# Acid-Base Balance

**O Siggaard-Andersen**, Medical Physiology, Panum Institute, University of Copenhagen, Denmark.

## Abstract

The acid-base balance or neutrality regulation maintains a pH around 7.4 in the extracellular fluid by excreting carbon dioxide in the lungs and non-carbonic acid or base in the kidneys. The result is a normal acid-base status in blood and extracellular fluid, i.e. a normal pH, a normal carbon dioxide tension ($pCO_2$), and a normal concentration of titratable hydrogen ion ($ctH^+$). A pH, log $pCO_2$ chart illustrates the acid-base status of the arterial blood. The chart shows normal values as well as values to be expected in typical acid-base disturbances, i.e. acute and chronic respiratory acidosis and alkalosis, and acute and chronic non-respiratory (metabolic) acidosis and alkalosis. The chart allows estimation of the concentration of titratable $H^+$ of the extended extracellular fluid (including erythrocytes), $ctH^+$Ecf. This quantity is also called standard base deficit but the term base does not directly indicate that the quantity refers to the excess or deficit of hydrogen ions. $ctH^+$Ecf is the preferred indicator of a non-respiratory acid-base disturbance being independent of acute changes in $pCO_2$ in vivo. While pH and $pCO_2$ are directly measured, $ctH^+$Ecf is calculated from pH and $pCO_2$ using the Henderson-Hasselbalch equation and the Van Slyke equation.

## Description

The acid-base balance or neutrality regulation maintains a pH around 7.4 in the extracellular fluid by excreting carbon dioxide in the lungs and non-carbonic acid or base in the kidneys. The result is a normal acid-base status in blood and extracellular fluid, i.e. a normal pH, a normal carbon dioxide tension ($pCO_2$), and a normal concentration of titratable hydrogen ion ($ctH^+$). A graphical illustration is an aid in the description of the acid-base status of the blood (Fig. 1).

### pH and the Hydrogen Ion Concentration ($cH^+$)

pH and $cH^+$ of the plasma are both indicated on the abscissa of the chart (Fig. 1). $cH^+$ is calculated as $10^{9-pH}$ nmol/L. pH and pOH are closely related: pH + pOH = p$K_w$ = 13.622 at 37 °C, where $K_w$ is the ionization constant of water. If $H^+$ is considered a key component of an aqueous solution, then $OH^-$ is a derived component. Accounting for $H^+$ and $H_2O$, indirectly accounts for $OH^-$ as well. It is the authors conviction that the relevant component is the hydrogen ion, not hydrogen ion binding groups (base) nor hydroxyl ions.

### Carbon Dioxide Tension of the Blood ($pCO_2$)

$pCO_2$, i.e. the partial pressure of carbon dioxide in a gas phase in equilibrium with the blood, is shown on the ordinate on a logarithmic scale. When $pCO_2$ increases, the concentration of dissolved carbon dioxide and carbonic acid increases, and hence the hydrogen ion concentration increases:
$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$.

### Concentration of Titratable Hydrogen Ion ($ctH^+$)

$ctH^+$ is indicated on the scale in the upper left corner of the chart. The amount of hydrogen ion added or removed in relation to a reference pH of 7.40 may be determined by titration to pH = 7.40 at $pCO_2$ = 5.33 kPa (= 40 mmHg) at 37 °C using strong acid or base, depending upon the initial pH. Titratable hydrogen ion or hydrogen ion excess, is also called base deficit, or with opposite sign base excess. Unfortunately, the term base is ambiguous (has been associated with cations) and does not directly indicate that the relevant chemical component is the hydrogen ion. If a nick name is needed it may be hydrogen ion excess; acronym: HX. Note: by definition $ctH^+$ of blood refers to the actual hemoglobin oxygen saturation, not the fully oxygenated blood.

Acid and base are defined by the equilibrium:
$Acid^z \leftrightarrows H^+ + Base^{z-1}$,
where $Acid^z$ and $Base^{z-1}$ is a conjugate acid-base pair. The charge number $z$ may be positive, zero, or negative. A strong acid, e.g. HCl, dissociates completely: $HCl \rightarrow H^+ + Cl^-$. A strong base, e.g. $OH^-$, associates completely with hydrogen ion: $OH^- + H^+ \rightarrow H_2O$. A weak acid (buffer acid) is in

equilibrium with its conjugate weak base (buffer base), e.g.

$H_2CO_3 \leftrightarrows H^+ + HCO_3^-$

$\text{hemoglobin}^z \leftrightarrows H^+ + \text{hemoglobin}^{z-1}$.

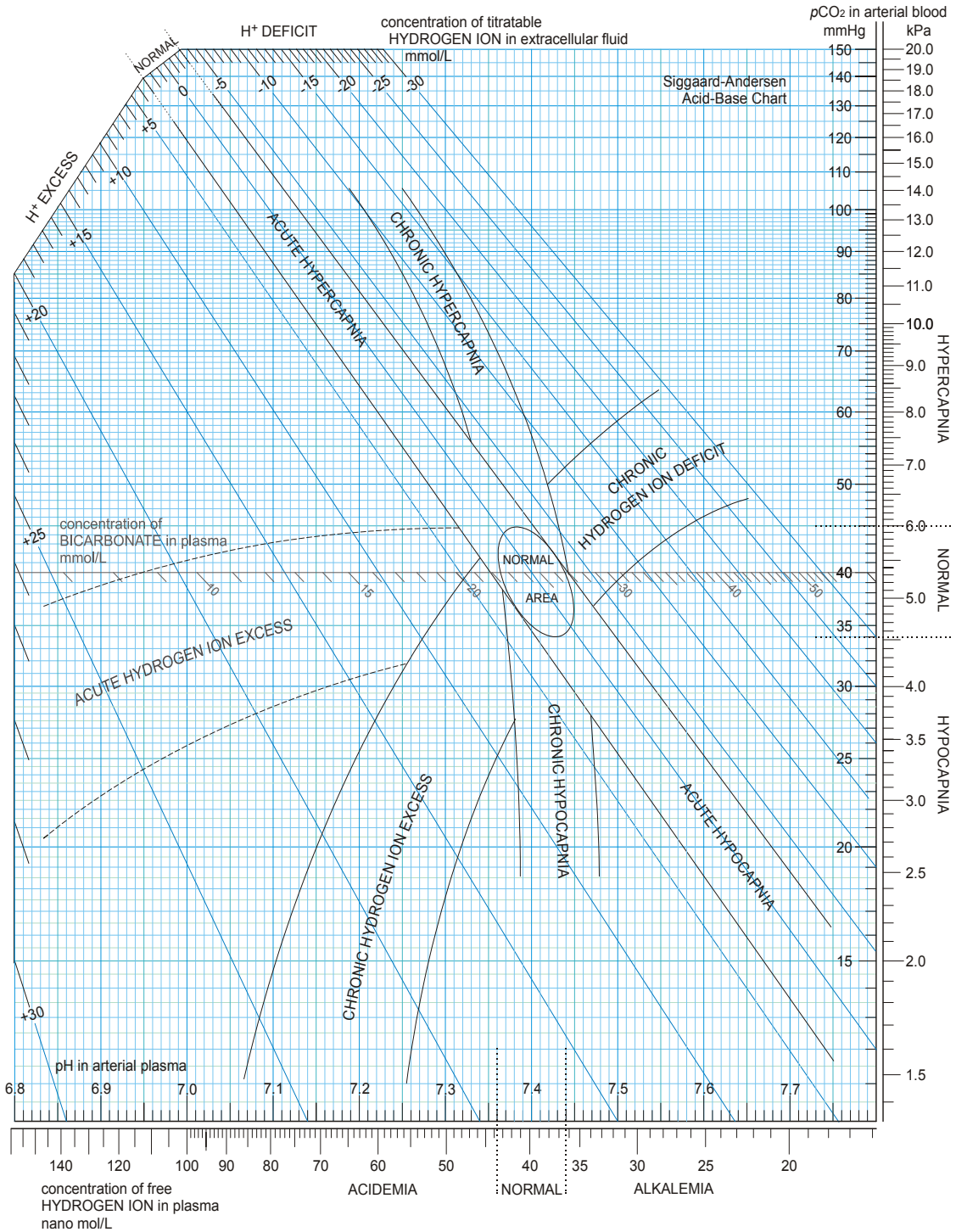


Fig. 1. Acid-base chart for arterial blood with normal and pathophysiological reference areas. The acid-base status is shown as a point with three coordinates: pH (abscissa), $pCO_2$ (ordinate), and $ctH^+$ (oblique coordinate). The bands radiating from the normal area show reference areas for typical acute and chronic, respiratory and non-respiratory, acid-base disturbances. Hyper- and hypocapnia are also called respiratory acidosis, respectively alkalosis. Hydrogen ion excess and deficit, i.e. increased and decreased $ctH^+$, are also called non-respiratory (or metabolic) acidosis, respectively alkalosis. 

An acute increase in $pCO_2$ in vivo causes a rise in $ctH^+_B$ and a fall in $ctH^+_P$ while $ctH^+_{Ecf}$ remains constant. The cause is a redistribution of hydrogen ions within the extended extracellular volume. Hydrogen ions diffuse from the poorly buffered interstitial fluid into the blood plasma and further into the erythrocytes. Very little transfer of hydrogen ions occurs between the intracellular space and the extracellular space, so $ctH^+_{Ecf}$ remains virtually constant during acute changes in $pCO_2$ in vivo. $ctH^+_{Ecf}$ is also called the standard base deficit (SBD), or with opposite sign the standard base excess (SBE), but the term base is deprecated by the author.

Projections to the $ctH^+$ scale in the upper left corner of the chart (Fig. 1) should be made along the slanting so-called vivo-$CO_2$ titration curves, which are virtually straight lines (slightly convex upwards). The slope of the lines depends on the concentration of non-bicarbonate buffers, i. e. mainly hemoglobin

In summary, the hydrogen ion status of the blood is described by a point in the acid-base chart: the *x,y* coordinates indicate $cH^+$ and $pCO_2$, the oblique coordinate is $ctH^+_{Ecf}$.

## The Henderson-Hasselbalch Equation

Often a description of acid base balance is based on the Henderson-Hasselbalch equation, derived from the law of mass action:

$pH = pK + \log_{10}(cHCO_3^-/(\alpha CO_2 \cdot pCO_2))$,

where $pK = 6.10$ and $\alpha CO_2 = 0.23$ mmol·L$^{-1}$·kPa$^{-1}$ = 0.0306 mmol·L$^{-1}$·mmHg$^{-1}$ (solubility coefficient of carbon dioxide in plasma at 37 °C). $\alpha CO_2 \cdot pCO_2$ gives the concentration of $H_2CO_3$ plus $CO_2$. pH is determined by two variables, $pCO_2$ and $cHCO_3^-$, representing respiratory and metabolic disturbances. $cHCO_3^-$ is shown in the acid-base chart on a horizontal logarithmic scale along the $pCO_2$ = 5.33 kPa line. Projections to the scale should be made at an angle of –45°. However, $cHCO_3^-$ is not independent of $pCO_2$. For this reason standard bicarbonate was introduced, i.e. the bicarbonate concentration in plasma of whole blood equilibrated with a gas mixture with a normal $pCO_2$ (5.33 kPa = 40 mmHg) at 37 °C. However, even the standard bicarbonate is not completely independent of acute changes in $pCO_2$ in vivo, decreasing slightly in acute hypercapnia. Projecting from a given point in the chart to the bicarbonate scale along the slanting vivo-$CO_2$ equilibration lines gives the standard bicarbonate concentration of the extended extracellular fluid.

## The Van Slyke Equation

Blood gas analyzers measure pH with a glass electrode and $pCO_2$ with a membrane covered glass electrode (Stow-Severinghaus electrode). $ctH^+Ecf$, is calculated from pH, $pCO_2$ and $cHb$ (concentration of hemoglobin) using a model of the titration curve called the Van Slyke equation (Table 1). The equation calculates the change in buffer base concentration (bicarbonate plus protein anion plus phosphate) from the value at the reference point: $pH^\circ = 7.40$, $pCO_2^\circ = 5.33$ kPa, and $T^\circ = 37$ °C.

Table 1. Van Slyke equation for calculation of the concentration of titratable hydrogen ion in the extended extracellular fluid, $ctH^+_{Ecf}$. Ecf refers to the extended extracellular fluid, B to whole blood, P to plasma. Replacing $cHb_{Ecf}$ by $cHb_B$ gives $ctH^+_B$; replacing $cHb_{Ecf}$ by zero gives $ctH^+_P$.

$ctH^+_{Ecf} = -(1 - cHb_{Ecf}/cHb^\circ)\cdot(\Delta cHCO_3^-{}_P + \beta H^+_{Ecf} \cdot \Delta pH_P)$.

| | |
|---|---|
| $cHb_{Ecf}$ | $= cHb_B \cdot V_B/V_{Ecf}$, concentration of hemoglobin in the extended extracellular fluid. |
| $V_B/V_{Ecf}$ | = 1/3 (default value), ratio between the volume of blood and volume of extended extracellular fluid. |
| $cHb^\circ$ | = 43 mmol/L, empirical parameter accounting for an unequal distribution of hydrogen ions between plasma and erythrocytes. |
| $\Delta cHCO_3^-{}_P$ | $= cHCO_3^-{}_P - cHCO_3^-{}_P{}^\circ$. |
| $cHCO_3^-{}_P{}^\circ$ | = 24.5 mmol/L, concentration of bicarbonate in plasma at $pHP^\circ = 7.40$, $pCO_2^\circ = 5.33$ kPa, $T^\circ = 37.0$ °C. |
| $\Delta pH_P$ | $= pH_P - pH_P{}^\circ$. |
| $\beta H^+_{Ecf}$ | $= \beta_m Hb^\circ \cdot cHb_{Ecf} + \beta_P$. |
| $\beta_m Hb^\circ$ | = 2.3, apparent molar buffer capacity of hemoglobin monomer in whole blood. |
| $\beta_P$ | = 7.7 mmol/L (default value), buffer value of non-bicarbonate buffers in plasma for a normal plasma protein (albumin) concentration. |
| $cHb_B$ | $= \rho Hb_B / M_m Hb$, (substance) concentration of hemoglobin in blood (unit: mmol/L) as a function of the mass concentration, $\rho Hb_B$ (unit: g/L). |
| $M_m Hb$ | = 16,114 g/mol, molar mass of hemoglobin monomer. |

Note: if $cHb_B$ = 9.0 mmol/l ⇔ $\rho Hb_B$ = 14.5 g/dL then the Van Slyke equation simplifies to:
$ctH^+_{Ecf} = -0.93 \cdot (\Delta cHCO_3^-P + \Delta pHP \cdot 14.6$ mmol/L).

Buffer base (BB) is the difference between the concentrations of buffer anions and buffer cations (the latter being virtually zero at physiological pH). Strong ion difference (SID) is the difference between the concentrations of non-buffer cations and non-buffer anions (see Fig. 2). According to the law of electro-neutrality the value of BB and SID must be identical. Buffer base is not a suitable indicator of a non-respiratory acid-base

disturbance; although independent of $pCO_2$, it varies with the albumin and hemoglobin concentrations, which are unrelated to acid-base disturbances.

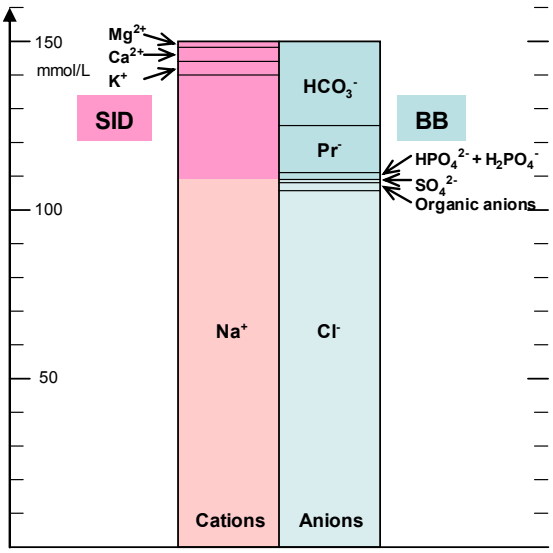


Fig. 2. Electrolyte balance of arterial plasma showing columns of cations and anions of equal height (law of electro-neutrality). The equality of the strong ion difference (SID) and buffer base (BB) is illustrated. The change in concentration of buffer base from normal (at pH = 7.40, $pCO_2$ = 5.3 kPa, and $T$ = 37 °C) with opposite sign equals the concentration of titratable hydrogen ion.

## Normal Acid-Base Balance

Acid-base balance refers to the balance between input (intake and production) and output (elimination) of hydrogen ion. The body is an open system in equilibrium with the alveolar air where the partial pressure of carbon dioxide ($pCO_2$) is identical with the carbon dioxide tension in the blood. $pCO_2$ is directly proportional with the $CO_2$ production rate (at constant alveolar ventilation and $CO_2$ free inspired air) and inversely proportional with the alveolar ventilation (at constant $CO_2$ production rate and $CO_2$ free inspired air). $CO_2$ is constantly produced in the oxidative metabolism at a rate of about 10 mmol/min (= 224 mL/min) and eliminated in the lungs at the same rate so that the $pCO_2$ remains about 5.33 kPa (= 40 mmHg). Hydrogen ions associated with any other anion than bicarbonate or exchanging with a cation are eliminated by the kidneys. In the oxidative metabolism of sulfur containing amino acids, hydrogen ions are produced together with sulfate ions at a rate of about 70 mmol/d, depending upon the protein intake. Amino acids are oxidized to carbon dioxide and water, and the amino nitrogen, liberated as $NH_3$, combines with carbon dioxide in the liver via the Krebs urea cycle to form neutral urea. Therefore there is no production of base (ammonia) except in the kidneys, where ammonia formed from glutamine, diffuses into the urine where it binds a hydrogen ion ($NH_3 + H^+ \rightarrow NH_4^+$) thereby preventing an excessively low urine pH.

Normal values for the acid-base status of arterial blood are given in Table 1. The values are independent of age except at birth, where babies tend to have higher $pCO_2$, lower pH, and slightly increased $ctH^+Ecf$, approaching normal values for adults in the course of few hours. In the last trimester of pregnancy the $pCO_2$ is lower (about 1 kPa = 7.5 mmHg), compensated by a slightly increased $ctH^+Ecf$. High altitude hypoxia stimulates ventilation; at 5 km $pCO_2$ is decreased to about 3.3 kPa = 25 mmHg. The hypocapnia is compensated by increased $ctH^+Ecf$, so pH is only slightly elevated. The values fall in the area of chronic hypocapnia in the acid-base chart (Fig. 1).

## Acid-Base Disturbances

### Respiratory Acid-Base Disturbances

Acute respiratory acid base disturbances are characterized by an acute change in $pCO_2$ associated with an acute change in pH but with unchanged $ctH^+Ecf$. The relationship between $pCO_2$ and pH is illustrated by the oblique in vivo $CO_2$ equilibration lines in the acid-base chart (Fig. 1).

Primary increase and decrease in $pCO_2$ are compensated by secondary renal decrease and increase in $ctH^+Ecf$, respectively. The acid-base chart shows the expected values in chronic hypercapnia and chronic hypocapnia. The effect of the compensation is a return of pH about two thirds towards normal, slightly more in acute hypocapnia.

Table 1. Reference values for arterial blood. $cH^+P$: conc. of (free) hydrogen ions in plasma; $ctH^+Ecf$ : conc. of titratable hydrogen ion in extracellular fluid (also called standard base deficit, SBD); $pCO_2$: tension of carbon dioxide; $cHCO_3^-P$: conc. of bicarbonate in plasma.

| | Women | Men |
|---|---|---|
| pH | 7.38 – 7.44 | 7.37 – 7.43 |
| $cH^+P$, nmol/L | 36.3 – 41.7 | 37.2 – 42.7 |
| $ctH^+Ecf$, mmol/L | –2.3 – +2.7 | –3.2 – +1.8 |
| $pCO_2$, mmHg | 33.8 – 42.4 | 36.8 – 46.2 |
| kPa | 4.59 – 5.76 | 4.91 – 6.16 |
| $cHCO_3^-P$,mmol/L | 21.2 – 27.0 | 22.2 – 28.3 |

## Non-Respiratory Acid-Base Disturbancies

Primary increase and decrease in $ctH^+Ecf$ are compensated by secondary decrease and increase in $pCO_2$. A very acute rise in $ctH^+Ecf$, for example due to anaerobic exercise with lactic acid formation, is only partly compensated because only peripheral chemoreceptors react promptly to a fall in blood pH. It takes about an hour before $H^+$ equilibrium between blood and brain extracellular fluid is achieved and the central chemoreceptors are maximally stimulated. The acid-base values in acute non-respiratory acidemia are illustrated in the acid-base chart by the area labeled acute hydrogen ion excess. The outline of the area is dotted because it is less well defined than the other areas of the chart. The compensations in more slowly developing non-respiratory acidemia or alkalemia are illustrated by the areas labeled chronic hydrogen ion excess and deficit, respectively. The effect of the respiratory compensation is a return of pH one third to halfway towards normal.

Once an increase in $ctH^+Ecf$ has been detected, the question is: what caused the metabolic acidosis? It may be a production of lactic acid due to anaerobic metabolism or acetoacetic acid (ketoacidosis) due to diabetes mellitus or starvation. In both cases the diagnosis may be verified by direct measurement of blood lactate or acetoacetate. When these analyses are unavailable, calculation of the concentration of undetermined anions may be useful, i.e. the sum of the concentrations of measured cations ($Na^+$ and $K^+$) minus the sum of the concentrations of measured and calculated anions ($Cl^-$ and $HCO_3^-$). This equals the sum of the concentrations of unmeasured anions (mainly $Protein^-$, $SO_4^{2-}$, $HPO_4^{2-}$, fatty carboxylate, lactate, acetoacetate) minus the sum of the concentrations of unmeasured cations ($Ca^{2+}$ and $Mg^{2+}$). A metabolic acidosis with a major increase in undetermined anions usually indicates organic acidosis. A hyperchloremic acidosis may be a renal acidosis with retention of $H^+$ and $Cl^-$ or an intestinal loss of $Na^+ + HCO_3^-$ with subsequent intake of saline ($Na^+ + Cl^-$). A hypochloremic alkalosis may be due to loss of $H^+$ and $Cl^-$ by vomiting. Hypokalemic alkalosis is due to inability of the kidneys to retain hydrogen ions in the presence of potassium depletion.

## Further Reading


Astup P, Severinghaus JW. The History of Blood Gases Acids and Bases. Copenhagen: Munksgaard International Publishers, 1986.

Davenport HW. The ABC of Acid-Base Chemistry. 5th ed. Chicago: The University of Chicago Press, 1969.

Grogono AW. Acid-Base Balance. International Anesthesiology Clinics, Problems and Advances in Respiratory Therapy, Vol. 24, No. 1, 1986.

Grogono AW. Acid-base balance: www.acid-base.com.

International Federation of Clinical Chemistry and International Union of Pure and Applied Chemistry. Approved Recommendation (1984) on Physico-Chemical Quantities and Units in Clinical Chemistry. J. Clin. Chem. Clin. Biochem. 25: 1987; 369-391.

Halperin ML and Goldstein MB. Fluid, Electrolyte, and Acid-Base Emergencies. Philadelphia: WB Saunders Company, 1988.

Hills AG. Acid-Base Balance. Chemistry, Physiology, and Pathophysiology. Baltimore: William & Wilkins, 1973.

Masoro EJ, Siegel PD. Acid-Base Regulation: Its Physiology and Pathophysiology. Philadelphia: Saunders, 1971.

Nahas G, Schaefer KE, eds. Carbon Dioxide and Metabolic Regulations. New York: Springer, 1974.

Rooth G. Acid-Base and Electrolyte Balance. Lund: Studentlitteratur, 1975.

Severinghaus JW, Astrup P. History of Blood Gas Analysis. Boston: Little, Brown and Company, 1987.

Shapiro BA, Peruzzi WT, Templin R. Clinical Application of Blood Gases. 5th ed. St. Louis: Mosby – Year Book, 1994.

Siggaard-Andersen O. The Acid-Base Status of the Blood. 4th ed. Copenhagen: Munksgaard, 1974, and Baltimore: William & Wilkins Company, 1974.

Siggaard-Andersen O. Hydrogen ions and blood gases. In: Brown SS, Mitchell FL, Young DS, eds. Chemical Diagnosis of Disease. London: Elsevier/North-Holland Biomedical Press, 1979. 181 – 245.

SiggaardAndersenO.The oxygen status algorithm: www.osa.suite.dk

Siggaard-Andersen O, Fogh-Andersen N. Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. Acta Anaest Scand 39, Suppl 107: 1995; 123-128.

Thomson WST, Adams JF, Cowan RA. Clinical Acid-Base Balance. New York: Oxford University Press, 1997.

West JB. Respiratory Physiology, the Essentials. Oxford: Blackwell, 1974.

West, JB. Pulmonary Physiology and Pathophysiology: An Integrated, Case-Based Approach. Philadelphia: Lippincott Williams & Wilkins, 2001.