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UNDERSTANDING THE DISEASE

Thomas Langer
Alberto Zanella
Pietro Caironi

Understanding the role of the cerebrospinal fluid in acid–base disorders

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T. Langer (✉) · P. Caironi
Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122 Milan, Italy
e-mail: tom.langer@hotmail.it
Tel.: +39 02 55033232

A. Zanella
Dipartimento di Scienze della Salute, Università degli Studi Milano, Bicocca, Monza, Italy

P. Caironi
Dipartimento di Fisiopatologia Medico, Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy

Introduction

The importance of acid–base interpretation is witnessed by the bulk of literature constantly being published on the topic [1, 2]. However, none of the recently published papers specifically addresses the acid–base equilibrium of the cerebrospinal fluid (CSF), which is an important compartment, since it influences the activity of the central controllers of respiration.

Here, we will briefly discuss the characteristics of CSF acid–base equilibrium and their implications on the control of breathing, basing our reasoning on Stewart's approach [3]. Moreover, we will highlight some clinical implications that, we believe, are usually not fully considered by clinicians.

Characteristics of CSF and blood–CSF barrier

According to Stewart's approach, pH in biologic fluids is independently regulated by three variables: (1) partial pressure of carbon dioxide (PCO_2), (2) strong ion difference (SID), the difference between the sum of strong cations and anions, and (3) the concentration of non-volatile weak acids (A_{TOT}), mainly albumin and phosphates [3].

Normal CSF is a clear fluid that surrounds brain and spinal cord, and fills the ventricular system and subarachnoid spaces. CSF is separated from plasma by the blood–CSF and blood–brain barriers, structures that are freely permeable to CO_2, while being impermeable to most polar substances, such as ions [4]. CSF is continuously produced at a rate of 0.4–0.5 %/min of its volume ($\sim$140 mL in adults) mainly by the choroid plexus, and is reabsorbed in the arachnoid villi. It is a protein-free solution and contains a negligible amount of other non-volatile buffers.

These aspects are responsible for a few important features of CSF and some differences from plasma (Fig. 1a, b):

1. CSF does not contain weak acids (A_{TOT}). Therefore, two are the variables regulating CSF pH: PCO_2 and SID.
2. CSF does not contain negative charges deriving from A_{TOT} (A^-); therefore, CSF SID and bicarbonate concentration are virtually identical.

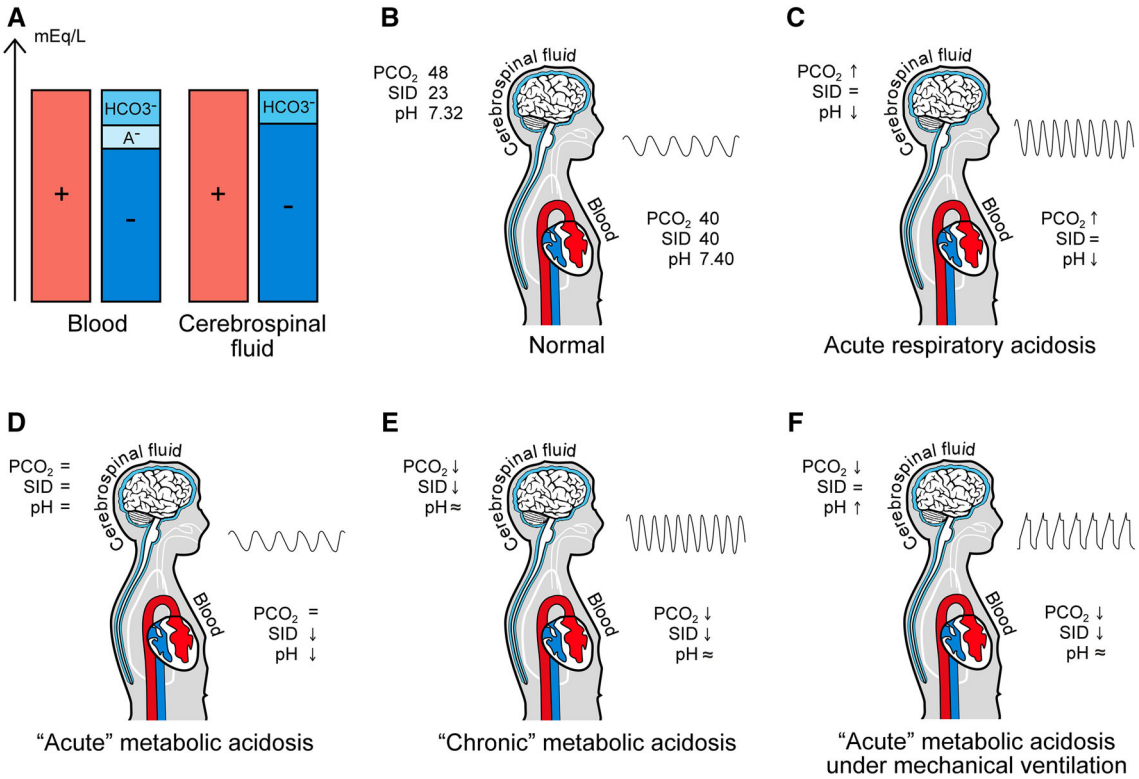

Fig. 1 Schematic representation of the interactions between blood, CSF and minute ventilation in normal and different conditions of altered acid–base equilibrium. **a** Normal Gamblegram of blood and CSF: positive charges (strong cations, *plus sign*) derive mainly from sodium, while negative charges (strong anions, *minus sign*) from chloride ions. Compared to plasma, normal CSF is characterized by the absence of proteins, and therefore by the lack of negative charges deriving from non-carbonic buffers (A^-), higher chloride concentration (115–120 mEq/L), and a lower SID (~23 mEq/L). **b** Normal: normal reference values of PCO_2, SID, pH and normal spirogram. **c** Acute respiratory acidosis: CO_2 increases and diffuses freely in CSF causing a reduction in both blood and CSF pH. Of note, in cases of respiratory acidosis caused by increased alveolar dead space, the respiratory drive will be increased and the spirogram will show an increased minute ventilation (despite a reduced alveolar ventilation). On the other side, minute ventilation would not be increased in cases of respiratory acidosis caused by failure of the respiratory muscles (despite an increased respiratory drive) or by a primary reduction of the respiratory drive (e.g., use of sedatives). **d** "Acute" metabolic acidosis: during the induction of metabolic acidosis, a disequilibrium is observed between blood and CSF. A reduction in blood SID causing acidemia is observed; the acid–base equilibrium of CSF is unvaried and the respiratory activity (during spontaneous breathing) unchanged, or only slightly increased. **e** "Chronic" metabolic acidosis: after 12–48 h from the onset of acute metabolic acid–base alteration, CSF equilibrates with blood, leading to a reduced CSF SID, and thereby to a ventilatory adaptation in order to maintain a normal CSF pH. **f** "Acute" metabolic acidosis under mechanical ventilation: in this condition, the control of breathing is taken over by the attending physician. The ventilator is usually set in order to achieve a blood pH close to normal values. This can, however, result in an acute hypocapnic alkalosis of the CSF. Of note, all the examples are simplifications that do not consider electrolyte shifts between red blood cells, interstitium and plasma [15] and between brain tissue and CSF

3. The in vitro buffer power of CSF against PCO_2 variations is lower as compared to blood, in which non-volatile buffers are well-represented [5].

CSF, systemic acid–base disturbances and control of breathing

The role of pH of cerebral fluids (CSF and interstitial cerebral fluid, ICF) in the control of breathing was identified through experiments in which variations of CSF pH were accomplished through direct perfusion of the ventriculocisternal system. It was clearly demonstrated that ventilation varied in order to restore normal pH in the cerebral milieu: it increased during CSF acidification, while it decreased during alkalinization [6–8]. However, these experimental settings, i.e., direct variation of CSF composition, bypassed the blood–brain and blood–CSF barriers, which, as discussed above, present different permeability to substances potentially altering acid–base.

In cases of respiratory acid–base derangements, i.e., derangements directly caused by CO_2 variations, plasma and CSF equilibrate immediately (Fig. 1c). Accordingly, the spontaneous ventilatory response will be an immediate increase in alveolar ventilation in cases of CO_2 load,

and a rapid reduction in ventilation in cases of reduced CO_2 production [9].

A different response is to be expected during the induction of acute systemic metabolic acid–base disorders, i.e., disorders in which plasma ions (such as lactate, ketoacids, chloride, and others) do not diffuse passively through the barriers, and an equilibrium between plasma and CSF is reached only after a delay (Fig. 1d). Experimental and clinical data demonstrate a transient disequilibrium between plasma and CSF composition during the induction of systemic metabolic acid–base disorders, which explains the time-lag normally observed for the respiratory response [10–12]. Depending on the rate at which fixed acids appear in plasma, ionic equilibrium between the two compartments is allegedly achieved after 12–48 h of steady-state acid–base imbalance, time during which a progressive respiratory response will be observed (Fig. 1e). Of note, other mechanisms, such as peripheral chemoreceptors, vagal pulmonary afferents and transient increases in CO_2 due to the HCO_3-buffering after addition of fixed acids to plasma, may as well activate the respiratory compensation. Nevertheless, these mechanisms normally account for a relatively minor proportion of the ventilatory adaptation [10].

Clinical implications

A clinical scenario recently published by Berend and colleagues [1] highlights the possible importance of CSF acid–base.

A healthy woman injured in an accident received a rapid and large infusion of 0.9 % NaCl with a consequent increase in plasma chloride concentration, decrease in plasma SID, and development of acute metabolic acidosis. The patient, while spontaneously breathing, had a normal PCO_2 (39 mmHg) despite marked acidemia (arterial pH of 7.28). The authors state that such "respiratory acidosis", i.e., failure in increasing alveolar ventilation to lower PCO_2 as a compensatory response, was likely due to inadequate chest-wall expansion. An alternative interpretation would be that the rapid increase in plasma chloride (up to 115 mEq/L) after the infusion of 6 l of 0.9 % NaCl was not paralleled by a consensual increase in CSF chloride concentration. CSF PCO_2, bicarbonate and pH remained unchanged, thus ensuing in a disequilibrium between plasma and CSF pH, and explaining the insufficient respiratory compensation.

What would happen if we would sedate, paralyze and mechanically ventilate the patient? First, we would take over the control of breathing and, second, we would likely regulate the ventilator in order to achieve an arterial pH close to 7.40 (Fig. 1f). This, however, would have the unrecognized side effect of inducing CSF hypocapnic alkalosis with consequent acute reduction in cerebral blood flow [13]. Of note, similar considerations can be made in cases of insufficient respiratory response erroneously attributed to sedation or excessive ventilation in central neurologic diseases, such as acute subarachnoid hemorrhage [14].

Conclusions

Bearing in mind the characteristics of CSF and the particularities of the barriers separating it from plasma might be useful in understanding the complexity of acid–base disorders. Indeed, an insufficient respiratory compensation of a normal respiratory system to a metabolic disorder could provide useful information about the onset of the derangement, suggesting a very acute phase. Finally, when "replacing" the respiratory centers, during controlled-mechanical ventilation, remember that patients are sensitive to CSF pH (which, sometimes, can be easily measured, especially in patients with a ventriculostomy), while we rely on arterial pH as a surrogate of it.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest regarding this commentary.

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