The 'Great Trans-Atlantic Acid-Base Debate: Current Status in the age of Artificial Intelligence

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Abstract

Blood gas analysis (BGA) is one of the most common investigations carried out in critically ill patients. All the results mentioned in the print-out from the BGA equipment are not measured directly but some are calculated using formulae devised by great scientists like Henderson and Hasselbalch. Similarly, in 1950s, interpretation rules were suggested by a group of scientists from Boston Massachusetts US. These rules were based on two BGA parameters i.e. partial pressure of arterial Carbon Dioxide ($PaCO_2$) and concentration of bicarbonate [HCO_3].These rules were, however, criticized on the plea that some 'extra luggage' has been added on a cognitively over-loaded plethora of symbols appearing 'Latin' to a novice. In Copenhagen (Denmark), on other side of the Atlantic Ocean, some parameters were proposed for quantitative assessment of metabolic acid-base abnormalities. These include Standard Bicarbonate ($stHCO_3$), Base Excess (BE) and Standard Base (SBE). These parameters were severely criticized by Boston Group mainly on the ground that these parameters are derived 'in vitro' and not valid for 'in vivo'. Such debates are quite desirable and must continue by the new generations of scientists to find a solution based on Artificial Intelligence, so that the machines should not only give the data (plethora of symbols) but also exact diagnosis of acid-base disorders, stoichiometric analysis and the amount of acid or base required to be given to the patient.

Keywords:

Metabolic Acidosis; Base Excess; Standard Bicarbonate; Standard Base Excess, The Great Trans-Atlantic Debate revolves around two schools of thought about the interpretation of Blood Gas Analysis (BGA) reports. The controversy in the words of Dr TJ Morgan is "at a given PaCO2 and pH, what is the best tool to delineate the separate respiratory and metabolic contributions to the overall acid-base status?"
(1) Let us examine this debate in some details:

Historical Perspective

As students of Clinical Biochemistry, we should be familiar with (as a neutral observer) this controversy spanning now over more than six decades and it continues in 2024, too.

The Parties Across the Atlantic

a. **Boston:** Schwartz, Relman and colleagues at Tufts University Boston Massachusetts US (Western side of Atlantic Ocean)

b**. Copenhagen:** K Jorgensen, Poul Astrup, Ole Siggaard-Andersen, N Fogh-Andersen (Eastern side of Atlantic Ocean). But this school of thought has big names to support from outside Denmark too, e.g. TJ Morgan (Australia) (his book chapter provided me the framework for this article) and JW Severinghaus (USA) (The inventor of CO_2 Electrode and BGA equipment). So, this debate is not limited to the Geographical boundaries.

c. **Canada:** Peter Stewart's 'Strong Ion Difference' - semi-quantitative analysis using principles of physical chemistry was a major conceptual shift. We worked on this system and found no additional advantage over traditional system, so for the sake of brevity, we will not include this school of thought in the present article (2) .

The Points of Agreement

Like a good arbitrator we must first bring forward the points agreed between the two parties:

a. Acidaemia as arterial pH<7.35,
b. Alkalaemia as pH>7.45.
c. Respiratory acidosis is when $PaCO_2$ > 45 mmHg
d. Respiratory alkalosis is $PaCO_2$ is < 35 mmHg.
e. Metabolic (non-respiratory) acid-base abnormalities manifest on blood gas analysis as a disturbed pH/ $PaCO_2$ relationship(1)

What exactly is the Controversy?

Background: when BGA report comes to a Chemical Pathologist or a Clinician, the primary disorders and compensatory changes are not marked on it, meaning the interpreter must delineate the metabolic and respiratory pathologies herself or himself.

The Difference: The debate is to select the best tool to find the compensatory change and whether the compensatory change is physiologic, or it is a double or triple ABD. Furthermore, the quantitative analysis of how much acidosis or alkalosis is present.

Rule of the Game

Let us first set the rule of the game i.e. the criteria of a good tool to find the compensatory change. Since we will use it on the bedside of patient, the ideal index for metabolic acid-base analysis should have following characteristics:

a. Simple and "user friendly"
b. Independent of $PaCO_2$ (CO_2-invariant).
c. Stoichiometric: This means that the index should be able to quantify the amount of strong acid or base (expressed as mmol/L extracellular fluid) which would correct any metabolic acid-base disturbance (3)

The Contending Parameters:

a. The $PaCO_2$/ $[HCO_3^-]$ based "rules" of the Boston school.
b. Standard base excess of Copenhagen school.

The Boston "Rules"

a. Six equations were developed by Schwartz, Relman and colleagues at Tufts University and are the foundation of Boston School (4)
b. The six equations examine either the $[HCO_3]$ in primary respiratory disturbances or the $PaCO_2$ in primary metabolic disturbances. (1).
c. These rules are widely used in medical set-ups. (5),(6),(7)
d. We have developed 'One Minute Decoder' based on Boston Rules for the interpretation of BGA reports by a novice (junior students).

'One Minute Decoder' (8)

Question 1: Acidosis or Alkalosis?

Look at pH

i. **Low pH**-----Acidosis
ii. **High pH**----Alkalosis

A. **If pH is Normal**--A normal pH does not rule out existence of an acid base disorder:

a. All three are normal –Normal Acid Base Status
b. PCO_2 and HCO_3 change grossly in the same direction ----mixed disorder of opposing type e.g. Metabolic acidosis and Respiratory alkalosis
c. Fully compensated Chronic Respiratory Alkalosis if HCO_3 decrease as per Boston equation for chronic respiratory alkalosis.

B. If pH is Abnormal

Question 2: Primary disorder is Metabolic or Respiratory??

Examine pH and HCO_3 relationship (For single disorders)

a. If pH and HCO_3 change in the same direction primary abnormality is metabolic

Examples:

- in metabolic acidosis both pH and HCO_3 decrease
- in metabolic alkalosis both pH and HCO3 increase

b. If pH and HCO_3 change in the opposite direction primary abnormality is respiratory

Examples:

- In respiratory acidosis pH decreases and HCO_3 increases
- In respiratory alkalosis pH increases and HCO_3 decreases

Question 3: Single or Double disorder???

This question requires some critical thinking. According to the primary disorder, an appropriate Boston rule is selected. Expected level of CO_2 is calculated for metabolic disorders and appropriate level of HCO_3 is calculated for respiratory disorders. The Bostonian Rules are as following:

a. Acute respiratory acidosis: Exp HCO 3= 24 + [(pCO2 − 40)/10]
b. Chronic Resp Acidosis: Exp HCO 3 = 24 + 3.5 [(pCO2 − 40)/10]
c. Acute Respiratory Alkalosis: Exp HCO 3 = 24 – 2 [(40 − pCO2)/10]
d. Chronic Respiratory Alkalosis: Exp HCO 3 = 24 – 5 [(40 − pCO2)/10]
e. Metabolic Acidosis: Exp PCO_2 = 1.5 × HCO3 + 8 (range: ±2)
f. Metabolic Alkalosis: Exp PCO_2 = 0.7 (HCO3) + 21 (range: ±2)

Figure 1: Acid Base Disorders - Animated

pH and HCO_3 Relationship

- pH and HCO3 are two friends studying in a university.
- Sometimes they are in good terms. They meet daily and go everywhere together. *'M' for 'Meet' and 'M' for 'Metabolic'*
- Other times they are not in good terms and repel each other's presence. If one goes to library, the other goes to cafeteria. *'R' for 'Repel' and 'R' for 'Respiratory'*

The Main Objections to Boston "Rules"

a. Difficult to Remember: The Boston "rules" need a lot of "rot memory" and too much 'cognitive load'
b. In my personal experience of nearly 30 years of teaching ABDs, only Winters Formula is easy to remember, so I encouraged my students to remember this formula for the metabolic acidosis [$PCO_2 = (1.5 \times HCO_3) + 8$]. By the way, Dr R.W. Winter was a Pediatrician from Columbia University, New York (Western side of Atlantic).
c. Not Stoichiometric: A big objection to these six equations was that one cannot find an amount of strong acid or base required to be added in vitro or in vivo to correct the disturbance.
d. Despite objections, these equations are hugely popular around the globe. But unfortunately "base excess" calculations have been removed in some part of the world from analyzer printouts (1).

The Copenhagen School of Thought:

The flagship parameter of Copenhagen group is 'Standard Base Excess' (SBE), but this parameter evolved gradually from 'Standard Bicarbonate' ($stHCO_3$) to 'Base Excess' (BE) and then SBE. The evolution took place in response to the objections raised from time to time from the Boston group.

Standard Bicarbonate ($stHCO_3$)

Initially devised by K Jørgensen, P Astrup in 1957, this parameter is calculated using Henderson and Hasselbeck Equation, keeping ($PaCO_2$ at 40 mmHg (9). It is still part of BGA reports, and helps the providers get an idea of presence or absence of respiratory ABD at one glance:

a. If actual HCO_3 (acHCO3) and $stHCO_3$ are close to each other, it indicates absence of a respiratory disorder.
b. If $acHCO_3$ is *lower* than $stHCO_3$, then respiratory alkalosis (compensatory decrease)
c. If $acHCO_3$ is *higher* than $stHCO_3$, then respiratory acidosis (compensatory increase)

There were two objections to this parameter:

a. The changes in [HCO_3] parameter are not stoichiometric i.e. one cannot quantitate the changes for providing treatment.
b. This parameter is developed in vitro and does not replicate in vivo pH/$PaCO_2$ relationship (1).

Base Excess:

Dr Ole Siggaard-Andersen, a Physician, and Dr Poul Astrup a Clinical Chemist, both from Copenhagen (Denmark) jointly invented the concepts of BE and SBE (10)

Definition of BE

- "Dose of acid or base required to return the pH of a blood sample to 7.40 measured at standard conditions - 37°C and 40 mmHg PaCO2".
- The purpose of this calculated parameter is to assess metabolic ABDs independent of respiratory ABDs.

Objection to BE by Boston Group

In 1963, Schwarz and Relman pointed out that BE is not CO2 -invariant in vivo. This is because for any specimen of arterial blood the in vitro plasma pH/$PaCO_2$ equilibration curve differs from the in vivo curve, since in vivo CO_2 equilibration occurs throughout the total extracellular compartment (11)

Definition of SBE

a. "Dose of acid or base required to return the pH of an anaemic blood sample to 7.40 measured at standard conditions - 37°C and 40mmHg PaCO2 calculated for a Hb of 50 g/L"
b. This parameter was devised to counter the objection on BE that it does not caters for the extra-cellular fluid (ECF) other than blood as haemoglobin buffers both the intravascular and the extravascular fluid. If blood is hypothetically mixed with other ECF, the haemoglobin will get diluted to about 50 g/L (5 g/dl).
c. Thus, SBE assesses the buffering of the whole ECF, not just the haemoglobin-rich intravascular fluid (1)

SBE Rules

Like "Boston Rules", Copenhagen Group has also developed four $PaCO_2$/SBE rules (SBE in mmol/L, $PaCO_2$ in mmHg) (12)

a. Acute respiratory acidosis and alkalosis SBE=0 x $\Delta PaCO_2$
b. Chronic respiratory acidosis and alkalosis SBE=0.4 x $\Delta PaCO_2$
c. Metabolic acidosis $PaCO_2$=SBE
d. Metabolic alkalosis $PaCO_2$=0.6 x ΔSBE

Application of SBE Rules

First determine Primary Disorder by using 'One Minute Decoder' or by directly examining $PaCO_2$ and pH (Table 1), then apply the rules mentioned above.

Table 1: Direct method of Finding Primary Acid Base Disorder

PaCO2	**pH**	**Primary processes**
Normal	Normal	None
Normal	High	Metabolic alkalosis, Respiratory alkalosis
Normal	Low	Metabolic acidosis, Respiratory acidosis
High	Normal	Respiratory acidosis, Metabolic alkalosis
High	High	Metabolic alkalosis
High	Low	Respiratory acidosis
Low	Normal	Chronic respiratory alkalosis
Low	High	Respiratory alkalosis
Low	Low	Metabolic acidosis

Novel Diagnostic BGA Interpretation Method in 2023

Dr Rajini Samuel has developed a novel method of BGA reports based on Hydrogen ion concentration. She has compared this method with Boston rules and found satisfactory correlation (13). So, Boston rules are still very much alive!!

Bostonian Rules, SBE and Copenhagen Rules in the Era of Artificial Intelligence

Presently stHCO_3, BE, SBE and Bostonian rules are widely used by the healthcare providers for the interpretation of BGA reports without having the slightest idea about 'The Great Debate'. Please consider following challenges and opportunities in BGA interpretation:

a. Imagine an Internist or Resident of specialty other than Anesthesia or Critical Care Medicine is on duty at 2:0 am in an Intensive Care Unit; a dozen patients are on ventilatory support and BGAs are carried out on hourly basis on a point-of-care-testing unit. What options he /she will have to interpret these reports? Literally very few. He / she will just make some superficial deductions about the patient condition based on his/her limited knowledge. He /she may start an insufficient or inappropriate patient treatment.
b. Can we develop algorithms for machine-learnings, so that the type of ABD, stoichiometric analysis and exact dose of the replacement or counteracting substance is instantly known?
c. Blood gas analysis is an expensive investigation requiring heavy funds even if the workload is not so much. We need to make it as meaningful as possible by adding AI in this system.
d. Lastly, almost all 'rules' classify the respiratory disorders in acute and chronic types because of delayed renal response to respiratory changes. This classification is arbitrary, blunt and discretionary. We must devise a crisp and unambiguous criteria for this division, so that AI can apply a specific rule of interpretation.

Conclusion

When you find BE, SBE, Standard HCO_3 and PCO2 and HCO3 rules, give a smile and remember 'The Great Trans-Atlantic Debate'. The present and next generations of Laboratory Specialists and Clinicians should initiate new debates , about adding Artificial Intelligence in BGA reports, so that, the future reports should contain an opinion about the acid base disorder present in the particular patient, the quantity of acid excess or deficit and calculated amount of antidote required.

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