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Cerebrospinal Fluid Acid-Base Physiology in Critical Illness: A Stewart Physicochemical Interpretation

Abstract

Cerebrospinal fluid (CSF) constitutes the physicochemical milieu bathing the brain and brainstem and can diverge from arterial blood in both magnitude and time course during critical illness. This review synthesizes human and experimental evidence relevant to a Stewart physicochemical interpretation of CSF acid-base physiology, emphasizing compartmental kinetics, blood–CSF barrier and choroid plexus transport, and methodological constraints that complicate measurement. Because CSF contains minimal weak-acid buffering under physiological conditions, CSF pH is often dominated by PCO_2 and strong ion difference (SID), making CSF a tractable compartment for compartment-aware physicochemical reasoning. Classical clinical observations and modern simultaneous CSF–arterial datasets in pregnancy and aneurysmal subarachnoid hemorrhage illustrate paired shifts in SID and PCO_2 that are not inferable from arterial blood gases alone. Transporter-dependent recovery from hypercapnia, pH-sensitive ion fluxes, and chloride-linked transport perturbation studies support that CSF acid-base homeostasis is actively regulated and plausibly vulnerable in neuroinflammation and brain injury. We outline ICU implications, focusing on why arterial normalization may not ensure central normalization and why time-resolved ventricular datasets are the key prerequisite for bedside translation.

Introduction

CSF is not merely a passive ultrafiltrate of plasma. It is the physicochemical environment bathing the brain and brainstem and therefore sits at the interface of two ICU priorities: ventilatory management and neurological physiology. In critically ill patients, particularly those with acute brain injury, clinicians routinely manipulate ventilation to control arterial pH and $PaCO_2$. Yet the therapeutic targets that matter for central chemosensitivity and cerebrovascular tone are more plausibly CSF and brain extracellular chemistry, which can diverge from arterial blood in both magnitude and time course[1].

The mechanistic basis for this dissociation is kinetic and compartmental. CO_2 crosses the blood–brain and blood–CSF interfaces rapidly, whereas ionic and other non-volatile components (for example chloride, lactate, and bicarbonate-equivalent handling) are constrained by barrier transport and therefore equilibrate more slowly and often incompletely. Clinically important mismatch states can follow: arterial blood gases appear corrected while CSF chemistry remains displaced (or vice versa), with potential consequences for respiratory drive and neurovascular regulation[1]. Classic clinical observations in systemic metabolic derangements similarly show that CSF acid-base relationships are not reliably inferable from plasma alone[2].

Pre-Stewart clinical work already anticipated the clinical relevance of the central compartment. Serial paired blood–CSF observations in severe systemic acid-base disorders showed that neurological status correlated more closely with CSF pH than with arterial acidemia alone, and that blood and CSF can evolve on different trajectories during illness and treatment[3]. These observations align with the ICU reality that arterial variables are readily manipulated, while central variables are coupled through barriers with distinct kinetics.

Stewart's physicochemical framework offers a coherent language for this compartmental problem because CSF composition differs from plasma. Under physiological conditions CSF has very low protein and weak-acid buffering, so CSF pH is often dominated by PCO_2 and strong ion difference (SID), with total weak non-volatile acids (ATOT) playing a smaller role than in blood[1]. This simplification is meaningful in contrast to plasma, where weak-acid (protein) charge chemistry complicates modeling and interpretation[4]. Within Stewart's formulation:

$$pH = f(\mathrm{PCO_2},\ \mathrm{SID},\ \mathrm{ATOT}), \tag{1}$$

and a pragmatic operational definition of CSF SID is:

$$\mathrm{SID_{CSF}} \approx \left([\mathrm{Na^+}] + [\mathrm{K^+}] + [\mathrm{Ca^{2+}}] + [\mathrm{Mg^{2+}}]\right) - \left([\mathrm{Cl^-}] + [\mathrm{Lactate^-}] + \ldots\right) \tag{2}$$

Because ATOT is typically small in normal CSF, bicarbonate is best treated as a dependent readout of electroneutrality and CO_2 chemistry rather than a controlling variable. This perspective is consistent with Stewart-quantitative development and clinical translation in critical care[5,6,7].

Recent simultaneous CSF–arterial studies provide clinically relevant constraints. In late pregnancy, sustained hypocapnia is accompanied by coordinated changes in CSF and plasma physicochemical variables and altered CSF–plasma gradients, consistent with compartment-specific setpoints and adaptation rather than simple arterial mirroring[8]. In neurocritical care, spontaneously breathing patients with aneurysmal subarachnoid hemorrhage (SAH) show CSF profiles interpretable as an interaction between lactate-associated SID shifts and CSF CO_2 dynamics, including a SID-lowering burden that can coexist with low CSF PCO_2 and near-normal CSF pH[9].

A Stewart interpretation must also be grounded in barrier biology. The choroid plexus and blood–CSF barrier express transport systems capable of shaping CSF composition and recovery kinetics. Experimental studies identify transporter-dependent contributions ranging from pH-sensitive Na^+/H^+ exchange-related fluxes during metabolic disturbances to bicarbonate-related transport required for recovery from

hypercapnia[10,11]. This review therefore aims to synthesize human and experimental evidence relevant to a Stewart interpretation of CSF acid-base physiology and to outline translational implications for ICU practice, including why ABG normalization may not guarantee central normalization and why higher-temporal-resolution CSF datasets are needed for bedside translation[1,12].

Methods

This is a focused narrative review integrating (i) human studies reporting CSF acid-base variables with sufficient data to interpret physicochemical determinants (including simultaneous CSF–arterial sampling in pregnancy and neurocritical illness)[8,9], (ii) classic clinical physiology in systemic metabolic derangements that illustrates blood–CSF dissociation[2,3,13], and (iii) mechanistic studies of choroid plexus and blood–CSF barrier transport relevant to CSF pH regulation and strong-ion composition[10,11,14,15,16]. We also cite integrative sources on cerebrovascular CO_2 responsiveness, chemoreflex physiology, and weak-acid modeling where they sharpen compartmental interpretation[4,17,18,19]. From each eligible study we extracted clinical/model context, sampling site (lumbar vs cisternal vs ventricular), measured variables (pH, PCO_2, electrolytes and lactate when available), and sampling/measurement methods, with particular attention to pre-analytical vulnerabilities of CSF pH/PCO_2[12]. Where feasible we interpreted coupling using gradients:

$$\Delta PCO_2 = PCO_2(\text{CSF}) - PCO_2(\text{arterial}) \tag{3}$$

and

$$\Delta SID = SID(\text{CSF}) - SID(\text{plasma}). \tag{4}$$

Because the goal is mechanistic integration and ICU framing rather than pooled effect estimates, no meta-analysis was attempted.

Physicochemical framework for CSF Acid-Base Interpretation

In ICU practice, bicarbonate-centered descriptors (bicarbonate, base excess, $PaCO_2$) remain clinically useful, but compartmental problems are often easier to reason about in terms of independent determinants and coupling time scales. Stewart's framework treats pH as determined by PCO_2, SID, and ATOT. In normal CSF, ATOT is typically small because protein buffering is minimal, which makes CSF a comparatively transparent compartment for physicochemical reasoning[1]. This is best understood relative to plasma, where weak-acid chemistry is more complex and protein charge modeling can materially affect pH interpretation[4].

Operationally, SID is an accounting of strong cations minus strong anions. In CSF, lactate and chloride are often the most clinically relevant strong anions, and their inclusion is necessary for interpretable SID calculations in pathology[9]. A practical advantage of this framework is that it makes gradients interpretable: ΔPCO_2 and ΔSID can be viewed as state variables that reflect blood–CSF coupling and transport-limited adaptation rather than as noise.

Because much transporter physiology is reported in bicarbonate/H^+-transport language, a consistent mapping is needed. In this review, we describe transporter findings in their native terms but interpret their acid-base consequences through changes in the strong-ion environment and electroneutrality, with bicarbonate treated as a dependent outcome. This avoids mixing causal and dependent variables and aligns with Stewart-quantitative and bedside physicochemical traditions[5,6,7].

Measurement Validity and Compartmental Constraints

CSF pH and PCO_2 are unusually sensitive to sampling artefacts because CSF has minimal non-volatile buffering. The dominant confounder is CO_2 loss during sampling and transfer, which increases measured pH and decreases measured PCO_2. Davies' *in vivo*/direct comparison demonstrated systematic, non-trivial error introduced by syringe technique, with PCO_2 underestimation increasing as true PCO_2 rises[12]. Such errors can materially distort small blood–CSF gradients and complicate inference about coupling.

Methodological rigor therefore becomes part of interpretation. Some classic studies provide relatively explicit sampling details; for example, Ohman *et al* reported anaerobic collection, cold handling, and rapid analysis in diabetic ketoacidosis, improving confidence that discordant blood–CSF trajectories reflect physiology rather than dominant artefact[13]. Contemporary studies should report anaerobic handling, time-to-analysis, temperature correction, and timing relative to changes in ventilation or drainage.

Sampling site is also a biological variable. Lumbar, cisternal, and ventricular CSF reflect different flow and exchange contexts; neurocritical studies frequently use ventricular access via external ventricular drains, whereas much older physiology is lumbar-based. Without explicit stratification by site and drainage conditions, apparent disease effects may partly reflect compartmental heterogeneity[9]. Finally, analytic completeness matters: lactate omission biases SID upward, and inconsistent inclusion of Ca^{2+}/Mg^{2+} or total vs ionized values limits cross-study comparability[9].

The remaining major gap is temporal resolution. Much human CSF literature is cross-sectional, yet the physiology is dynamic: CO_2 equilibrates rapidly, while strong-ion/strong-anion adjustment is transport-limited and slower[1]. Continuous *in vivo* CSF pH recording has been demonstrated experimentally and resolves recovery kinetics during hypercapnia and transporter perturbation[11], but analogous high-temporal-resolution human ICU datasets remain scarce.

Human and Disease Evidence: Coupling Patterns that Matter Clinically

A Stewart-oriented reading is most useful when it asks where the perturbation originates and how coupling unfolds over time. Classic clinical studies already show that blood and CSF can behave differently in severe systemic disorders. Posner and Plum demonstrated that neurological status correlated more closely with CSF pH than with arterial acidemia alone, supporting a central-compartment focus in interpreting neurologic consequences of systemic acid-base disturbances[3]. Ohman *et al* further showed discordant blood–CSF trajectories during treatment of diabetic ketoacidosis, including blood pH improvement while CSF pH fell in early treatment in several cases, alongside persistent differences in PCO_2 and bicarbonate and slower equilibration of glucose and ketoacids[13]. These pre-Stewart observations are consistent with barrier-limited coupling and non-identical time constants.

Pregnancy provides a relatively clean human model of sustained hypocapnia. Simultaneous sampling in late pregnancy shows coordinated adaptation across compartments with altered CSF–plasma gradients rather than simple arterial mirroring[8]. From an ICU perspective, the transferable principle is that sustained ventilatory shifts can drive compartment-specific setpoints and transport-limited adaptation, and that gradients may be informative descriptors of coupling (Figure 1; Figure 2).

In neurocritical illness, SAH illustrates a clinically instructive trade-off pat-

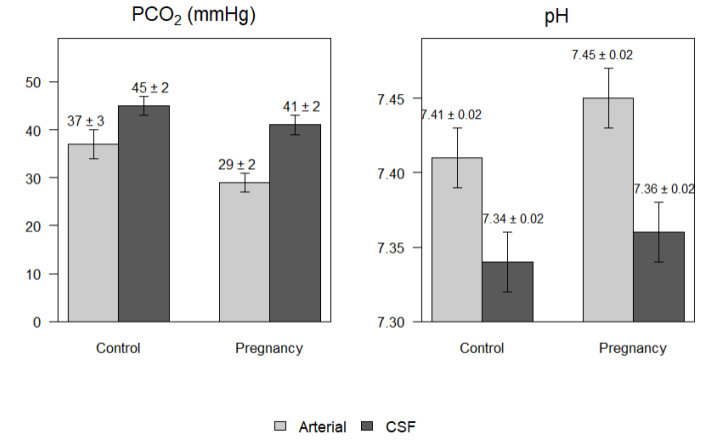

Figure 1. Arterial and cerebrospinal fluid acid–base variables in third-trimester pregnancy and non-pregnant controls. Bars show mean (SD) of simultaneously collected arterial blood and CSF samples obtained at the time of spinal anesthesia (controls, $n = 13$; pregnancy, $n = 20$). Variables shown are arterial and CSF pH (dimensionless) and PCO_2 (mmHg). Values are extracted from Zadek *et al.* (Br J Anaesth, 2022), Tables 1–2.

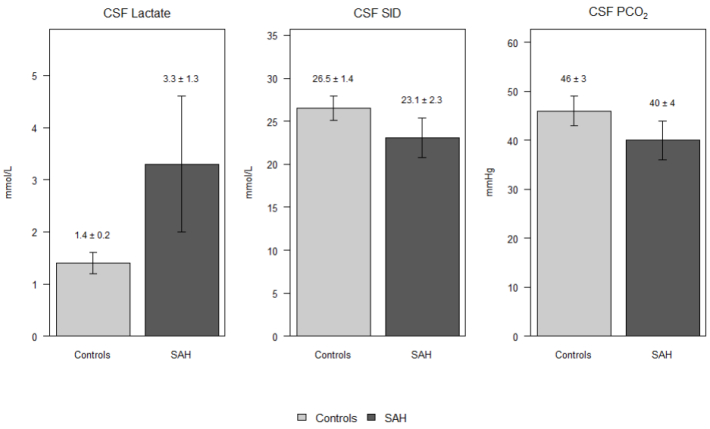

Figure 2. Blood–CSF coupling gradients in third-trimester pregnancy and non-pregnant controls. Bars show mean (SD) of ΔPCO_2 and ΔSID computed as CSF minus plasma values from simultaneously collected samples obtained at the time of spinal anesthesia (controls, $n = 13$; pregnancy, $n = 20$). ΔPCO_2 is expressed in mmHg. ΔSID is expressed in mM and is negative when plasma SID exceeds CSF SID. Values are extracted from Zadek *et al.* (Br J Anaesth, 2022), Table 2.

tern. In spontaneously breathing SAH patients, CSF SID is reduced largely due to higher CSF lactate, while CSF PCO_2 is also reduced; CSF pH may remain near normal and ATOT does not differ materially from controls[9]. Interpreted physicochemically, a SID-lowering strong-anion burden coexists with hypocapnia that counterbalances acidification (Figure 3). This cautions against treating normal CSF pH as evidence of metabolic neutrality and highlights why ABG-only reasoning can miss clinically relevant central states[1,9].

Classic systemic metabolic acidoses further support a strong-anion burden framing. Marks *et al* reported a strong inverse relationship between CSF bicarbonate and total CSF organic acids[2]:

$$\left[HCO_3^-\right]_{CSF} = 13.0 - 0.82\,(\text{total organic acids}),\quad r = -0.93,\quad p < 0.001. \tag{5}$$

This relationship supports interpretation of CSF bicarbonate as a dependent consequence of organic acid burden rather than a primary controller. Together, the DKA datasets[13] and organic-acid relationship[2] provide a consistent narrative: coupling is constrained by barriers, and ionic/strong-anion components may persist after arterial correction.

Infectious CNS disease remains relevant as a high-metabolic-load translational scenario. Experimental meningitis produces major derangements in respiration and circulation consistent with a central chemical environment capable of influencing ventilatory output[20]. Although older datasets often lack complete ion panels required for full Stewart decomposition, they emphasize that CNS pathology can alter CSF chemistry, barrier properties, and coupling in clinically meaningful ways.

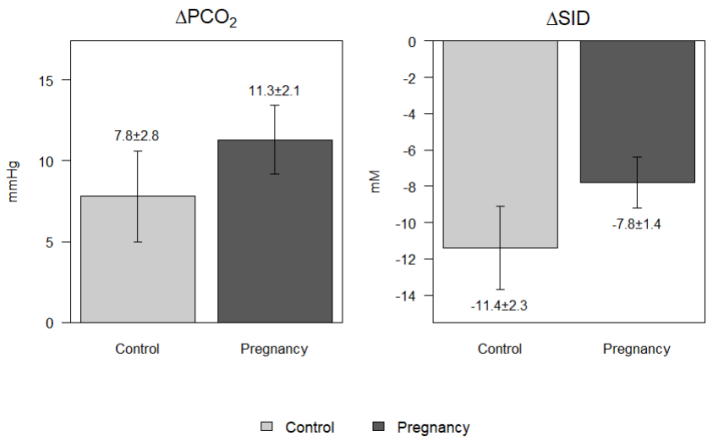

Figure 3. Cerebrospinal fluid strong-anion/strong-ion and CO_2-related variables in aneurysmal subarachnoid hemorrhage and controls. Bars show mean (SD) of ventricular CSF samples collected simultaneously with arterial blood in spontaneously breathing SAH patients ($n = 20$) and control subjects undergoing elective surgery under spinal anesthesia ($n = 25$). Variables shown are CSF lactate (mmol/L), CSF strong ion difference (SID, mmol/L), and CSF PCO_2 (mmHg). Values are extracted from Langer *et al.* (Neurocrit Care, 2022), Table 1.

Across these settings, a useful synthesis is to classify disturbances along two axes: perturbation origin (systemic/peripheral vs central/local) and propagation mechanism (CO_2-dominant rapid diffusion vs transport-limited ionic/strong-anion adjustment). This avoids over-rigid phenotype labels while retaining the clinically relevant kinetic asymmetry.

Mechanistic Substrate: Transport, SID Shaping, and Recovery Kinetics

A Stewart interpretation gains translational traction only if independent determinants map to mechanisms. In CSF, two levers dominate: fast CO_2 coupling and transport-limited shaping of the strong-ion environment. The choroid plexus and blood–CSF barrier regulate CSF composition through coordinated transport of bicarbonate equivalents and strong ions, particularly Na^+ and Cl^-[1,14].

Evidence for pH-sensitive Na^+ flux pathways consistent with Na^+/H^+ exchange comes from Murphy and Johanson, who demonstrated pH-dependent Na^+ flux with an amiloride-inhibitable component during acute metabolic disturbances[10]. In Stewart terms, such fluxes contribute to transport-limited reorganization of the strong-ion environment rather than passive buffering alone.

Ion-transport perturbation studies provide additional mechanistic anchors that are directly interpretable in strong-ion terms. Johnson, Frankel, and Kazemi showed that during hypercapnia, cerebroventricular (but not intravenous) furosemide altered the expected CSF chloride–bicarbonate pattern, producing a greater fall in CSF chloride without the usual rise in CSF bicarbonate during CO_2 exposure[16]. Although reported in bicarbonate/chloride language, the key implication is that furosemide-sensitive transport processes can reshape the strong-ion environment during CO_2 loading and thereby shape the dependent bicarbonate response.

Recovery kinetics during hypercapnia provide a causal link from trans-

porter capacity to CSF pH resilience. Christensen *et al* used continuous *in vivo* CSF pH recording and demonstrated that disruption of the choroid plexus sodium–bicarbonate cotransporter NBCe2 markedly attenuates CSF pH recovery during sustained hypercapnia[11]. This finding is particularly important for ICU translation because it implies that the same ventilatory perturbation could yield different central trajectories depending on barrier transport capacity.

Broader epithelial machinery plausibly contributes to disease-dependent kinetics. The expression of luminal membrane acid-extrusion related components such as ClC-7 and NHE6 in murine choroid plexus strengthens biological plausibility for an active epithelial toolkit that could be modulated by inflammation or injury[15]. Direct quantitative mapping from specific components to bedside SID trajectories remains limited, but the existence of this machinery supports the view that CSF acid-base homeostasis is actively regulated and therefore vulnerable under pathology.

Ventilatory Control and Chemosensitivity: Supported Inferences and Boundaries

The translational promise of applying Stewart to CSF is a clearer bridge from chemistry to ventilatory control. Central chemoreception responds to the chemical environment of the CNS/CSF rather than arterial bicarbonate per se[1,5,6]. Within a Stewart framework, strong ions influence ventilation indirectly by altering $[H^+]$ via SID at a given PCO_2, with chemosensitive networks transducing the resulting chemical signal.

A physiologically realistic interpretation must also acknowledge integration of central and peripheral chemoreflex mechanisms. The carotid body provides major peripheral input via multimodal sensing of blood O_2, CO_2, pH, and metabolites including lactate[18]. This boundary condition matters clinically because ventilatory output reflects integrated drives, and central compartment chemistry is a key component but not necessarily the sole determinant in all contexts.

Within this integrated view, SAH provides a compelling example of why pH alone can mislead. A lactate-associated SID-lowering burden can coexist with hypocapnia and near-normal CSF pH[9]. Clinically, ABG-only reasoning can miss this paired central state, and $PaCO_2$ manipulation could shift central pH rapidly before transport-limited SID adaptation occurs[1,9].

Experimental physiology supports plausibility that ionic state can alter ventilatory control. In potassium depletion, Nattie and Tenney demonstrated altered control of breathing in awake rats[21]. Although not framed in Stewart terms and not providing full CSF strong-ion panels, this work supports the general principle that electrolyte states can modulate ventilatory regulation, motivating more direct tests that isolate SID changes at controlled CO_2.

Modern circuit-level work, particularly on the retrotrapezoid nucleus (RTN), has advanced understanding of central CO_2/H^+ chemoreception and emphasizes multicellular contributions to chemosensory function[19]. However, current circuit-level evidence remains primarily CO_2/H^+-centric and does not yet provide direct tests that isolated CSF SID manipulation at constant CO_2 alters defined circuit output *in vivo*, particularly in humans. Circuit-specific claims about SID modulation should therefore remain hypothesis-level.

ICU Implications: Toward Compartment-Aware Interpretation

The ICU relevance of a CSF Stewart framework is not to replace ABG analysis, but to clarify when ABG normalization is an incomplete proxy for the central physicochemical environment governing respiratory drive and potentially cerebrovascular physiology[19]. Because CSF has minimal weak-acid buffering and is shaped by barrier transport with distinct time constants, CSF pH can be maintained near normal by hypocapnia despite a substantial SID-lowering burden, and conversely CSF may remain displaced despite apparent arterial correction.

A practical prediction is kinetic: $PaCO_2$ changes transmit quickly to CSF, while transport-limited ionic adaptation is slower[1]. In patients who already carry a SID-lowering burden, such as lactate-associated changes in neurocritical illness[9], $PaCO_2$ adjustment may shift central pH rapidly before meaningful strong-ion compensation develops. This reframes the clinical question from "is $PaCO_2$ corrected" to "what is the paired central state (PCO_2, SID), and how will an intervention move it over time."

$PaCO_2$ manipulation also has parallel cerebrovascular consequences. Human data show nonlinear cerebrovascular responses to CO_2 and pressure-coupled effects at higher CO_2 ranges, reinforcing that ventilatory interventions can simultaneously alter central chemistry and cerebral hemodynamics[17]. This strengthens the case for cautious, compartment-aware interpretation rather than ABG-only reasoning.

Mechanistic studies further imply potential heterogeneity in central recovery capacity. $NBCe_2$-dependent recovery during hypercapnia[11] and pH-sensitive Na^+ flux pathways consistent with exchanger activity[10] support the idea that barrier transport capacity can determine the time constant and completeness of central compensation. In neuroinflammation, hemorrhage, or injury, transporter function and permeability may change, plausibly contributing to variable CSF responses to similar arterial interventions.

A clinically usable CSF Stewart bedside framework would minimally require standardized sampling to minimize CO_2 loss and enable reliable gradients[12], a core chemistry panel enabling SID computation (Na^+, K^+, Cl^-, lactate $\pm$ Ca^{2+}/Mg^{2+}), ideally paired with simultaneous arterial sampling[8,9], and dynamic data rather than snapshots. Experimental proof of principle exists for continuous CSF pH recording[11]. Consistent with ICU bedside physicochemical pedagogy[22], clinically usable outputs would likely be simple descriptors such as $\Delta PCO_2(t)$, $\Delta SID(t)$, and their relation to CSF pH trajectories, rather than opaque multi-equation summaries.

Limitations and Gaps

Despite conceptual clarity, the literature remains constrained by methodological heterogeneity, limited temporal resolution, and incomplete mechanistic integration.

First, pre-analytical and analytical heterogeneity limits cross-study comparability. CO_2 loss during sampling can materially bias CSF pH and PCO_2 and thereby distort gradients and coupling inference[12]. Variation in measured ion panels and SID definitions further limits comparability, especially if lactate is omitted[9].

Second, compartmental heterogeneity matters. Lumbar, cisternal, and ventricular compartments are not interchangeable; drainage conditions and local metabolism can shift composition. ICU translation often relies on ventricular access, whereas many historical datasets are lumbar-based[9].

Third, most human evidence remains cross-sectional. Yet time con-

stants are central to CSF Stewart interpretation: CO_2 equilibrates rapidly, while strong-ion/strong-anion adjustment is transport-limited and slower[1]. High-temporal-resolution human datasets that couple ventilator changes to CSF pH/PCO_2 and electrolytes remain rare, and this is a major barrier to bedside translation.

Fourth, mechanistic integration under ICU-relevant pathologies is incomplete. Transporter dependence is established for recovery from hypercapnia[11], exchanger-like fluxes are demonstrable in metabolic disturbances[10], and chloride-linked transport perturbation studies support transport-regulated ionic rearrangement during CO_2 loading[16]. However, direct linking of specific critical illness pathologies to quantitative changes in transporter function and CSF SID trajectories remains limited[15].

Fifth, ventilatory-control circuitry integration in Stewart terms is undertested. Modern RTN-centered work advances CO_2/H^+ circuit models[19], but direct tests isolating SID changes at controlled CO_2 with parallel circuit readouts remain scarce. Thus, SID-specific circuit claims should remain hypothesis-level.

Finally, language accessibility and selection bias remain practical limitations. Relevant historical work exists in non-English sources (including German-language physiology)[23]. English-only synthesis may therefore underrepresent certain early observations. In addition, although CSF is often low-ATOT under physiological conditions, this simplification may weaken when CSF protein increases, and plasma-side weak-acid complexity provides a cautionary parallel[4].

Future Directions

Four priorities follow directly from the current evidence base. First, high-temporal-resolution human ventriculostomy datasets are needed, coupling ventilator changes to CSF pH, PCO_2, electrolytes, lactate, and paired arterial sampling. Second, studies should connect ICU-relevant pathologies (SAH, TBI, neuroinflammation) to barrier transport capacity and CSF physicochemical trajectories using chemistry plus transporter biomarkers or physiologic surrogates. Third, integration with chemosensory circuitry should test whether Stewart-defined ionic state variables alter ventilatory response curves or circuit output at controlled CO_2, leveraging modern RTN/network paradigms[19]. Fourth, broader inclusion of non-English historical literature may improve continuity of mechanistic synthesis[23].

Conclusion

CSF acid-base physiology in critical illness is best understood as a compartmental, transport-coupled problem rather than a simple extension of arterial blood gas interpretation. A Stewart framework is particularly useful in CSF because low weak-acid buffering makes PCO_2 and SID the dominant determinants of pH in many conditions, while barrier transport provides a mechanistic basis for delayed and pathology-sensitive compensation. Classic clinical observations[3,13] and modern paired CSF–arterial datasets[8,9] converge on the practical point that blood and CSF can move on different trajectories. Mechanistic work supports that these trajectories are actively regulated rather than passive[10,11,16]. At present, CSF Stewart analysis is best regarded as an interpretive framework that strengthens mechanistic reasoning and hypothesis generation. Its transition into a validated bedside tool will require time-resolved human data, standardized measurement, and tighter linkage between physicochemical state variables, barrier transport, and ventilatory-control circuitry.

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