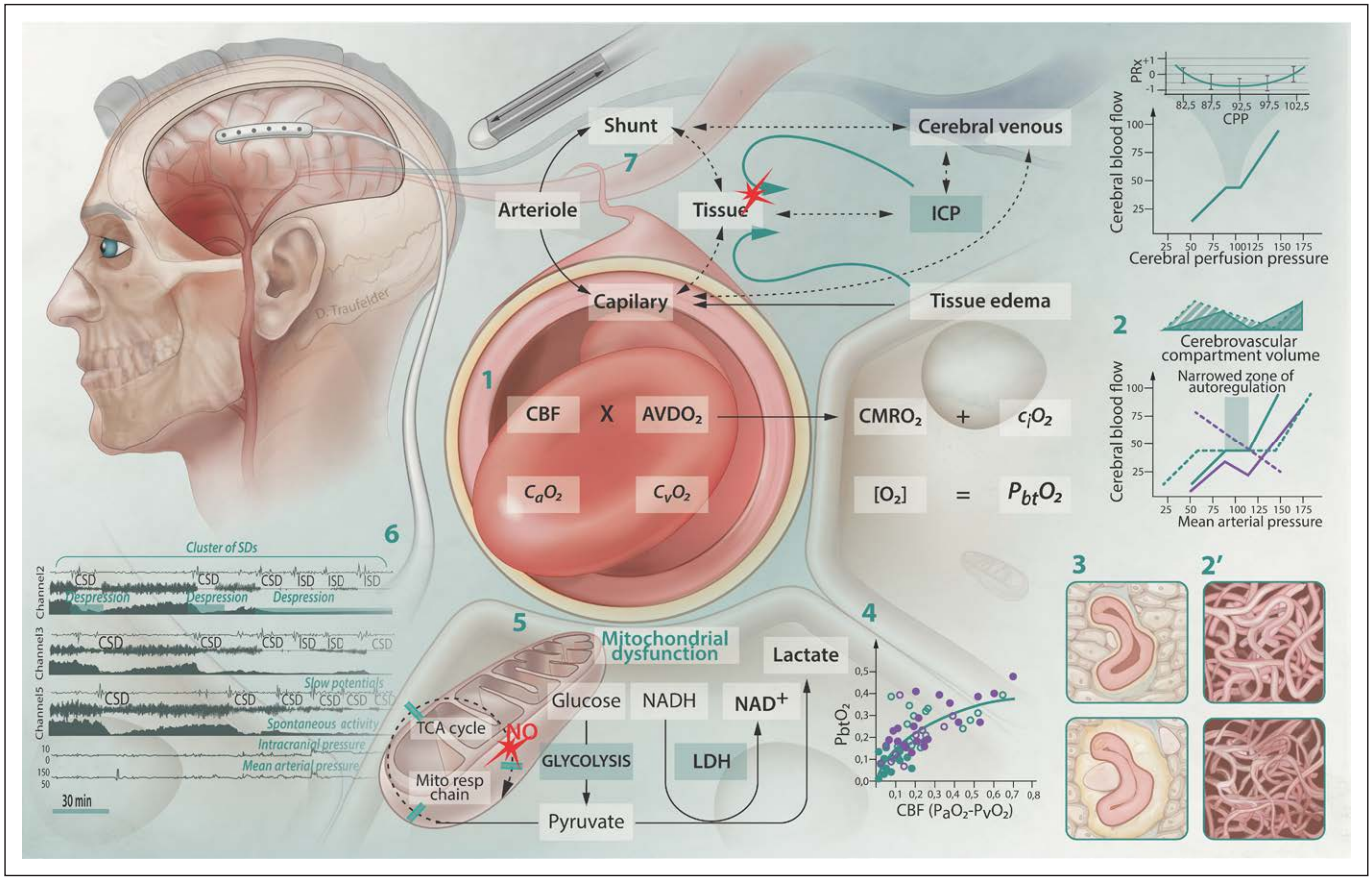


**Figure 1.** Mechanisms of secondary injury after brain trauma. Illustration of the various mechanisms discussed in the text. 1. According to the Fick principle, the total amount of oxygen that crosses the blood-brain barrier into the cerebral tissue must be equal to the product of the cerebral blood flow (CBF) and the arteriovenous oxygen content difference ($AVDo_2$) (see Rosenthal et al [12]); 2. The Lassen CBF pressure autoregulation curve is depicted with *right* and *left shifts*, as well as U-shape relationship described between the pressure reactive index (PRx) and cerebral perfusion pressure (CPP) (see Aries et al [13]); 2′. Depiction of normal (pressure-reactive) versus partially collapsed (pressure-passive) microvasculature; 3. Illustration of barrier to oxygen diffusion (see Menon et al [14]); 4. Relationship between CBF and arteriovenous oxygen tension difference (see Rosenthal et al [12]); 5. Mitochondrial dysfunction; 6. Cortical spreading depolarization and depression (see Hartings et al [15]); 7. Shunt physiology due to increased capillary transit time heterogeneity (see Bragin et al [16]). $Cao_2$ = arterial oxygen content, $C_iO_2$ = concentration of interstitial oxygen, $CMRo_2$ = cerebral metabolic rate of oxygen consumption, CSD = cortical spreading depression, $C_vO_2$ = cerebral venous oxygen content, ISD = isoelectric spreading depression, LDH = lactate dehydrogenase, NAD = nicotinamide adenine dinucleotide, NADH = nicotinamide adenine dinucleotide + hydrogen, ICP = intracranial pressure, $Pbto_2$ = partial brain tissue oxygen tension, $P_vO_2$ = partial venous oxygen tension, TCA = tricarboxylic acid.

**TABLE 1.**
**Brain Shock: Pathophysiologic Types, Neuromonitoring Signatures, and Management**

| Type | Pathophysiology | Neuromonitoring Pattern | Management |
|---|---|---|---|
| Flow-dependent | Inadequate CBF | ↓$Pbto_2$ ↓glucose ↓pyruvate<br>↑Lactate<br>↑LPR | Cerebral perfusion pressure augmentation; optimize hemodynamics; assess pressure reactivity; improve rheology |
| Flow-independent, diffusion barrier | Intracellular and/or interstitial edema; microvascular failure | ↓$Pbto_2$<br>≅ Glucose<br>↑Lactate<br>↑LPR | Decrease cerebral edema; hyperoxia(?) |
| Flow-independent, mitochondrial failure | Primary mitochondrial failure | ≅ $Pbto_2$<br>↓Glucose<br>≅↑Pyruvate<br>↑Lactate<br>↑LPR | Cyclosporine and succinate have been tried; hyperoxia (?); ketones (?) |
| Flow-independent, capillary transit time heterogeneity | Microvascular shunting; luxury perfusion | ↑CBF⇒↓$Pbto_2$<br>(↑Glucose↑lactate?) | Intracranial pressure control; hyperventilation; hypothermia |
| Low extraction | Low $Pao_2$ low hemoglobin<br>Low pressure at 50% hemoglobin saturation | ↓$Pbto_2$<br>≅ Glucose ↓pyruvate<br>↑Lactate<br>↑LPR | Improve oxygenation; transfuse; optimize conditions for hemoglobin oxygen offloading |
| Hypermetabolic | Pathologic increase in substrate demand | ↓$Pbto_2$ ↓glucose ↓pyruvate<br>↑Lactate<br>↑LPR | Temperature control; sedation; monitor and control seizures and cortical spreading depression and cortical spreading depolarizations; glucose-sparing hypertonic lactate or ketones (?) |

≅ = denotes no change or cannot predict, CBF = cerebral blood flow, LPR = lactate pyruvate ratio, $Pbto_2$ = partial brain tissue oxygen tension.

in real time the status of cerebrovascular pressure reactivity, and to determine patient-specific optimal CPP (19, 20). Flow dependency is not only an issue for oxygen but also for glucose delivery; neuroglycopenia can be an independent cause for energy crisis (21). Recent studies employing multimodality imaging and invasive tissue monitoring suggest that flow-dependent cerebral energy crisis—that is, ischemia due to low CPP/CBF—is not the sole and may not be the dominant SBI mechanism beyond the resuscitative phase (21–23).

## FLOW-INDEPENDENT

Augmenting CBF may not correct critically low $CMRo_2$ in the presence of a barrier to oxygen diffusion or a primary failure in oxygen utilization due to mitochondrial dysfunction (14,24). These mechanisms are being deciphered by combining neuroimaging (MRI, PET) and tissue monitoring modalities that provide partial brain tissue oxygen tension ($Pbto_2$) and biochemical parameters via cerebral microdialysis (CMD) (22, 25). The latter, by assaying brain tissue lactate and pyruvate provides for an indicator of cellular redox state, the lactate/pyruvate ratio (LPR), as well as cerebral glucose (23, 26). Shunt physiology is characterized by reductions in $CMRo_2$ without corresponding increase in oxygen extraction fraction (OEF). Explanations for this failure to enhance OEF could fit with diffusion limitation or uncoupling hypoxia resulting from

mitochondrial failure (27). Differentiating could have clinical implications if hyperoxia, as has been proposed, may be used to overcome diffusion limitation (28), whereas mitochondrial failure could be a target for novel neurotherapeutics (29–31). The biochemical pattern obtained during mitochondrial dysfunction has been described both in experimental animal and clinical human studies (24, 32, 33). In a flow-dependent state where flow is inadequate, one expects decrease in $Pbto_2$ and rapid increase in LPR. This is due to anaerobic consumption of pyruvate and production of lactate. In addition, as delivery of glucose is also interrupted, pyruvate further decreases (LPR thresholds of > 25 and > 40 have been identified as critical in the literature; cerebral glucose is considered critically low below a threshold of 0.8–1 mM) (34). Flow-dependency can then be classified by high LPR accompanied by low glucose and pyruvate and high lactate.

In primary (vs secondary post-ischemic) mitochondrial dysfunction, $Pbto_2$ should remain largely unaffected; nevertheless, there is a failure of oxidative metabolism and energy crisis. Hyperglycolysis ensues leading to large production of lactate driving a high LPR; however, tissue pyruvate is not consumed and remains normal or even slightly increases. Other causes for LPR elevation should also be considered particularly in mixed patterns or when responses to targeted interventions do not follow expectations (35). Another mechanism of more direct, anatomical, and functional shunting accords with observations of altered capillary flow patterns during intracranial hypertension and how they affect local oxygen delivery (16, 36). Extreme heterogeneity of RBC transit times across cerebral capillaries has been observed, a phenomenon known as capillary transit time heterogeneity (CTTH) (37). Increases in CTTH were shown to reduce the maximum achievable OEF for a given CBF and tissue oxygen tension. This creates arteriovenous shunting, where an increasing proportion of erythrocytes pass through the capillary at transit times too short to permit proper oxygen extraction. Microvascular shunting has been shown to occur under experimental conditions of raised ICP or due to capillary collapse, vasospasm, or microthrombosis (37). Luxury perfusion syndrome is caused by increased CTTH coupled with high CBF leading to a reduction in OEF that may either fail to improve tissue oxygenation or lead to a paradoxical reduction in $Pbto_2$ during episodes of increased CBF (38).

## LOW EXTRACTION

Low-extraction hypoxia refers to situations of low $Pao_2$ (hypoxemic hypoxia), low hemoglobin concentration (anemic hypoxia), or low half-saturation tension (high-affinity hypoxia) (11). The main determinants of $Pbto_2$ are thought to be CBF and cerebral arteriovenous oxygen tension difference, establishing a strong association between brain tissue oxygen tension and diffusion of dissolved plasma oxygen across the blood-brain barrier (12). It follows, both CBF and $Pao_2$ ought to be optimized when targeting $Pbto_2$ levels.

## HYPERMETABOLIC

The hallmark here is demand exceeding supply. Characteristic causes are seizures and hyperthermia. Another electrical phenomenon, not captured by surface electroencephalography, relates to cortical spreading depression (CSD), resulting from self-propagating waves of neural and astrocyte depolarization known as cortical spreading depolarizations; CSD can be elicited by focal ischemic injury, TBI, and hemorrhage. These waves may lead to depressed spontaneous cortical activity for periods lasting minutes to hours, can precipitate energy crisis, and have prognostic implications (15). Elevated cerebral glucose demand, if not met will lead to a reduction of the cerebral metabolic rate of glucose (CMRgluc) and a decreased availability of cerebral extracellular glucose (another possible issue is glucose diversion to the pentose phosphate cycle during cellular stress [39]). Lactate supplementation may be used to compensate for decreased CMRgluc acting as a glucose-sparing substrate (40–42). There is increasing interest in exploring alternative cerebral energy substrates—such as lactate and ketone bodies (β-hydroxybutyrate and acetoacetate) that may further improve mitochondrial function (43). Some authors, on the basis that the metabolic efficacy of lactate supplementation depends on functional mitochondria, recommend that a prior assessment of oxidative capability would be required before exogenous lactate supplementation (44).

## LIMITATIONS

Advances in multimodality neuromonitoring aspire to move treatments from a one-size-fits-all approach toward patient-specific precision. Nevertheless, there are several difficulties that should be considered moving forward. **Local Measurements Systemic Actions:** Indices such as $Pbto_2$ and LPR are derived from regional probes sampling a small volume of brain tissue. Therefore, caution is needed as one combines local with global (e.g., ICP/CPP) data and in employing regional data to inform interventions that have systemic effects. This becomes further salient in situations where regional heterogeneity would in fact lead to conflicting treatment plans (a situation where different parts of the brain demonstrate divergent and opposing physiology, e.g., hyperemia and ischemia coexisting [25]). **Time and Space Heterogeneity:** There is also a temporal component that needs attention and should lead to frequent reassessments and dynamic treatment decisions. A problem for CMD is that until recently, it is implemented via hourly samples. There is also though the issue of temporal associations in how the different variables interact that may affect interpretation of observed patterns (e.g., see change-point analysis looking at temporal association of high-frequency periodic discharges onset and $Pbto_2$ reduction [45]). **Tissue And Patient Outcomes:** Local tissue monitoring and targeted interventions may be expected to improve the observed local physiology; however, this may not translate to improved patient outcomes. The information collected is several steps removed from the many factors that interplay in delivering long-term clinical outcomes. The aims should primarily be understood as deciphering pathophysiologic states and informing interventions with favorable benefit-risk ratios.

## CONCLUSIONS

TBI is a highly heterogeneous pathophysiologic entity where multiple interacting mechanisms are operating. This becomes evident in examining the known or hypothesized routes of neuronal oxidative metabolic compromise. These mechanisms can be usefully classified via analysis of the different classes of tissue hypoxia and substrate delivery, and several of them can now be investigated and monitored at the bedside in real time. This approach could lead to an alternative treatment paradigm toward $CMRo_2$ targeting and energy crisis avoidance to supplement the conventional ICP/CPP targets. The common measures of augmenting blood flow, increasing perfusion pressure and decreasing ICP are going to be appropriate only for certain patients but will have no effect or can be harmful for others. Furthermore, measures such as hyperoxia, control of abnormal electrical phenomena, and novel neurotherapeutics may require further attention to reverse flow-independent mechanisms of energy crisis. It is becoming evident that to improve neuronal and clinical outcomes, we should move away from "one-size-fits-all" and toward precision strategies. Our bedside approach to TBI should respect the pathophysiologic diversity involved; operationalizing it in types of "brain shock" can be one such approach.

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