

## RELATION BETWEEN pH AND THE STRONG ION DIFFERENCE (SID) IN BODY FLUIDS

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Acid-base balance evaluation according to the Henderson-Hasselbalch equation enable us to assess the contribution of respiratory ( $p\text{CO}_2$ ) and/or non-respiratory (metabolic,  $\text{HCO}_3^-$ ) components to the acid-base balance status. A new approach to acid-base balance evaluation according to Stewart-Fencl, which is based on a detailed physical-chemical analysis of body fluids shows that metabolic acid-base balance disorders are characterized not only by  $[\text{HCO}_3^-]$ . According to this concept independent variables must be taken into an account. The abnormality of concentration of one or more of the independent variable(s) determines the pH of a solution. The independent variables are: 1. strong ion difference (SID); 2. total concentration of nonvolatile weak acids  $[\text{A}_{\text{tot}}^-]$ ; 3. in agreement with the Henderson-Hasselbalch concept also  $p\text{CO}_2$ . Traditional evaluation of acid-base balance disorders is based on the pH of body fluids (though pH may be within normal range if several acid-base balance disturbances are present). In order to maintain this view and simultaneously to respect the Stewart-Fencl principle, we invented a new equation, which uses only the independent variables to define the pH of body fluids. This analysis shows that for a given value of  $p\text{CO}_2$ , the pH of body fluids is determined by a difference between SID and  $[\text{A}_{\text{tot}}^-]$ .

$$\text{pH} = 6.1 + \log \frac{\text{SID} - [\text{A}_{\text{tot}}^-]}{0,03p\text{CO}_2}$$

or in itemized form:

$$\text{pH} = 6.1 + \log \frac{([\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] - [\text{Cl}^-] - [\text{UA}^-]) - (k_1[\text{Alb}] + k_2[\text{P}_i])}{0.03 \times p\text{CO}_2}$$

Evaluation of the individual components of this equation enables us to detect, which of the independent variable (or a combination of independent variables) deviates from the normal range and therefore which one or ones is a cause of the acid-base balance disorder. At the end of this paper we give examples of a practical application of this equation.

### ABBREVIATIONS

$[\text{Na}^+]$ ,  $[\text{K}^+]$ ,  $[\text{Ca}^{2+}]$ ,  $[\text{Mg}^{2+}]$ ,  $[\text{Cl}^-]$ ,  $[\text{UA}^-]$ ...concentrations of ions,  $\text{UA}^-$  means ions that are not routinely measured (lactate, ketoacids, sulphates, exogenous anions)

SID ... strong ion difference, e.g. net electric charge of the strong electrolytes

$[\text{Alb}]$ ,  $[\text{P}_i]$  ... total albumin (g/l) and inorganic phosphate concentration (mmol/l)

$[\text{Alb}^-]$ ,  $[\text{P}_i^-]$  ... electric charge on albumin and inorganic phosphate (mmol/l)

$[\text{A}_{\text{tot}}^-]$  ... total concentration of the weak, non-volatile acids (i.e. albumin and inorganic phosphate)

$[\text{A}_{\text{tot}}^-]$  ... charge on the weak non-volatile acids (i.e.  $[\text{Alb}^-] + [\text{P}_i^-]$ ) (mmol/l)

The acid-base status of body fluids is traditionally assessed according to the variables in the Henderson-Hasselbalch equation. This equation is a logarithmic expression of the dissociation equilibrium of carbonic acid. Metabolic disorders of acid-base balance are assessed according to serum bicarbonate concentration while non-metabolic

(respiratory) disorders according to  $p\text{CO}_2$ . Astrup (1) elaborated this approach for clinical use.

For a long time, it has been established that acid base status is influenced by chloride concentration and that saline solution displays acidification properties. This fact does not follow from the Henderson-Hasselbalch equation. Principles which determine the influence of strong ions on the acid-base status were defined at the beginning of the eighties of the last century by Stewart (2) and for clinical use they were elaborated by Fencel (3, 4, 5). On the basis of a detailed physical-chemical analysis of body fluids, Stewart defined two independent variables that enable us to define metabolic disturbances of the acid-base balance exactly

- a) strong ion difference – SID
- b) total concentrations of the weak non-volatile acids ( $[A_{\text{tot}}^-]$ , represented mainly by albumin and inorganic phosphate)

Respiratory acid-base balance disturbances are assessed according to  $p\text{CO}_2$ , in the same way as in a conventional approach.

According to Stewart, SID is calculated by the equation [1]:

$$\text{SID} = [\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] - [\text{Cl}^-] - [\text{UA}^-] \quad [1]$$

In this equation,  $[\text{UA}^-]$  means concentration of the unidentified strong anions (e.g. ketoacids, lactate and exogenous substances etc.)

Normal value of SID is  $39 \pm 1$  mmol/l (6). Values lower than 38 express metabolic acidosis and values over 40 mean metabolic alkalosis.

Exact assessment of SID is difficult because of difficulties to measure  $[\text{UA}^-]$ . Fencel's et al. (5) contribution is a new equation allowing us to calculate SID easily on the basis of the principle of the electroneutrality of body fluids:

$$\text{SID} = [\text{HCO}_3^-] + k_1[\text{Alb}] + k_2[\text{P}_i] \quad [2]$$

In this equation,  $k_1$  a  $k_2$  are factors which are dependent on pH (see below). These determine the electric charge (in mmol/l) on albumin and inorganic phosphates. The sum  $k_1[\text{Alb}] + k_2[\text{P}_i]$  is designated as  $[A_{\text{tot}}^-]$ . This is the total concentration of dissociated weak non-volatile acids (see below).

The electric charge on albumin is calculated on the basis of equation [3]:

$$[\text{Alb}^-] = [\text{Alb}] \times (0.123\text{pH} - 0.631) \quad [3]$$

and a charge on inorganic phosphate according to the equation [4]:

$$[\text{P}_i^-] = [\text{P}_i] \times (0.309 \times \text{pH} - 0.469) \quad [4]$$

For pH value 7.40 is  $k_1 = 0.28$  a  $k_2 = 1.8$

A differential diagnosis of causes of acidosis and alkalosis is more precise when we use the Stewart-Fencel principle, while the true cause may remain uncovered if conventional method is applied. In a clinical practice (see case 2 at the end of this manuscript) may, e.g. pH indicates alkalosis while a value of SID documents metabolic acidosis. Therefore, it is questionable, which of two approaches of acid-base disturbances evaluation is more accurate, or if this disaccord is simply a consequence of the imprecise terminology. More detailed information about a clinical usefulness of the Stewart's methods in a clinical praxis was published elsewhere. (7, 8, 9, 10, 11, 12, 13).

There is no doubt from a physiological and biochemical points of view that the activity of enzymes is evaluated on the basis of pH. It is questionable if the enzyme activity may be evaluated on the basis of SID (in complex with other independent variables that determine pH of a solution). It is well known that an enzyme activity is dependent on some strong ion(s) concentration(s). More studies on these problems at molecular levels are necessary.

In this study aimed at a clinical use, we tried to find out what is the relation among pH, SID and  $[A_{\text{tot}}^-]$  in the body fluids. The mathematical statement of this relation would be of a practical importance because it would enable to define an influence of the strong ions (and also the weak non-volatile acids  $[A_{\text{tot}}^-]$ ) on the pH of the body fluids (12, 13, 14).

We solved this problem as it follows:

1. We came out from the Henderson-Hasselbalch equation:

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \times p\text{CO}_2} \quad [5]$$

2. We feel, that a possibility to calculate SID by two ways (either by the equation [1] or by the Fencel method – equation [2]) is very useful. We can calculate  $[\text{HCO}_3^-]$  concentration from the equation [2]:

$$[\text{HCO}_3^-] = \text{SID} - (k_1[\text{Alb}] + k_2[\text{P}_i]) = \text{SID} - [A_{\text{tot}}^-] \quad [6]$$

If pH of the body fluids fluctuate around the value of 7.40, the equation [6] may be rewritten as:

$$[\text{HCO}_3^-] = \text{SID} - (0.28[\text{Alb}] + 1.8[\text{P}_i]) \quad [7]$$

3. The total serum albumin and inorganic phosphates are designated as the weak non-volatile acids. They are considered as the third independent variable in the Stewart-Fencel's theory (the others are  $p\text{CO}_2$  and SID), which affects the acid-base status. The sum of concentrations of these substances is designated as the  $[A_{\text{tot}}^-]$  and the sum of electric charge carried by them is designated as the  $[A_{\text{tot}}^-]$ :

$$[A_{\text{tot}}^-] = k_1[\text{Alb}] + k_2[\text{P}_i] \quad [8]$$

From the equation [7], it follows one important conclusion on a significance of  $[A_{\text{tot}}^-]$ : if we institute the normal values of hydro carbonate (24 mmol/l) and SID (39 mmol/l) in the equation [7], we may calculate easily that  $[A_{\text{tot}}^-]$  is equal to 15 mmol/l. Therefore,  $[A_{\text{tot}}^-]$  contributes to a metabolic component of acid-base status significantly, as it follows from comparison with the normal value for SID (39 mmol/l).

4. With a respect to above-mentioned facts, we can rewrite the original Henderson-Hasselbalch equation as follows:

$$\text{pH} = 6.1 + \log \frac{\text{SID} - [A_{\text{tot}}^-]}{0,03 \times \text{pCO}_2} \quad [9]$$

or in an itemized form on the basis of the equations [1] a [8]:

$$\text{pH} = 6.1 + \log \frac{([\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] - [\text{Cl}^-] - [\text{UA}^-]) - (k_1[\text{Alb}] + k_2[\text{P}_i])}{0.03 \times \text{pCO}_2} \quad [10]$$

where  $k_1$  a  $k_2$  are constants determined by the equations [3] a [4].

It is apparent from the equation [9], that for a particular value of  $\text{pCO}_2$ , pH is determined by a difference between  $\text{SID} - [A_{\text{tot}}^-]$ . On the basis of the equation [10] we can characterize deviations, which caused a change of pH.

Therefore, we believe that in a clinical praxis the modified Henderson-Hasselbalch equation may be used in the following way:

1. The value of SID is calculated by the Fencel's equation [2], but this value is interpreted according to the Stewards theory [1]. The calculation of SID according to the Fencel's equation is easier, because it does not use the value  $[\text{UA}^-]$ , which is hardly possible to assess in the laboratory.

It is apparent from the Stewart equation for SID calculation [1] that, from the quantitative point of view, a significant role plays  $[\text{Na}^+]$ , but also concentrations of other cations (kalium, calcium, magnesium) cannot be neglected. As for anions,  $[\text{Cl}^-]$  is a decisive ion, but in pathologic conditions the increased concentrations of  $[\text{UA}^-]$  may be important. A value of  $[\text{UA}^-]$  may not be measured and therefore its value is estimated indirectly from the value of an anion gap (AG):

$$\text{AG} = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]) \quad [11]$$

In individuals with an abnormal serum albumin concentration, it is necessary to correct a calculated value of AG according to the following equation:

$$\text{AG}_{\text{corrected}} = \text{AG}_{\text{calculated}} + 0.25 \times ([\text{Alb}]_{\text{normal}} - [\text{Alb}]_{\text{measured}}) \quad [12]$$

Normal range for AG is  $16 \pm 2$  mmol/l.

2. The value of  $[A_{\text{tot}}^-]$  is determined by the sum of net electric charge carried by albumin and inorganic phosphate:

$$\begin{aligned} [A_{\text{tot}}^-] &= \\ &= [\text{Alb}] \times (0.123\text{pH} - 0.631) + [\text{P}_i] \times (0.309\text{pH} - 0.469) \end{aligned} \quad [13]$$

Under normal conditions, the value of  $[A_{\text{tot}}^-]$  is equal to 15 mmol/l. The deviations of the serum albumin concentrations are quantitatively more effective than  $[\text{P}_i]$  deviations.

3. In the corrected Henderson-Hasselbalch equation,  $\text{pCO}_2$  has the same meaning as in its original form of this equation. It follows, that like in a conventional approach, the corrected equation enables to distinguish between compensatory and lung diseases induced deviations of  $\text{pCO}_2$  (15). If a respiratory compensation of metabolic acidosis is in play, then a decrease of  $\text{SID} - [A_{\text{tot}}^-]$  by each 1 mmol/l below 24 mmol/l, is compensated by a decrease of  $\text{pCO}_2$  by 1 mmHg below 40 mmHg. In case of a respiratory compensation of metabolic alkalosis, an increase of  $\text{SID} - [A_{\text{tot}}^-]$  by 1 mmol/l above 24 mmol/l is compensated by an increase of  $\text{pCO}_2$  by 0,7 mmHg above 40 mmHg

The above-mentioned view unifies a conventional and Stewart-Fencel concept of the acid-base balance disturbances. In the numerator of Henderson-Hasselbalch equation,  $[\text{HCO}_3^-]$  is replaced by  $\text{SID} - [A_{\text{tot}}^-]$ . This new equation enables to understand to the kaleidoscope of causes of pH deviations from the normal and, moreover, to correct these abnormalities by an adjustment of values of the three independent variables, e.g. SID,  $A_{\text{tot}}$  a  $\text{pCO}_2$ .

Two cases of acid-base balance disturbances and a practical application of a modified Henderson-Hasselbalch equation are given below (Table 1)

**Table 1** Examples of acid-base dysbalances

	normal	Case 1	Case 2
Na <sup>+</sup> mmol/l	142 ± 2	117	159
K <sup>+</sup> mmol/l	4.1 ± 0,3	3.9	3.6
Ca <sup>2+</sup> mmol/l	2.3 ± 0,1	3	4.2
Mg <sup>2+</sup> mmol/l	0.8 ± 0,05	1.4	2.2
Cl <sup>-</sup> mmol/l	106 ± 2	92	121
Pi mmol/l	1 ± 0,2	0,6	0.5
Alb g/l	44 ± 3	6	9
pH	7.422 ± 0.015	7.33	7.55
pCO <sub>2</sub> mmHg	38 ± 1.5	30	29
HCO <sub>3</sub> <sup>-</sup> mmol/l	24.5 ± 0.5	15	25.5
AG <sub>measured</sub> mmol/l	16 ± 2	13	16
AG <sub>corrected</sub> mmol/l	16±2	23	25
BE mmol/l	0.3 ± 0.5	- 10	2
SID mmol/l	39 ± 1	18	29
Cl <sup>-</sup> <sub>corrected</sub> mmol/l	106 ± 2	112	108
UA <sup>-</sup> mmol/l	8 ± 2	14.8	19
UA <sup>-</sup> <sub>korig</sub> mmol/l	8 ± 2	18	17
A <sup>-</sup> <sub>tot</sub> mmol/l	15	2.7	3.6

The examples in Table 1 are taken from a publication: Fencl, V., Jabor, A., Kazda, A, Figge, J.: Diagnosis of metabolic acid-base disturbances in critically ill patients. Am. J.Resp. Crit Care Med. 162, 2000, s. 2246-2251

Comment to the case 1:

- a) On the basis of a traditional approach to acid-base balance assessment, an evaluation of this case is as follows: pH value is below of a normal limit, therefore acidosis is in play. The value of pCO<sub>2</sub> is also below normal range, so that it is not respiratory but metabolic acidosis. This assumption is supported by a significant decrease of [HCO<sub>3</sub><sup>-</sup>]. AG<sub>corrected</sub> (e. g. correction for serum albumin level) is increased. Therefore, metabolic acidosis caused by unidentified anions is the cause of disorder. Furthermore, we can determine, if a decrease in pCO<sub>2</sub> is only compensatory or if metabolic acidosis is combined with a primary respiratory disorder (pCO<sub>2</sub> is decreased, therefore primary respiratory alkalosis is possible). The difference 24 - [HCO<sub>3</sub><sup>-</sup>] measured is 24 - 15 = 9 mmol/l. The difference of measured value of pCO<sub>2</sub> from normal is 40 - 30 = 10 mmHg. Therefore, a decrease in pCO<sub>2</sub> is a consequence of a respiratory compensation of metabolic acidosis.
- b) Now, we will analyze this case using Henderson-Hasselbalch equation modified by Stewart-Fencl concept.

It is evident that SID (calculated according the Fencl's equation) is markedly decreased. A difference between normal and measured value ( $\Delta$ SID) is: 39 - 18 = 21 mmol/l. This decrease in SID itself causes decrease of pH, which is in this case small (pH = 7.33). On the basis of equation [1] we can determine, which strong ions operate in a decrease of SID. It is a pronounced decrease of [Na<sup>+</sup>]. Its concentration is 117 mmol/l only. Concentrations of Ca<sup>2+</sup> and Mg<sup>2+</sup> are increased, but their increases only marginally antagonize the effect of [Na<sup>+</sup>] decrease. A concentration of chlorides is moderately decreased but the difference [Na<sup>+</sup>] - [Cl<sup>-</sup>] = 25 mmol/l (normal value is 36) determines total SID decrease significantly. According to the value of AG<sub>corrected</sub> we may find out if [UA<sup>-</sup>] anions accumulate in the body fluids (like in a conventional method). Our conclusion is: there is an accumulation of unidentified strong anions. Therefore, a decrease in SID is caused by three factors: by a decrease in [Na<sup>+</sup>] and by a decrease of [Na<sup>+</sup>] - [Cl<sup>-</sup>] and by retention of unidentified strong anions [UA<sup>-</sup>] (deduced from an increase in AG<sub>corrected</sub>). A decrease in SID is slightly counteracted by an increase in [Ca<sup>2+</sup>] and [Mg<sup>2+</sup>] in this case.

As it follows from the modified Henderson-Hasselbalch equation, only SID itself can not determine the final pH value, because a value [A<sup>-</sup><sub>tot</sub>] either pronounce or suppress the effect of SID. A value [A<sup>-</sup><sub>tot</sub>] is decreased in this case and therefore it has alkalinizing effect. A difference between normal average value and measured value is ( $\Delta$ [A<sup>-</sup><sub>tot</sub>]) is 15 - 2.7 = 12.3 mmol/l. This difference is markedly lower than above mentioned value  $\Delta$ SID (= 21 mmol/l) and therefore metabolic acidosis is a consequence. Mainly a decrease of serum albumin concentration determines this decrease of [A<sup>-</sup><sub>tot</sub>].

The value of pCO<sub>2</sub> is interpreted in the same way as in the conventional approach.

General evaluation of this case is as follows: metabolic acidosis because SID - [A<sup>-</sup><sub>tot</sub>] is decreased in the modified Henderson-Hasselbalch equation.  $\Delta$ SID -  $\Delta$ [A<sup>-</sup><sub>tot</sub>] = 21 - 12.3 = 8.7 mmol/l, and this value approaches hydrogen carbonate deficit (24 - 15 = 9 mmol/l). An accumulation of unidentified strong anions and severe hyponatremia with a relatively lower decrease in chloride concentration contribute to this metabolic acidosis. Severity of this metabolic acidosis is suppressed by a decrease of [A<sup>-</sup><sub>tot</sub>], which is mainly caused by hypoalbuminemia and much less by a decrease in inorganic phosphate concentration. A deviation of pCO<sub>2</sub> has only compensatory character. Altogether, as a consequence of a combination of all mentioned factors, the pH is not decreased proportionally to SID.

Comment to case 2:

- a) A traditional approach comes out from pH value, that shows alkalosis. This alkalosis can hardly be described as a metabolic one, because [HCO<sub>3</sub><sup>-</sup>] displays

normal value (25,5 mmol/l). Value of  $p\text{CO}_2$  is markedly decreased (29 mmHg), which points at a respiratory alkalosis, which is corrected by a compensatory decrease of  $[\text{HCO}_3^-]$ . It is remarkable, that value of  $\text{AG}_{\text{corrected}}$  is markedly increased. Therefore, the traditional approach points at a combination of respiratory alkalosis and metabolic acidosis.

- b) If we interpret these findings according to a new approach, then SID is markedly decreased. This contributes to a metabolic acidosis. The value of SID is determined by hypernatremia (159 mmol/l). The value  $[\text{Na}^+] - [\text{Cl}^-]$  is within normal range (38 mmol/l, normal value is 36). Apparently, retention of the strong unidentified anions  $[\text{UA}^-]$  is in the play as shown by an increased  $\text{AG}_{\text{corrected}}$ .

The difference  $\text{SID}_{\text{normal}} - \text{SID}_{\text{measured}}$  is  $39 - 29 = 10$  mmol/l. A decrease of SID is mostly determined by strong unidentified anions retention, because the difference  $[\text{Na}^+] - [\text{Cl}^-]$  is within a normal range. The decrease in SID is partially suppressed by an increases in  $[\text{Ca}^{2+}]$  a  $[\text{Mg}^{2+}]$ . The evaluation of SID unequivocally shows metabolic acidosis.

A value of  $[\text{A}_{\text{tot}}^-]$  is decreased to 3.6 mmol/l in this case, so that  $\Delta[\text{A}_{\text{tot}}^-] = 15.0 - 3.6 = 11.4$  mmol/l. this difference is determined mostly by a decrease of serum albumin concentration and partially also by a decrease of  $[\text{P}_i]$ . From the point of interpretation of these findings it is notable that  $\Delta\text{SID}$  is almost identical with  $\Delta[\text{A}_{\text{tot}}^-]$ , so that resulting metabolic changes are cancelled and have no any influence on pH value. Therefore, the value of  $p\text{CO}_2$  is the main determinant of the pH value.

We can summarize, that pH value is mostly determined by respiration alkalosis. The new approach of interpretation extends the conclusion: the metabolic changes are the sum of a decreased value of SID and hypalbuminemia. Their influence on pH is inverse and cancels one another.

This example also shows an apparent discrepancy between traditional view (which shows alkalosis) and new methods of acid-base balance evaluation. A more detailed new approach discovers principals and interrelation of factors involved in metabolic disturbances of the acid-base balance. The corrected Henderson-Hasselbalch equation enables to span this virtual discrepancy between the two approaches, because it defines pH of body fluids as a function of SID,  $\text{A}_{\text{tot}}$  a  $p\text{CO}_2$ .

## CONCLUSION

The presented theoretical analysis suggests that the proposed modification of Henderson-Hasselbalch equation by Stewart-Fencel approach could help in the interpretation of biochemical causes responsible for changes in plasma bicarbonate concentration.

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