

The significance of base excess (BE_B) and base excess in the extra cellular fluid compartment (BE_{Ecf})

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Background

Besides actual pH, base excess (ctH^+_B (mmol/L)) is of major importance since it is meant to reflect lactate acidosis due to fetal hypoxia; in vivo BE_B is not independent from pCO_2 .

Independence is achieved by using the extended extracellular fluid (Ecf) for dilution of hemoglobin (cHb_B), reducing cHb_B to $cHb_B / 3$ (in the fetus to 1/4). Correction of ctH^+_B from the normally low fetal oxygen saturation by reoxygenation of Hb increases ctH^+_B resulting in four different variables: $ctH^+_{B,act}$ ($= BE_B$), $ctH^+_{Ecf,act}$ (Standard BE), $ctH^+_{B,ox}$ and $ctH^+_{Ecf,ox}$. The question is which variable is most appropriate for perinatal acid-base studies?

Methods

The APGAR 1 min. and the WAS score were used, thus measuring neonatal vigor and FHR (Fetal Heart Rate)

characteristics during the last 30 minutes of 475 fetuses all delivered vaginally.

FHR was evaluated by computation of the WAS index.

The WAS index refers to: $(f_{hm} \times w1) \times (ozf \times w2) \times (oza \times w3)^{-1}$ where f_{hm} is mean heart frequency (bpm), ozf is the number of turning points (N/min.) and oza denotes oscillation amplitude/min. (bpm). The weighting functions $w1$, $w2$ and $w3$ were computed using optimizing software. The WAS score denotes the mean of the WAS indices of the last 30 minutes of delivery.

Results

In vivo fetal $ctH^+_{B,act}$ (UA) is closely correlated with pCO_2 , UA: $r = -0.288$, $P < 10^{-4}$, $N = 475$, whereas $ctH^+_{Ecf,act}$ (Standard BE) becomes definitely independent from pCO_2 : $r = -0.0068$, $P = 0.881$.

In UA blood there is no independence of the two blood gases $p\text{CO}_2$ and $p\text{O}_2$: both are inversely correlated: $r = -0.291$, $P < 10^{-4}$. $p\text{O}_2$ shows no correlation with $\text{ctH}^+_{\text{B,act}}$ ($r = -0.074$, $P = 0.105$) but correlates well with $\text{ctH}^+_{\text{Ecf,act}}$: $r = -0.1722$, $P = 0.0002$.

The APGAR score is best correlated with pH_{UA} ($r = 0.4078$, $P < 10^{-4}$, $N = 475$, Spearman's $\text{Rho} = 0.307$, $P < 10^{-4}$). Correction of $\text{ctH}^+_{\text{B,act}}$ or $\text{ctH}^+_{\text{Ecf,act}}$ to 100 % oxygen saturation always leads to higher coefficients.

Using $\text{ctH}^+_{\text{B,ox}}$, $\text{ctH}^+_{\text{B,act}}$, $\text{ctH}^+_{\text{Ecf,ox}}$ and $\text{ctH}^+_{\text{Ecf,act}}$: $\text{Rho} = 0.2597$, 0.2394 , 0.1838 and 0.1763 , respectively; P all $< 10^{-4}$. The same holds true for APGAR 5 min. $\text{Rho} = 0.2307$, 0.2168 , 0.1811 and 0.1771 , respectively ($P < 10^{-4}$ for all).

The WAS score is closely correlated with pH_{UA} : $r = 0.656$, $P < 10^{-4}$, $N = 475$. The correlation with the four variables under investigation: $\text{ctH}^+_{\text{B,ox}}$, $\text{ctH}^+_{\text{B,act}}$, $\text{ctH}^+_{\text{Ecf,ox}}$ and $\text{ctH}^+_{\text{Ecf,act}}$ leads to $r = -0.587$, $r = -0.565$, $r = -0.437$ and $r = -0.427$, respectively ($P < 10^{-4}$ for all).

Conclusions

Actual pH (CH^+) offers the closest correlation with two essential clinical parameters: FHF and APGAR scores; the advantages of ctH^+_{B} and $\text{ctH}^+_{\text{Ecf}}$ are not evident; if determination of a metabolic component becomes necessary, Standard BE, ($\text{ctH}^+_{\text{Ecf}}$) should be used with correction to 100 % oxygen saturation ($\text{ctH}^+_{\text{Ecf,ox}}$) of hemoglobin (HbF), because this quantity correlates best with clinical indices.

Introduction

Assessment of the acid-base status of the neonate immediately after birth is important because it provides us with information about the consequences of any decrease in oxygen delivery to the fetus.

Simply measuring $p\text{O}_2$ in umbilical blood (venous or arterial) will neither tell us reliably that the fetus is hypoxic [1, 2] nor can we estimate the degree of hypoxia [3, 1, 4]. In the adult, hydrogen ion concentration (CH^+)

gives a true insight not only into the consequences of hypoxia (metabolic component) but also into respiration disorders (non-metabolic component, i.e. $p\text{CO}_2$).

In the fetus $p\text{CO}_2$ and base excess (BE) are not independent but closely combined because the fetus has no pulmonary respiration; for example, cord encirclements (Fig. 1) may lead to hypercapnia together with hypoxia and therefore nearly always to a mixed acidosis.

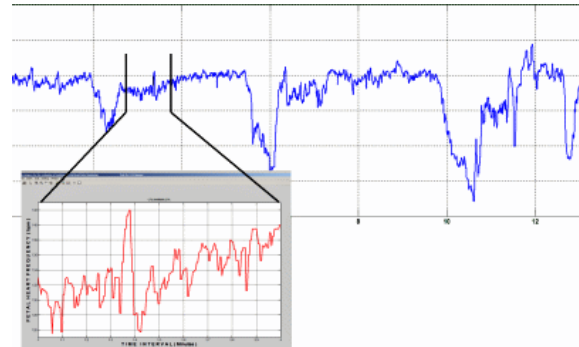


FIG. 1: Foetal heart frequency with amplification of 1 Min. - Typical FHR recording with variable decelerations due to cord encirclements. One base-line Minute is amplified electronically.

In vitro, the metabolic component of an acidosis, BE, is defined as the titratable (t) base (mmol/L), using e.g. NaOH when titrating an acidotic blood sample to the reference $\text{pH} = 7.40$, at $p\text{CO}_2 = 40$ mmHg, at $T = 37^\circ\text{C}$ without changing the actual sO_2 (%). When BE refers to fully *in vitro* oxygenated blood it should be specified as BE_{ox} .

Recently Siggaard-Andersen proposed [5] to use the term ctH^+_{B} rather than BE_{B} because the relevant chemical component is the hydrogen ion, not hydrogen-ion-binding groups (base) nor hydroxyl ions (COH^-).

Both in the adult and in the fetus ctH^+_{B} (BE_{B}) *in vitro* is independent of $p\text{CO}_2$ changes [6, 5], because the change in bicarbonate is completely balanced by an opposite change in other buffer anions (albuminate and hemoglobinate); *in vivo*, however, ctH^+_{B} does not remain constant [6]:

In vivo, with a rise in $p\text{CO}_2$ the pH falls more and the bicarbonate produced rises less than in blood *in vitro* [7].

This means that ctH^+ of whole blood rises *in vivo* because hydrogen ions move from the poorly buffered interstitial fluid into blood plasma and further into the red cells, where they are buffered by hemoglobin; the result is a redistribution of hydrogen ions throughout the whole extracellular space [6] in which $\text{ctH}^+_{\text{Ecf}}$ remains unchanged. In this context extracellular space refers to interstitial fluid, lymph, plasma and fluid in erythrocytes and other formed elements in blood.

If we want a quantity which is independent of $p\text{CO}_2$ changes *in vivo*, we need to use a model of the extended extracellular fluid (Ecf) since it is not accessible for direct sampling.

We can create such a model assuming that the red cells are evenly distributed throughout this extended Ecf. The hemoglobin concentration (cHb) of this model equals the hemoglobin concentration of the blood times the ratio of the volume of blood divided by the volume of the extended Ecf. It is generally assumed that this ratio normally is around 1/3 and therefore $\text{cHb}_{\text{Ecf}} = \text{cHb}_B / 3 = 5.0 \text{ g\%}$. In the fetus/newborn, however, the interstitial volume is larger and the ratio may be close to 1/4 [8].

Blood BE originally referred to fully oxygenated blood because the blood sample was equilibrated *in vitro* with a gas mixture of 94.4 % O_2 and 5.6 % CO_2 . Later on, in 1964, it was redefined to the actual hemoglobin oxygen saturation (%).

In 1964 Crawford and Holaday [9] recognized a significant effect on BE of fully oxygenated blood according to the degree of deoxygenation: In umbilical artery (UA) blood, where oxygenation normally is low ($p\text{O}_2$ about 18 mmHg only [16]), BE_{ox} values are lower (e.g. -10.0 instead of -7.0 mmol/L ($-10 < -8$)) when compared to BE values referring to actual (act) oxygenation; in consequence $\text{ctH}^+_{B,\text{ox}}$ is higher than $\text{ctH}^+_{B,\text{act}}$.

Reoxygenation of hemoglobin therefore causes an increase in net titratable hydrogen ion because hydrogen ions are liberated from so-called oxygen-linked buffer groups (NH^+ , NH_2^+ or NH_3^+ groups of the globin); an

effect which traditionally is called the HALDANE effect [10, 11].

If we denote BE, which we normally get from the analyzer, $\text{BE}_{\text{act,ox}}$. (not knowing the degree of oxygen desaturation *in vivo*) and BE after complete reoxygenation (experimentally *in vitro* or by computation).

$\text{BE}_{\text{fully ox.}}$, the following equation was verified by Siggaard-Andersen [10]:

$$\text{BE}_{\text{act,ox.}} = \text{BE}_{\text{fully ox.}} + 0.3 \times \text{cHb} \times (1 - s\text{O}_2), \text{ and rearranged}$$

$$\text{BE}_{\text{fully ox.}} = \text{BE}_{\text{act,ox.}} - 0.3 \times \text{cHb} \times (1 - s\text{O}_2)$$

This equation looks simple but is not so easily understood because $\text{BE}_B = (\text{ctH}^+_B) \times -1$ leading to:

$$-\text{ctH}^+_{\text{fully ox.}} = -\text{ctH}^+_{\text{act ox.}} - 0.3 \times \text{cHb} \times (1 - s\text{O}_2), \text{ multiplied with } -1:$$

$$\text{ctH}^+_{\text{fully ox.}} = \text{ctH}^+_{\text{act ox.}} + 0.3 \times \text{cHb} \times (1 - s\text{O}_2)$$

Now it becomes clear that $\text{ctH}^+_{\text{fully ox.}}$ is the sum of two components: $\text{ctH}^+_{\text{act ox.}}$ ($\text{BE}_{\text{act ox.}}$) and the term: $0.3 \times \text{cHb} \times (1 - s\text{O}_2)$ representing the hydrogen ions hidden in the hemoglobin molecules.

Numerically $\text{BE}_{\text{fully ox.}}$ therefore is besides the bulk of solved hydrogen ions ($\text{BE}_{\text{act ox.}}$), a function both of cHb (mmol/L) and oxygen saturation of hemoglobin ranging between 0.0 (when $s\text{O}_2 = 1.0$, i.e. 100 %) and approx. 5.0 mmol/L (when $s\text{O}_2 = 0$ %: $15 \times 0.3 = 5$).

Full oxygenation liberates hydrogen ions from hemoglobin corresponding to about 0.3 mol/mol, i.e. 0.3 mol H^+ per mol oxygen.

The figure 0.3 is called the Haldane coefficient. (Note: If cHb is measured in g/dL, the Haldane coefficient (0.306) must be divided by 1.6114 to convert to mmol/L; thus $0.3 / 1.6114 = 0.19$, (the molar mass of hemoglobin monomer being 16.114 g/mol)).

To be shorter in the following we denote: $BE_{act\ ox.} = BE_{act}$ and $BE_{fully\ ox.} = BE_{ox.}$ Note that generally: $ctH^+_{B,ox.} > ctH^+_{B,act}$ because due to reoxygenation all hydrogen ions in the sample are available, i.e. they become titratable and consequently $BE_{ox.} < BE_{act}$ ($-6 < -2$).

For example: If the actual oxygen saturation is 50 % ($sO_2 = 0.5$) and the initial pH is 7.40 with $pCO_2 = 40$ mmHg (therefore per definition $BE_{act} = 0$) and the hemoglobin concentration amounts to 10 mmol/L (16.1 g%), complete oxygenation in vitro would produce 1.5 mmol of hydrogen ions and $BE_{ox.} = -1.5$ since: $0 - 0.30 \times 10 \times (1 - 0.5) = -1.5$;

In vivo, however, the 1.5 mmol of hydrogen ions ($BE_{ox.} = -1.5$) are quickly distributed throughout the whole extracellular space and therefore the rise in ctH^+ would be only $1.5 / 3 = 0.5$ mmol/L; in the fetus/neonate the increase in ctH^+ will be even less (e.g. $1.5 / 4 = 0.37$ mmol/L) since the extracellular space in the fetus is significantly larger when compared with the space in an adult [12, 8]:

$$BE_{Ecf,act} = BE_{Ecf,ox.} + 0.3 \times cHb_{Ecf} \times (1 - sO_2)$$

This is the main reason for using $ctH^+_{Ecf,act}$ ($BE_{Ecf,act}$), currently called Standard BE (SBE) indicating the true, i.e. reduced accumulation of cH^+ in the extended extracellular fluid compartment (Ecf).

For the clinician it is necessary to understand the difference between ctH^+_B referring to whole blood ($B, (in\ vitro)$) and ctH^+_{Ecf} referring to a model of the Ecf *in vivo*; moreover, the clinician should be aware of the reoxygenation effect leading to: $ctH^+_{B,ox.}$ and $ctH^+_{Ecf,ox.}$

Furthermore, in fetal acid-base studies it is of interest to evaluate the correlation of clinical parameters (e.g. the APGAR score and the fetal heart frequency (FHF)) to the spectrum of these four metabolic acid-base variables, the "base excess family" (Table I). Therefore the question must arise: Which base excess should preferably be used?

$BE_{B,act}$	$ctH^+_{B,act}$	Normal BE_B
$BE_{Ecf,act}$	$ctH^+_{Ecf,act}$	Standard BE
$BE_{B,ox.}$	$ctH^+_{B,ox.}$	"Corrected" to 100 % oxygen saturation of Hb
$BE_{Ecf,ox.}$	$ctH^+_{Ecf,ox.}$	"Corrected" to 100 % oxygen saturation of Hb

TABLE I - The base excess family.
All in mmol/L.

The second column refers to the new nomenclature according to Siggaard-Andersen [3] where c = concentration, t = titratable and H^+ = hydrogen ions. B = Whole blood, Ecf = Extracellular fluid compartment, act = actual oxygenation of hemoglobin, $ox.$ = fully oxygenated blood.

Note: $-ctH^+ = BE$.

Methods

The FHR signals (i.e. R-R intervals) of 637 fetuses were recorded by a computer. During a period of 10 years (2000-2009) all recordings were realized in the Frauenklinik of the Klinikum Lippe Detmold GmbH (East Westfalia/Lippe, Germany, (Head: Prof. Dr. med. V. M. Roemer)) including also some premature infants.

To enter the study all fetuses must have been delivered by the vaginal route – thus without a significant loss of FHR signals. During forceps/vacuum delivery recordings were continued. Short-lasting (< 20 sec.) signal losses were overcome by signal-repair algorithms developed in this institution [13].

If necessary, a new electrode was inserted. Recordings of fetuses with chorioamnionitis and tracings of malformed neonates were excluded. No drugs were given during the time of recording. Thus 475 recordings were left. In this study only the last 30 minutes were analyzed using our own MATLAB programs [14].

FHF can be evaluated quantitatively by computer using a new formula:

$$\text{WAS index} = (f_{hm} \times w1) \times (ozf \times w2) \times (oza \times w3)^{-1},$$

where f_{hm} is mean heart frequency/min. (bpm), ozf is the number of turning points (N/min.) and oza denotes oscillation amplitude/min. (bpm) (Figs. 1 and 2).

The weighting functions $w1$, $w2$ and $w3$ can hardly be guessed by intuition and therefore were determined by an optimization program designed to maximize the correlation coefficient, r between actual pH_{UA} and the WAS score.

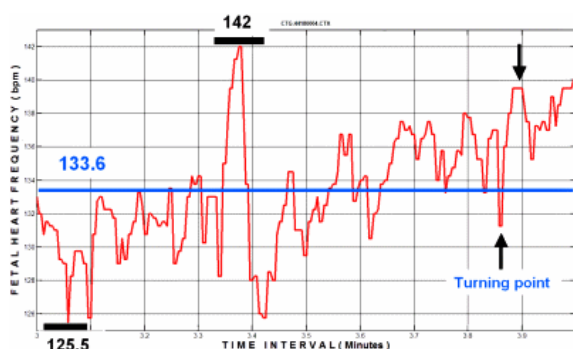


FIG. 2: FHF: Mean frequency (133.6 bpm), Osc.- amplitude : (142 – 125.5 = 16.5 bpm), Number of turning points (labelled with arrows): $N = 61 / \text{Min.}$ - The three variables constituting the WAS index are computed; two turns (of 61 in this minute) are labelled with arrows.

The mean of the WAS index, determined for the last 30 minutes before delivery was denoted **“WAS score”** [14].

Acid-base variables including actual blood gases were determined in blood of the umbilical artery (and vein) immediately after delivery by trained personal. Radiometer (Copenhagen) equipment was used (ABL500).

APGAR scores after 1, 5 and 10 minutes refer to the fetal reaction pattern mirroring the whole birth process including hypoxia and acidosis, using five variables of neonatal vigor. No fetus delivered with general anesthesia was included in this study.

The Van Slyke equation

Base excess is defined as the negative value of the concentration (c) of titratable (t) hydrogen ion in blood (B); thus $BE = -ctH^+_B$. It may be determined directly experimentally.

The endpoint of *in vitro* titration is $pH = 7.40$ at $pCO_2 = 5.33 \text{ kPa}$ (40 mmHg) at $T = 37.0^\circ \text{C}$. The concentration of total oxygen must be held constant during this procedure.

In daily practice ctH^+_B is determined by calculation using a formula first given by Siggaard-Andersen in his doctoral thesis in 1963.

In 1976 Siggaard-Andersen renamed the equation after Donald Dexter Van Slyke, Rockefeller Institute N.Y. (1883-1971), honoring the outstanding contributions of his compatriot to acid-base physiology [15, 8]. Originally [15] the formula given in 1963 (Hb in mmol/L) is:

$$cHCO_3^- - 24.4 = -(2.3 \times cHb_B + 7.7) \times (pH_p - 7.4) + BE_B \times (1 - 0.023 \times cHb_B)^{-1}$$

using $cHCO_3^- - 24.4 = \Delta cHCO_3^-$, $pH_p - 7.4 = \Delta pH$ and $(2.3 \times cHb_B + 7.7) = \beta$

simplifies the equation to

$$BE_B = (1 - 0.023 \times cHb_B) \times [\beta \times \Delta pH + \Delta cHCO_3^-]$$

BE_{Ecf} is calculated using cHb_B multiplied by the volume fraction of blood in the extended extracellular space, i.e. 0.33 by default as mentioned before. A somewhat lower value, e.g. 0.25 should be used in the newborn [12] because the Ecf in the fetus and thus the dilution effect is larger.

A very simplified and thus practical equation for calculating ctH^+_{Ecf} is:

$$ctH^+_{Ecf} = -14.0 \times \Delta pH - \Delta cHCO_3^-$$

where fetal hemoglobin concentration as a true variable is ignored and bicarbonate is not 24.4 (see above) but 25.0 mmol/L. If hemoglobin and the low fetal protein concentration are taken into account, the factor 14 changes to $\beta = 5.5$ (7.7 in the adult) + $0.4 \times cHb_B$, i.e. 11.5 with $cHb_B = 15.0 \text{ g/dL}$ [16].

In this version we have ignored the fact that bicarbonate refers to plasma bicarbonate, which is higher than the

bicarbonate concentration of whole blood. If we take this into account also, we should multiply the result with 0.93 or the term $(1 - 0.005 \times \text{cHb}_b \text{ (g/dL)})$ since $1 - 0.005 \times 15.0 = 0.925$ [16].

Fetal bicarbonate (CHCO_3^-) in plasma (P) is always determined using the **Henderson-Hasselbalch** equation:

$$\text{cHCO}_3^-_p = 0.0306 \times p\text{CO}_2 \times 10^{(\text{pH} - 6.1)}$$

where $p\text{CO}_2$ is given in mmHg (if $p\text{CO}_2$ is given in kPa, 0.0306 changes to 0.231).

For example: Given a pH of 7.0, $p\text{CO}_2 = 84.0$ mmHg, $\text{cHb} = 15.2$ g/dL, and assuming that the blood volume constitute 1/3 of the extended extracellular fluid volume, computation for the adult (!) leads to $\text{ctH}^+_{B,\text{act}} = 14.6$ and $\text{ctH}^+_{\text{Ecf,act}} = 10.3$ (both in mmol/L).

Applying fetal conditions ($p\text{O}_2 = 18.0$ mmHg, $s\text{O}_2 = 12.3\%$ ([17], $\text{cHb} = 15.2$ g% [1]), and assuming that blood constitutes 1/4 of the extended extracellular space), $\text{ctH}^+_{\text{Ecf,act}}$ will be 9.7, i.e. 0.6 lower than for the adult due to the larger dilution effect of cHb in the extracellular fetal space, and $\text{ctH}^+_{\text{Ecf,act}}$ will increase from 9.7 to 10.4 ($\text{ctH}^+_{\text{Ecf,ox}}$) when "correction" to 100 % oxygen saturation is performed.

The values in the adult are in excellent accordance with the figures derived from the Siggaard-Andersen curve nomogram [18] and the Siggaard-Andersen acid-base chart [19].

Using the simplified formula for computation of $\text{BE}_{\text{Ecf,act}}$ ($= -\text{ctH}^+_{\text{Ecf,act}}$) and the same data in an adult: $\text{CHCO}_3^-_p = 0.0306 \times 84 \times 100.9 = 2.57 \times 7.943 = 20.4$ and $\Delta\text{CHCO}_3^- = 20.4 - 25.0 = -4.6$; with $\Delta\text{pH} = -0.4$

$\text{BE}_{\text{Ecf,act}}$ becomes: $-(14 \times 0.4) - 4.6 = -10.2$ which is close (see above) to -10.3 (both in mmol/L).

In all computations in this study a cHb_{UA} of 15.2 g%, and thus a Haldane coefficient of 0.19 and a divisor of 0.25 for approximation of fetal extracellular fluid compartment, was used [20]. $s\text{O}_2$ was computed for

HbF according to Ruiz *et al.* [17]. The JMP software was used for graphical design.

Results

Fetal $p\text{O}_2$, $p\text{CO}_2$ and BE: Normally *in vivo* fetal BE, which we get from the analyzer, ($\text{ctH}^+_{B,\text{act}}$) is closely correlated with $p\text{CO}_2$ both measured in UA blood: $r = -0.288$, $P < 10^{-4}$, $N = 475$. Fig. 3 shows that in the extended extracellular fetal fluid compartment $\text{ctH}^+_{\text{Ecf,act}}$ ($\text{BE}_{\text{Ecf,act}}$) becomes definitely independent from $p\text{CO}_2$: $r = -0.0068$, $P = 0.881$, $N = 475$.

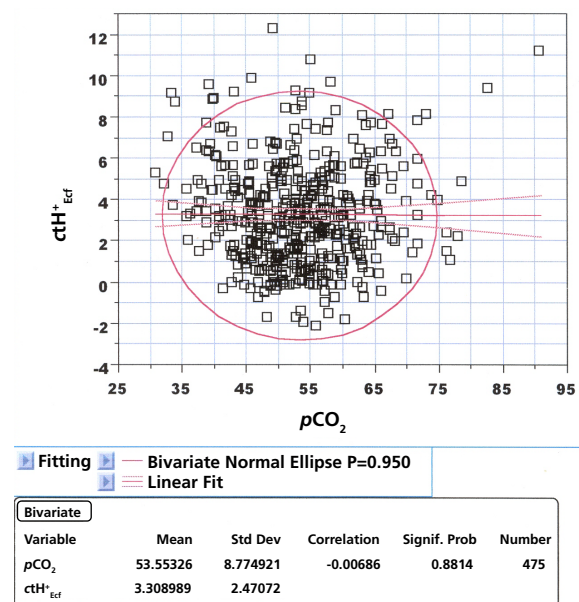


FIG. 3: Correlation diagram between $p\text{CO}_2$ (mmHg) and ctH^+ (mmol/L) computed for the extended extracellular fluid compartment ($\text{ctH}^+_{\text{Ecf,act}}$): *In vivo* both variables are independent from each other: $r = 0$.

Moreover, it is interesting to note that this correlation becomes insignificant ($P < 0.05$) already with a divisor of 2 (not 3 or even 4 (accounting for diluted fetal cHb_{Ecf}): $r = -0.094$, $P = 0.040$, $N = 475$. The lowest correlation coefficient is achieved in fetal blood with a divisor of 3.3: $r = -0.0015$, $P = 0.974$.

However, with a divisor of about 1000, setting $\text{cHb} = 0$ mmol/L (ctH^+_p) the coefficient is (steadily) increased again to -0.155 , $P = 0.0007$, $N = 475$.

UA blood is dependent of $p\text{CO}_2$ and $p\text{O}_2$: both blood gases are closely and inversely correlated: $r = -0.291$, $P < 10^{-4}$, $N = 475$.

Moreover, pO_2 (mmHg) shows no correlation with $ctH^+_{B,act}$ ($r = -0.074$, $P = 0.105$) but correlates well again with $ctH^+_{Ecf,act}$: $r = -0.1722$, $P = 0.0002$. pCO_2 , however, shows a complementary reaction pattern: pCO_2 is closely correlated with $ctH^+_{B,act}$: $r = -0.288$ (see above) and is definitely independent from $ctH^+_{Ecf,act}$ (see above) due to the redistribution effect *in vivo*.

If $ctH^+_{B,act}$ (BE_B) is "corrected" to full oxygen saturation, named $ctH^+_{B,ox}$, the coefficient r with pCO_2 will increase numerically from -0.288 to -0.345 and with pO_2 it will decrease numerically from -0.074 to -0.049 .

APGAR scores and ctH^+/ctH^+_{Ecf} : In this sample the APGAR score 1 min. is best correlated with actual pH_{UA} ($r = 0.4078$, $P < 10^{-4}$, $N = 475$ and Spearman's Rho = 0.307 , $P < 10^{-4}$).

The metabolic components of a fetal acidosis are less closely correlated with this index and "correction" to 100 % oxygen saturation in UA blood always leads to higher coefficients: Using again Spearman's Rho: $ctH^+_{B,ox}$, $ctH^+_{B,act}$, $ctH^+_{Ecf,ox}$ and $ctH^+_{Ecf,act}$ provide Rho values of 0.2597, 0.2394, 0.1838 and 0.1763, respectively; P all $< 10^{-4}$.

The same holds true for APGAR 5 min.: Rho = 0.2307, 0.2168, 0.1811 and 0.1771, respectively.

pCO_2 is also closely associated with APGAR 1 min. (Rho = -0.258 , $P < 10^{-4}$) and APGAR 5 min. (Rho = -0.214 , $P < 10^{-4}$).

Fetal heart frequency and ctH^+_B/ctH^+_{Ecf} :

The same reaction pattern as in APGAR scores can be observed when using computer-evaluated FHR characteristics during the last 30 minutes of delivery: The best correlation is achieved with actual pH_{UA} : $r = 0.656$, $P < 10^{-4}$, $N = 475$ (Fig. 4).

Again, the correlation coefficients (r) with the four metabolic components (Table 1) referring to fetal hypoxia are of minor importance and depend in UA blood again "correction" to fetal oxygen saturation to 100 %:

$ctH^+_{B,ox}$, $ctH^+_{B,act}$, $ctH^+_{Ecf,ox}$ and $ctH^+_{Ecf,act}$ lead to $r = -0.587$, $r = -0.565$, $r = -0.437$ and $r = -0.427$, respectively ($P < 10^{-4}$ for all). Figs. 4 and 5 show the correlations of the WAS score with pH_{UA} and $ctH^+_{Ecf,act}$ respectively.

In consequence, "correction" of the prevailing fetal oxygen status ($sO_{2,UA}$) to 100 %, UA seems to be important, yielding always numerically higher coefficients.

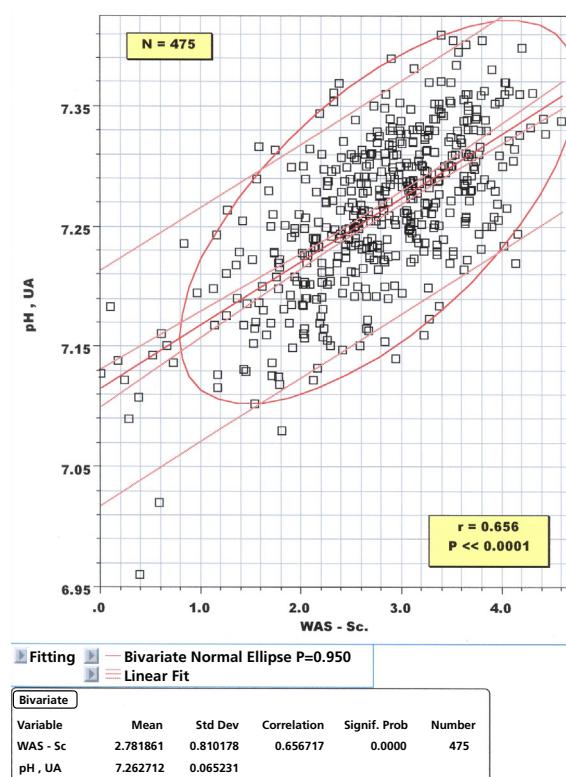


FIG. 4: Correlation diagram between pH in umbilical artery blood and the WAS score: The correlation is highly significant: $r = 0.656$, $P < 10^{-4}$ and may be used for clinical purposes.

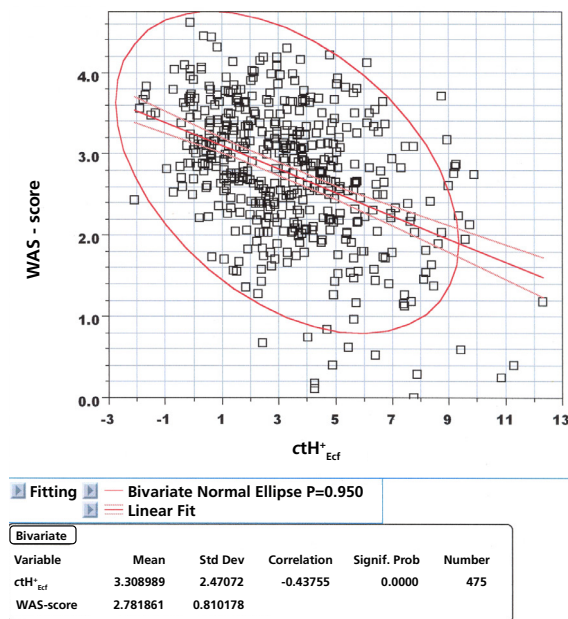


FIG. 5: Correlation diagram between the WAS score and $\text{ctH}^+_{\text{Ecf,act}}$, i.e. Standard BE: The correlation coefficient: r is only -0.427 , $P < 10^{-4}$ which is significantly less than with actual pH_{UA} (see Fig. 4).

The remaining variables of the fetal acid-base balance determined in UA blood will result in the following four coefficients (r) when correlated with the WAS score: pH : $r = 0.657$, pCO_2 : $r = -0.501$, pO_2 : $r = 0.122$ and sO_2 : $r = 0.274$, $P \text{ all} < 10^{-4}$, except pO_2 : $P = 0.0076$.

These highly significant correlations indicate that FHF is an extremely sensitive clinical parameter if it is quantified adequately (WAS index) using electronic devices.

COMMENTS

1) On first sight it seems impossible to draw any valid clinical conclusions concerning "normal" BE ($\text{ctH}^+_{\text{B,act}}$), standard BE ($\text{ctH}^+_{\text{Ecf,act}}$) and the possible need for "correction" to full oxygen saturation of fetal hemoglobin (HbF).

Basically the question must arise [21] if in fetal blood it really makes sense to discern between a metabolic and non-metabolic acidosis since until delivery (i.e. clamping the cord) there is definitely no fetal respiration although breathing movements are visible in sonography.

In fact, the obstetrician is confronted with the strange

situation to artificially separate the influence of pCO_2 (hypercarbia) and O_2 (normally meaning hypoxia) upon $\text{ctH}^+_{\text{B,act}}$ (i.e. pH) using $\text{ctH}^+_{\text{B,act}}$ ($\text{BE}_{\text{B,act}}$) and furthermore to eliminate the pCO_2 effect on $\text{ctH}^+_{\text{B,act}}$ *in vivo* introducing $\text{ctH}^+_{\text{Ecf,act}}$ (i.e. SBE) whereas *in utero* definitely no separation is given by nature.

Moreover, there seems to exist no clinical situation in which knowledge of $\text{ctH}^+_{\text{B,act}}$ or $\text{ctH}^+_{\text{Ecf,act}}$ is truly superior to the measurement of only ctH^+ , i.e. actual pH . Only in very severe fetal acidosis the rise of pCO_2 is not further increased ($> 110 \text{ mmHg}$), most probably due to hypoxic impairment of the whole cellular metabolism.

In summary, from a clinical point of view the obstetrician needs actual pH but not necessarily $\text{ctH}^+_{\text{Ecf,act}}$, i.e. Standard BE nor $\text{BE}_{\text{B,act}}$, i.e. "normal" BE. Today, if necessary, lactate can be measured separately [22].

If isolated alterations of fetal pCO_2 occur – this would simulate pure fetal "respiratory" acidosis/alkalosis – maternal hypercarbia (or alternatively hypocarbia due to maternal **hyperventilation**) seems to be a possible reason often encountered [23]: The correlations between fetal venous (UV) and maternal arterial (art. radialis) blood gases *sub partu* are very strong (e.g. maternal art. pCO_2 vs. pCO_2 , UV blood: $r = 0.514$, $P < 10^{-4}$, $N = 101$ [23]).

Already in 1962 Saling [24] pointed out that actual pH should be used in fetal acid-base studies instead of pH40 ($= \text{BE}_{\text{B,act}}$), still not knowing in 1962 the concept of BE_{Ecf} [6].

2) The hydrogen ion in imperceptible concentrations is a potent effector to liberate oxygen from the hemoglobin molecules for fetal tissue oxygen supply.

Deoxygenation thus leads to the appearance of NH^+ , NH_2^+ or NH_3^+ groups in the Hb molecule whereas free titratable hydrogen ions disappear.

If severe hypoxia occurs, the fetal hemoglobin molecules are soaked with hydrogen ions like a sponge filled with

water and hemoglobin saturation becomes very low (e.g. around 3.0 % [25]); thus oxygen is delivered to fetal tissues, avoiding at least temporarily hypoxic injuries.

Therefore using the new and logical nomenclature proposed by Siggaard-Andersen [5], abandoning the mentally uncomfortable term BE and remembering again that $BE_B = -ctH^+_B$:

$ctH^+_{Ecf,act} = ctH^+_{Ecf,ox} - 0.3 \times cHb_{Ecf} \times (1 - sO_2)$,
rearranged:

$$ctH^+_{Ecf,ox} = ctH^+_{Ecf,act} + 0.3 \times cHb_{Ecf} \times (1 - sO_2),$$

where cHb is given in mmol/L and sO_2 as fraction.

Most probably this (i.e. $ctH^+_{B,ox} > ctH^+_{B,act}$ and $BE_{B,ox} < BE_{B,act}$

($-6 < -3$)) is the reason why in all computations with the "base excess family", using completely different clinical variables, "correction" (i.e. addition of the term $0.3 \times cHb_{Ecf} \times (1 - sO_2)$) invariably leads to better, i.e. more significant coefficients; the differences between the coefficients being also highly significant (not shown). Therefore it is tempting to generally recommend "correction" of $BE_{B,act}$ or $BE_{Ecf,act}$ to 100 % oxygen saturation in obstetrical acid-base studies [20, 26].

This correction procedure, however, might not entirely reflect reality since it combines *in vivo* and *in vitro* conditions: *In vivo* the hydrogen ions liberated by reoxygenation are quickly redistributed.

Therefore ctH^+_B (BE_B) should refer to actual oxygen saturation, i.e. $ctH^+_{B,act}$, not to fully oxygenated blood, i.e. $ctH^+_{B,ox}$, simulating *in vitro* conditions. This was not taken into account in our last study [20].

Moreover, the link to fetal oxygen status needs the additional measurement (computation) of sO_2 (%) for HbF; clinically this might not be worthwhile.

Additionally, $ctH^+_{B,ox}$ ($BE_{B,ox}$) greatly overestimates the metabolic component [25] of an acidosis *in vivo* when

compared with $BE_{B,act}$, the latter being used in the majority of all perinatal acid-base studies in the past:

In a large sample the median ΔctH^+_B due to oxygen "correction" (*in vitro* (!)) amounts to +2.74 mmol/L, the maximum being 5.2 mmol/L [20]. Thus a computed BE_B of -20.0 might change to -25.2 mmol/L ($BE_{B,ox}$) with acidotic fetal hemoconcentration.

However, if one would adhere to real fetal oxygen status, it is possible to "correct" ctH^+_{Ecf} using the same equation but with

$$cHb_{Ecf} = cHb_B / 4 \text{ (g\%)}$$

$$ctH^+_{Ecf,ox} = ctH^+_{Ecf,act} + 0.3 \times cHb_{Ecf} \times (1 - sO_2)$$

Using this concept, however, the difference ($\Delta ctH^+_{Ecf} = ctH^+_{Ecf,ox} - ctH^+_{Ecf,act}$) becomes clinically more or less unimportant:

Mean $\Delta ctH^+_{Ecf} = 0.548 \pm 0.090$, median = 0.563, range: 0.200-0.710 (mmol/L), N = 475.

This was to be expected since dilution of cHb in the expanded extracellular fetal space (cHb_{Ecf}) must reduce the correction effect numerically to about 1/4.

Nevertheless it reflects reality since intrauterine reanimation (always *in vivo* conditions) possibly with full reoxygenation will result in increased ctH^+_{Ecf} values, i.e. $ctH^+_{Ecf,ox}$.

In summary: Fetal Standard BE ($ctH^+_{Ecf,act}$) should be used instead of BE_B ("normal" BE) and "correction" to 100 % oxygen saturation makes sense if one would virtually separate fetal hypercarbia from fetal hypoxia *in vivo*.

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