Rapid Analysis—Blood Gases and More

Dr. Patrizia Mikulcik

siemens-healthineers.com

SIEMENS Healthineers

Table of contents

History

Today the conduct of blood gas analysis in the broader sense represents a key part of clinical diagnostics, especially in critical care or intensive care situations. Its origin dates back to the early 19th century.

Henderson was the first to recognize the correlation between acid-base parameters in 1909, representing the relationship between proton (hydrogen ion) concentration, carbonic acid and its corresponding base (bicarbonate) in the following formula:

$$[H^+] = K \times \frac{[H_2CO_3]}{[HCO_3^-]}$$

Shortly thereafter, Hasselbalch (1916) modified the equation for use with respect to the pH value of the blood. From then on, it was as follows:

$$pH = pKa + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

Note: Subsequent to the development of the Severinghaus-Bradley electrode for measuring partial pressure of carbon dioxide (PCO_2), the equation uses the term 0.031 x PCO_2 instead of 'H_2CO_3'

The basis for the measuring technique was laid parallel with these insights. Barely ten years after the "Henderson-Hasselbalch" equation was published, Kerridge measured the pH value of human blood by means of a gas electrode for the first time in 1925. However, the direct measurement of PCO_2 did not materialize until 1952 when Stow described an electrode capable of direct measurement. The modification of this electrode by Severinghaus shortly thereafter is still being used to this day.

The oxygen electrode, which is still being used in modified form, was developed by Clark in 1956.

The 1970s experienced a rapid development from the first manual blood gas analyzer with an electronic acid-base calculator to a single sample chamber model (Corning M165) to a model with automatic calibration and error detection (Corning M175).

In the 1980s, the parameters hemoglobin and the main electrolytes (Na^+, K^+, Ca^{++}, and Cl-) obtained from a capillary blood specimen were introduced to patient-centered diagnostics.

The additional determination of glucose and lactate has been possible since 1994. It was in the same year that the CO-oximetry for the determination of hemoglobin and its derivatives revolutionized the possible evaluations of the oxygen supply.

And the development goes on...

Pre-Examination considerations

Recently developed analytical systems allow the complete analytical procedure to be performed with small specimen volumes. To guarantee good quality emergency analysis, and to minimize unnecessary sources of error, an analysis must be preceded by proper pre-analytical examinations. This is the only way to ensure that the measured values correspond to the actual blood status. The key to accurately measured results is the correct preparation, and conduct of the blood withdrawal, and handling of the specimens.

The suitable specimen type and withdrawal site should be monitored by a clinician.

To simplify the specimen collection, manufacturers offer ideally equipped and prepared specimen collection systems.

Several points need to be taken into account when handling specimens because analytical emergency procedures in the broadest sense (including oxygen status) represent particularly sensitive diagnostic procedures: the values of individual parameters are altered at every instant as a result of respiration and metabolism, and the gas exchange of a blood specimen with ambient air significantly affects the blood gases PO_2 and PCO_2.

“Collection, handling, and transport of blood specimens are key factors for the accuracy of clinical laboratory analysis, and ultimately for the quality of the patient care.”

Clinical and Laboratory Standards Institute (CLSI), formerly National Committee for Clinical Laboratory Standards (NCCLS)

Specimen types

The selection of a suitable site for the withdrawal of blood specimens should be monitored by a clinician. The puncture site must be cleaned with a dermal antiseptic and be dried completely with a sterile swab because traces of antiseptic on the skin will hemolyze the blood.

Arterial blood

The complete physiological picture is based on arterial blood. As a result, specimens collected anaerobically from the artery, and heparinized specimens, represent the preferred specimen material for the reliable assessment of the acid-base metabolism and the oxygen status. This specimen material will provide evidence of any diffusion, ventilation, or perfusion disorders the patient may experience.

Arterial blood can be collected by:

• Puncture of the femoral artery, brachial artery, and radial artery (Fig. 1), or

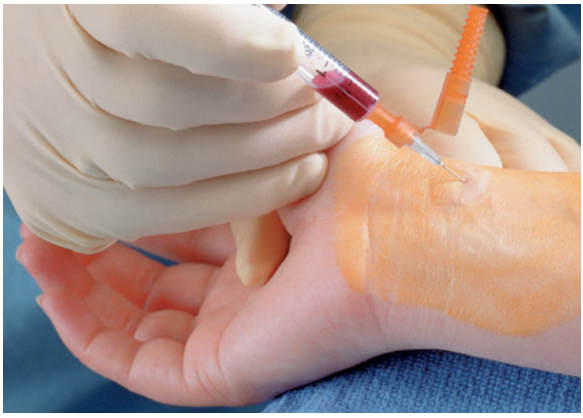


Fig. 1: Puncture of the radial artery

Note:
Election of certain arteries by anyone other than a licensed physician may be proscribed by law in some jurisdictions.

• Aspiration from an indwelling arterial catheter (Fig. 2) or arterial cannula.

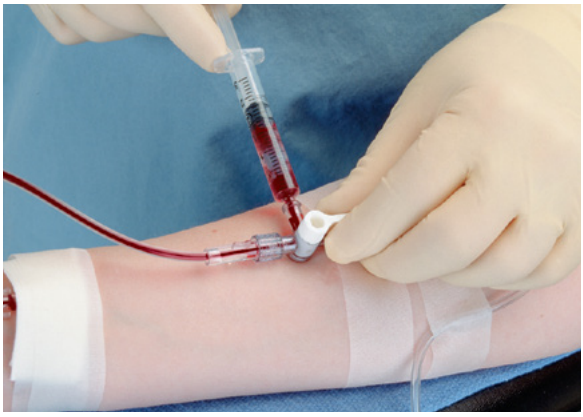


Fig. 2: Aspiration from an indwelling arterial catheter.

The key advantage consists in the homogeneity of arterial blood from the aorta to the peripheral circulation. The simultaneous specimen withdrawal from the brachial, radial, and femoral arteries at identical conditions will provide identical pH, PCO_2, and PO_2 values.

Always ensure the anaerobic withdrawal and the use of anticoagulants.

Capillary blood

In stable circulatory conditions, capillary blood sampling has been proven to be a practical and suitable alternative to arterial puncture, provided the following criteria are observed:

- Capillary blood is generally withdrawn from the earlobe or the heel of the foot (neonatology only). The selected area of skin should be warmed up prior to the puncture or the arterial circulation increased by other means to ensure the proper blood gas and pH measurement. FINALGON ointment (nicotinic acid ester) is commonly used to stimulate localized capillary blood flow.

Remember to sterilize the corresponding skin area prior to the puncture to enlarge the capillaries and increase the blood flow within the capillary vessel, e.g., with the application of Finalgon ointment.

- The puncture should be sufficiently deep to provide an unobstructed and rapid blood flow.
- The end of the capillary tube should have direct contact with the drop of blood to minimize the gas exchange of the specimen with air (Fig. 3). The risk of contamination with ambient air, and the resulting falsification of the values, is particularly high in this instance.

Fig. 3: Capillary blood withdrawal from the sterilized earlobe.

Important: If the patient is experiencing circulatory shock, and the peripheral circulation is insufficient as a result, the content of the blood contained in the peripheral arteries and arterioles differs from the blood of the major arteries. In this case, collect the blood specimens by means of arterial puncture, especially puncture of the femoral artery. In infants younger than 1 year, the blood can be collected by puncturing the heel (following compression).

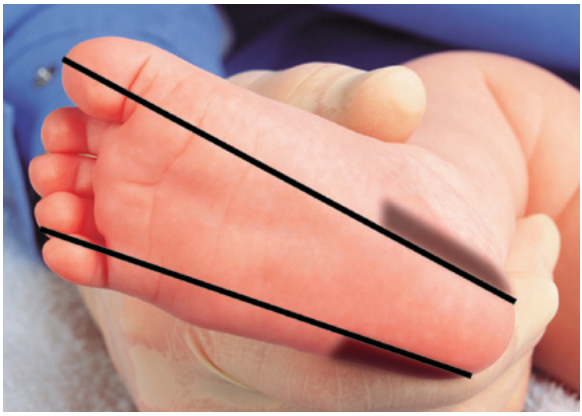


Fig. 4: Lateral or medial area of the heel suitable for puncture in infants (hatched area).

Venous blood

Venous blood is not suitable for blood gas analysis because the oxygen exchange in the various regions of the body can lead to extreme differences of the values.

Venous blood can be used to determine the parameters hemoglobin, electrolytes, and metabolites as well as pH and PCO_2 (with due correction for expected and consistent a-v differences).

Mixed venous blood

To answer special questions, mixed venous blood can be used that was collected from an indwelling catheter in the pulmonary artery that was carefully cleared of infusion fluid.

For example, PCO_2, PO_2, and sO_2 are relevant for the evaluation of the oxygen supply and oxygen exhaustion (heart surgery or heart catheterization).

Specimen withdrawal

Specimen containers

The following containers can be used:

- glass syringes
- synthetic syringes
- capillary tubes

Glass syringes

In glass syringes, the exposure to contamination by air is lower than synthetic ones as the walls are resistant against air diffusion.

Synthetic syringes

Synthetic syringes are easy to use. The gas dissolved in the synthetic materials—especially with respect to CO_2 and O_2—constitutes a potential source of error when the time between withdrawal and evaluation is prolonged. Therefore, the specimen must be analyzed immediately upon withdrawal to minimize this influence.

Capillary tubes

The manufacturers generally add an adequate amount of heparin to capillary tubes. Please refrain from using mixing rods because the hemolysis, and consequently the falsification of the potassium values, represent a source of error.

Anticoagulants

Important: Only use specimen containers for whole blood specimens that contain calcium-titrated (balanced) lithium-heparin as an anticoagulant. Other anticoagulants such as benzalkonium heparin, EDTA, citrate, oxalate, and fluoride significantly affect the results for pH, sodium, potassium, chloride, and ionized calcium.

The frequently employed sodium heparin must not be used if the specimen will also be used to determine the electrolytes. Due to its molecular structure, heparin binds cations, where Ca^{++} has the highest affinity to heparin among the measured electrolytes.

In high-quality syringes or capillary tubes, this effect is negligible because heparin was pre-titrated, and the free binding sites are occupied as a result. In no situations should one use heparin intended for therapeutic use, since its concentration and electrolyte content will vary and affect analytical results.

Ca^{++} titrated lithium heparin reduces the electrolyte binding, thus optimizing the accuracy of the analysis.

Prior to specimen collection, estimate the amount of arterial blood to be collected, then add sufficient heparin so that the final concentration in the specimen will be between 50 and 100 IU/mL of blood.

Specimen collection and patient's body temperature

Blood gas analyzers are set at 37°C. Interpretation errors caused by different patient temperatures can occur. However, different medical diagnostic questions require the patient's body temperature.

Therefore, the patient's temperature should be determined at the time the specimen is drawn. All state-of-the-art systems allow you to enter the patient's body temperature, and update the measured pH, PO_2, PCO_2 values, and the oxygen saturation with respect to the patient's actual body temperature.

Sometimes, the measured values for PO_2 and PCO_2 change proportionally with the temperature, while the pH changes reverse proportionally with respect to the body temperature (Fig. 5). It should be noted that there are no established "normal" or "expected" values for pH and blood gases for temperatures other than 37°C. Thus many believe that 37°C measured values should be reported and labeled as such when reporting patient temperature corrected values.

°C	pH	PCO_2	PO_2
29	+ 0.120	x 0.720	x 0.560
30	+ 0.105	x 0.750	x 0.600
31	+ 0.090	x 0.780	x 0.650
32	+ 0.075	x 0.815	x 0.700
33	+ 0.060	x 0.850	x 0.750
34	+ 0.045	x 0.885	x 0.805
35	+ 0.030	x 0.920	x 0.865
36	+ 0.015	x 0.960	x 0.930
37	+ 0.000	x 1.000	x 1.000
38	– 0.015	x 1.040	x 1.070
39	– 0.030	x 1.080	x 1.145
40	– 0.045	x 1.125	x 1.225
41	– 0.060	x 1.170	x 1.310

Fig. 5: Temperature dependence of the measured blood gas parameters

Handling specimens

The observance of the following points is crucial:

- Mix the specimen after the collection and before conducting the measurement.
- Prevent the contamination of the specimen with ambient air.
- Remember the influence of metabolic activities.
- Prevent hemolysis.

Mix the specimen after the collection and before conducting the measurement

Roll the specimen collection system between your hands after collecting the specimen, and turn it gently to ensure the thorough mixture of the blood with the heparin (Fig. 6).

The sedimentation of erythrocytes causes the specimen to segregate, resulting in incorrect measurements for hemoglobin and hematocrit. To ensure the homogeneity of the blood specimen, carefully mix the specimen once more before conducting the measurement.

Fig. 6: Mixing the specimen by rolling it between the palms of your hands.

Prevent the contamination of the specimen with ambient air

The contamination of the specimen with air represents one of the most common sources of pre-examination error. Gas exchange caused by the presence of air is generally possible:

- During the collection of capillary specimens or by accidental aspiration of air during the specimen collection.
- During the collection of specimens from an indwelling arterial catheter: please observe the dead space.
- Due to the diffusion of air through the wall of (synthetic) syringes—time-dependent.
- On contact between the blood and the air, the small CO_2 concentration and the higher O_2 concentration of air cause the shift in the values of the blood you wish to analyze into the respective direction of the air concentration.

This is due to the equilibration tendency between the two media involving the risk of a decrease of the PCO_2 in the specimen and an change of PO_2 under normal conditions.

If the PO_2 in the blood is $<PO_2$ in the air → the measured result for PO_2 is falsely elevated.

If the PCO_2 in the blood is $>PCO_2$ in the air → the measured result for PCO_2 is falsely decreased.

The effect is both time and temperature dependent. Therefore, the appearance of air bubbles should be prevented by:

- Exercising care when collecting the specimen with the careful retraction of the syringe plunger or by using self-filling syringes.
- Using precisely fitting syringes.
- Closing the specimen container. If air bubbles do occur, remove them prior to mixing the specimen.

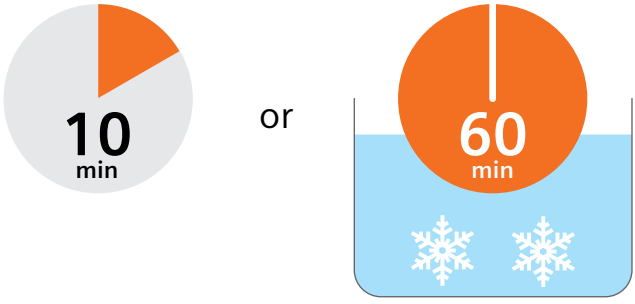
Air bubbles can be removed by squirting out the air, e.g., into a swab, etc. (Note: Risk of infection.) Or modern ventilation systems allow the safe removal of air bubbles.

Remember the influence of metabolic activities

The effect of metabolic activities increases proportionately with the time elapsed between the withdrawal and the conduct of the analysis. Therefore, the specimen should be measured without delay. Blood is a living medium: oxygen continues to be consumed even after the specimen has been collected. This particularly affects the parameters PO_2, glucose, and lactate.

The analytical procedures described in this document relate to emergency parameters. Therapeutic measures can be derived immediately from their findings. Ideally, the measurements are conducted immediately.

If the analysis is not performed within 30 minutes of specimen withdrawal, the specimen can be stored for a maximum of one hour at 0 to + 4°C—in ice water, not directly placed on ice. Avoid the exposure to direct sunlight.



Mix the specimen once more prior to conducting the measurement.

Any storage will affect the values in spite of the above.

Prevent hemolysis

Hemolysis can occur as a result of:

- Freezing of the specimen.
- Strong shaking of the specimen.
- Forceful aspiration of the specimen (application of excessive underpressure during aspiration).

Hemolysis of the specimen provides falsely elevated potassium values and falsely decreased hematocrit values, depending on the system.

Acid-base metabolism

The chemical basis of the acid-base metabolism

Acids and bases

Based on the definition by Bronstedt, acids are substances that release protons (H^+ or hydrogen ions) in aqueous solution, and bases are substances that take up protons. In other words, there is an interaction between the undissociated acid (HA) and the corresponding base (A^-) in accordance with $HA \rightleftarrows A^- + H^+$.

For strong acids, such as HCl, the equilibrium is on the right side, i.e., it is strongly dissociated, while the equilibrium is on the left side for weak acids. To guarantee the electrical neutrality of the solution during dissociation, an equal number of positively charged cations (H^+) and negatively charged anions (A^-) is always formed.

pH value

The acidic or alkaline reaction of an aqueous solution depends on the concentration of free protons. The term pH value was introduced with an exponential scale by Sorensen in 1909. It is an expression of very low H^+ ion concentrations (pH for potentia Hydrogenii). The pH value is the negative decadic logarithm (p) of the hydrogen ion's molar concentration (H^+).

This negative decadic logarithm allowed the expression of concentrations ranging from 1 to 10^{-14} with the pH values 0 to 14. As a result, pure water with an H^+ ion concentration of 0.0000001 or 10^{-7} mol had a value of 7 on his scale.

At this pH value, the proton concentration corresponds to the one of hydroxide ions $[OH^-] = [H^+]$.

A pH value of 7 is referred to as neutral pH. Solutions with a pH of <7 are referred to as acids, and solutions with a pH of >7 are referred to as bases.

H^+ [mol/l]	OH^- [mol/l]	pH-value	Examples	pH	
10^{-14}	10^{-0}	14	Unobstructed drain	Highly alkaline	
10^{-13}	10^{-1}	13			
10^{-12}	10^{-2}	12	Toilet bowl cleaner		
10^{-11}	10^{-3}	11	Laundry detergent		
10^{-10}	10^{-4}	10			
10^{-9}	10^{-5}	9	Suds	Alkaline	
10^{-8}	10^{-6}	8	Sea water		
10^{-7}	10^{-7}	7	Blood, water	Neutral	} Blood
10^{-6}	10^{-8}	6	Saliva		} Urine
10^{-5}	10^{-9}	5	Spoiled milk		
10^{-4}	10^{-10}	4	Sauerkraut	Acidic	
10^{-3}	10^{-11}	3	Coke		
10^{-2}	10^{-12}	2	Lemon juice		
10^{-1}	10^{-13}	1	Gastric juice	Very acidic	Gastric juice

Examples of pH values

0.0001 mol H^+-ions/1 ≃ pH4 → acid
0.0000000001 mol +1$^+$-ions/1 ≃ PH10 → base.

Buffer solutions/buffer systems/buffer mixtures

When an acid or base is added to an aqueous solution, its pH normally changes. However, if an acid or base is added to a buffer solution, most protons are bound. Buffer mixtures consist of a weak acid and its corresponding alkaline salt. Within certain limits, they are insensitive toward acids and bases. A buffer solution is defined as a solution with a pH that changes only slightly despite the addition of H^+- or OH^- ions.

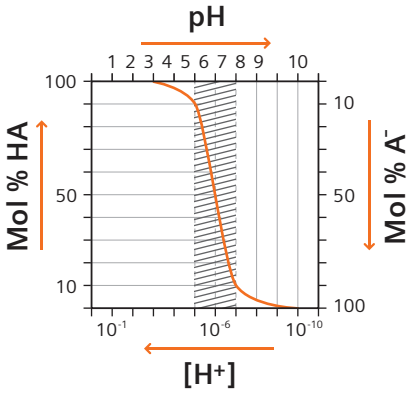


Fig. 2: Buffer systems—with the change of the molar ratio between acid/base (HA/A-) between 10:1 and 1:10; the pH value only changes slightly.

As shown in Fig. 2, neutralizing the acid (HA) with base (A^-) at a molar ratio of 10:1 to 1:10 (hatched part) only results in a minor change of the pH: in this example, the pH is elevated from 5 to 7.

Buffer mixtures are of particular significance with respect to chemical processes in living organisms, which generally occur within a narrow pH range. For example, the pH range of human blood is maintained at a constant value between 7.3 and 7.5 by active buffer systems.

The buffer capacity describes the effectiveness of a buffer system. A 0.1 molar system buffers approximately 5 times less H^+ or OH^- ions than a 0.5 molar system.

Physiology of the acid-base metabolism

Development of acids

The acid-base metabolism expresses the attempt to maintain the pH value as a measure for the degree of acidity. As a result of food intake and metabolism, acidic metabolites such as lactate and "carbonic acid" constantly accumulate, and protons (H^+ ions) are continuously released. The maintenance of the pH value at a constant level is particularly important for the organism.

- The structure of proteins and cell components, the cell membrane permeability as well as the effect of enzymes, are all dependent on a neutral pH value.

Larger deviations in the pH value contribute to metabolic disorders, permeability of membranes, and displacements in the electrolyte distribution. For adults blood pH values below 7.0, and above 7.8, are incompatible with life.

Based on the regulation of the H^+ ion concentration (buffer systems) within specified limits, different mechanisms are responsible for maintaining controlled enzymatic reactions (biochemical reaction sequences) which require a certain pH value. The blood is the responsible transport organ for energy-supplying nutrients and waste products.

The blood is predominantly responsible for the:

- Supply of cells with oxygen and nutrients.
- Removal of carbon dioxide.
- Regulation of the acid-base metabolism.

All generated protons are first buffered in blood, and then eliminated mainly via the two most important organs involved in the regulation of the acid-base metabolism of the body, i.e., the lungs and kidneys (Fig. 3). The most important acid included in the acid-base metabolism is carbonic acid. However, carbonic acid is not measured by itself, but dissociated into carbon dioxide and water. Carbon dioxide is eliminated by the lungs, while the kidneys secrete all non-volatile acids.

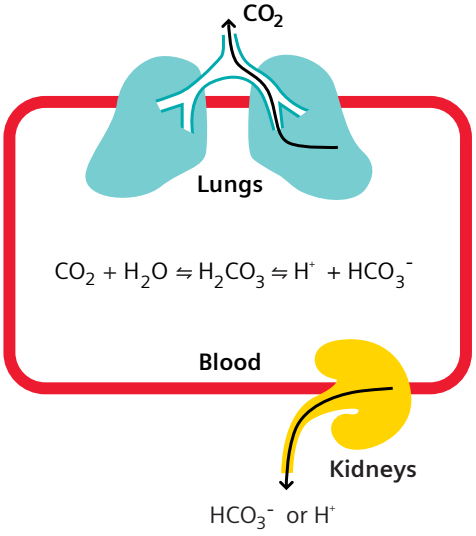


Fig. 3: Regulation of the blood pH

The following metabolic processes are responsible for the continuous formation of acid and the development of protons (H^+ ions):

Breakdown of lipids and carbohydrates

Under regular conditions, the lipid and carbohydrate metabolism forms more than 13,000 mmol of carbon dioxide (CO_2) a day. With a food intake of 3000 kcal, the number increases to more than 25,000 mmol of CO_2/day. CO_2 reacts with water to become carbonic acid (H_2CO_3). Through dissociation, the latter develops into H^+ ions and bicarbonate (HCO_3^-).

Ketogenesis

Fatty acids are broken down into diacetic acid and, β-hydroxybutyric acid, which completely dissociate into acetoacetate and β-hydroxybutyrate at a physiological pH. Approximately 600 mmol of H^+ ions are formed per day during this process.

Glycolysis

During anaerobic glucose degradation, approximately 1400 mmol of lactic acid are formed every day which dissociate into lactate and H^+ ions at a physiological pH.

Breakdown of sulphuric amino acids and phospholipids

~ 80 mmol of H^+ ions in the form of nonvolatile acids secreted via kidneys in urine develop as a result of the breakdown of sulphuric amino acids (e.g., methionine and cysteine) and phospholipids.

The quantity of acid produced daily is approximately equivalent to 20L of 1 mol/L hydrochloric acid.

From physiology to the mathematical basis of blood gas analysis, the Henderson-Hasselbalch equation

1 Acids ⇋ H^+ + base
$CO_2 + H_2O \leftrightharpoons H_2CO_3 \leftrightharpoons H^+ + HCO_3^-$

According to Guldberg and Waage's law of mass action, the product of the concentrations on the right side is constant in relation to the starting materials on the left side, i.e.:

2 $$K = \frac{[H^+] \times [HCO_3^-]}{[H_2CO_3]}$$

Instead of carbonic acid, which cannot be measured due to the dissociation (see equation (1), PCO_2 —multiplied by the molar solubility coefficient 0.0307 (a)— is used. Its concentration is directly proportional in respect to the acid, yielding the following modified equation:

3 $$K = \frac{[H^+] \times [HCO_3^-]}{a \times [CO_2]}$$

Forming the decadic logarithm on both sides, taking into account that logarithm:

4 $$\log K = \log \frac{[H^+] \times [HCO_3^-]}{a \times [CO_2]}$$

of a product equals the sum of logarithms of the individual factors, the following is determined:

5 $$\log K = \log [H^+] + \log \frac{[HCO_3^-]}{a \times [CO_2]}$$

Conversion and solving for log [H+] yields:

6 $$\log [H^+] = \log K - \log \frac{[HCO_3^-]}{a \times [CO_2]}$$

Multiplied by -1, the result is:

7 $$- \log [H^+] = - \log K + \log \frac{[HCO_3^-]}{a \times [CO_2]}$$

The negative decadic logarithm of the protons corresponds to the pH value, while the negative decadic logarithm of constant K corresponds to the pK value:

8 $$pH = pKa + \log \frac{[HCO_3^-]}{a \times [CO_2]}$$

The pK value represents the dissociation constant of a solution, where p represents the negative decadic logarithm and K the ion product of the solution.

The frequently used pKa value refers to the constant of an acid. The pKa value in the serum is 6.11 and is therefore a solid component of the physiology.

9 $$pH = 6.11 + \log \frac{[HCO_3^-]}{a \times [CO_2]}$$

This equation, established for the first time by Henderson and Hasselbalch, and named after them, contains all the information required to determine the acid-base status:

$$pH = 6.11 + \log \frac{[HCO_3^-]}{a \times [CO_2]}$$

or

$$pH = 6.11 + \log \frac{[kidneys]}{[lungs]}$$

Consequently, the pH value depends on

- The renal function (HCO_3^-).
- The pulmonary function (PCO_2).

The two buffer systems of the blood

The buffer system carbonic acid-bicarbonate corresponds to the classical definition of a buffer solution, involving a weak acid with its salts, whereby its change in pH is limited to a minimum.

In addition, the key significance of this buffer system consists in the fact that it is not only capable of buffering off H^+ ions, but that the concentrations of the two buffer components can be modified almost independently from one another:

- CO_2 via respiration.
- HCO_3^- via liver and kidneys.

Respiratory influences

Hydration turns carbon dioxide into carbonic acid. This process is controlled by the lungs, i.e., the respiration. Consequently, carbonic acid can be referred to as the respiratory factor of the buffer pair.

$CO_2 \uparrow + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$

Changes in the carbonic acid concentrations can occur within seconds as a reaction to hyper- or hypoventilation.

Hypoventilation

If the inhaled CO_2 quantity is smaller than the quantity produced, resulting in an increase of PCO_2 (hypercapnia, >46 mmHg), the pH value drops (respiratory acidosis).

Hyperventilation

If the eliminated CO_2 quantity is greater than the quantity produced, resulting in a decrease of PCO_2 (hypocapnia, <35 mmHg), the pH value rises (respiratory alkalosis).

Metabolic influences

The HCO_3^- buffer system represents the metabolic factor. It is predominantly controlled by the kidneys. Any disorders in this region of the body will result in a deviation of the buffer capacity. A metabolic change cannot occur at the same speed as it can be achieved with respiration. Periods lasting hours and days can be involved. The changes are the result of an altered retention rate, i.e., the tubular reabsorption of H^+, HCO_3^- or the new formation of organic acids in the tissue.

The pH value in the blood is indicated by the ratio of HCO_3^- with the corresponding acid CO_2. In healthy subjects, the ratio between base and acid is approximately 24 to 1.2 20:1). The pH for these "normal values" is 7.41 (see Fig. 4):

A $pH = 6.11 + \log \frac{24}{1.2} = 7.41$

If one of the concentrations is changed, the ratio of 20:1 changes too, causing a change in the pH value. For example, if the carbonic acid concentration rises to double the value due to hypoventilation, i.e., to 2.4 mmol, the pH changes to 7.11.

B $pH = 6.11 + \log \frac{24}{2.4} = 7.11$

However, the same value would be obtained if the metabolic side would be reduced to half, i.e., 12 mmol.

C $pH = 6.11 + \log \frac{12}{1.2} = 7.11$

Likewise, the pH value changes to the opposite direction if the carbonic acid (H_2CO_3) content is reduced or bicarbonate (HCO_3^-) increased.

D $pH = 6.11 + \log \frac{48}{1.2} = 7.71$

Due to its reciprocal relationship, the metabolic/respiratory buffer pair (HCO_3^--/PCO_2) is capable of compensating disorders on one side with steps on the other side, resulting in a rapid response to minor pH changes.

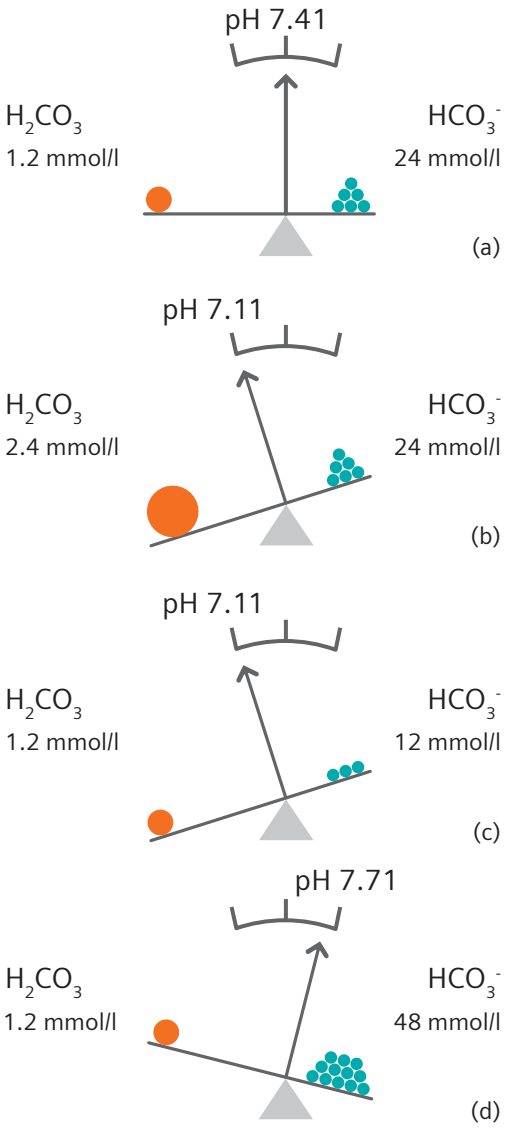


Fig. 4: The "buffer scale"—changes of the buffer systems in the human body.

In addition to the bicarbonate buffer, which is predominantly found in plasma, the group of "non-bicarbonate buffers," which are mainly located in the erythrocytes, are responsible for maintaining the pH value in the blood at a constant level.

The bicarbonate buffer HCO_3^- accounts for 50% of the buffering substance. The ratio of "non-bicarbonate buffers" is mainly composed of hemoglobin, proteins (especially albumin and globulins), and phosphates (in the blood cells). However, the buffer capacities are distributed differently: for HCO_3^-, the capacity is 75%. For "non-bicarbonate buffers," the capacity is 25%, where hemoglobin accounts for 24%, and proteins and phosphates only account for 1%.

Bicarbonate buffers	Ratio	Capacity
HCO_3^-	50%	75%
Non-bicarbonate buffers	**Ratio**	**Capacity**
Hemoglobin	50%	24%
Proteins/phosphate	—	1%

With respect to observations of the acid-base metabolism, proteins and phosphates are negligible due to their small buffer capacities. Hemoglobin, with its primary responsibility of transporting gas, requires its complete buffer capacity for the gas exchange. As a result, it is not available as an effective metabolic buffer.

Both buffer systems are included in the term "buffer bases." The total concentration is 48 mmol/L. According to the distribution outlined above:

- 50% of the concentration is allotted to bicarbonate, and
- 50% to hemoglobin, i.e., 24 mmol/L each.

Parameters

Measured and calculated

Parameters—introduction

pH and *P*CO_2 are the most important parameters to determine the acid-base metabolism. The following values can be calculated based on these two analytes:

- Actual HCO_3^- from the Henderson-Hasselbalch equation as dimension for the total buffer capacity of the blood.
- Standard HCO_3^- (this application is declining because it does not supply any information in addition to the actual bicarbonate and excess base value).
- B.E. (base excess)
  - A negative base excess indicates the presence of metabolic acidosis
  - A positive base excess indicates the presence of metabolic alkalosis
  - B.E. allows the calculation of the buffer quantity that needs to be infused in a patient with impaired acid-base balance

Other parameters include:

- Total CO_2 content.
- CO_2 binding capacity.

If the *P*O_2 value is determined within the conduct of a blood gas analysis, the following parameters can be calculated, assuming the generally applicable O_2 bonding curve of available hemoglobin:

- Oxygen saturation, *s*O_2, and
- Oxygen concentration, ctO_2.

Besides pH and *P*CO_2, the most important parameters for the acid-base metabolism are the actual bicarbonate and base excess levels, as well as the oxygen parameters *P*O_2, *s*O_2, and ctO_2 (the latter are discussed in detail in chapter “oxygen status”).

Although most blood gas analytical systems also determine the different electrolytes, they are not part of the classical acid-base metabolism. However, they should be included in the analysis (see chapter “Electrolytes”). With the exception of lactate, the “nonvolatile” acids (e.g., “sulphuric acid”) are not measured. But their concentration can be calculated based on the so-called anion gap.

The Henderson-Hasselbalch formula was first stated in 1909 and modified in 1916. Astrup developed the indirect PCO_2 determination in 1956. From that time until the 1970s, this nomogram was used. (“Anästhesiologie” [Hrsg.: E. Kochs, H.A. Adams, C. Spies], Thieme Verlag, 2001) (Fig. 5).

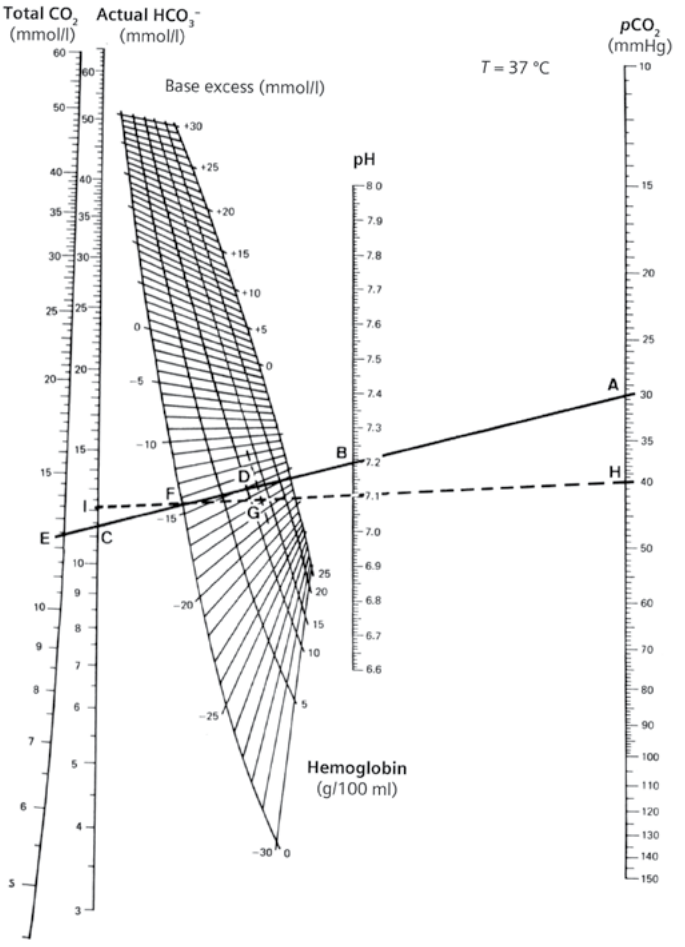


Fig. 5: Siggaard-Andersen nomogram: the application of a straight line through the measured values for PCO_2 (a) and pH (b) with previously specified Hb, bicarbonate (c) and total CO_2 (e) values allows you to read off the values for the base excess (d).

The measured parameters pH value

pH value

The pH describes the hydrogen ion activity of a solution as negative decadic logarithm of the hydrogen ion concentration (pH = - log H^+). The cellular metabolism requires an environment in which the hydrogen ion concentration is within narrow limits. The lungs and kidneys are responsible for regulating the balance.

$CO_2 \uparrow + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$
lungs kidneys

The kidneys regulate the bicarbonate buffer, and as a result 75% of the total buffer capacity. One bicarbonate ion remains in the body for each H^+ ion eliminated by the kidneys. This mechanism is not earmarked for rapid reactions.

Respiration affects the CO_2 concentration. If the pH drops, the CO_2 concentration increases. If the pH increases, the CO_2 concentration drops. The respiration reacts to changes in the H^+ ion concentration within several minutes.

Clinical significance

The extracellular pH closely correlates with the intracellular pH. Therefore, it is particularly important with respect to the intracellular acid-base status. It is used to record acid base disorders as a result of serious pathological causes such as impaired respiratory function as well as renal or gastrointestinal insufficiency.

Regular range 7.37–7.45

Elevated values

- Respiratory alkalosis
  – alveolar hyperventilation
- Metabolic alkalosis
  – gastrointestinal acid loss
  – often with concomitant hypokalemia

Decreased values

- Respiratory acidosis
  – alveolar hypoventilation
  – elevated metabolism
- Metabolic acidosis
  – often with concomitant hyperkalemia
  – renal failure
  – diabetes or alcohol-induced acidosis
  – pancreatic or biliar fistula, diarrhea

Measurement principle

The pH electrode is equipped with ion selective electrode (ISE) technology. It is a half-cell; combined with a reference electrode, it forms a complete electrochemical cell.

The pH electrode contains a silver/silver chloride wire covered by buffer solution (electrolyte with known pH). A glass membrane permeable for hydrogen ions separates the specimen from the solution.

If the specimen comes into contact with the membrane of the pH electrode, a membrane potential forms in the membrane due to the exchange of the hydrogen ions. The potential difference between the inner and outer solution based on this reaction is proportional to the hydrogen ion concentration.

Consequently, it equals 0, if the hydrogen ion concentrations of the reference and measured solution are identical.

The inner silver/silver chloride conductor transmits the potential difference to a voltmeter where it is compared to the constant potential of the reference electrode. The ultimately measured potential reflects the hydrogen ion concentration of the specimen, and is used to indicate the pH value.

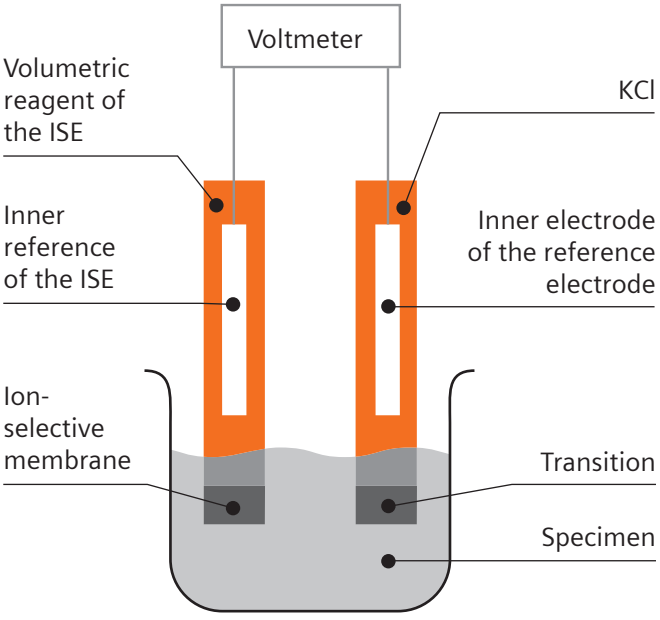


Fig. 6: Design of an ion selective electrode (ISE).

PCO_2

Carbon dioxide (CO_2) is a metabolic product, and is absorbed into the blood to be transported to the kidneys and lungs. CO_2 is transported in the blood as bicarbonate (HCO_3^-), dissolved CO_2 , and carbonic acid (H_2CO_3). CO_2 is present in the blood in a dynamic state as seen in the equation given in the introductory part:

$CO_2 + H_2O\ H_2CO_3\ H^+ + HCO_3^-$

Clinical significance

The partial carbon dioxide pressure (PCO_2) mainly depends on the pulmonary function and the associated elimination of CO_2. Changes in the PCO_2 indicate a change in the respiratory status. Combining the PCO_2 measurement with the pH measurement allows you to determine the bicarbonate (HCO_3^-) value by means of the Henderson-Hasselbalch equation. Because the PCO_2 value is proportionate to the content of dissolved CO_2/HCO_3^- (the proportionality constant is 0.03), the PCO_2 value in combination with the pH can also be useful for the differentiation of acid-base disorders.

Regular range

35–46 mmHg (4.7–6.1 kPa)

In the field of medicine, the conventional unit mmHg is generally used instead of the SI unit Pascal. The conversion factors are as follows:

1 mmHg = 133.3 Pa

1 Pascal = 7.5 x 103 mmHg

Elevated values

- Sign of poor gas exchange in the lungs.

Decreased values

- Sign for overly fast or deep respiration.
- Compensated metabolic acidosis.

Measurement method

The PCO_2 sensor is based on an electrode according to Severinghaus. This electrochemical cell consists of a measuring electrode and an inner reference electrode. The measurement electrode is a pH electrode surrounded by buffer solution. The internal reference electrode, surrounded by chloride-bicarbonate solution, supplies a constant potential. A CO_2-permeable membrane separates this solution from the specimen.

When the specimen comes into contact with the membrane, CO_2 diffuses into the internal chloride bicarbonate solution and triggers a change of the hydrogen ion activity (Fig. 7). The internal pH-electrode detects this change in potential. It leads to a measurement signal, which reflects the pH change in the internal bicarbonate solution of the sensor. The change in pH corresponds to the partial CO_2 pressure (= PCO_2).

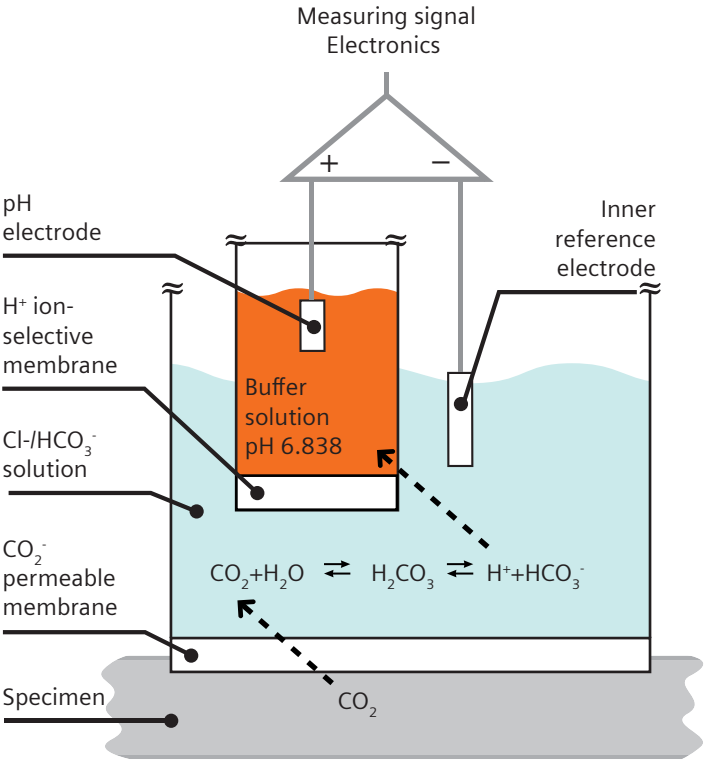


Fig. 7: Measuring method of the PCO_2-electrode according to Severinghaus.

The calculated parameters

Most blood gas analytical systems calculate the parameters recorded below directly without any "other requirements," and are therefore available. Nevertheless, the different calculation basics are explained below for better understanding.

HCO_3^- (bicarbonate)

The bicarbonate ion (HCO_3^-) is the main buffer substance in the body, and plays a key role in maintaining the pH value in the blood.

Due to the dynamic CO_2 balance, it is available in the blood in large quantities. CO_2 is transported in the blood as bicarbonate (HCO_3^-), dissolved CO_2, and carbonic acid (H_2CO_3).

$CO_2 + H_2O \; H_2CO_3 \; H^+ + HCO_3^-$

The equation emphasizes the relationship between HCO_3^- and pH: if HCO_3^- increases, the pH value increases too; if HCO_3^- decreases, the pH decreases.

Clinical significance

The kidneys are the main organs that control the bicarbonate ion. The HCO_3^- concentration is clinically significant for the determination of the non-respiratory, renal, and metabolic component in acid-base disorders. For example, changes of the HCO_3^- concentration in connection with pH values are used for the determination of whether an acidosis or alkalosis of metabolic origin is present (see chapter "Pathophysiology").

Two bicarbonate versions exist:

• HCO_3^- (actual bicarbonate)

The actual bicarbonate defines the bicarbonate concentration that is actually present with known or measured pH and PCO_2 values. The calculation is based on the Henderson-Hasselbalch equation (formula (9) on page 17), solved for according to the logarithm of the bicarbonate concentration:

$\text{Log } [HCO_3^-] = pH + \log(PCO_2 \times 0.0307) - 6.11$

Or

$[HCO_3^-] = 10(pH-6.11) \times PCO_2 \times 0.0307$

Regular range

21 – 26 mmol

• HCO_3^- std (standard bicarbonate)

This refers to the bicarbonate content of plasma, which would be present in blood equilibrated to a PCO_2 of 40 mmHg. The equation described by Vanslyke and Cullin is used to calculate the standard bicarbonate. The significance of this term dates back to the early days of blood gas analysis, using manometric technology, and estimation of "normal" plasma (the sample used):

$[HCO_3^-] = 24.5 + 0.9A + (A - 2.9)^2 \times x \times (2.65 + 0.31 \text{ cHb})/1.000$

Where $A = BE(B) + 0.2 \text{ Chb } (100 - O_2sat)/100$

The standardization makes this parameter independent of the PCO_2. However, it depends on the hemoglobin content (cHb) of the blood specimen.

Regular range

23 – 27 mmol

Total CO_2

(Content of tCO_2 or $ctCO_2$)

The total CO_2 quantity or total CO_2 is a classical parameter of the acid-base metabolism. In some regions, it is hardly used anymore because its informational value is only relevant in connection with the HCO_3^- std parameter.

$tCO_2 = H_2CO_3 + HCO_3^-$

Clinical significance

Combined with the pH and PCO_2 values, tCO_2 is used to evaluate the correlation between respiratory and metabolic factors.

Generally, this value alone is not helpful because the individual itemization of the metabolic and respiratory components is desired. The informational value is greater in connection with HCO_3^- std because HCO_3^- std only takes into account the metabolic component.

Regular range

23 – 28 mmol

The term base "excess" is not doing justice to the fact that the base deviation can be positive or negative; it may therefore be misleading.

The base "deviation" is always connected to the "regular range" of the buffer base. The buffer base is defined as the sum of all anionic buffer factors in the blood (HCO_3^-, Hb, protein, phosphate) capable of taking up H^+ ions.

The "regular value" is 48 mmol/L, about half of it is allotted to the bicarbonate in the plasma (see page 17: "The two buffer systems of the blood").

Regular range

- 2 to + 2 mmol/L

Thus, B.E. always indicates the deviation of the buffer base with respect to the "regular value," and determines the acid or base quantity in mmol/L required to bring the metabolic part to a pH of 7.4. For example, if the B.E. was calculated to be + 4.5 mmol/L, 4.5 mmol/L of acid are required to titrate the specimen back to "0," and to a pH of 7.4 at a PCO_2 of 40 mmHg.

The quantity of acid or base in mmol/L given to the patient can be calculated using the correction formula B.E. x 0.3 x body weight [kg].

Clinical significance

The base deviation is suitable for evaluating the respective non-respiratory (metabolic, renal, etc.) share of the acid-base balance.

The causes for the base deviation include:

- Metabolic causes (metabolic disorder, e.g., diabetes mellitus).
- Renal causes (renal function impairment, e.g., anuria).
- Intestinal causes (loss of gastric juice (H^+) or duodenal secretion (HCO_3^-).
- Hepatic causes (impaired hepatic function).
- Iatrogenic causes (use of infusions with anions that can be metabolized, such as lactate, malate, etc.).

Similar to bicarbonate, two versions are available here:

- Base excess of the extracellular fluid, referred to as BE(ecf) or BE(vv) for in vivo base excess in older blood gas analytical systems.
  - BE(ecf) or BE(vv).
    The base excess of extracellular fluid is calculated via HCO_3^- and pH value.
- Base excess of the blood, referred to as BE(B) or BE(vt) for in vitro base excess in older blood gas analytical systems.
  - BE(B) or BE(vt).
    In addition to the parameters HCO_3^- and pH value, the base excess of the blood takes into account an estimation of the buffer effect of the blood.

CO_2-binding capacity

The CO_2-binding capacity or CO_2 combining power differs from the tCO_2 in that a PCO_2 of 40 mmHg is assumed here. The patient's actual PCO_2 is not taken into account, meaning that the acid product H_2CO_3 in the formula remains constant, and that changes in the CO_2 binding capacity only change the bicarbonate concentration as a result. The parameter is only rarely used in the diagnostics of the acid-base metabolism.

All measurements and calculations are based on the standard patient temperature of 37° C. When analyzing the specimens, the current patient temperature can be entered additionally. The system then displays all pH and PCO_2 values, based on both temperatures.

Pathophysiology of the acid-base metabolism

Depending on the change in pH, disorders of the acid-base metabolism can be divided into:

- Acidoses (pH <7.35), and
- Alkaloses (pH >7.45).

They indicate the extent to which the buffer and regulation systems mentioned above (buffering in the blood, respiratory function, and renal function) are no longer capable of maintaining the pH value of the blood at a constant level.

- If the cause is a primary change of the PCO_2 in the blood, it is referred to as respiratory disorder, while changes in the HCO_3^- and buffer base concentrations cause metabolic disorders.

Respiratory disorders are always due to changes in the respiratory behavior:

- A primary change of the CO_2 partial pressure (PCO_2 ↑ in case of hypoventilation, and PCO_2 ↓ in case of hyperventilation).
- Primarily unchanged base deviations (B.E. = 0).

In contrast, metabolic disorders of the acid-base metabolism indicate:

- An increase/decrease of non-volatile acids in the blood (HCO_3^- or HCO_3^-), and a correspondingly changed base deviation (B.E. positive or negative).
- A generally regular CO_2 partial pressure.

A blood gas analysis and the evaluation of the parameters pH, PCO_2, bicarbonate, and base deviation are required to determine whether a respiratory or metabolic disorder is present.

Altered values of the energy metabolism (metabolites) and the electrolyte metabolism are closely related to these changes.

IMPORTANT: Renal function impairment (e.g., anuria) can also lead to changes in the pH value. Therefore, renal and metabolic disorders are frequently summarized under "non-respiratory" disorders.

These disorders can be partially or completely compensated as a result of the interaction between the buffer pair, i.e., metabolic disorders can be subject to respiratory compensation, and vice versa. Compensation refers to an active organ function. Based on the term, it is separate from the buffering as a physiochemical process.

While the maximum metabolic compensation of respiratory compensation can take several days, the maximum of the respiratory compensation of metabolic disorders (e.g., hyperventilation due to ketoacidosis) is achieved within several hours.

Metabolic acidosis

Metabolic acidosis is defined by a lack of bicarbonate and the associated negative base deviation. In the Henderson-Hasselbalch equation (formula 9 on page 17), the ratio is reduced by the decrease in HCO_3^-, and the pH value is decreased as a result.

9 $$pH = 6.11 + \log \frac{[HCO_3^-]}{a \times [CO_2]}$$

The decrease in the pH stimulates the respiration (hyperventilation), and results in the respiratory elimination of CO_2, used by the organism in an attempt to restore the balance and to compensate the change in pH.

Laboratory findings				
Type	**pH**	***P*CO$_2$ [mmHg]**	**HCO_3^- [mmol/L]**	**B.E.[mmol/L]**
Not compensated	<7.35	Regular	<21	<-2
Partially compensated	<(regular)	Decreased (<35) → pH ↑	<21	<-2
Examples				
Non-compensated ketoacidosis (46-year-old diabetic)				
	7.18	39.9	14.4	-13.2
In addition: potassium: 8.8 mmol/L, glucose: 1.280 mg/dL, lactate: 1.8 mmol/L				
Completely compensated renal acidosis (70-year-old male)				
	7.39	31.1	18.2	-4.7
In addition: potassium: 4.9 mmol/L				

Further diagnostic procedures:

Determination of lactate and electrolytes (hyperkalemia? hyperchloridemia?)

Possible causes

- Renal failure (→ missing or reduced renal acid elimination)
- Ketoacidosis due to decompensated type I diabetes
- Hunger (→ increase in ketonic acids in the blood)
- Alcohol poisoning (→ elevated concentration of non-volatile acids, here acetic acid)
- Diarrhea, pancreatic or biliary fistula (→ loss of bicarbonate-rich secretion)

The exact determination of the extent of metabolic acidosis and the timely therapy are required to prevent serious effects on endocrine and immune functions, bone metabolism, cellular activities, and on the amino acid protein metabolism.

Metabolic alkalosis

Metabolic alkalosis is defined by an excess of bicarbonate or a loss of H^+ ions, and the associated positive base deviation.

9 $$pH = 6.11 + \log \frac{[HCO_3^-]\uparrow}{a \times [CO_2]}$$

The resulting pH increase causes respiratory dullness, thus leading to an increase in PCO_2, which is however limited due to the resulting lack of oxygen. If the alkalosis is not of renal origin, it can be compensated by an increased HCO_3^- output.

Laboratory findings				
Type	**pH**	***P*CO$_2$ [mmHg]**	**HCO$_3^-$ [mmol/L]**	**B.E.[mmol/L]**
Not compensated	>7.45	Regular	>26	>+3
Partially compensated	>(regular)	Elevated (>46) → pH ↓	>26	>+3
Example				
Repeated vomiting (75-year-old male)				
Not compensated	7.52	41.1	32.4	+10.9
Partially compensated (Begin)	7.52	46.1	45.9	+13.9

Further diagnostic procedures:

Determination of lactate and electrolytes (hyperkalemia? hyperchloridemia?)

Metabolic alkalosis is always associated with hypokalemia, i.e., a decrease in the potassium value because the H^+ ions are substituted by K^+ ions.

Metabolic alkalosis is far less common than metabolic acidosis.

Possible causes

- vomiting (loss of gastric juice)
- stomach probe
- hypokalemia (laxative abuse, malabsorption)
- therapy of metabolic acidosis (e.g., intake of bicarbonate)

Respiratory acidosis

Respiratory acidosis is defined by an elevated PCO_2 due to reduced CO_2 output of the lungs (hypoventilation).

$$\text{9} \quad pH = 6.11 + \log \frac{[HCO_3^-]}{a \times [CO_2]}$$

In the Henderson-Hasselbalch equation (9) the ratio is reduced due to the CO_2 increase, and the pH is decreased as a result. After a start-up time of one to two days, this degradation causes increased renal back-resorption of bicarbonate and an increased acid secretion (output of H^+ ions).

Possible causes

- Blocked respiratory system (foreign body aspiration, bronchial asthma)
- Cardiovascular insufficiency
- Lung disease (extended pneumonia, pulmonary edema, pulmonary emphysema)
- Incorrectly adjusted respiration
- CNS (skull-brain trauma, encephalitis, Pickwick syndrome, narcotics)
- Thorax (rib fracture)

Respiratory acidosis is a life-threatening condition, because:

- The delayed renal compensation causes severely decreased pH values.
- The underlying hypoventilation is always associated with an acute lack of oxygen.
- Carbon dioxide is immediately diffused into the cells due to hypercapnia (good penetration capability).

Laboratory findings			
Type	**pH**	***P*CO$_2$ [mmHg]**	**HCO_3^- [mmol/L]**
Not compensated	<7.35	Elevated (>46)	Regular
Partially compensated	<(regular)	Elevated	Elevated >26 → pH ↑
Example			
Chronic obstructive respiratory disease and lung emphysema (52-year-old female)			
Partially compensated	7.33	67.5	34.8

Respiratory alkalosis

Respiratory alkalosis is defined by a decreased PCO_2 due to increased CO_2 output by the lungs (hyperventilation).

$$\text{9} \quad pH = 6.11 + \log \frac{[HCO_3^-]}{a \times [CO_2]}$$

According to equation 9, an elevation of the pH occurs which is compensated renally through increased bicarbonate output. As mentioned above, a start-up time of one to two days is required for renal compensation. The acid-to-base ratio normalizes again. Respiratory alkalosis is always associated with hypokalemia, i.e., a decrease in the potassium level.

Possible causes

- Psychological reasons such as excitement, fear (→ stimulated respiration)
- Mechanically-induced hyperventilation/incorrectly adjusted respiration
- Pulmonary fibrosis (gasping)
- Stay at elevated altitudes

Laboratory findings			
Type	**pH**	***P*CO$_2$ [mmHg]**	**HCO$_3^-$ [mmol/L]**
Not compensated	>7.45	Decreased (<35)	Regular
Partially compensated	>(regular)	Regular	Decreased <21 → pH ↓
Example			
Hyperventilation caused by O_2-enriched air (61-year-old male)			
Not compensated*	7.51	27.7	21.4

**Metabolic compensation takes longer.*

See Fig. 9, Müller-Plathe nomogram on page 37.

The laboratory value constellations for disorders involving the acid-base metabolism are summarized in the diagram (Fig. 8): the primarily altered parameters are characterized by bold arrows. The resulting pH changes and compensatory measures are represented by thin arrows, while the dotted arches mark the direction of the pH value tendency or the compensation events toward the regular value (horizontal line).

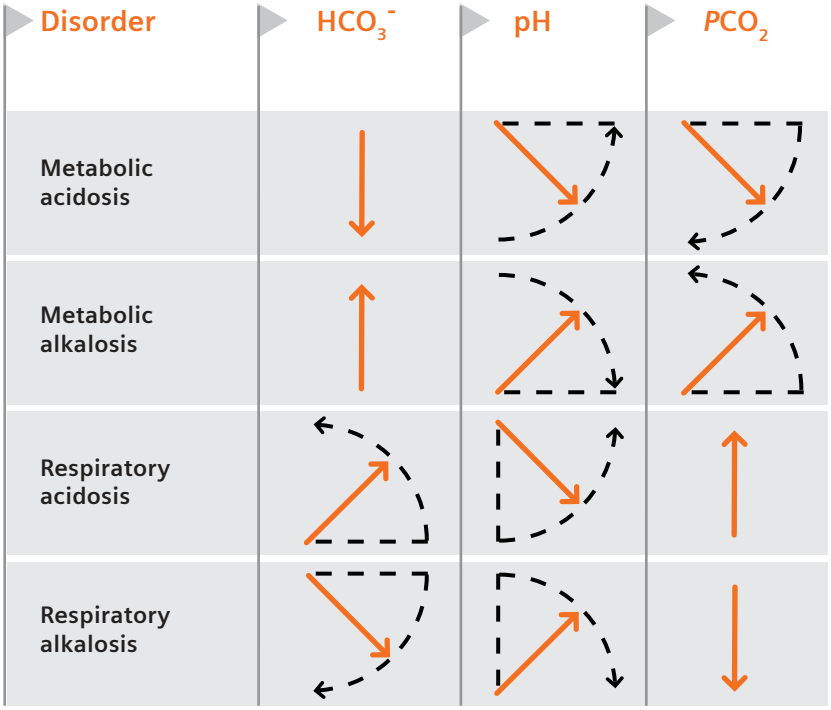


Fig. 8: Disorders of the acid-base metabolism.

Combined disorders

The evaluation becomes difficult if more than one cause for the disorder or a concomitant disease involving the compensation organs—lungs, kidneys, or liver—are present simultaneously. This may be the case in a patient with chronic lung disease (respiratory acidosis) who is experiencing vomiting (metabolic alkalosis) at the same time. In this case, the diagram above does not apply because the disorders partially compensate one another with respect to the pH, thus making it more difficult to establish a diagnosis.

This emphasizes the necessity to take into account the patient's overall status as well as other parameters when interpreting the acid-base metabolism:

- Clinical pattern and anamnesis, state of awareness, state of hydration, medication
- Electrolytes (in particular K^+, Cl^-, and anion gap)
- Parameters PO_2 and sO_2
- pH value in urine, ketone bodies, blood glucose, serum creatinine, lactate in the blood, etc.

The nomogram (Fig. 9) developed by Müller-Plathe is useful for the classification of a potential combined disorder: the point of intersection of the respective values for PCO_2 (X-axis) and $cHCO_3^-$ (Y-axis) allows the allocation as pure or combined disorder.

pH — reference range: 7.35 – 7.45

- Below 7.1 life-threatening acidosis
- 7.1 – 7.3 serious decompensated acidosis
- 7.3 – 7.5 minor deviations that require further evaluation
- 7.5 – 7.6 serious decompensated alkalosis
- Above 7.6 life-threatening alkalosis

PCO_2 — reference range: 35 – 46 mmHg (4.7–6.1 kPa)

- 30–50 mmHg (4.0 – 6.7 kPa). Primarily caused deviations within this range are deemed minor, but require further evaluation.
- 25 mmHg/above 60 mmHg (<3.3/ >8.0 kPa). Acute and therefore not yet renally compensated PCO_2 deviations extending into these ranges are life-threatening.

$cHCO_3^-$ — reference range: 21–26 mmol/L

The degree of risk caused by a deviating bicarbonate concentration is measured based on the resulting pH shift.

Base deviation reference range: -2 to +3 mmol/L

As an expression of a lack or excess of base, the significance of the base deviation is therapeutic rather than diagnostic.

Acid-Base Diagnostic Nomogram (O. Müller-Plathe, 1987).

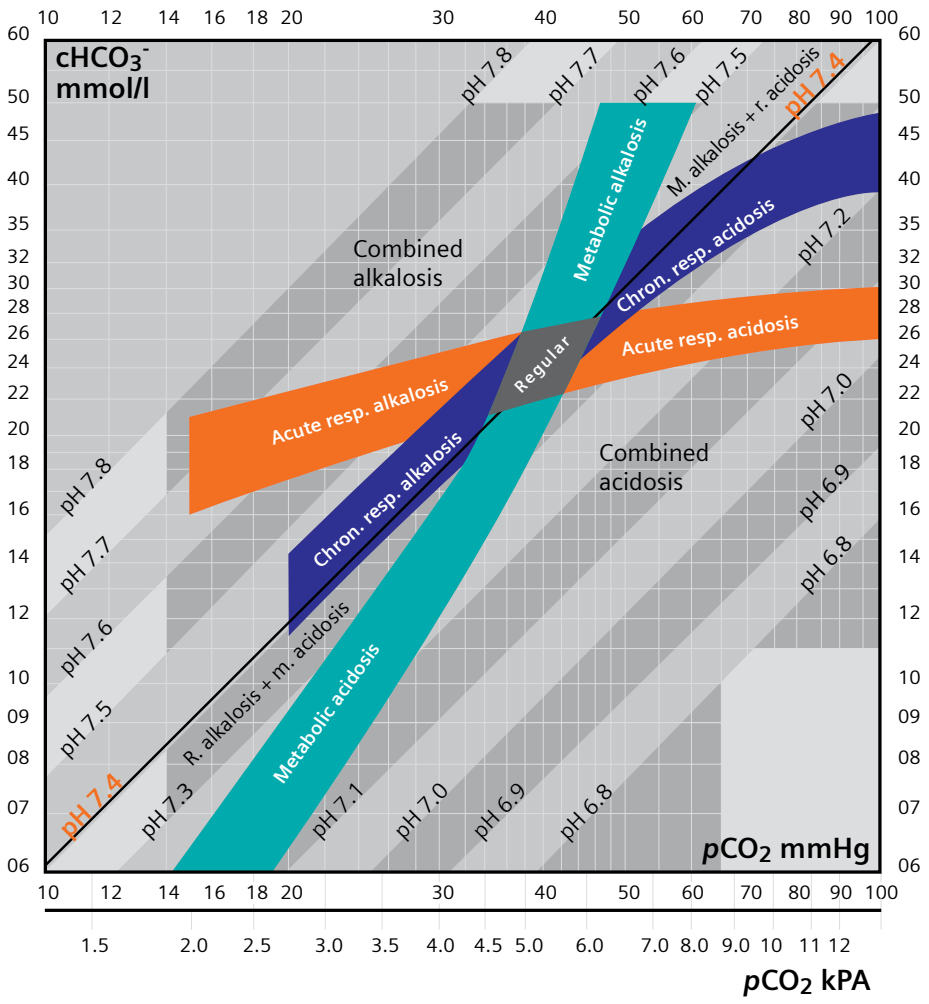


Fig. 9: Müller-Plathe nomogram for the classification of combined disorders of the acid-base metabolism.

Oxygen status

Physiology of respiration

Oxygen plays a major role with respect to the vitality of all body cells and, hence, the viability of the human organism.

Based on the simplified formula:

nutrition + O_2 → energy + CO_2 + H_2O

oxygen is constantly metabolized for energy recovery (ATP synthesis), but it cannot be stored in the organism. As a result, the continuous re-supply must be guaranteed at any time. An interruption of the oxygen supply, for example as a result of respiratory or cardiac arrest lasting 5 to 10 minutes, can lead to irreversible organ damage (in particular brain damage) and lead to death. On the other hand, excess oxygen can equally be toxic and damage, for example the endothelial membrane of the lung.

The oxygen supply is dependent on:

- Heart and metabolism
- Lungs
- Blood transport (in particular the carrier properties of hemoglobin)

In other words, oxygen covers a long distance from the utilization to the mitochondria. In the blood, 98% of the oxygen is chemically bound to hemoglobin. The remainder is physically dissolved.

The following parameters are available to evaluate the sufficient oxygen supply and hence the optimal function of the organism:

- *P*O_2 (oxygen partial pressure, indicator for the oxygen uptake in the lungs)
- *s*O_2 (oxygen saturation, oxygen transport indicator)
- *c*tO_2 (oxygen concentration, oxygen supply indicator)
- Determination of the hemoglobin derivatives (indicator for the hemoglobin/oxygen affinity of the tissue)

Depending on the diagnosis and type of malfunction, it is possible to introduce procedures to support the regular function, such as increasing the O_2 concentration of the inspiration air or using a respirator to assume the natural function.

Inspiration gas

The gas mixture available in the atmosphere serves as gas for spontaneous respiration. Room air contains ~78% of nitrogen and ~21% of oxygen in addition to minor quantities of CO_2 and other gases, generally noble gases (Fig. 1).

Partial pressure is allocated to each individual gas according to its volume ratio as a result of air pressure (1 atm. = 760 mmHg). This pressure is referred to as partial pressure (p) and is equal to the product of total pressure and volume fraction of the gases (Dalton's law).

Dalton's law: Partial pressure = % of ratio in the gas mixture x 760.

Example: PO_2 = 21% (= 0.21) x 760 = 160 mmHg/21.17kPa

Gas	Volumetric content	Partial pressure at sea level (kPA) (mmHg)	
O_2	0.21 (21.0%)	21.17	160
CO_2	0.003 (0.3%)	0.03	0.23
N_2 + noble gases	0.79 (79.0%)	80.1	600
	1.0	**101.3**	**760**

Fig. 1: Dry outside air with volumetric content and partial pressures of the gases.

Oxygen uptake, gas exchange, and partial pressure of oxygen

We distinguish between exterior and interior respiration when describing gas exchange processes.

Exterior respiration refers to the pulmonary gas exchange. The most important function of the lung consists in the uptake of oxygen from the inspiration air and the supply of the organism via blood as the transport organ. At the same time, the metabolic product carbon dioxide is going the opposite way, namely from venous blood to air in the lungs.

Interior respiration describes the release of oxygen into the cells and the oxidation of food according to $C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O$.

This brochure deals with the exterior respiration and the basics of blood gas analysis.

Exterior respiration (pulmonary gas exchange)
= Uptake of O_2 and output of CO_2 in alveoli and capillaries

Respiration = Gas exchange

Interior respiration
= Output of O_2 and uptake of CO_2 in the tissues

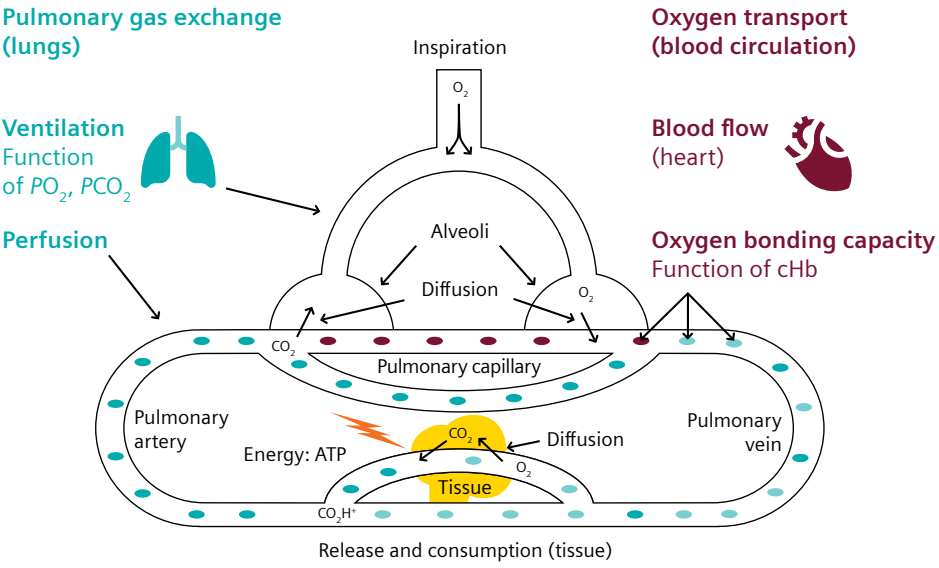


Fig. 2: Diagram illustrating the path of "oxygen in the air to the mitochondria." The pulmonary function includes the air supply via upper respiratory system (ventilation), the gas exchange between the alveoli and blood (diffusion), pulmonary perfusion and exhalation. Diagram © R.F. Moran.

In turn, the pulmonary gas exchange is based on the following four basic functions:

Ventilation (ventilation of the alveoli)

Ventilation refers to the oxygen transport based on the gas flow to places with lower pressure from the atmosphere to the pulmonary alveoli. The pressure difference is the result of the periodic enlargement and reduction of the pulmonary content caused by the contraction of the diaphragm and the intercostal and abdominal musculature. A major gradient in the partial pressure of oxygen occurs en route to the alveoli, reducing it from initially 160 mmHg in room air to 100 mmHg in the alveolar region.

Fig. 3: O_2 gradient between outside air and alveolar air.

The decrease is caused by the moisturization of the inspired air during its passage through the nose and bronchi, which serves to protect the alveoli from drying out (the water vapor pressure [47 mmHg at 37° C] does not depend on the total pressure, but only on the temperature).

Tracheal PO_2 = (760 - 47 mmHg) x 0.21 = 150 mmHg

In addition, there is the the so-called dead space (nasal area, mouth, neck, trachea, bronchial tree, and terminal bronchi) in which no gas exchange takes place, but which is ventilated.

Inspiration air (mmHg)	Alveolar air (mmHg)
PO_2 = ~160.0	PO_2 = ~100
PCO_2 = ~0.3	PCO_2 = ~40
pH_2O = ~5.7	pH_2O = ~47

The inspired air is mixed with the functional residual capacity contained in the lungs, resulting in the two important consequences:

- The pressure in the alveoli is largely constant (PO_2 = 100 mmHg and PCO_2 = 40 mmHg).
- The blood temperature is kept constant as a result of the dilation and mixing effect.

PCO_2 is the most important parameter with respect to the respiratory center—via chemoreceptors in the wall of the aorta and carotid aorta.

Respiratory regulation

Elevated PCO_2 values in the arterial blood lead to an increased urge to inspire and deepening of the respiration. A decreased pH value of <7.37 (acidosis) has the same effect. Thirdly, a lack of O_2 causes an increased respiratory activity, although manifested in acceleration of the breathing rate rather than a deepening.

Perfusion (of the lungs)

To achieve an optimal gas exchange, the lung requires adequate perfusion with blood. In a resting state, 5 L of alveolar air are renewed by ventilation every minute; at the same time, 5 L of blood flow through the lungs (cardiac output). In this ideal case, the ventilation-perfusion ratio (VPR) ranges from 0.8 to 1.0 (5/5). When exercising, the ventilation increases faster (up to 20 times) than the perfusion (up to 5 times); the VPR increases up to 4 times.

Distribution

This term summarizes the ventilation and perfusion which are matched to one another. The VPR of 0.8–1.0 mentioned above applies to the whole lung and is on principle valid for all pulmonary segments up to and including the individual alveoli. However, different distribution ratios occur in the various pulmonary segments even under regular conditions, and the VPR varies as a result.

For example, it is possible that certain regions are less ventilated, while the perfusion is not reduced (ventilation distribution impairment). On the other hand, the irregular blood distribution in the lung is possible, while the ventilation is not altered (circulatory distribution impairment). Please see chapter “Pathophysiology” for more explanations and examples.

Diffusion

Diffusion refers to the movement of molecules along a certain concentration gradient due to their temperature-dependent, kinetic energy. This concentration gradient occurs between alveoli and mixed-venous blood:

Pulmonary artery (venous) (mmHg)	Alveolus (mmHg)
$PO_2 = 40$	$PO_2 = 100$
$PCO_2 = 46$	$PCO_2 = 40$
$pH_2O = 47$	$pH_2O = 47$

The partial pressure differences for oxygen (Δ = 60 mmHg) and carbon dioxide (Δ = 6 mmHg) are the driving forces for the pulmonary gas exchange (Fig. 4).

The diffusion path (alveolar epithelium—interstitium—capillary endothelium—plasma—erythrocyte membrane) is approximately 1 mm. To balance the smaller partial pressure difference, carbon dioxide is capable of overcoming the diffusion path 23 times easier compared to oxygen (better diffusion conductivity).

Consequently, respiratory gases are transported, alternating by convection across long distances (ventilation, circulation) and diffusion on thin interfaces (gas/fluid in the case of alveoli and blood/tissue at the periphery).

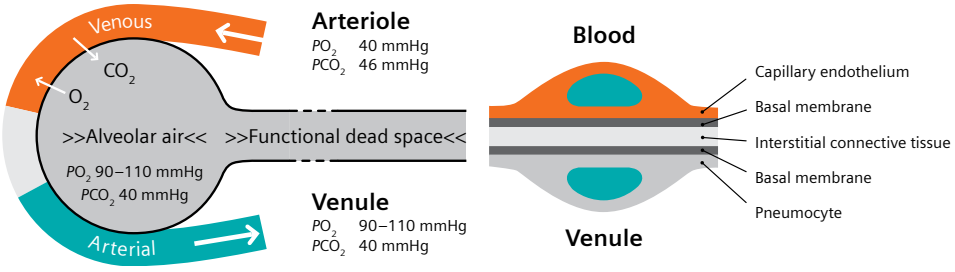


Fig. 4: Alveolar pulmonary diffusion—the respiratory oxygen is transported from the alveolar air into the capillary blood along a pressure gradient of the O_2 partial pressure between the venous capillary channel (40 mmHg) and mixed alveolar air (100 mmHg).

Oxygen transport

Composition and properties of hemoglobin

The main responsibility of the blood as a transport system consists in the supply of all cells and tissue of the body with oxygen and the simultaneous elimination of the metabolic product carbon dioxide. In the blood, 98% of oxygen is chemically bound to hemoglobin. For lack of erythrocytes, either a cardiac output of 100 L/min. or oxygen supply under/over pressure of 3 atm. would be required to maintain the oxygen supply.

The hemoglobin molecule (Hb) consists of four protein chains (2 α-, 2 β-chains) with a pigment component each (heme). The bivalent charged iron ion in the heme structure is relevant with respect to the oxygen transport. An oxygen molecule is coordinatively absorbed in the pulmonary capillaries. As a result, 1 mol of Hb is capable of binding 4mol of oxygen. The process of oxygen absorption is referred to as oxygenation and the product as oxyhemoglobin (O_2Hb). Conversely, deoxygenation yields deoxyhemoglobin (HHb). A proton (H^+) is reversibly absorbed in the free bonding site of the Hb molecule.

The term "Oxygenation" indicates that the O_2 absorption takes place wihout a change in the oxidation numbers, i.e., iron remains bivalent and oxygen remains at oxidation level "0."

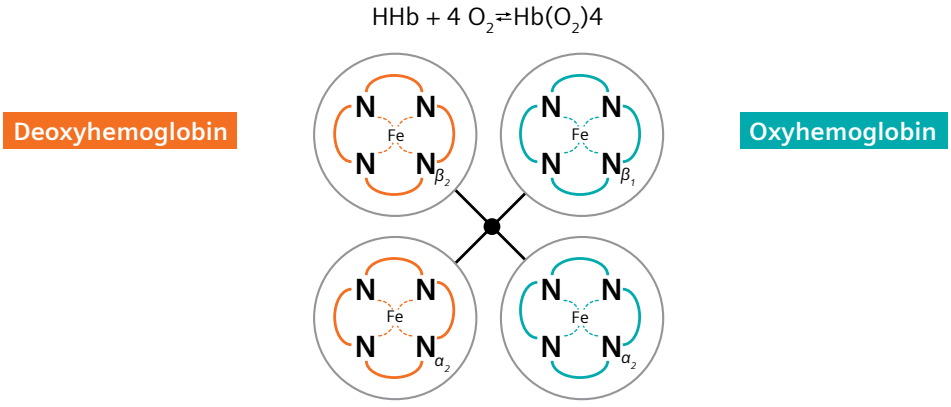


Fig. 5: Illustration of the hemoglobin structure. Each of the 4 protein chains contains a heme structure consisting of 4 pyrrole rings (symbolized by ⌖) and an iron (Fe) ion in the middle.

The bonding capability (capacity) of hemoglobin with oxygen is described by means of Hüfner's number and amounts to 1.34 mL of O_2 per g of Hb (in the practice, the theoretical value of 1.39 is never achieved due to the presence of non-oxygenizeable hemoglobins). For a hemoglobin concentration of 15 g/dL, it is 20 mL of O_2 per 100 mL of blood. A maximum of 1 L of oxygen can be transported with a blood volume of 5 L.

The oxygen binding capability of hemoglobin depends on the pH, PCO_2, PO_2, the erythrocyte metabolite 2,3-Diphosphoglycerate (DPG) and the temperature (see Fig. 7 on page 47, oxygen dissociation curve).

Calculation of Hüfner's number:[1]
Molecular weight of hemoglobin:

64,458 g/mol

Each hemoglobin molecule is capable of absorbing four oxygen molecules:

1 x 64,458 g/mol binds 4 x 22,400 mL/mol = 1.39 mL/g

In addition, hemoglobin is capable of binding part of the carbon dioxide that develops during the cellular metabolism and of releasing it again in the lungs. Consequently, hemoglobin plays a central role in the transport chain for respiratory gases, and is a unique example for an energy supplier that directly recycles the accumulated waste product.

Hemoglobin and its derivatives

The hemoglobin analysis supplies important information for the evaluation of the function of the oxygen transport system. The requirement to determine the Hb levels leads to the development of various methods to concentrate the total Hb, Hb types, and dyshemoglobins. The hemoglobin capacity, and hence the transport capability of oxygen, is altered by the presence of dyshemoglobins and toxins.

Human hemoglobin consists of:

- 97–98% of HbA_1 (2 α- and 2 β-protein chains)
- <3% of HbA_2 (2 α- and 2 Δ-chains)
- <1% of HbF (2 α- and 2 γ-chains) and reacts with various substances to become complexes or fractions

The fractions oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb), available for oxygen transport, were described above.

Up to the 3rd month of pregnancy, embryos have almost 100% of fetal hemoglobin (HbF), while the number for a five-month-old infant is only 10%. The oxygen affinity of HbF is higher compared to the adult hemoglobin HbA_1 found in the blood of adults. In addition to oxygenation, oxidation of iron (Fe^{++}) to iron (Fe^{+++}) is also possible; as a result, this so-called methemoglobin[2] (MetHb) is no longer available for oxygen transport. The content of methemoglobin in human blood is normally very small (approximately 1%); exposure to certain toxins and medications, or certain illnesses, can cause cyanosis[3] or hypoxemia. Carbon monoxide is bound to hemoglobin at the same position as the oxygen molecule to form carboxyhemoglobin (COHb). However, the affinity of carbon monoxide to hemoglobin is greater compared to oxygen by a factor of >200x.[4]

References:

1. Hüfner's number or factor. Hüfner's number expresses the amount of oxygen that can be bound to hemoglobin in mL O_2 / mol of available hemoglobin.
2. Methemoglobin is also referred to as 'hemiglobin' (Hi), but this term is deprecated to minimize confusion with the term "hemoglobin."
3. Note that cyanosis is a condition of the patient, while hypoxemia is a condition of the blood.
4. West, JB, in Respiratory Physiology-the essentials, 5th ed. Williams & Wilkins, 1995, p 76, uses 240 as the factor.

When inhaling a gas mixture containing CO, in addition to O_2, the formation of oxy--and carboxyhemoglobin depends on the ratio of the partial pressures of both gases according to:

$COHb/O_2Hb = M \times pCO/PO_2$

where M = 300 (according to Haldane), meaning that the affinity of CO to Hb is 300 times greater compared to O_2. CO bound to hemoglobin is released from the Hb bond much slower compared to O_2. The CO affinity is pH-dependent and peaks at pH 7.35. Carbon monoxide intoxication is very dangerous, because CO is odorless, and the early symptoms such as headache, nausea, and dizziness are unspecific. As little as 0.5% of carbon monoxide in the surrounding air (inspiration air) can block 90% of the hemoglobin for oxygen transport.

Dyshemoglobins impair the bonding capability of oxygen.

Abbreviation	Name	Bonding partner	Valence of iron	Ratio in %
Physiological Hemoglobin types				
tHb	Total Hemoglobin			
HbA	Adult Hemoglobin			
HbF	Fetal Hemoglobin			
Hemoglobin fractions				
O_2Hb	OxyHemoglobin	$+O_2$	Fe^{2+}	} 98%
HHb	DeoxyHemoglobin	$-O_2$	Fe^{2+}	} 2%
MetHb	MetHemoglobin	—	Fe^{3+}	} <1%
COHb	CarboxyHemoglobin	+CO	Fe^{2+}	} <1%

Fig. 6: Physiological hemoglobin types and hemoglobin fractions.

Correlation between oxygen uptake and transport: the oxygen dissociation curve (ODC)

The oxygenation of hemoglobin depends on the partial pressure of the oxygen dissolved in the blood.

The quantitative relationship between the physically dissolved oxygen affecting the hemoglobin (measurable as partial pressure of oxygen, PO_2) and oxygen uptake of hemoglobin (measurable as oxygen saturation, sO_2) is illustrated with the oxygen bonding curve, or oxygen dissociation curve (ODC) (Fig. 7).

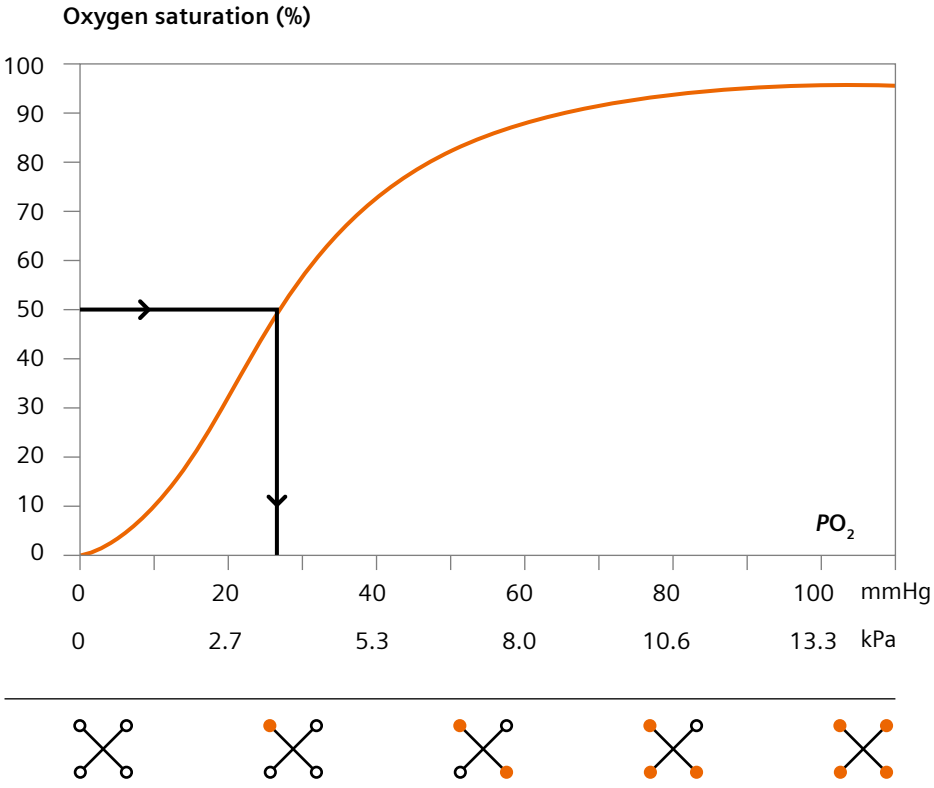


Fig. 7: Oxygen dissociation curve (ODC) and illustration of the oxygenation steps of hemoglobin (below the curve). As seen in the upper part of the figure, the oxygen saturation practically no longer increases when the PO_2 increases from 80 to100 mmHg.

Explanation of the X's: The saturation, of course, applies only to the available hemoglobins. If significant amounts of dyshemoglobins are present, the total hemoglobin is not a good indicator of oxygen transport capacity.

The correlation between saturation and partial pressure is not linear. It is described by a sigmoid curve, the so-called oxygen dissociation curve (OCD). A possible explanation for the sigmoid development is the gradual oxygenation due to different affinities of the four heme groups for O_2 (Fig. 7, bottom): the flat start of the curve signifies the difficult oxygenation of the first α- chain; an increasing conformation change in the total Hb molecule facilitates the further oxygenation, which is expressed in the steeper ascent. With the decrease of the coordinates available for oxygenation, the course of the ODC increasingly approaches the horizontal line. Each additional PO_2 increase only results in a minor increase in saturation. This characteristic sigmoid development of the ODC is a key condition for the O_2 transport function of the blood.

• The flat gradient in the higher PO_2 range provides an effective security against a saturation deficit of the arterial blood, because a significant O_2 saturation (oxygen uptake) is also guaranteed with decreased alveolar PO_2. For example, a saturation of 90% can still be achieved with a PO_2 of 60 mmHg.

• The steep development of the ODC in the center is particularly favorable with respect to the oxygen release in tissue, because the oxygen saturation changes significantly, with minor changes in the PO_2. This leads to increased O_2 desaturation of the blood, and to an improved supply to the tissue as a result.

Significance and influence factors:

The ODC offers the possibility to see how oxygen is absorbed in the lung and released to metabolically active cells in the capillaries. A range of factors including:

• temperature

• pH-value
• PCO_2
} "Bohr-effect"

• 2.3-Diphosphoglycerate (2,3-DPG) concentration = erythrocytic glycolysis metabolite cause deviations and alterations of the oxygen affinity of the hemoglobin in the ODC (see Fig. 8)

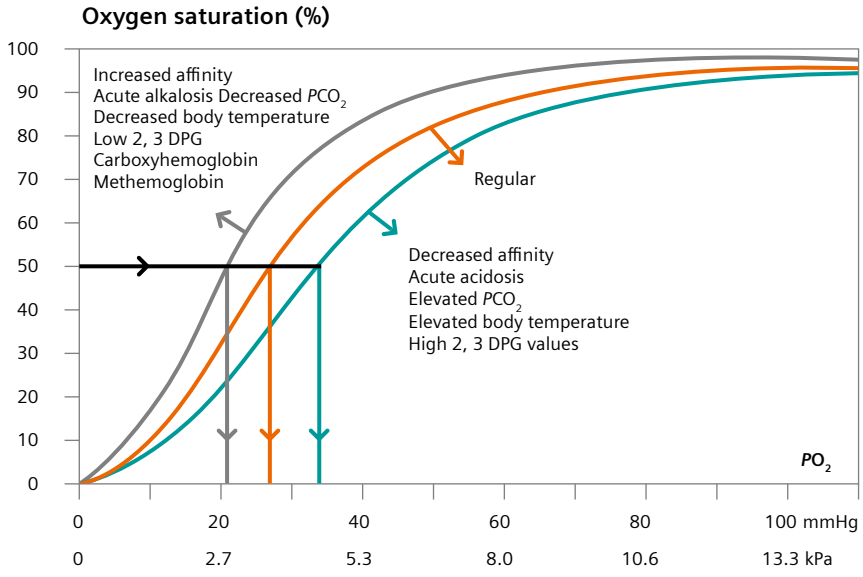


Fig. 8: Left and right shift of the oxygen dissociation curve caused by various factors. In addition to the mentioned factors, different hemoglobin types, such as fetal hemoglobin (HbF), also play a significant role.

- High pH value, low PCO_2, low body temperature (hypothermia during heart surgery), and decreased 2, 3-DPG values (typical characteristics during perfusion of the lung), cause a left shift and steep gradient of the curve.
  → High sO_2 with relatively low PO_2. Under these conditions, the O_2-charge of hemoglobin is facilitated (O_2-accumulation in the lungs).
- Low pH value, high PCO_2, elevated body temperature (fever) and high 2,3-DPG value (conditions in the capillaries) cause a right shift and flatter gradient of the curve.
  → Low sO_2, with relatively high PO_2. The O_2-release from the hemoglobin is facilitated (release of O_2 in the tissue).

While flowing through tissue-supplying capillaries, the blood can be enriched with CO_2, while the release of O_2 to the tissue along this path is eased (elevated PCO_2, shift of the ODC to the right, so-called Bohr effect).

Conversely, the blood in the lung is continuously freed of CO_2 , and the charge with O_2 is continuously eased, thanks to the growing hemoglobin affinity (decreased PCO_2, left shift of the ODC).

Fetal hemoglobin binds more oxygen with low PO_2 than adult hemoglobin, allowing a high arterial saturation of the fetal blood during the passage through the placenta, which has a low PO_2. However, HbF is less efficient and adjustable with respect to the O_2 release in the capillary region.

The presence of COHb and MetHb not only results in the partial alteration of the Hb molecule, and hence blocks the O_2-transport, but causes an additional left shift of the ODC. Consequently, the O_2 release of hemoglobin is made more difficult.

These changes in the position can be illustrated particularly well using the so-called half-saturation pressure (p50, PO_2 [0.5]): p50 reflects the O_2 affinity alterations of hemoglobin, without the need to review the complete ODC. In Fig. 8, the left shift as a result of the presence of COHb or MetHb (blue curve) can be seen clearly. In this case, p50 is approximately 21 mmHg (2.7 kPa).

Parameters

PO_2 (partial pressure of oxygen)

PO_2 refers to the physically dissolved oxygen in the blood. Because the intracellular measurement of the oxygen pressure is impossible, the arterial PO_2 becomes the standard for clinical evaluation of the oxygen status. The PO_2 (a) measurement indicates the oxygen pressure in the arterial blood, and reflects the pressure that transports the oxygen from one place to the next, due to the pressure difference, and is not a measurement of the O_2 content.

Based on Henry's law, the quantity of a gas dissolved at a constant temperature in a unit of fluid is directly proportional to its partial pressure. The oxygen quantity soluble in plasma is 0.023 mL/mL. With respect to the PO_2 in the alveoli, the dissolved quantity is calculated according to (0.023/760) x 100 = 0.003 mL of O_2/mL of plasma, i.e., 0.3 percent by volume with respect to 100 mL of plasma.

Solubility of O_2 in blood: 0.003 mL of O_2/mL of plasma	Bonding of O_2 to hemoglobin: 0.2 mL of O_2/mL of plasma

Corresponds to a ratio of 1:70

The solubility of oxygen in blood is so poor that no adequate oxygen supply of the organism would be guaranteed without the bonding of O_2 to hemoglobin (transports 200 mL/L, i.e., about 70 times the quantity).

Nevertheless, this status has a major biological significance. Before gases enter into a chemical bond, they must diffuse to the reaction partners (erythrocyte, hemoglobin) in dissolved form. Each O_2/CO_2 molecule substituted in the lungs or tissue will have to have passed the status of physical solution first.

Clinical significance

The partial pressure of oxygen in arterial blood is a parameter for the ability of the lungs to enrich the blood with oxygen, thus evaluating changes in the pulmonary function. This parameter has a major significance for the evaluation of the degree of oxygen saturation in a patient, in particular with respect to the degree of hypoxemia (lack of oxygen in arterial blood).

Regular range

The laboratory reference range of PO_2 in arterial blood, in a healthy adult at sea level, is normally 70–100 mmHg (9.5–13.3 kPa). But the PO_2 depends on a number of factors, including:

- Age
- Newborns: 40–70 mmHg (5.3–9.3 kPa)
- People aged 50 and up experience a deterioration of the pulmonary function and hence a reduction of the "regular" PO_2 value of ~ 1 mmHg (~ 0.13 kPa) per year (rule of thumb: PO_2 [mmHg] = 102–0.33 x years of age. PO_2 [kPA] = 13.6–0.044 x years of age*)
- Stress: the PO_2 rises as a result of hyperventilation (PCO_2 decreases, pH rises)
- Position-dependent (subject to the same withdrawal site): in young adults in a sitting position: approximately 90–98 mmHg, in a supine position: 85–95 mmHg, while sleeping: 70–85 mmHg

When determining the PO_2, the strong "age dependence" of the analyte should be taken into account, as mentioned above. In subjects over the age of 65, a decrease of the PO_2 to below 60 mmHg is not considered dramatic.

In medicine, the conventional unit mmHg is still widely used instead of the S.I. unit Pascal. The conversion factors are as follows:

1 mmHg = 133.3 Pa
1 Pascal = 7.5 x 103 mmHg

Elevated values

- Risk of oxygen toxicosis (damaging the lungs) caused by free oxygen radicals (in newborns and premature babies, the arterial PO_2 should not exceed 75 mmHg).

Decreased values

- Inadequate oxygen uptake in the lungs (→ examination of the pulmonary function).
- If the PO_2 is below approximately 40 mmHg, the subject is expected to experience unconsciousness.

**Patrizia: R. Zander, F.O. Mertzlufft "Oxygen Status of Arterial Blood," Karger Verlag, 1988.*

Principle of measurement

The PO_2 sensor is based on an electrode according to Clark. It is a complete electro-chemical cell, based on the amperometric principle of measurement (Fig. 9).

The sensor contains a platinum (Pt) cathode, a silver (Ag) anode, an electrolyte solution and a gas-permeable membrane. Constant voltage is maintained between the anode and cathode. If dissolved oxygen from the specimen penetrates the membrane and enters the electrolyte solution, it is reduced at the cathode:

$$O_2 + 2\ H_2O + 4\ e^- \rightarrow 4\ OH^-$$

The quantity of reduced oxygen is directly proportional to the number of electrons used at the cathode. Therefore, the oxygen quantity in the electrolyte solution can be determined by measuring the current (electron flow) between the anode and cathode.

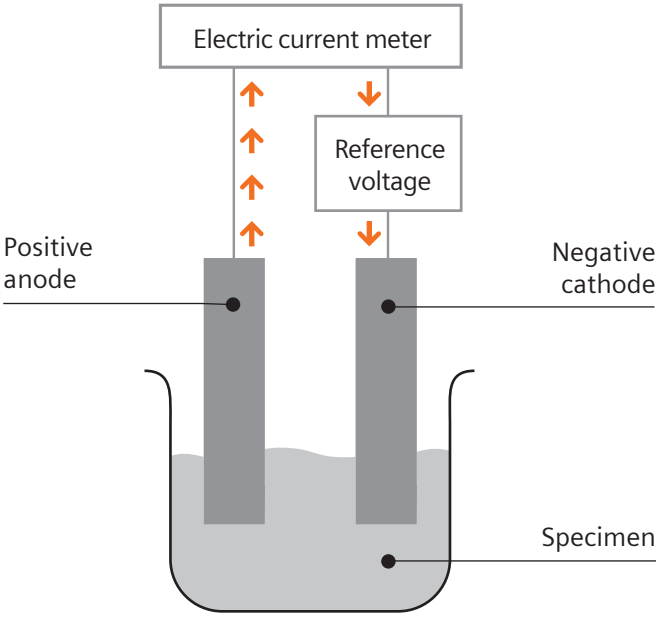


Fig. 9: Composition of an amperometric cell.

sO_2 (or O_2SAT, oxygen saturation)

The measured oxygen saturation sO_2 indicates the ratio of oxygenated (O_2-bonded) hemoglobin to oxygenizeable (O_2-bondable) hemoglobin:

$$sO_2 = \frac{cO_2Hb\ (x100)}{cO_2Hb + cHHb} = \frac{\text{Oxyhemoglobin}}{\text{Oxyhemoglobin + Deoxyhemoglobin}}$$

$$FO_2Hb = \frac{cO_2Hb\ (x100)}{cO_2Hb + cHHb + cCOHb + cMetHb + \ldots} = \frac{\text{Oxyhemoglobin}}{\text{Total hemoglobin}}$$

Clinical significance

The oxygen saturation sO_2 allows the evaluation of the oxygenation and dissociation of the oxyhemoglobin, and is an indicator for the capability of the lungs to supply the blood with oxygen.

It would make more sense to call it "partial O_2 saturation," where the term "partial" is meant to emphasize that only the O_2Hb and HHb fractions are used in the calculation.

Regular range

>96% (0.96)

Elevated values

- adequate oxygen transport capacity
- possible risk of hyperoxia

Decreased values

- deteriorated oxygen uptake
- right shift of the ODC

FO_2Hb (oxyhemoglobin fraction)
Ratio of oxygenated (O_2-bonded) hemoglobin to total hemoglobin (sum of all measured hemoglobin fractions).

Clinical significance

While the regular range of the COHb fraction is around <2%, values of up to 10% are found in heavy smokers, people living close to a major road in a large city, or heavy industry workers. The affinity of CO to hemoglobin is approximately 300 times higher than the one of oxygen to hemoglobin.

Significant deviations between the *s*O_2 values and *F*O_2Hb are expected, particularly in burn victims, as illustrated in the example below:

cHb = 16.0 g/dL

cHHb = 0.3 g/dL

cO_2Hb = 11.0 g/dL

cCOHb = 4.7 g/dL

$$FO_2Hb = \frac{cO_2Hb \times 100}{cO_2Hb + cHHb + cCOHb + cMetHb + \ldots} = \frac{11.0}{11.0 + 0.3 + 4.7} = 69\%$$

$$sO_2 = \frac{cO_2Hb \times 100}{cO_2Hb + cHHb} = \frac{11.0}{11.0 + 0.3} = 97\%$$

Without considering the dyshemoglobins, the saturation would be ideal and would not reveal that only 69% of hemoglobin is available for bonding with oxygen.

Regular range

>96% (0.96)

Elevated values

- adequate oxygen transport capacity
- potential risk or hyperoxia

Decreased values

- deteriorated oxygen uptake
- presence of non-oxygenizeable hemoglobins (dyshemoglobin)
- right shift of the ODC

Differentiation of O_2SAT vs. sO_2

O_2SAT
Calculates the oxygen saturation via empirical equation which approximately describes the gradient of the oxygen dissociation curve. The parameters temperature (T), pH, PO_2, PCO_2, cHb are used in this equation; it does not take into account any other Hb fractions.

***s*O_2**
The O_2 saturation measured by means of the CO oxymeter indicates the ratio of oxygenated (O_2-bonded) hemoglobin to oxygenizeable (O_2-bondable) hemoglobin. In the presence of non-oxygenizeable hemoglobin derivatives or 2,3-Diphosphoglycerate, it deviates from FO_2Hb (and O_2SAT).

***F*O_2Hb**
Calculates the ratio of oxygenated (O_2-bonded) hemoglobin to total hemoglobin and takes into account the sum of all measured hemoglobin fractions.

---

cHb (hemoglobin concentration) and hemoglobin fractions

Generally, hemoglobin is determined either:

- Directly via photometry using
  – the cyanmethemoglobin method or
  – CO-oxymetry
- indirectly via conductivity measurement (see hematocrit)

Cyanmethemoglobin method

All hemoglobin derivatives are oxidized to methemoglobin using potassium hexacyanoferrate (III) and transformed into cyanmethemoglobin via potassium cyanide. The intensity of the resulting brownish color is measured photometrically at λ = 546 nm.

$$Hb(Fe^{+2}) \xrightarrow{[Fe(CN)_6]^{+3}} Hb(Fe^{3+}) \xrightarrow{CN^-} Hb(Fe^{+3})\text{-}CN$$

Clinical significance

The parameter is used to evaluate the oxygen transport as well as anemias. However, a regular hemoglobin concentration does not necessarily guarantee a regular oxygen transport capacity. Dyshemoglobins in high concentrations significantly reduce the ability (Fig. 10). Moreover, non-oxygenizeable hemoglobins (dyshemoglobins) can be recorded in the total hemoglobin concentration via CO-oxymetry (see page 58).

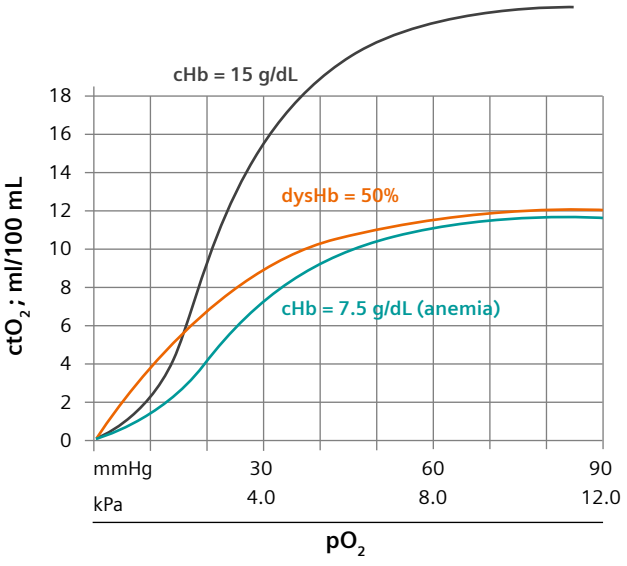


Fig. 10: Influence of non-oxygenizeable hemoglobin fractions (dyshemoglobins) on the oxygen content compared to the effects of anemia.

Regular range

Females: 12–16 g/dL (7.5–9.9 mmol/L)

Males: 14–18 g/dL (8.7–11.2 mmol/L)

(1 mmol/L = 0.621 g/dL)

Elevated values

→ High blood viscosity (cardiac stress)

- Polycytemia
- Dehydratization
- Chronic lung/heart disease
- Living at high altitudes
- Trained athletes

Decreased values (anemia)

- Hemolysis
- Hemorrhages
- Blood thinning
- Reduced erythrocyte production

CO-oxymetry—total hemoglobin and hemoglobin fractions

The total hemoglobin is the sum of all measured hemoglobin fractions and hence a measurement for the potential oxygen transport capacity.

$cHb = cO_2Hb + cHHb + cMetHb + cCOHb$

Different Hb fractions absorb light at different wavelengths (Fig. 11).

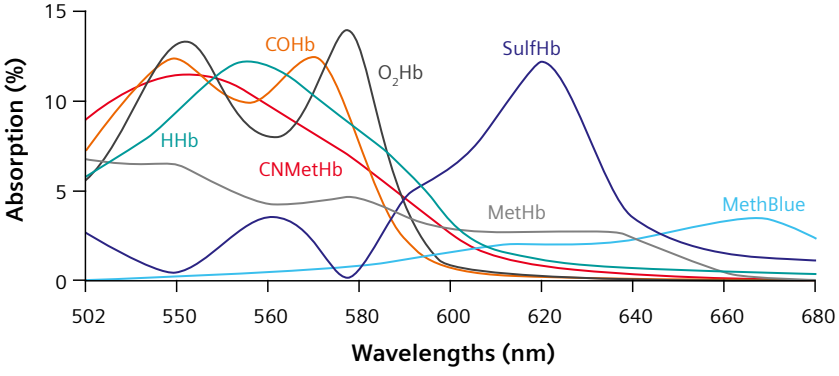


Fig. 11: Hemoglobin fraction absorption spectrum.

The spectral absorption method determines the concentration by means of matrix equations. For each fraction, absorption A at a specific wavelength is equal to the product of distance covered l, concentration c and a molar absorption coefficient e.

$A = l \times e \times c$

In two measured substances, the measured absorption is the sum of the individual absorptions. To be able to determine the concentrations, measurements need to be conducted with two different wavelengths:

$A_1 = l \times (e_{1.1}\, c_1 + e_{1.2}\, c_2)$

$A_2 = l \times (e_{2.1}\, c_1 + e_{2.2}\, c_2)$

The process is analogous for all Hb fractions. Each Hb fraction is determined individually, via absorption measurement, using the (spectrophotometer) at characteristic wavelengths; interferences by pigmented molecules such as bilirubin or turbidities are recognized and eliminated.

FO_2Hb (oxyhemoglobin fraction) see page 54

*F*HHb (deoxyhemoglobin fraction)

*F*HHb refers to the ratio of oxygenizeable, not oxygen-charged hemoglobin, with respect to the total hemoglobin.

$$FHHb = \frac{cHHb}{cHb} (\times 100)$$

Clinical significance

The parameter is used to calculate the partial saturation sO_2.

Regular range

0.0–5.0% (0.0–0.05)

FMetHb (methemoglobin fraction)

In MetHb, bivalent iron is oxidized to trivalent iron; therefore, it is no longer capable of a reversible oxygen bond.

$$FMetHb \frac{cmetHb}{cHb} (\times 100)$$

Clinical significance

High methemoglobin concentrations prevent and inhibit the oxygen transporting ability of hemoglobin and can cause hypoxias and cyanosis. In the case of methemoglobinemis, the cyanosis is due to the actual color of the methemoglobin as well as the decreased amounts of oxyhemoglobin.

Regular range

<1.5% (<0.015)

Elevated values

- In congenital methemoglobinemia (various forms)
- Due to exposure to toxic substances (nitrates, nitrites, aniline dyes and their derivatives)
- Due to diagnostic or therapeutic exposure (certain local anesthetics such as prilocaine, resorcine, phenacetine, nitroglycerin, nitro-containing substances)

*F*COHb (carboxyhemoglobin fraction)

COHb refers to the hemoglobin linked to carbon monoxide via covalent bond, blocking the bonding site for oxygen. The hemoglobin affinity to carbon monoxide is 300 times greater than to oxygen. The "elimination" of the carbon monoxide from the hemoglobin bond can be achieved faster under high partial oxygen pressures than under regular pressure conditions (see Fig. 12).

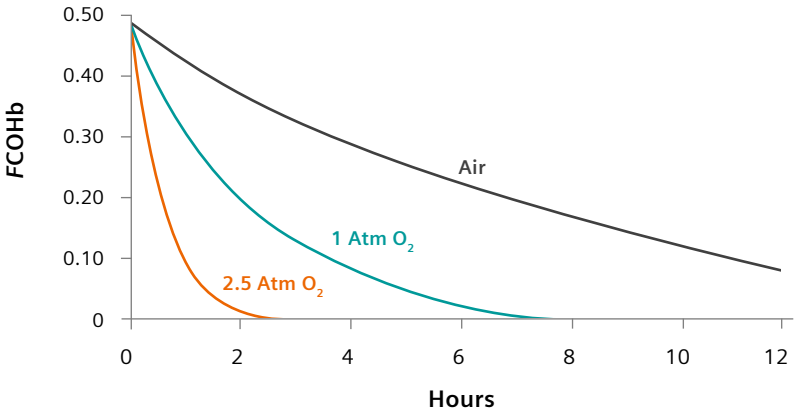


Fig. 12: CO-elimination—the greater the pressure of the administered oxygen, the faster CO is eliminated from the Hb-bond.

$$FCOHb = \frac{cCOHb}{cHb} (x\ 100)$$

Clinical significance

High carboxyhemoglobin concentrations prevent and inhibit the oxygen transporting ability of hemoglobin and can cause hypoxias and cyanosis.

Regular range

<2% (<0.02)

Elevated values

- In smokers and burn victims
- Due to household, industrial, and agricultural exposure

FSulfHb (sulfhemoglobin fraction)

SulfHb is a stable bond between hemoglobin and sulphur. It is characterized by a very low affinity to oxygen. Usually accompanied by methemoglobinemia, this dyshemoglobin affects the oxyhemoglobin values.

Because the sulfhemoglobin absorption spectrum does not show discrete peaks, which would allow the reliable registration of the parameter, FSulfHb is not measured.

$$FSulfHb = \frac{sSulfHb}{cHb} (x\ 100)$$

Elevated values

- Exposure to hydrogen sulphide (H_2S)
- Sulphonamides
- Oral antidiabetic agents

Regular range

0.0–2.2% (0.0–0.022)

HCT (hematocrit)

Hematocrit is the ratio of erythrocyte volume to the whole blood volume. It is:

- Measured via centrifugation,
- Measured via conductivity by means of an Hct sensor, or
- Calculated based on the total hemoglobin determined by photometry (tHb x 2.941). The factor 2.941 assumes a regular mean corpuscular hemoglobin concentration (MCHC).

Limitations of the determination using conductivity measurements are due to factors, which equally affect the conductivity of the specimen:

- Anticoagulants
- Replacement of the blood plasma by saline solutions (in major surgeries)
- Leukocyte concentration (reduced conductivity) is outside the regular range

Clinical significance

Hematocrit is useful for the evaluation of anemia but it should not be used as the sole criterion to diagnose hematological function impairment.

Regular range

Females: 37–47%

Males: 42–52%

Elevated values

- Reduced plasma volume
- Diarrhea, vomiting, excessive sweating, inadequate water intake
- Polyuria
- Increased red blood cell mass
- Polycythemia, polyglobulia (→ elevated Hb concentration)
- Thalassemia (→ increased erythrocyte count)

Decreased values

- Anemia

CTO_2 (O_2CT, oxygen content, oxygen concentration)

The oxygen concentration of the blood (B), referred to as total oxygen content in some regions, includes both hemoglobin-bonded and physically dissolved oxygen. It is calculated according to the following formula:

$$ctO_2\ (B) = \frac{FO_2Hb \times cHb \times 1.39 + 0.0031 \times PO_2}{\text{bonded } O_2 + \text{dissolved } O_2}$$

Sometimes, the following term is used:

CTO_2 (Hb) = $FO_2Hb \times cHb \times 1.39$

It only takes into account the oxygen content of hemoglobin

Particularly in patients with very low hemoglobin concentrations, patients undergoing overpressure therapy or oxygen therapy, the dissolved oxygen can account for a significant share of the oxygen content, and hence for the oxygen transport.

Clinical significance

The oxygen content of the blood reflects the effects of changes in the arterial PO_2, the hemoglobin concentration, and hemoglobin affinity for oxygen, and includes all components involved in the oxygen supply.

Regular range

20 mL/dL

Elevated values

- With regular PO_2: cause for high cHb (cardiac stress)

Decreased values

- Risk of reduced oxygen supply of the tissue (hypoxia)
  → further diagnostic procedures: examine the lactate value
- With regular PO_2: cause for decreased cHb or presence of non-oxygenizeable hemoglobin

p50 (PO_2 [0.5], half-saturation pressure)

The semi-saturation of hemoglobin by oxygen indicates the PO_2 at which hemoglobin is semi-charged ("saturated") with oxygen, and reflects the affinity of oxygen to hemoglobin.

$$p50 = \frac{26.6 \times (PO_2 \times 10\text{-}0.48^{(7.4\text{-}pH + 0.0013\ BE(vt))})}{PO_2S}$$

PO_2S = PO_2 depending on the measured sO_2 (between 20 and 90%)

PO_2 = adjusted to pH 7.4 and 37° C

Clinical significance

The semi-saturation pressure provides information about the oxygen release in the tissue.

Regular value

26.6 mmHg (~ 3.6 kPa)

Elevated values

→ Decreased O_2 affinity of hemoglobin (increased semi-saturation pressure p50 to >26.6 mmHg = right shift of the ODC [red curve in Fig. 8]), can indicate:

- Respiratory acidosis (elevated PCO_2, pH <7.37)
- Elevated body temperature
- Elevated 2.3-DPG
- Anemia
- Pregnancy
- Respiratory insufficiency

Decreased values

→ Increased O_2 affinity of hemoglobin (decreased semi-saturation pressure p50 to <26.6 mmHg = left shift of the ODC [blue curve in Fig. 8]), can indicate:

- Presence of dyshemoglobins
- Decreased body temperature
- Respiratory alkalosis (decreased PCO_2, pH >7.45)
- Massive transfusion
- CO poisoning

The unnecessary increase of the oxygen content in the respiration is preventable.

O_2 CAP (CO_2[max], O_2 capacity, BO_2, Maximum oxygen bonding capacity)

The maximum oxygen capacity refers to the maximum oxygen quantity hemoglobin is capable of transporting within a given blood quantity. This value illustrates the potential of hemoglobin to bond oxygen and contains the total oxygen quantity that can be bound to the available hemoglobin.

$$O_2CAP = 1{,}xxx = \frac{FO_2Hb + FHHb}{100} \times cHb$$

where 1.xx represents the oxygen bonding factor of hemoglobin. It can be set at a value ranging from 1.30 to 1.40 on some blood gas systems.

Clinical significance

Together with the oxyhemoglobin fraction and the oxygen content, the hemoglobinoxygen capacity represents a helpful parameter to determine the oxygen quantity in the blood that is actually available to the tissue and to determine the effectiveness of oxygen therapy.

Regular range

17.6 to 23.6 mL/dL

FiO_2 (oxygen content of the inspiration air)

Refers to the oxygen content in the inspiration air offered to the patient, approximately 21% in room air. The *F*iO_2 is entered by the user. The calculation of the alveolar/arterial pressure differences is only possible after this entry (see below).

PO_2(A)T (alveolar partial pressure of oxygen according to patient temperature)

Refers to the partial pressure of oxygen in alveolar gas. It is a primary component in the detection of the gas exchange indices.

$PO_2(A)T = piO_2 - pACO_2 \times (FiO_2 + (1-FiO_2)/R)$

$piO_2 = FiO_2 \times (760 - 47)$

Regular barometric pressure: 760 mmHg partial pressure of water vapor: 47 mmHg *F*iO_2: oxygen content of inspiration air (21% in room air)

R: gas exchange ratio

Clinical significance

The value is important for the calculation of the alveolar-arterial partial pressure difference PO_2 (A-a) and the arterial-alveolar oxygenation index.

Regular value

105 mmHg

PO_2 (A-a) ($AaDO_2$, alveolar-arterial difference of the partial pressure of O_2)

The alveolar-arterial difference or alveolar-arterial difference of the partial pressure of O_2 allows the relatively FiO_2-independent interpretation of the PO_2 values. This parameter is calculated as follows, using the values for alveolar oxygen and the measured arterial oxygen:

PO_2 (A-a)T = PO_2 (A)T - PO_2 (a)T

PO_2 (A) = temperature-adjusted oxygen pressure of alveolar gas; calculated

PO_2 (a)T = temperature-adjusted oxygen pressure of arterial gas; measured

Regular range

10–12 mmHg by FiO_2 21%

Clinical significance

The partial pressure difference indicates the efficiency of the oxygenation process in the lungs; consequently, it is crucial for the evaluation of the oxygen conversion in the lungs under respiration.

PO_2 (a/A) (a/A, alveolar-arterial oxygenation index)

The alveolar-arterial oxygenation index indicates the ratio of arterial to alveolar oxygen at patient temperature, and remains relatively stable during changes of the FiO_2.

PO_2 (A)T = temperature-adjusted oxygen pressure of alveolar gas; calculated

$$PO_2(a/A)T = \frac{PO_2(a)T}{PO_2(A)T}$$

PO_2(a)T = temperature-adjusted oxygen pressure of arterial gas; measured

RI (T) respiratory index

Quotient of the alveolar-arterial difference of PO_2 and the PO_2 in the arterial blood at patient temperature; can be used instead of the alveolar–arterial oxygen pressure difference.

RI(T) = PO_2(A-a)T/PO_2(a)T

$avDO_2$ (ctO_2(a-v), arterial-venous oxygen difference)

Difference of the oxygen content between arteries and veins. It determines the oxygen quantity released to the tissue per blood volume.

$avDO_2 = ctO_2(a) - ctO_2(v)$

ctO_2(a) = arterial oxygen content; measured

ctO_2(v) = venous oxygen content; measured

Clinical significance

This parameter reflects the oxygen consumption of the organism. Cardiac insufficiency is more common in adult patients than pulmonary insufficiency; for this purpose, the arterial-venous oxygen difference is a suitable parameter to evaluate the cardiac and metabolic factors as direct reaction to altered cardiac performance and oxygen absorption in the organism.

Alternatively, the difference between arterial and venous oxygen content can be displayed as partial pressures (PO_2) or saturations (sO_2). However, the concentration units of the $avDO_2$ are most significant, because a conclusion about the O_2 consumption of the whole organism, or individual organs, is only possible in this case.

Regular value

5 mL/dL

AV (extraction index)

The AV extraction index (ctO_2(a-v)/a) is used for the interpretation of the arterial-venous oxygen difference, and can indicate an inadequate oxygen content in the arterial blood or inadequate cardiac performance.

The value is most accurately determined using an arterial and mixed-venous blood specimen.

$AV = (ctO_2(a) - ctO_2(v))/ctO_2(a)$

VO_2 (oxygen consumption, oxygen uptake)

Refers to the oxygen volume consumed by the body per minute. It is calculated as follows:

$VO_2 = ctO_2(a\text{-}v) \times Qt \times 10$

Qt = total blood flow through the lungs

DO_2 (oxygen supply, oxygen transport)

Refers to the oxygen volume transported to the tissue per minute.
It is calculated as follows:

$DO_2 = ctO_2(a) \times Qt \times 10$

Qt = total blood flow through the lungs

Qs/Qt (physiological shunt)

Describes the quantity of mixed-venous blood that is not oxygenized during the passage through the pulmonary capillaries. The calculation of the shunt represents the best option to describe the extent the pulmonary system contributes to the development of hypoxemia.

$$\text{Shunt volume} = \frac{Qs}{Qt} = \frac{ctO_2(c) - ctO_2(a)}{ctO_2(c) - ctO_2(v)}$$

Qs = shunt blood flow (blood quantity per minute not involved in the gas exchange)

Qt = total blood flow through the lungs (cardiac output)

Ideally, the shunt volume is quantified by measuring the oxygen content in pulmonary capillary blood ($ctO_2(c)$), as well as arterial ($ctO_2(a)$) and mixed-venous blood ($ctO_2(v)$). Because measurements of end-capillary and mixed-venous blood are impossible (during regular blood gas analysis), ctO_2 (c) and ctO_2 (v) are calculated as follows:

$ctO_2(c) = [1.39 \times cHb \times (1\text{-}FCOHb - FMetHb)] + (0.00314 \times A)$;

$A = [(FiO_2/100) \times (pAtm - pH_2O)] - \{PCO_2 \times [1.25 - (0.25 \times FiO_2/100)]\}$

$ctO_2(v) = 1.39 \times cHb$

Clinical significance

The shunt can be elevated as a result of both chronic and acute illnesses; the sudden increase can have serious consequences.

We distinguish between:
• Real shunts (the blood is not exposed to any gas exchange during the passage from the right to the left half of the heart due to heart-septum defects), or

• Ventilation/perfusion impairments due to lung diseases.

Regular range

2–8%

This parameter supplies the most important information during heart surgery, where the value is output by the heart-lung machine.

Pathophysiology

The pathophysiological influences on the oxygen supply of the organism vary greatly. Below is an overview of the most common impairments of the oxygen status and the associated conditions.

Impaired cardiac/metabolic function

- Shock/collapse due to reduced venous reflux
- Impaired stimulus formation or stimulus conduction (tachycardia, arrhythmia, atrial flutter and atrial fibrillation cause a decrease in cardiac output)
- Elevated pressure and volume load due to heart defects, right/left shunt (venous blood is mixed directly with arterial blood while bypassing the lungs)
- Cardiomyopathies, myocarditis, toxic myocardial impairments impaired pulmonary function (impaired O_2 uptake)

Impaired pulmonary function (impaired O_2 uptake)

- Ventilation (impaired respiratory mechanism)
- Restrictive (impairment of lung volume or elasticity and associated limitation of the gas exchange surface): pulmonary fibrosis, pulmonary resection
- Obstructive (congestion/narrowing of the respiratory system causing impaired air flow): stenoses of the upper respiratory tract (nasopharyngeal region), bronchial asthma
- Perfusion (impaired perfusion)
- Right/left shunts (venoarterial bypasses) due to cardiac malformation (heart defects)
- Reduced pulmonary tissue due to surgery
- Impaired perfusion due to acute and chronic pulmonary embolisms
- Distribution (impaired gas transfer)
- Ventilation of non-perfused alveoli (pulmonary embolism)
- Perfusion of non-ventilated alveoli (shunt due to pneumonia)
- Diffusion (difficult gas transfer between blood and lungs)
- Enlarged diffusion distance (pulmonary edema, pulmonary fibrosis)

Impaired blood transport function (impaired O_2 supply)

- Hypoxia (reduced partial pressure of oxygen in blood), e.g., due to lack of oxygen in the respiration air (high altitudes; the PO_2 is reduced by half every 5500 m)
- Hypoxemia (reduced oxygen concentration per volume unit of blood)
- Hypoxygenation (reduced blood saturation)

Arterial hypoxia (PO_2 too low) always requires arterial hypoxygenation (sO_2 too low)—sO_2 is determined by the bonding curve of PO_2—which in turn is expressed as hypoxemia (ctO_2 too low). The correlation of the parameters PO_2, sO_2 (FO_2Hb) and ctO_2 is illustrated in Fig. 13.

Partial pressure of oxygen	Oxygen saturation	Hemoglobin concentration	Hüfner number	Phys. charged oxygen	Oxygen content
PO_2	**FO_2Hb (sO_2)**	**cHb**			**ctO_2**
[mmHg, kPa]	%	[g/dL]	[mL/g]	[mL/dL]	[mL/dL]
PO_2 $\xrightarrow{ODC}$ FO_2Hb		x cHb	x 1.39	+ O_2 Physically charged	= ctO_2

$$FO_2Hb \quad \frac{(= \quad cO_2Hb \quad)}{cO_2Hb + cHHb + cCOHb + cMetHb}$$

Fig. 13: Correlation and dependence of the parameters PO_2, FO_2Hb, ctO_2 among one another—modified according to Zander, 1988.

All impairments of the cardio-pulmonary gas exchange mentioned above cause a decrease in arterial PO_2 and lead to hypoxia (decreased ctO_2) as a result.

Example of hypoxic hypoxemia:

68-year-old male with pneumonia

pH = 7.36

PCO_2 = 43.2 mmHg

PO_2 = 68.4 mmHg ↓

cHb = 14.3 g/dL

ctO_2 = 17.5 mL/dL ↓

sO_2 = 87.5% ↓

The oxygen binding capacity of hemoglobin decreases with elevated COHb and MetHb concentrations, manifesting itself in a left shift of the O_2 dissociation curve and an increase of the O_2 affinity of the intact hemoglobin. The result is hypoxygenation and toxic hypoxemia.

Likewise, the use of stored blood can cause a left shift of the ODC due to the decreased 2.3 DPG concentration, resulting in elevated O_2 affinity (the anaerobic glycolysis of erythrocytes causes the degradation of 2.3 DPG; the O_2 affinity in stored blood increases strongly during the first week).

Example of toxic hypoxemia:

40-year-old male with smoke poisoning

pH = 7.40

PCO_2 = 40.0 mmHg

PO_2 = 100.0 mmHg

cHb = 15.7 g/dL

ctO_2 = 12.7 mL/dL ↓

sO_2 = 99.8%

FCOHb = 42.8% ↓

FO_2Hb = 56.6% ↑

This example highlights the difference between sO_2 and FO_2Hb. At 99.8%, the saturation (sO_2) is excellent; but taking into account the COHb share, the FO_2Hb at 56.6% is severely decreased and requires treatment.

Anemias of various genesis (e.g., hemorrhagic anemia, iron deficiency anemia, impaired heme or Hb synthesis, hemeolytic anemia) impair the oxygen supply and cause anemic hypoxemia. This causes a right shift of the ODC, decreased O_2 affinity, resulting in increased oxygen extraction in the tissue due to an increase in 2.3-DPG.

Example of anemic hypoxemia:

75-year-old female with hemeorrhagic anemia

pH = 7.40

PCO_2 = 40.0 mmHg

PO_2 = 80.0 mmHg

cHb = 9.07 g/dL ↓

ctO_2 = 12.4 mL/dL ↓

sO_2 = 97.0%

	PO_2	sO_2	FO_2Hb	cHb	ctO_2
Hypoxic hypoxemia	↓	↓	↓	→	↓
Toxic hypoxemia	→	→	↓	→	↓
Anaemic hypoxemia	→	→	→	↓	↓

Fig. 14: Visualization of the altered parameters caused by impaired oxygen transport (→ means "regular," ↓ means "decreased"). Please note the sO_2 and FO_2Hb parameters in toxic hypoxemia—modified according to Zander, 1988.

Electrolytes

Physiology of the electrolyte and water metabolism

In aqueous solutions, electrolytes dissociate into electrically charged particles (ions). Cations (positively charged) and anions (negatively charged) develop in the process.

Example:
Sodium chloride dissociates into sodium and chloride ions:

$NaCl \rightarrow Na^+ + Cl^-$

Sodium is the positively charged cation (Na^+); it migrates to the negative pole, the cathode.

Chloride is the negatively charged anion (Cl^-); it migrates to the positive pole, the anode.

Distribution of electrolytes and water in the human body

Water and salts (electrolytes in dissolved state) are the components of all life. Approximately 50–60% of the body weight of adults (75% in newborns, the water content decreases with increasing age) consists of water. A dynamic balance generally exists between the uptake and output of water. It is primarily maintained by the kidneys: depending on the available water quantity, the pair-wise arranged organs produce maximally diluted to maximally concentrated urine.

Water is taken up through liquid and solid food and by the formation of oxidation water when the food is burnt. Water is excreted through urine and feces as well as via skin and lungs.

The water in the body is not equally distributed across the body; it is stored in so-called extra- and intracellular spaces.

The extracellular space (ECS) includes any water outside the cells, i.e., approximately 40% of the total water content in the body:

- Blood plasma (the fluid surrounding the blood cells)
- Interstitial fluid (all cells except the ones surrounding the blood cells)
- Transcellular fluids (fluid-filled spaces surrounded by epithelium, such as gastrointestinal tract, sweat and salivary glands, renal tubes, etc.)

Correspondingly, about 60% of the water in the body is stored in the intracellular space (ICS).

Selective separation walls (semi-permeable membranes) between the distribution spaces offer the possibility to exchange (diffuse) osmotically active components (electrolytes) dissolved in the water, but not—or only to a very limited degree—the diffusion of proteins. A certain pressure, the osmotic pressure, builds up during this process, also known as osmosis, due to the developing differences in the concentration.

The distribution of the electrolytes in the body and hence their concentration (osmolarity in [mmol/L] or osmolarity in [mmol/kg]) represents a sensitive balance that is crucial to a number of biological control mechanisms, the induction of enzymatic activities, transfer of action potentials via nerve fibers, etc. The electrolyte and water metabolisms are intrinsically tied to one another.

In the blood plasma and interstitial fluid compartments, Na^+, Cl^- and HCO_3^- in small concentrations prevail. They differ in the respective protein concentrations. Their quantities in blood plasma are much higher compared to the interstitium. In contrast, K^+, hydrogen phosphate and proteins are the osmotically most important components of the intracellular fluid (Fig. 1).

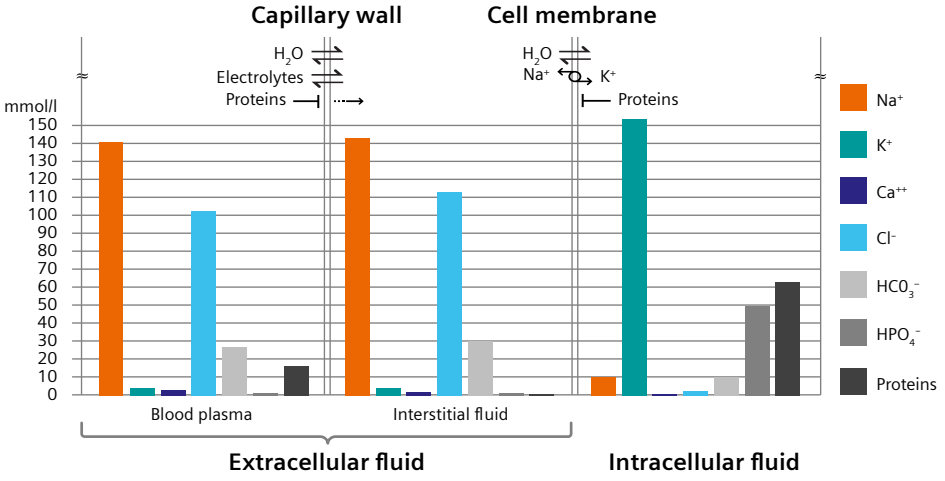


Fig. 1: Distribution of ions in blood plasma, interstitial and intracellular fluids.

The electrolyte and water metabolism can be impaired in a life-threatening manner by various illnesses. Generally, water deficit causes dehydration and too much water causes hyperhydration.

The concentration of sodium ions in the body is by far the greatest; consequently, their influence is the highest. Depending on the concomitant sodium loss or excess, the disorders are further divided into three types each (Fig. 2).

	Dehydration		Hyperhydration	
Hypotonic	Water ↓	Electrolytes ↓↓	Water ↑↑	Electrolytes ↑
Isotonic	Water ↓	Electrolytes ↓	Water ↑	Electrolytes ↑
Hypertonic	Water ↓↓	Electrolytes ↓	Water ↑	Electrolytes ↑↑

Fig. 2: Impaired water and electrolyte metabolism (means elevation, means decrease of volume).

Isotonic disorder refers to regular osmolarity (loss and excess of sodium and water are balanced).

Hypotonic disorders cause reduced osmolarity (sodium concentration is decreased compared to the available water supply), and hypertonic disorders result in increased osmolarity (the sodium concentration exceeds the regular range).

Electrolyte concentrations

The body's own membranes are water permeable; therefore, the osmolarity (= concentration of osmotically active substances) is identical in the ECS and ICS. On principal, electrolyte shifts occur in compliance with electric neutrality, either as opposite movement of ions with the same charge, or as movement in the same direction of ions with opposing charge. The ion concentration in the various body fluids (isoiony) is maintained constant by ion-specific mechanisms.

Absolute quantities of extracellular sodium and intracellular potassium determine the distribution of the water in the body between the two fluid-filled spaces. Outside the cell, the concentration of sodium is about 20 times higher than the intracellular concentration, while the potassium concentration in the cells is about 35 times higher than outside the cell. This concentration gradient in the cell membrane is maintained by an active process using energy (Fig. 3).

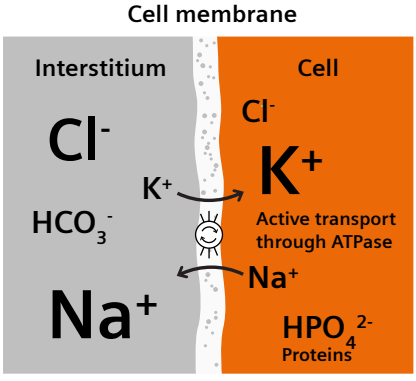


Fig. 3: The "sodium-potassium pump".

Na-K-ATPase is "pumping" sodium ions out of the cell and potassium ions into the cell. The so-called ion pump is most important with respect to the conduction of nerve impulses.

In addition to the ion pump, the glucose also plays a role with respect to the exchange of potassium between ICS and ECS. When glucose enters the cell, potassium is taken along. The sodium transport is closely related to the potassium transport. The differences in the concentration of both cations in the cell membrane are essential to the functionality of the cell and the information transfer between the cells.

In addition to sodium, chloride is also responsible for the maintenance of the osmotic pressure. The chloride concentration is higher in the ECS than in the cell. Depending on the requirements of the acid-base metabolism, chloride can be replaced by bicarbonate with the renal output.

Calcium is present in the serum freely ionized, or as citrate, phosphate or in protein-bound form. It plays a key role for the coagulation and intracellular for the stimulation of nerve and muscle cells as well as the electromechanical coupling of muscle cells. Both the extra and intracellular distribution of calcium ions is controlled via calcium ATPase.

In view of the various compositions of the different body cells, the concentrations of all electrolytes illustrated in Fig. 4 with respect to the intracellular and interstitial fluid have purely exploratory character.

Electrolytes mmol/L	Plasma	Interstitial space	Intracellular space
Na^+	142	144	7
K^+	4	4	155
Ca^{++} (total)	2.5	1.25	0.001
Ca^{++} (ionized)	1.25	1.25	0.001
Cl^-	103	114	2
HCO_3^-	27	30	10

Fig. 4: Comparison of approximate electrolyte concentrations in blood plasma, interstitium and cells.

Measuring methods and their limits

The serum electrolyte concentration can be determined using different methods:

Flame-Atomic-Emission-Spectrometry (FAES)

When an alkali metal solution is held into a flame, the fluid evaporates and the salt ions are atomized. Each atom absorbs energy. As excitation energy, it directs the outer-shell electron of the alkali metal atom to a different orbital. Upon return to the original orbital, the electron releases the energy in the form of light at a wavelength that is characteristic for the atom. The intensity of the emitted light depends on the number of atoms of the corresponding element in the flame and is therefore proportional to the concentration.

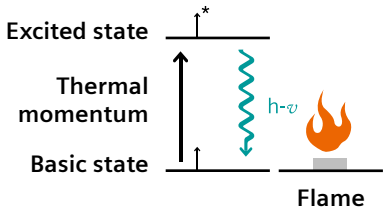


Fig. 5: Illustration of the FAES measuring principle.

To conduct the measurement, the ion strength of the diluted specimen (serum or plasma) is adjusted to the calibration solution and the electrolyte-free compartment of macromolecules is reduced to below 1% of the total volume. Similar to indirect potentiometry, the measured signals are converted into concentrations by comparing them with the calibration solution.

The macromolecule (proteins, lipids, etc.) concentrations affect the measurement and hence the determination of the concentration. As a result, these measurements are only applicable to a certain lipid and protein concentration. When determining the electrolytes according to this method, the values for total protein and lipids should always be determined too, to allow the correct interpretation of the results.

	Wavelength
Sodium	580 nm
Lithium	732 nm
Potassium	765 nm
At 1.800°C with propane gas	
Calcium	555 nm
At 2.900°C with propane gas	

Coulometry—conductivity measurement: chloride

Today, coulometry is used to determine chloride in serum, urine and other body fluids. In this highly sensitive electrochemical analysis method, the electrical current is measured over time between two electrodes through which it is flowing. The consumed amount of electricity can be calculated based on this analysis.

$Q = I \times t$

where Q = quantity of electricity (current)

I = electric current in amperes

t = time in seconds, during which the current is flowing

According to Faraday's Law, this amount of electricity Q is equivalent to the amount of converted chloride (N), in accordance with

$Q = a \times N$

where a = device-specific constant.

Potentiometry (Ion-Selective Electrodes, "ISE")

Potentiometry measures the voltage or potential generated between two electrodes in an electrochemical cell when no current is flowing. The electrochemical cell consists of two electrodes (a measuring and a reference electrode), an electrolyte solution (specimen) and a measurement system, e.g., a voltmeter.

The electrochemical cell can measure the concentration or activity of a substance in a solution.

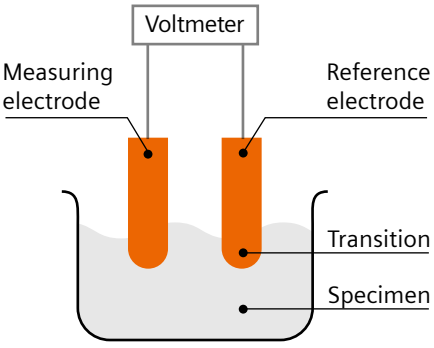


Fig. 6: Illustration of a potentiometric cell.

Together with the measuring electrode, the reference sensor of the system forms an electrochemical cell within the measurement module (E-cell). It supplies a constant potential that is dependent on the analytical activity. The system compares the constant potential of the reference sensor (E-Ref) with the measured potential of the measuring electrode (E-Meas) for the respective analyte.

The reference sensor contains a silver wire coated with silver chloride (AgCl) and an ion-permeable polymer surrounded by a saturated potassium chloride (KCl) solution. As a result, the chloride concentration in the solution remains unchanged and the reference sensor maintains a constant electrical potential. The chamber of the reference sensor contains a potassium chloride (KCl) donor to ensure the saturation of the solution.

The fluid potential (EFI), a small but significant voltage, develops at the transition of the fluid from the reference electrode, between the saturated potassium chloride solution on the inside and the specimen solution on the outside. This potential is the result of different speeds at which the chemical components diffuse through the borders between the fluids and needs to be deducted from the measured potential.

$E_{Cell} = E_{Meas} - (E_{Ref} + E_{FI})$

Direct potentiometry ("direct ISE") in emergency analytical systems (without dilution) measures the ion activity. The macromolecule concentrations (proteins, lipids) do not affect this measurement. Because the extracellular water phase (plasma or serum water) is measured here, the correct interpretation of the results is also possible without knowing the lipid or protein content. The ion activity is independent hereof. Contrary to the determination of the concentration (flame photometry and indirect ISE), direct ISE records the medically relevant parameter. To simplify interpretation of electrolyte results, many direct-reading systems are designed to have their values correspond to the indirect/diluted systems when proteins and lipids are at typical levels. These systems will then differ when there are disturbances in plasma water—the direct reading systems being physiologically correct.

Indirect potentiometry ("indirect ISE") in clinical-chemical analytical systems (with dilution) determines the concentration and only represents an estimate of the activity or free molar concentration. The water content is decreased in hyperlipidemia or hyperproteinemia.

Consequence: It is possible that "pseudohyponatremia" or "chloridemia" are simulated with regular electrolyte concentration in the serum. (The effect of hyperlipidemia or hyperproteinemia with respect to potassium is less pronounced due to the relatively large reference interval).

Important:
Flame-atomic-emission-spectrometry (FAES), coulometry and indirect potentiometry ("indirect ISE") determine the ion concentrations. If the extracellular water share decreases due to hyperlipidemia or hyperproteinemia, the essentially regular electrolyte concentration appears to be decreased as well, thus causing "pseudohyponatremia" and "pseudohypochloridemia." Due to the large reference interval, the effect is not as pronounced with respect to potassium.

The ion activity is determined by means of direct potentiometry ("direct ISE"). This measurement is not affected and allows the correct interpretation.

Parameters

Sodium

Na^+ is the most important cation in the extracellular fluid (blood plasma and interstitial space). It plays a central role in the regulation of the body's fluid volume. In this context, it is responsible for maintaining the osmolarity (rough estimate: Na^+ [mmol/L] x 2 = osmolarity of plasma in mmol/L). Two regulating hormones, aldosterone and adiuretin (ADH), influence the renal function and hence the sodium balance. Aldosterone stimulates the kidneys to reabsorb Na^+, while ADH stimulates the kidneys to reabsorb water.

Clinical significance

Sodium is mainly responsible for the regulation of the body fluids, maintenance of the electrical potential in the muscle cells and control of the cellular membrane permeability.

Disorders of sodium metabolism are the result of inadequate sodium intake or output, frequently in connection with disorders of the water metabolism. Both hypo- and hypernatremia can cause clouding of consciousness, seizures and vomiting.

Regular range

135–145 mmol/L

Alarm limits

<125 and >155 mmol/L

Elevated values

(Hypernatremia)

Hypertonic impairment of the water and electrolyte metabolism: the osmolarity (osmotic pressure) of the plasma increases as a result of reduced water intake or increased water output.

- Hypertonic dehydration (lack of water) caused by inadequate fluid intake in seriously ill patients or high loss of water, e.g., in diabetes mellitus/insipidus, watery diarrhea, serious febrile illnesses
- Hypertonic hyperhydration (sodium surplus exceeds water surplus)
- Infusion with hypertonic sodium chloride solutions or
- Hyperaldosteronism (Conn's syndrome: Na^+ retention)

Decreased values

(Hyponatremia)

= most common electrolyte shift (< 130 mmol/L)

Hypotonic impairment of the water and electrolyte metabolism:

- Decreased plasma osmolarity

Hypotonic dehydration (sodium loss exceeds lack of water) caused by:

- Loss of salt in patients with renal illnesses (impaired NaCl resorption in the loop of Henle)
- Diuretics (renal loss of NaCl and water)
- Vomiting or diarrhea (gastrointestinal loss of water)
- Excessive sweating
- Inadequate electrolyte supply under infusion therapy
- Hypotonic hyperhydration (water surplus)
- Infusion with electrolyte-free glucose solutions
- Polydipsia
- Renal and cardiac insufficiency

In the two following cases, the sodium concentration in the serum does not indicate an impairment of the water metabolism:

- Isotonic dehydration (concomitant with lack of water, causing a reduction in the osmotically active substances) due to loss of isotonic body fluids (diarrhea, vomiting, blood loss)
- Isotonic hyperhydration (increased extracellular fluid volume) due to excess supply of isotonic solutions in illnesses with generalized formation of edema such as cardiac and renal insufficiency

Important: with respect to the interpretation

- In serious losses of water, the sodium value within regular range may simulate normal sodium content in the body. Conversely, the decreased sodium concentration as a result of serious hyperhydration (renal, cardiac insufficiency) may simulate a lack of sodium that is not actually present.
- If flame photometry or indirect ISE are used for the determination, the Na^+ concentration depends on the size of the electrolyte-free compartment, i.e., on the concentration of macromolecules such as proteins and lipids. In unchanged sodium concentration, the increase of the electrolyte-free compartment (hyperlipid-/-proteinemia) results in the corresponding decrease of the Na^+ concentration (“pseudohyponatremia”). This constellation is clinically more significant than the opposite case where the decrease causes an increase (“pseudohypernatremia”). If the specimen material is determined by means of direct ISE in undiluted status, these errors will not occur.

Na^+ sensor

The sodium sensor is a half-cell forming a complete electrochemical half-cell together with the external reference sensor. The sensor is equipped with an $Ag/AgCl^-$ wire, surrounded by an electrolyte solution with defined sodium ion and chloride ion concentrations. The membrane that separates the electrolyte solution from the specimen consists of a glass or PVC capillary tube and is highly selective for sodium ions.

When the specimen comes into contact with the membrane, a potential develops due to the sodium ion exchange. The membrane potential is compared to the constant potential of the reference sensor. The measured potential difference is proportional to the sodium ion concentration in the specimen and changes with the ion activity.

Potassium

Potassium is the most important intracellular cation in the human body. It maintains the cellular resting membrane potential and the osmotic pressure and plays a significant role in electrical events involving excitable tissue (muscles, especially the heart muscle). Potassium is responsible for the fluid content (osmotic pressure) in the cell, because it is most prevalent there.

The concentration of potassium is very high (155 mmol/L) inside the cell and very low (4 mmol/L) outside the cell. The serum potassium value does not reflect the intracellular potassium supply of the body.

Clinical significance

The regulation of the potassium metabolism is by far less adaptable compared to sodium. As a result, the body compensates potassium imbalances comparatively poorly. Due to the important function of potassium, any impairments of the K^+ metabolism, irrespective of the direction (hyper- and hypokalemia) are always life-threatening. Disorders can be caused by inadequate K^+ supply, or output or shift between the extra- and intracellular spaces. The control of the potassium levels is especially important for patients suffering from cardiac arrhythmia or acute renal insufficiency and in those scheduled to undergo surgery or receive diuretic treatment as well as patients on digoxin monitoring and dialysis.

Regular range

3.6–4.8 mmol/L

Alarm limits <2.5 and >6.5 mmol/L

Elevated values

(Hyperkalemia)

Impairment of vital muscle functions: heart muscle (arrhythmia, ventricular fibrillation, cardiac arrest), intestinal muscles (spasms), respiratory muscles (paralysis)

- Excess K^+ or decreased K^+ output
- Renal failure (acute and chronic) with oliguria/anuria
- Incorrect infusion therapy (massive administration of solutions containing K^+)
- Medications (Heparin, Digoxin, Succinylcholine, potassium-saving diuretics)
- Mineral corticoid deficiency within the scope of adrenal gland insufficiency
- K^+-distribution disorders (for examples, see p. 36)
- Respiratory/metabolic acidosis
- Serious tissue destruction with K^+ release from the cells
- Hemolysis

Discourse on dialysis

Renal insufficiency in dialysis patients leads to elevated potassium concentrations in the plasma. Values of 6.0 mmol/L and more are common. A further increase causes a decrease in the cardiac output as a result of reduced heart rate (bradycardia). Vital organs are no longer adequately perfused. The adrenal gland secretes adrenaline as an emergency reaction to elevate the blood pressure. However, the response of the hyperkalaemic heart to adrenaline is immediate ventricular fibrillation and cardiac arrest.

After dialysis, the potassium level is approximately 2 to 3 mmol/L. Consequently, potassium is the most important electrolyte in dialysis.

Decreased values

(Hypokalemia)

Impairment of vital muscle functions: heart muscle (tachycardia, cardiac arrest), intestinal muscles (paralysis, ileus), respiratory muscles (paralysis), renal function (renal acidosis).

Differentiating between K^+ deficiency and K^+ shift is important for therapeutic reasons.

- K^+ loss or deficiency
  - Undernourishment in anorexic patients and alcoholics
  - Gastrointestinal: loss of K^+ containing digestive juices due to vomiting, diarrhea, laxative abuse, potassium-poor infusion
  - Renal: diuretics, renal tubular acidosis, renal illnesses with increased salt output
    → additional diagnostic procedures: examine the chloride levels (hyperchloridemia)
  - Hyperaldosteronism
  - Cutaneous: extensive burns
- Impaired K^+ distribution
  - Respiratory/metabolic alkalosis
  - Elevated insulin concentration
  - Elevated catecholamine concentration
  - Pernicious (vitamin B12 deficiency) anemia

In case of potassium losses, e.g., due to diarrhea, the serum potassium content can quickly be compensated by means of the storage inside the cells. This process is associated with the risk that a relevant potassium deficiency in the cells is not determined for a long time because the serum potassium levels are regular.

Similarly, potassium deficiency in the ICS can be compensated with the inflow of H^+ ions; this results in alkalosis in the plasma, while acidosis is present in the ICS.

Important: with respect to the interpretation

- Identical to sodium, the potassium concentration in the serum depends on the size of the electrolyte-free space. Due to the large reference range, the clinical significance for the potassium determination is even smaller.
- When interpreting potassium values, the acid-base metabolism should be taken into account because the potassium levels are closely related to it (influence on the potassium distribution between inner and outer space of the cell).

K^+ sensor

The potassium sensor is a half-cell. Together with the external reference sensor, it forms a complete electrochemical half-cell. The sensor is equipped with an Ag/AgCl wire, surrounded by electrolyte solution with a defined concentration of potassium ions. The membrane consists of ionophoric valinomycin in plasticized PVC. It separates the electrolyte solution from the specimen. Valinomycin is a neutral ion carrier and highly-selective for potassium ions.

The contact between the specimen and the membrane results in a potential due to the potassium ion diffusion through the membrane. The membrane potential is compared to the constant potential of the reference sensor. The measured potential difference is proportional to the potassium ion concentration in the specimen. Consequently, it changes based on the ion activity.

Calcium

99% of the calcium content (approximately 1 kg) is found extracellularly in the bone substance in crystalline form as calcium hydroxylapatite. Approximately 50% of the remaining percent is located in the ECS in ionized form (1.25 mmol/L); only this fraction is biologically active and integrated in the normal regulation. 35% are bound to protein (mainly albumin and globulin), while 15% are complex-bound (citrate, lactate, phosphate, bicarbonate).

Calcium plays an important role in the electromechanical coupling in the cell (conversion of nerve impulses into muscular activities) and regulates the membrane permeability of sodium and potassium (ATPase). Moreover, it plays a key role in the coagulation, in enzymatic activities and the secretion of hormones such as adrenaline. This broad range of responsibilities requires an extensive control of this ion with multiple security levels. Hormones (parathormone, calcitonin), the acid-base metabolism, the vitamin D metabolism and the phosphate metabolism affect the serum calcium levels.

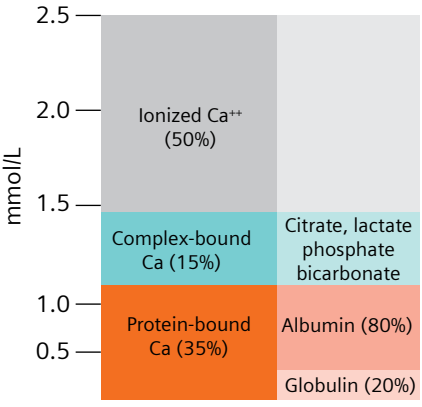


Fig. 7: Serum calcium fractions.

The concentration of calcium in the cell is very low (0.001 mmol/L). At an overall concentration of 2.5 mmol/L in the space outside the cells, the concentration gradient of calcium is the greatest of all ions in the cellular wall. Therefore, it flows into the cell with minimal changes in the permeability of the cellular wall, giving the signal for important and various functional changes in the cell.

Clinical significance

Impairments of the calcium metabolism occur due to an imbalance between the calcium intake and output or due to pathological alterations of the calcium deposits in the skeleton. The ionized calcium level of patients in intensive care must be carefully monitored, especially if they require blood transfusions, because the anticoagulants (citrates) contained in the blood concentrate bind calcium, thus lowering the level of ionized calcium in the blood. This can lead to cardiac or neuromuscular disorders.

Regular range

1.15–1.35 mmol/L (ionized)

Alarm limits

<0.9 and >1.75 mmol/L

2.20–2.65 mmol/L (overall)

Alarm limits

<1.7 and >3.5 mmol/L

Elevated values

(Hypercalcemia)

80% of serious hypercalcemias are due to osteolysis associated with malignant tumors (bone metastases) or primary hyperparathyroidism (pPHT).

- The Ca^{++} release exceeds the Ca^{++} bonding in primary hyperparathyroidism tumors (especially in breast, lung, prostate and kidney cancer), prolonged restraint (e.g., due to pelvic fractures), loss of fluid (diarrhea, alcohol, vomiting)
- Increased Ca^{++} uptake due to vitamin A and D overdose, intake of special drugs (lithium, antiestrogens, certain diuretics), sarkoidosis, morbus addison

Chronic hypercalcemias can lead to calcifications in different organs and formation of renal calculus.

Decreased values

(Hypocalcemia)

- Decreased Ca^{++} supply due to
  – Hypoalbuminia
  – Vitamin D deficiency or reduced vitamin D effect
  – Intake of special drugs (antiepileptic substances, certain diuretics)
- The Ca^{++} bonding exceeds the Ca^{++} release in
  – (pseudo) hypoparathyroidism
  – Acute pancreatitis
- Ca^{++} loss due to
  – Chronic renal insufficiency
  – Chronic pancreatitis (impaired calcium resorption)

Extreme deficiency (below 0.8 mmol/L) causes muscle cramps (tetany).

Important: with respect to the interpretation

- If the plasma pH changes, the affinity of proteins to calcium changes too. In other words, the ratio of ionized calcium in plasma changes based on the pH. To obtain a clear indication of the ionized calcium, it is recommended to print out the value calculated for pH 7.4 in addition to the measured calcium value.
- The total calcium concentration in the serum is directly dependent on the albumin concentration. The total calcium concentration decreases in illnesses associated with hypoalbuminia (cirrhosis of the liver or nephrotic syndrome). However, the biologically more important ionized form remains unaffected in this “pseudohypocalcemia.” For this reason, it is preferable to measure the ionized calcium.

Ca^{++} sensor:

The calcium sensor is a half-cell. Together with the external reference sensor it forms a complete electrochemical half-cell. The sensor contains an Ag/AgCl wire, surrounded by an electrolyte solution with a defined concentration of calcium ions. The membrane consists of an ionophore, embedded in a PVC membrane. It separates the electrolyte solution from the specimen.

The contact between the specimen and the membrane results in a potential due to the potassium ion diffusion through the membrane. The membrane potential is compared to the constant potential of the reference sensor. The measured potential difference is proportional to the potassium ion concentration in the specimen. Consequently, it changes based on the ion activity.

Chloride

Chloride is the most important anion in body fluids. It occurs mainly in extracellular spaces. Together with a host of other factors, it regulates the water distribution within the spaces in the body. Chloride is the counter-ion to sodium. Its metabolism is therefore closely related to the one of sodium: both are ingested as common salt (NaCl) with the food and secreted together via kidneys. Therefore, the change is usually identical.

Clinical significance

The chloride metabolism is usually impaired to the same extent as the sodium metabolism and is determined by impairments of the sodium and water balance. Isolated chloride deviations are found in disorders of the acid-base metabolism. Bicarbonate and chloride concentrations change conversely because chloride is replaced by bicarbonate during the renal output. Here, chloride is required to calculate the anion gap.

Regular range

95–105 mmol/L

Alarm limits: <80 and >118 mmol/L

Elevated values

(Hyperchloridemia)

Hypertonic impairment of the water and electrolyte metabolism (elevated plasma osmolarity due to reduced water intake or increased loss of water)

- Hypertonic dehydration (water deficiency) due to
  - Inadequate fluid supply in very ill patients
  - High loss of water, e.g., in diabetes mellitus/insipidus, chronic watery diarrhea (chloride retention in the kidneys to compensate the bicarbonate loss → metabolic acidosis, hypokalemia), serious febrile illnesses
- Hypertonic hyperhydration (excess sodium exceeds overhydration) due to
  - Infusion with hypertonic sodium chloride solutions or
  - Hyperaldosteronism (Conn syndrome: Na^+ retention).
- Renal tubular acidosis → further diagnostic procedures: examine the potassium levels (hyper- or hypokalemia, depending on the type)
  - Hyperventilation (respiratory alkalosis → compensatory chloride retention in the kidneys → metabolic acidosis)

Decreased values

(Hypochloridemia)

- Generally identical symptoms as described for sodium
- Hypotonic dehydration (the sodium and chloride loss exceeds the water deficiency) due to
  – Loss of salt in patients with kidney disease (impaired NaCl resorption in the Henle loop), diuretics (renal loss of NaCl and water)
  – Vomiting or diarrhea (gastrointestinal chloride-rich loss of water)
  – Excessive sweating
  – Inadequate electrolyte supply during infusion therapy
- Hypotonic hyperhydration (overhydration)
  – Infusion with electrolyte-free glucose solutions
  – Polydipsy
  – Renal or cardiac insufficiency
- Metabolic alkalosis (hyperaldosteronism, Cushing syndrome, ACTH forming tumors, Bartter syndrome):
  → Further diagnostic procedures: examine the potassium levels (hypokalemia)

Symptoms may include thirst, drowsiness, water deposit in tissue and tendency to collapse (similar to sodium deficiency).

Important: with respect to the interpretation
- If the specimen is measured by means of coulometry or indirect ISE, hyperproteinemia or hyperlipidemia can cause "pseudohypochloridemia" due to the small reference interval of chloride. Conversely, hypoproteinemia and hypolipidemia can cause "pseudohyperchloridemia. The determination of chloride by means of ion-selective methods without diluting the specimen is dependent on the water content of the specimen and allows the proper interpretation.

Cl^- sensor

The chloride sensor is a half-cell. Together with the external reference sensor, it forms a complete electrochemical half-cell. The sensor is equipped with an Ag/AgCl wire, surrounded by electrolyte solution with a defined concentration of chloride ions. A membrane made of a PVC matrix in quarternary amine, a highly selective ion exchanger for chloride ions, separates the electrolyte solution from the specimen.

The contact between the specimen and the membrane results in a membrane potential due to the chloride ion exchange. The potential is compared to the constant potential of the reference sensor. The measured potential difference is proportional to the chloride ion concentration in the specimen and changes based on the ion activity.

Anion gap

Anions	
Chloride	103 mmol/L
Bicarbonate	27 mmol/L
Sum	130 mmol/L
Cations	
Sodium	142 mmol/L
Sum	142 mmol/L

Fig. 7: Serum calcium fractions.

Anion gap = $[Na^+]$ - ($[Cl^-]$ + $[HCO_3^-]$)

Regular range

8–16 mmol/L

The anion gap refers to the difference between cations and anions. It is used to measure the routinely not determined and not determinable anions (mainly negatively charged plasma proteins, phosphate, sulphate and organic acid residues such as lactate, acetoacetate, β-hydroxybutyrate). Although it is not a sensitive or specific procedure, the determination of the anion gap has achieved a firm position in emergency and intensive care within the scope of the differential diagnosis of metabolic acidoses. In particular, it is possible to distinguish life-threatening metabolic acidoses due to intoxication from other clinical symptoms.

Metabolic acidosis with enlarged anion gap

- Diabetic acidosis (primarily acetoacetate due to lipolysis)
- Alcoholic acidosis (primarily β-hydroxybutyrate due to lipolysis)
- Lactacidosis (due to shock or Biguanide therapy)
- Uremia (retention of organic acids from the metabolism
- Intoxication
  - Salicylate (→ combined metabolic acidosis and respiratory alkalosis)
  - Methanol: Formiate
  - Ethyleneglycol: Glycolate and Oxalate (crystals in the urine)

Metabolic acidosis with regular anion gap (hyperchloridemic metabolic acidosis)

- Diarrhea (hypokalemia)
- Primary metabolic acidosis: renal tubular acidosis (hyper- or hypokalemia, depending on the type)
- Primary respiratory alkalosis with secondary metabolic acidosis (e.g., hyperventilation)
- Therapy with carboanhydrase inhibitors
- Ureterosigmoidostomy (hypokalemia)

Important: with respect to the interpretation

- The anion gap can be reduced under concomitant pronounced hypercalcemia or high bromide concentrations (abuse of bromium-containing barbiturates).

Metabolites

Carbohydrates act as energy supplier

Carbohydrates, fats and proteins are the three most important nutrients we ingest in our diets. They are the main energy suppliers and key components for the organism.

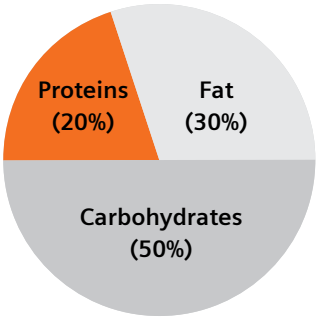


Fig. 1: Energy distribution target values.

During not physically challenging work, half of the energy requirement is provided by carbohydrates. Their digestion (decomposition into simple sugar molecules) starts in the mouth with the help of ptyalin (commonly known as salivary amlylase), an enzyme produced by the salivary glands. Those metabolically converted substances are referred to as metabolites. They include the intermediate products of the intermediary metabolism or compounds synthesized by the organism.

One of these metabolites is glucose, the most important energy source and molecule of the carbohydrate group. It is generated during the enzymatic cleavage of more complex carbohydrates and resorbed in the small intestine.

From here, three basic metabolic paths are possible: if energy is not required immediately, glucose can be stored in the liver and musculature as glycogen.

In addition, glucose can be converted into other sugars or into intermediate products linked to the metabolism of fatty acids and triglycerides, or the formation of amino acids. To obtain its key position within the energy metabolism of the human body, the metabolite glucose is decomposed.

The oxidative glucose decomposition takes place under aerobic conditions, yielding energy and the end products carbon dioxide and water:

$C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O +$

Energy (36 mol ATP)

An alternative decomposition path under anaerobic conditions exists too: it generates lactate and a much smaller energy recovery:

$C_6H_{12}O_6 \rightarrow 2\ C_3H_6O_3 +$ Energy (2 mol ATP)

$C_3H_6O_3 \rightleftarrows C_3H_5O_3^- + H^+$

This anaerobic glycolysis represents the main energy supply of cells and tissue, which sometimes require large amounts of energy under anaerobic conditions (skeletal musculature) or are poorly supplied with oxygen (retina, cartilage).

Glycolysis is especially important for the erythrocytes, because they are lacking the cell organelles (mitochondria) required for the aerobic energy recovery.

Glucose

Biochemistry, Physiology and Pathophysiology

The objective of oxidative glucose decomposition and glycolysis is the energy recovery through:

- Conversion of adenosine diphosphate (ADP) into adenosine triphosphate (ATP, the most important energy supplier of the intermediary metabolism) and
- The provision of pyruvate, required for the citrate cycle (this only applies to the oxidative glucose decomposition).

During glycolysis, the glucose molecule consisting of six carbon molecules is split into two pyruvate molecules with three carbon atoms each, where 5% of the energy contained in the glucose molecule is released. The remaining 95% of the glucose energy are recovered with the burning of the two pyruvate molecules through infiltration into the citrate cycle and the respiratory chain.

Pyruvate forms the junction of the metabolic paths that are taken depending on the presence (citrate cycle and respiratory chain) or absence (lactate) of oxygen (Fig. 2).

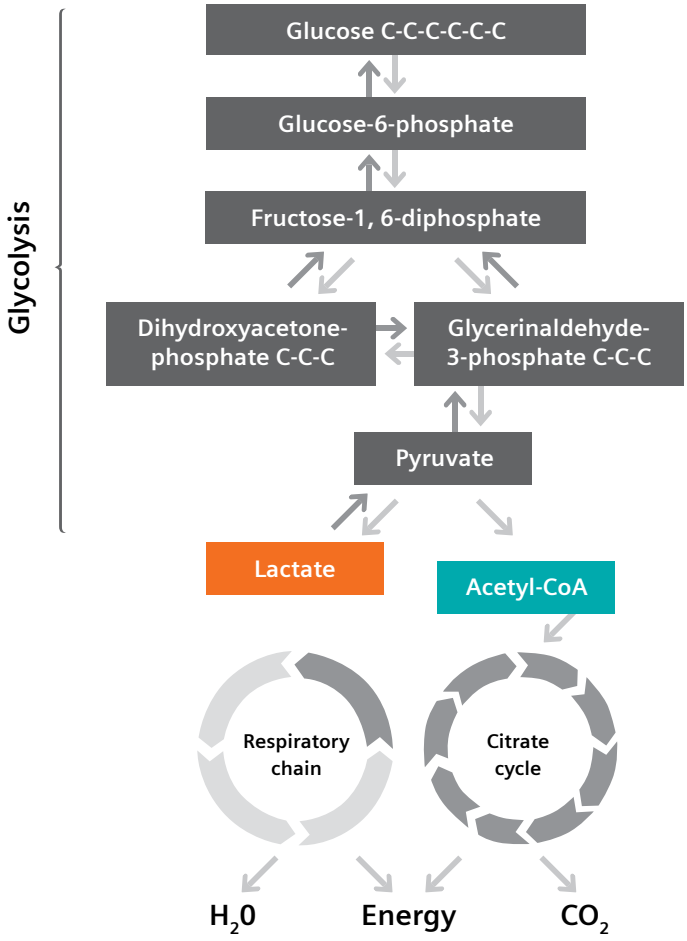


Fig. 2: Decomposition of glucose.

The blood glucose concentration can fluctuate significantly depending on the food intake. The glucose uptake into many tissue cells (muscle and fatty tissue) is regulated by the hormone insulin. Insulin is produced by the islets of Langerhans in the pancreas The hormone is secreted based on the stimulus associated with elevated blood glucose levels (due to food intake) and has a blood glucose-lowering action.

Other cells, such as the erythrocytes, cells of the lymphatic tissue, nerve cells, liver cells and the retina are insulin-independent. They possess so-called carriers which transport glucose through the cell membrane.

An elevated blood glucose concentration (hyperglycemia) over an extended time usually indicates an insufficient concentration or action of insulin and is referred to as diabetes mellitus. We generally distinguish between two basic types of this disease:

• In type I diabetes mellitus, the pancreas has lost its ability to produce insulin due to genetic disorders or as a result of infections. Glucose cannot be absorbed into the cells and the blood glucose levels remain elevated. Type I diabetics (approximately 10% of all diabetics) therefore rely on exogenous insulin applications.

• In type II diabetes mellitus, the islets of Langerhans in the pancreas produce insulin, but the body's cells are incapable of "recognizing" insulin. The cause for this "insulin resistance" can be excess food supply across an extended period of time with concomitant genetic predisposition. The consequence is again an elevated blood glucose concentration with simultaneously elevated blood insulin concentration (Fig. 3).

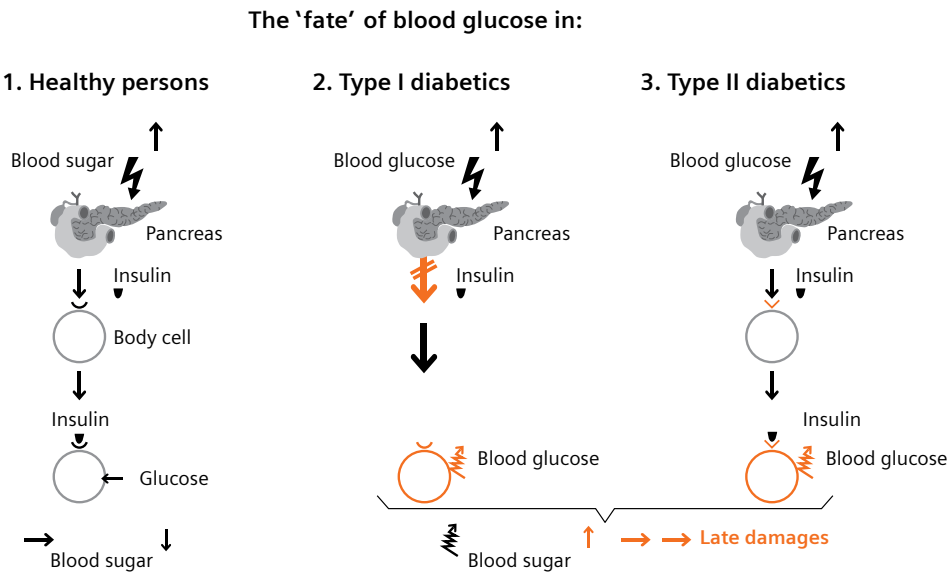


Fig. 3: The 'fate' of blood glucose in 1. healthy persons, 2. type I and 3. type II diabetics.

Approximately 90% of all diabetics are type II diabetics; a majority of them also suffer from high blood pressure, elevated blood lipids and are overweight ("metabolic syndrome").

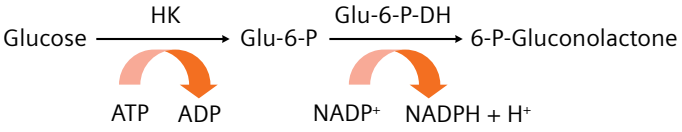
Glucose is mobilized by the insulin antagonists glucagon, cortisol and adrenaline. These hormones have a blood glucose-elevating effect by catabolizing the glycogen stored in the liver and releasing glucose to the blood (glycogenolysis). Increased glucose requirements, e.g., due to illnesses and physical or mental stress, can be directly balanced this way.

The concentration ratio between glucagon and insulin is characteristic for the status of the organism with respect to its nutritional and energy storage status: after eating (resorption phase), the glucagon/insulin ratio is low (a lot of insulin), and the excess amount of glucose is stored. During the post-resorption phase, the ratio is high (less insulin), and the storage is emptied again.

Measuring methods

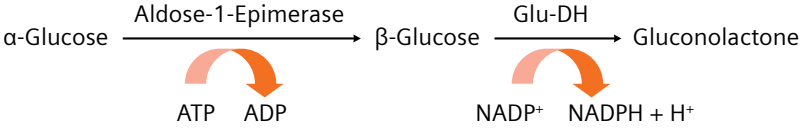
Different measuring methods are available for blood glucose, the most frequently determined analyte. Certain factors need to be considered, depending on the method, specimen type and area of application, to obtain correct and precise results.

Hexokinase
Glucose is transformed by hexokinase (HK) into Glucose-6-phosphate (Glu-6-P), which is transformed to phosphogluconolactone by Glucose-6-phosphate-dehydrogenase (Glu-6-P-DH) under reduction of the coenzyme $NADP^+$:



The increase of NADPH is proportional to the glucose quantity and is determined by means of photometry. This method is deemed the reference method.

Glucose dehydrogenase
Glucose is present in solution in both forms (a : β = 1 : 2). Glucose-dehydrogenase (Glu-DH) is a β-glucose-specific enzyme. The α-share is transformed into the β-form via Aldose-1-epimerase enzyme. The addition of this enzyme allows the acceleration of the speed-determining step and hence the duration of the analysis:



The NADPH increase is proportional to the glucose content and is determined by means of photometry. Besides glucose, it also registers the Xylose levels, which do not cause an impairment at regular concentrations (<2.5 mg/dL). This method to determine the glucose levels cannot be used during a Xylose absorption test.

Glucose oxidase

In the first step, glucose is oxidized to Gluconolactone by means of oxygen in the air and the presence of the Glucose oxidase enzyme (GOD). The second step varies, depending on the method:

Glucose oxidase-peroxidase

In common urine test strips (“dry chemistry”) as well as certain older blood glucose measuring devices, the action of peroxidase (POD) reduces the resulting hydrogen peroxide.

The color intensity of the concomitantly developing color indicator D_2 (oxidation of the added chromogen D-H_2) is proportional to the glucose content and is determined by means of photometry/reflectometry:

$$\text{Glucose} + H_2O + O_2 \xrightarrow{\text{GOD}} \text{Gluconolactone} + H_2O_2$$

$$H_2O_2 + \text{D-}H_2 \xrightarrow{\text{POD}} \text{Dye } (D_2)$$

Amperometry/biosensors

The hydrogen peroxide generated during the first step is anodically oxidized to oxygen by the polarization voltage. The quantity of released electrons is proportional to the glucose content (see glucose sensor in the chapter ”Metabolites”).

$$\text{Glucose} + H_2O + O_2 \xrightarrow{\text{GOD}} \text{Gluconolactone} + H_2O_2$$

$$H_2O_2 \longrightarrow 2\,H^+ + O_2 + 2e^-$$

One mole of oxidized hydrogen peroxide corresponds to one mol of glucose. The current is electronically converted into concentration.

Lactate

Biochemistry, Physiology and Pathophysiology

Lactate is the salt of lactic acid and an end product of the glucose metabolism. It is formed during glycolysis, when energy (ATP) is recovered under anaerobic conditions (see Fig. 2).

When resting, the metabolism produces approximately 1,400 mmol of lactate per day (20 mmol/kg/day) in the brain, skin, gastrointestinal tract, erythrocytes and muscle tissue.

Lactate diffuses from the cells of the body into the blood and is transformed back into glucose (gluconeogenesis) mainly in the liver and in small quantities in the kidneys. The medical term for this process is the Cori cycle (Fig. 4).

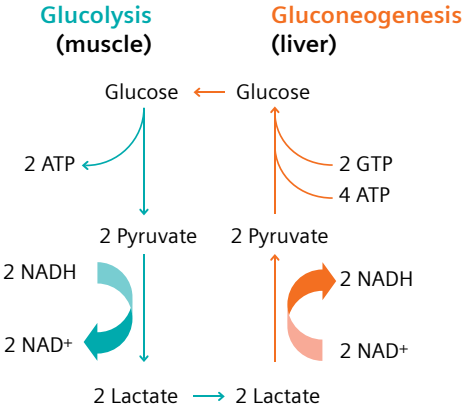


Fig. 4: Cori cycle—the gluconeogenesis requires three times more energy (2 GTP and 4 ATP) than the quantity generated during the decomposition of glucose to lactate (2 ATP).

Under regular conditions, the production and metabolism of lactate is balanced. Lactate maintains a blood concentration of below 2.0 mmol/L and neutralizes the developing H^+ ions (protons) by means of the buffer system in the blood.

In healthy subjects, lactate is produced when energy is required for the short term due to excessive physical strain and the energy—in the form of ATP—needs to be recovered from the glycolysis process under anaerobic conditions. The lactate concentration increases significantly and cannot be broken down at the same speed as it is produced.

The consequences are:

- An increase in the lactate concentration to >2.0 mmol/L (= hyperlactatemia) and
- An increase in the proton concentration (resulting in a pH of <7.35) = lactic acidosis.

The lactate concentration depends on the metabolic rate and the oxygen debt of the cells. Oxygen deficiency causes lactic acidosis and indicates overstrain of the muscles.

In critically ill intensive care patients, elevated lactate levels indicate tissue hypoxia, which can lead to multiple organ failure in the worst case. For lack of oxygen, the body is forced to the anaerobic generation of energy. Similar to healthy persons (see above), this process leads to an excess of lactate (→ hyperlactatemia) and the simultaneous accumulation of H^+ ions (→ lactacidosis). Organs that have been damaged due to the protracted course of an illness, such as the heart, liver and kidneys, prevent the decomposition of the metabolite.

In the clinic, this can indicate that the respiration was terminated too soon (cardiac decompensation and associated overstrain of the heart muscle) or that the hepatic function is impaired.

Outside the clinic, the lactate value is a parameter used to determine the training status of athletes.

Measuring Methods

Enzymatic method
Lactate is oxidized to pyruvate by the lactate-dehydrogenase enzyme in the presence of the coenzyme NAD^+. Because the reaction balance is much more pronounced on the lactate side, certain reaction conditions (alkaline milieu, recovery of the formed pyruvate) need to be ensured for the quantitative oxidation:

$$\text{Lactate} + NAD^+ \rightleftarrows \text{pyruvate} + NADH + H^+$$
$$\text{pyruvate} + \text{L-Glutamate} \rightleftarrows \text{L-Alanine} + \alpha\text{-Ketoglutarate}$$

The increase of NADH is proportional to the lactate quantity and is determined by means of photometry.

Amperometry/biosensors
Lactate is transformed into pyruvate through lactate oxidase (LOD). The hydrogen peroxide generated in the process is oxidized to oxygen by the polarization voltage. The quantity of nascent electrons is proportional to the lactate quantity in the specimen (see lactate sensor in the chapter “Lactate Parameters”).

$$\text{Lactate} + H_2O + O_2 \xrightarrow{\text{LOD}} \text{pyruvate} + H_2O_2$$

$$H_2O_2 \longrightarrow 2\,H^+ + O_2 + 2\,e^-$$

One mol of oxidized hydrogen peroxide corresponds to one mol of lactate. The current is electronically converted into concentration.

Total bilirubin in neonates

Biochemistry, Physiology and Pathophysiology

Bilirubin is an essential bile pigment formed as a result of the hemoglobin degradation. The pigment is released during the destruction of aging or damaged erythrocytes. Hemoglobin breaks down into the heme-part, which in turn is transformed into unconjugated bilirubin, and the globin part, which is broken down into amino acids.

In healthy subjects, the quantity of bilirubin in the blood is small because bilirubin is broken down in the liver and eliminated. Unconjugated bilirubin is fat-soluble and can only be eliminated after binding to albumin and transported into the liver where it is conjugated by the enzyme glucuronyl transferase and converted into a water-soluble form.

The majority of conjugated bilirubin is eliminated in the small intestine via the gall bladder. However, a small part is broken down in the large intestine, while another part is reabsorbed and eliminated with the urine. The conjugation of bilirubin in the liver can be affected either by glucuronyl transferase deficiency or by medications interfering with this enzyme, thus causing elevated bilirubin levels in the blood.

Elevated bilirubin values in the blood (hyperbilirubinemia) cause jaundice

(Discoloration of body tissue)

Generally, jaundice in neonates is completely harmless and the result of a not yet fully developed liver function as well as the fetal hemoglobin degradation during the exchange with hemoglobin from adults.

Caution!

Severe jaundice in neonates can indicate the presence of a serious illness such as erythrocyte hemolysis (fetal erythroblastosis), usually caused by blood incompatibilities between the mother and child. Extremely high bilirubin values in newborns can trigger bilirubin-induced encephalopathy (also known as nuclear icterus), an impairment of the brain.

Warning

Exposure to light affects the bilirubin concentration. Therefore, protect the samples from light immediately after the collection until they are analyzed. In addition, please make sure that the samples are free of fibrin, other suspended matter and air bubbles. Refer to the recommendations issued by the “Clinical and Laboratory Standards Institute” (formerly NCCLS) concerning the handling and storage of samples in the chapter Blood Gas and pH Analysis and Related Measurements; Approved Standard; CLSI Document C46-A; (Vol. 21); 2001.

Measuring methods

RAPIDLab® 1200 system uses a spectrophotometer (CO-oximetry) with several wavelengths to measure the light transmission of a sample of neonatal whole blood and to determine the concentration of hemoglobin derivatives and bilirubin. The whole blood sample is aspirated in the RAPIDLab 1200 system at the sample input and transferred to the CO-ox module. The sample flows through an optical chamber, and the optical unit of the CO-ox module transmits light through the sample to a polychromator used to measure the light intensity at 256 wavelengths. The data is evaluated with 47 selected wavelengths. The bilirubin values are determined by a residual least squares analysis. To determine the nBili results, the raw data is corrected depending on the hematocrit value.

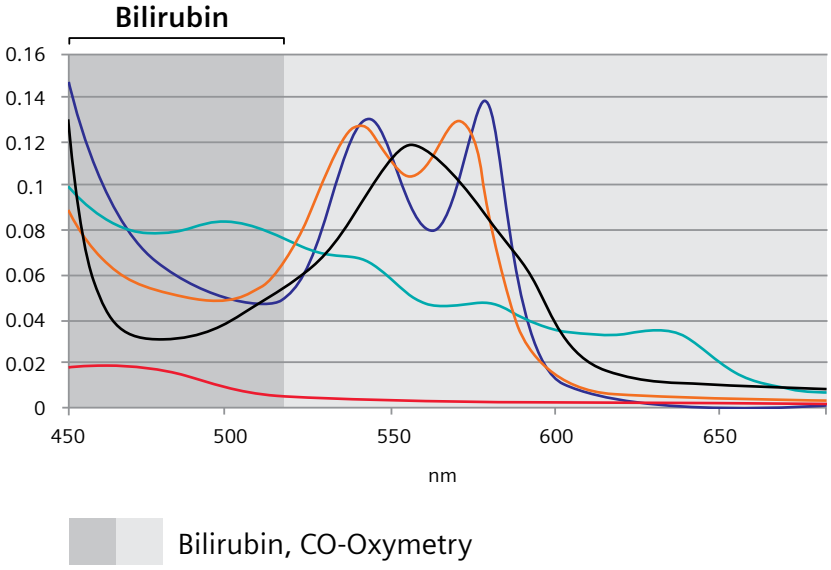


Fig. 5: Wavelengths for total bilirubin values in neonates.

$$\text{nBili measured} = \frac{\text{bili Rcmess} * \text{bili Scaler}}{(1 - \text{tHb*HctFactor}) * \text{btr Slope} + \text{btr Offset}}$$

- tHb*Hct Factor is an estimate of Hct
- btr Slope and btr Offset define the bias-to-reference correction
- bili Scaler defines the adjustment scale of the raw data to the plasma/serum reference
- bili Rcmess is the result measured

Parameters

Glucose

Glucose is the most important molecule in the carbohydrate metabolism and is fed into the cells as the most significant energy supplier.

The glucose concentration in the blood is affected by a number of factors, primarily by the nutrition: the blood glucose concentration increases as a result of food intake. The hormone insulin is secreted as a direct reaction to the increase. It plays an important role in the regulation of the blood glucose concentration: the blood glucose concentration is decreased as a result of the promotion of glycogenesis (glycogen formation from glucose) and increase of the cell permeability for glucose.

Clinical significance

The determination of the blood glucose concentration is helpful for the diagnosis of a number of metabolic diseases.

Due to the constant increase in diseases of the carbohydrate metabolism and improved quality of analytical procedures, the blood glucose concentration remains to be the most commonly determined parameter both in the central (laboratory) and local (wards) area of the clinic.

Regular range in adults

- 70–100 mg/dL (3.89–5.55 mmol/L) in capillary whole blood
- 70–115 mg/dL (3.9–6.38 mmol/L) in venous plasma

Elevated values

Hyperglycemias
(>100 mg of glucose/dL of whole blood, postprandial >160 mg/dL) can generally be triggered by

- Insulin deficiency
  – absolutely in type I diabetes mellitus (absent pancreatic insulin production) or
  – relative in type II diabetes mellitus (peripheral insulin resistance)
- Increased glucose intake
- Decreased glucose tolerance
- Post-aggression metabolism

We distinguish between two forms of hyperglycemias, depending on the type of insulin deficiency:

Ketoacidotic diabetic coma (>400 mg of glucose/dL of blood or >22.2 mmol/L)
Due to the absolute insulin deficiency in type I diabetics, hyperglycemia under inadequate blood glucose control or an acute serious crisis can lead to ketoacidotic diabetic coma. Because the hormone insulin is absent, which feeds glucose into the cells and generates energy reservoirs, a compensatory build-up of fatty acids takes place to provide energy. The ketone bodies generated during this process cause metabolic acidosis (elevated acetoacetate, β-hydroxybutyrate levels in the blood with simultaneous drop in pH, Kussmaul's breathing, acetone, and odor). See example on p. 102

→ Further diagnostic procedures: enlarged anion gap, decreased bicarbonate levels, blood pH of <7.37, PCO_2 <35 mmHg, increased osmolarity: up to approximately 350 mosm/kg, ketone bodies in the serum and urine are severely elevated, glucose levels in the urine are elevated.

Hyperosmolar diabetic coma
(usually >1000 mg of glucose/dL of blood or >55.5 mmol/L)

The relative insulin deficiency in type II diabetics can lead to hyperglycemia and hyperosmolar (non-ketoacidotic) diabetic coma, if left untreated. The elevated osmotic diuresis associated with this condition results in exsiccosis. In most patients, the insulin levels are measurable. Extreme dehydration, hypovolemia and hyperosmolarity lead to tissue hypoxia, anaerobic metabolism and ultimately to the possible lactacidosis.

→ Further diagnostic procedures: blood pH 7.37–7.45, PCO_2 35–46 mmHg, regular to slightly elevated ketone bodies in the serum and urine, elevated glucose in the urine, severely elevated osmolarity: >350 mosm/kg

The typical findings in diabetic coma are summarized in Fig. 8 on page 102.

Non-diabetic causes:

- Reduced glucose tolerance due to a major surgical procedure or trauma (stress situation) as a result of the inhibited insulin secretion and/or increased glucose supply caused by the release of catecholamines (Adrenaline and Noradrenaline) and Glucocorticoids
- Hyperglycemias as a result of reduced glucose tolerance in intensive care patients due to the use of Suprarenin® and, to a lesser extent, Arterenol®

The body compensates this situation by increasing the renal output to reduce the glucose level. This can lead to dehydration and loss of electrolytes.

→ Further diagnostic procedures: electrolytes, especially potassium (decreased)—see chapter "Electrolytes"—blood pH, analyze ketone bodies and test urine glucose (all regular).

Decreased values

Hypoglycemias
(<70 mg of glucose/dL of whole blood or <3.9 mmol/L) are triggered by:

- Increased peripheral glucose requirement due to physical activities.
- Insulin overdose/endogenic hyperinsulinism (Morbus Addison, hypopituitarism, Sulfonylurea therapy).
- Reduced hepatic gluconeogenesis (terminal cirrhosis of the liver, alcohol intoxication, poisoning).

→ Further diagnostic procedures: elevated lactate, β-Hydroxybutyrate and free fatty acids in the blood, positive ketone bodies in the urine

- Malabsorption
- Polycythemia vera (unbalanced glucose distribution between erythrocytes and plasma and/or excessive glycolysis caused by erythrocytes)
- Leukemia (excessive leukocytic glycolysis or glycolysis as a result of serious erythroblast propagation, e.g., in a hemeolytic crisis)
- Dumping syndrome (gastrectomy). The body tries to compensate it through energy recovery from other substances (lypolysis)

It increases the cerebral perfusion to protect the brain.

Important: with respect to the interpretation

- **Capillary venous differences—**
  As expected, the glucose concentration is higher in the arterial blood than in the venous blood. The extent of the capillary venous differences is subject to significant fluctuations: while differences from "not measurable" to approximately 10 mg/dL or 0.6 mmol/L occur in fasting measurements, the values in capillary blood can be 50% higher than in the venous blood after food intake (postprandial) or after an oral glucose tolerance test.
- Differences between plasma/serum and whole blood In blood specimens, glucose is dissolved in the aqueous component. Erythrocytes have a water content of 71%, while it is 93% for plasma. This leads to a difference of 12% between the glucose value in plasma and in whole blood with regular hematocrit. The relation and conversion of the two values is illustrated with the following equation:

[Glucose]Whole blood = [Glucose]Plasma

x [1.0 - (0.0024 x hematocrit [%])]

Interferences: If given at therapeutic concentrations, most medications do not cause any interferences. Fig. 6 shows some substances that do not affect the glucose measurement (e.g., measured with the RAPIDLab® 860/865 analytical system). The respective specified concentrations result in a deviation of less than 6 mg/dL (0.3 mmol/L) with respect to the recovery of the glucose concentration.

Medications	
Substance	**Concentration**
Chlorpromazine	5 mg/dL
Dopamine*	0.5 mg/dL
Ethanol	350 mg/dL
Salicylate	50 mg/dL
Sodium nitroprusside	70 mg/dL
Thiocyanate	80 mg/dL
Ascorbic acid	6 mg/dL

Endogenous substances	
Substance	**Concentration**
Urea	500 mg/dL
Uric acid	10 mg/dL
Lactate	100 mg/dL
Acetoacetate	40 mg/dL
β-hydroxybutyrate	200 mg/dL
Creatinine	30 mg/dL
Bilirubin (direct)	30 mg/dL
Bilirubin (total)	34 mg/dL
Hematocrit	70%

Anticoagulants	
Substance	**Concentration**
Heparin	20,000 U/dL

Fig. 6: Substances without detectable interference on the glucose value— measured using the RAPIDLab 860 analytical system.

For more information about the specimen preparation, please see chapter "Pre-Examination considerations."

Fig. 7 Contains a list of substances that may affect the glucose measurement.

Substance	Analyzed concentration	Interference level
Sodium fluoride	1.000 mg/dL	25 mg/dL (1.4 mmol/L)
Acetaminophen	2 mg/dL	7 mg/dL (0.4 mmol/L)
Sodium fluoride/potassium oxalate	1.000 mg/dL each	25 mg/dL (1.4 mmol/L)

Fig. 7: Substances affecting the glucose measurement with the deviation listed under "Interference level".

Glucose sensor

The glucose sensor by Siemens Healthineers is a complete electrochemical cell used to determine the concentration of a specimen by means of amperometry; it is referred to as biosensor. Biosensors consist of a biologically active component, in this case an enzyme and a conversion unit that converts the reaction between the biological material and the analyte into a measurable electrical signal. The biosensor allows the measurement in undiluted materials.

The biosensor is equipped with four electrodes:

- The platinum measurement electrode applied to the glucose oxidase (GOD) enzyme,
- The Ag/AgCl reference electrode,
- A platinum counter electrode for the stabilization of a constant potential, and
- An additional platinum measurement electrode determines the substances which may interfere with the enzymatic reaction process. The potential of the interfering substance is eliminated by the differential measurement. A microporous membrane separates the electrodes from the specimen.

A constant polarized voltage is applied during the measurement. Glucose is oxidized to D-Gluconate at the surface of the measurement electrode through the enzyme GOD; hydrogen peroxide is generated in the process:

$C_6H_{12}O_6 + H_2O + O_2 \rightarrow C_6H_{12}O_7 + H_2O_2$

Hydrogen peroxide oxidizes to become oxygen as a result of the polarization voltage:

$H_2O_2 \rightarrow 2\ H^+ + O_2 + 2\ e^-$

The electrons that were released during the oxidation increase the current flow proportional to the glucose concentration of the specimen.

Lactate

Lactate is an end product of the anaerobic glucose metabolism. It is normally formed during muscle contractions. During physical strain, the lactate concentration increases significantly, and the metabolite is transported to the liver via blood and metabolized. Under regular aerobic conditions, lactate is oxidized to pyruvate, which in turn is decomposed into CO_2 and H_2O during the next step.

The lactate concentration in the blood is affected by the production rate, the metabolic rate and the oxygen availability in the cells.

Clinical significance

The determination of the blood lactate concentration is helpful for the evaluation of the oxygen supply of the tissue and as an indicator, in particular, for the assessment of perfusion disorders and regional oxygen deficiencies. As oxygen deficiency becomes greater it may cause severe lactic acidosis.

Regular range

<1.8 mmol/L

Values of up to 15 mmol/L are tolerable with short-term strain (exercise). Values of more than 4 mmol/L for an extended period of time in intensive care patients are associated with a higher predicted mortality rate.

Elevated values

(Hyperlactatemia)

- Impaired oxygen supply
  - Hypoxic hypoxemia
  - Cardiac decompensation
  - Pulmonary insufficiency
  - CO-poisoning
  - Trauma/shock
- Metabolic causes
  - Competitive sports (increased accumulation of pyruvate as a result of increased glycolysis due to muscle activities)
  - Diabetic* or alcoholic ketoacidosis (increased fatty acid metabolism)
  - Sepsis, infections such as malaria, cholera
  - Renal insufficiency, impaired hepatic function
- Medications (including biguanidine, salicylates, cocaine, theophylline) and toxic substances (cyanide, methanol, ethylene glycol, etc.)

→ Further diagnostic procedures: to evaluate the pathological quality of the hyperlactatemia: blood pH, bicarbonate, PCO_2, PO_2, anion gap, ketone body concentration in the serum/urine (not elevated in pure lactic acidosis), creatinine, urea.

**In diabetics, the rare complication of lactate acidotic coma is not caused directly by diabetic metabolic disorders, but in connection with the anti-diabetic therapy using Biguanides. In this case, the pH, PCO_2 and bicarbonate values are decreased and the anion gap increased, while the blood glucose is regular to low (Fig. 8).*

Significant lactacidosis

- Lactate concentration of >45 mg/dL of blood (5.0 mmol/L)
- Blood pH of <7.25

	Ketoacidotic coma	Hyperosmolar coma	Lactate acidotic coma
Clinical findings			
Respiration	Deep and rapid (Kussmauls's type)	Regular	Deep and rapid
Reflexes	Reduced	Reduced	Atypical
Muscle tone	Low	High, tendency to seizures	Atypical
Laboratory findings			
Blood glucose	Elevated (>400 mg/dL or 22.2 mmol/L)	Severely elevated (>1.000 mg/dL or 55.5 mmol/L)	Regular/low
Lactate	Regular (to elevated)	Regular (to elevated)	Severely elevated
pH, PCO_2, bicarbonate	Decreased	Regular	Decreased
Ketonuria	Pronounced	Absent/minor	Absent/minor
Osmolarity	Regular to elevated	Severely elevated (>350 mosm/kg)	Regular

Fig. 8: Diabetic comas.

Important: with respect to the interpretation

- Take into account the hepatic and renal functions. Although the basal values in patients with an impaired function of these organs are regular, their lactate clearance is reduced.
- Lactate should not be considered as an individual value but in the overall clinical context. This applies in particular to the perfusion disorders applicable to the main area of indication, but also to inadequate metabolization (impaired uptake in the liver), regional deficiencies (surgical field, sepsis, shunts) and increased lactate output into the circulation, e.g., due to limited blood flow (wash-out effect).
- Interferences (Fig. 9) lists substances that do not affect the lactate measurement. In the specified concentrations, these compounds produce an error of less than 6 mg/dL (0.7 mmol/L) with respect to the recovery of the lactate concentration.

Medications	
Substance	**Concentration**
Chlorpromazine	17 mg/dL
Dopamine	1 mg/dL
Ethanol	350 mg/dL
Salicylate	50 mg/dL
Sodium nitroprusside	70 mg/dL
Thiocyanate	80 mg/dL
Epinephrine	2 mg/dL
Norepinephrine	2 mg/dL
Phenobarbital	15 mg/dL
Glutamate	16 mg/dL
Hydroxyethyl starch	30%
Ascorbic acid	8 mg/dL
Dilantin	14 mg/dL
Theophylline	9 mg/dL
D-Penicillamine	25 mg/dL
Isonicotinic acid hydrazide	2 mg/dL

Endogenous substances	
Substance	**Concentration**
Bilirubin (direct)	30 mg/dL
Bilirubin (total)	35 mg/dL
Creatinine	30 mg/dL
Glucose	1000 mg/dL
Acetoacetate	40 mg/dL
β-hydroxybutyrate	200 mg/dL
Urea	500 mg/dL
Pyruvate	9 mg/dL
Uric acid	10 mg/dL

Anticoagulants	
Substance	**Concentration**
Heparin	20,000 U/dL

Fig. 9: Substances without detectable interference on the lactate value—measured using the RAPIDLab 860 analytical system*.

*D'Orazio, P. A.: Interference by Thiocyanate on Electrochemical Biosensors for Blood Glucose. Clin. Chem. 42(7), 1124–1126, 1996

Krouwer, J., Maley, T. C., Moran, R. F., Rossi, D., Silvia, M.: Lactate Performance Comparison: The CibaCorning 860 System versus Reference Methods, Reference Materials and the Ektachem 700 System. Bayerinterne Unterlagen, 1996 (Bayer-internal documents, 1996)

Please see the chapter “Pre-Examination considerations” for more information about the requirements for handling the specimens and anticoagulants.

Substance	Analyzed concentration	Interference level
Sodium fluoride	1.000 mg/dL	9 mg/dL (1.0 mmol/L)
Acetaminophen	2 mg/dL	3.2 mg/dL (0.4 mmol/L)
Sodium fluoride/potassium oxalate	1.000 mg/dL each	9 mg/dL (1.0 mmol/L)

Fig. 10: Substances that affect the lactate measurement with the deviation listed under the heading “Interference level”.

Lactate sensor

The lactate sensor by Siemens Healthineers is a complete electrochemical cell used to determine the concentration of the specimen by means of amperometry; it is referred to as biosensor.

> Biosensors consist of a biologically active component, in this case, an enzyme and a conversion unit that converts the reaction between the biological material and the analyte into a measurable electrical signal. The biosensor allows the measurement in undiluted materials.

The sensor is equipped with four electrodes:

- The platinum measurement electrode applied to the lactate oxidase enzyme (measures the extent of change in oxygen in the sample, as it results from the action of the lactate oxidase enzyme),
- An Ag/AgCl reference electrode,
- A platinum counter electrode for the stabilization of a constant potential, and
- An additional platinum measurement electrode without enzyme determines substances which might interfere with the enzymatic reaction process. The potential of the interfering substance is eliminated by the differential measurement.

A constant polarized voltage is applied during the measurement. Lactate from the specimen is oxidized to pyruvate (salt of the pyruvic acid) at the surface of the measurement electrode through the lactate oxidase enzyme; hydrogen peroxide is generated in the process:

$$C_3H_6O_3 + H_2O + O_2 \rightarrow C_3H_4O_3 + H_2O_2$$

Hydrogen peroxide is oxidized to oxygen by the polarization voltage:

$$H_2O_2 \rightarrow 2\ H^+ + O_2 + 2\ e^-$$

The electrons that were released during the oxidation increase the current flow proportional to the lactate concentration of the specimen.

Regular values (adults)

Acid-base metabolism[1]	
pH	7.35–7.45
PCO_2	35–46 mmHg (4.7–6.1 kPa)
HCO_3^- (act)	21–26 mmol/L
B.E.	+2 – + 3 mmol/L
tCO_2	23–28 mmol/L

Oxygen status[2]		
PO_2	70–100 mmHg 9.5–13.3 kPa	Age-dependent[1] PO_2 (mmHg) = 102 - 0.33 x years of age PO_2 (kPa) = 13.6 - 0.044 x years of age
cHb	12–16 g/dL (f) 7.5–9.9 mmol/L (f)	14–18 g/dL (m) 8.7–11.2 mmol/L (m)
Hct	37–47% (f)	42–52% (m)
ctO_2	20 mL/dL	
sO_2	>96% (0.96)	
FO_2Hb	>96% (0.96)	
*F*COHb	<2.0% (0.02)	
*F*MetHb	<1.5% (0.015)	
*F*HHb	0.0–5.0% (0.0–0.05)	
p5O	26.6 mmHg (3.6 kPa)	
PO_2(A)T	105 mmHg	
PO_2(A-a)	10–12 mmHg with FiO_2 0.21	
$AvDO_2$	5 mL/dL	
Qs/Qt	2–8%	
VO_2[3]	130–150 mL/min /m²	
DO_2[3]	520–720 mL/min /m²	

Electrolytes[1]	
Na^+	135–145 mmol/L
K^+	3.6–4.8 mmol/L
Ca^{++} (ionized)	1.15–1.35 mmol/L
Cl^-	95–105 mmol/L
Anion gap	8–16 mmol/L

Metabolites[1]	
Glucose **Capillary** whole blood	70–100 mg/dL (3.9–5.5 mmol/L)
Glucose **Venous** plasma	70–115 mg/dL (3.9–6.4 mmol/L)
Lactate **Arterial** whole blood/plasma	<16 mg/dL (<1.8 mmol/L)
Lactate **Venous** whole blood/plasma	4.5–20 mg/dL (0.5–2.2 mmol/L)

References:

1. Thomas, L.: Labor und Diagnose. (Laboratory tests and diagnosis) TH Books Verlagsgesellschaft (5th edition), Frankfurt a. M., 1998
2. Leuwer, M., Schürmeyer, T. H., Trappe, H.-J., Zuzan, O.: Checkliste Interdisziplinäre Intensivmedizin. (Checklist for interdisciplinary intensive medicine) Georg Thieme Verlag, Stuttgart, 1999
3. Beale, R.: VO_2 und DO_2 während des kardiogenen Schocks und der Sepsis. (VO_2 and DO_2 during cardiogenic shock and sepsis). Anästhesiol. Intensivmed. Notfallmed. Schmerzther. Sonderheft 1/31, 22–25, 1996 (Anaesthesiol. intensive and emergency medical pain management, special issue 1/31, 22-25, 1996).

Regular values (newborns/infants/children)*

Acid-base metabolism[1]

Newborns/infants/children	pH	PCO_2	
		mmHg	kPa
Umbilical artery	7.09–7.40	35.0–80.0	4.7–10.7
Umbilical vein	7.15–7.45	30.0–57.0	4.0–7.6
Newborns, 1 day	7.20–7.41	29.4–60.6	4.0–8.0
10–90 days	7.34–7.45	26.5–42.5	3.5–5.7
4–12 months	7.38–7.45	27.0–39.8	3.6–5.3

Oxygen status[1]

Newborns/infants/children	Hemoglobin		Hematocrit
	g/dL	mmol/L	%
Blood from the umbilical cord	13.5–20.7	8.4–12.9	48–56
1 day	15.2–23.5	9.4–14.6	—
2–6 days	15.0–24.0	9.3–14.9	40–70
14–23 days	12.7–18.7	7.9–11.6	38–60
24–37 days	10.3–17.9	6.4–11.1	36–46
40–50 days	9.0–16.6	5.6–10.3	—
2–2.5 months	9.2–15.0	5.7–9.3	—
3.0–3.5 months	9.6–12.8	6.0–7.9	—
5–7 months	10.1–12.9	6.3–8.0	—
10–12 months	10.7–13.1	6.6–8.1	35–43
1.5–3.0 years	10.8–12.8	6.7–7.9	—
5 years	11.1–14.3	6.9–8.9	32–40
10 years	11.9–14.7	7.4–9.1	32–41
12 years	11.8–15.0	7.3–9.3	34–44
15 years	12.8–16.8	7.9–10.4	35–49

Acid-base metabolism[1]

Newborns/infants/children	PCO_2		Standard bicarbonate
	mmHg	kPa	
Umbilical artery	0–22	0–2.9	—
Umbilical vein	16–35	2.2–4.7	11.8–21.4
Newborns, 1 day	—	—	18.6–22.6
10–90 days	70–85	9.3–11.4	18.5–24.5
4–12 months	—	—	19.8–24.2

Electrolytes[1]

Newborns/infants/children	Sodium	Potassium	Calcium (ionized)	Chloride
	mmol/L			
0–7 days	133–146	3.2–5.5	1.10 ± 0.059	96–111
7–31 days	134–144	3.4–6.0	1.22 ± 0.053	96–110
1–6 months	134–142	3.5–5.6	—	96–110
6 months–1 year	133–142	3.5–6.1	—	96–108
>1 year	134–143	3.3–4.6	1.18 ± 0.069	96–109

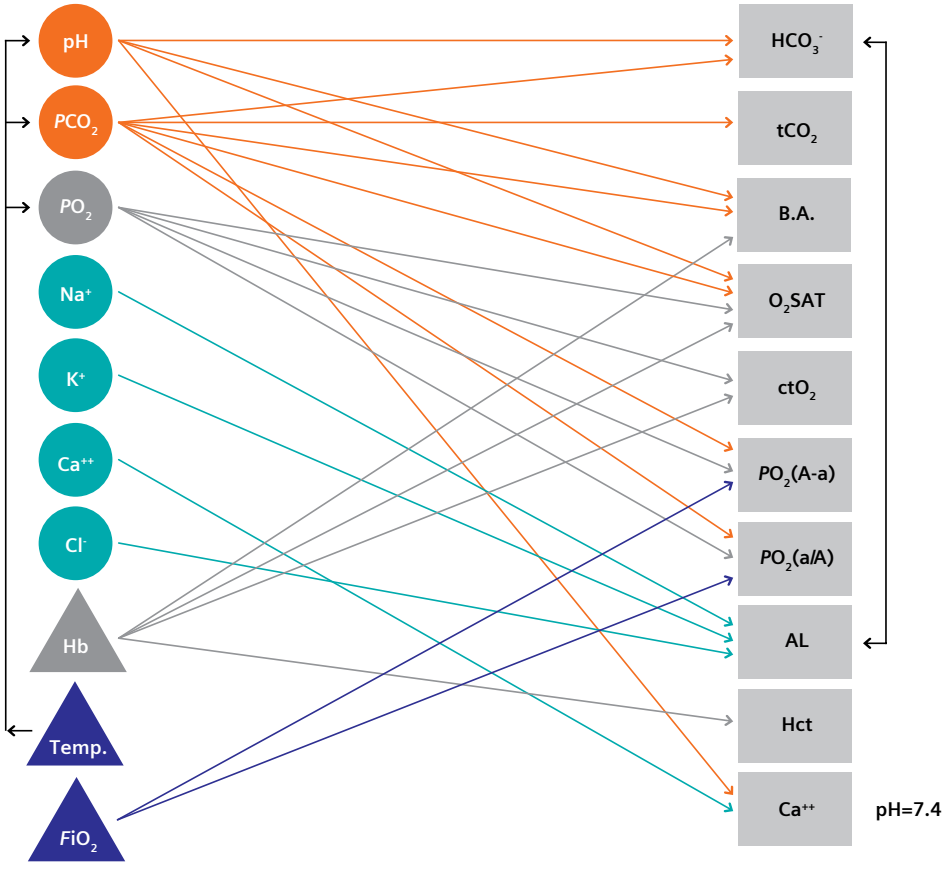
Metabolites[1]

Newborns/infants/children	Glucose	
	mg/dL	mmol/L
Blood from the umbilical cord	63–158	3.5–8.8
1 hour	36–99	2.0–5.5
2 hours	39–89	2.2–4.9
5–14 hours	34–77	1.9–4.3
20–28 hours	46–81	2.6–4.5
44–52 hours	48–79	2.7–4.4

References:

1. Thomas, L.: Labor und Diagnose. (Laboratory tests and diagnosis) TH Books Verlagsgesellschaft (5th edition), Frankfurt a. M., 1998
2. Leuwer, M., Schürmeyer, T. H., Trappe, H.-J., Zuzan, O.: Checkliste Interdisziplinäre Intensivmedizin. (Checklist for interdisciplinary intensive medicine) Georg Thieme Verlag, Stuttgart, 1999
3. Beale, R.: VO_2 und DO_2 während des kardiogenen Schocks und der Sepsis. (VO_2 and DO_2 during cardiogenic shock and sepsis). Anästhesiol. Intensivmed. Notfallmed. Schmerzther. Sonderheft 1/31, 22–25, 1996 (Anaesthesiol. intensive and emergency medical pain management, special issue 1/31, 22-25, 1996).

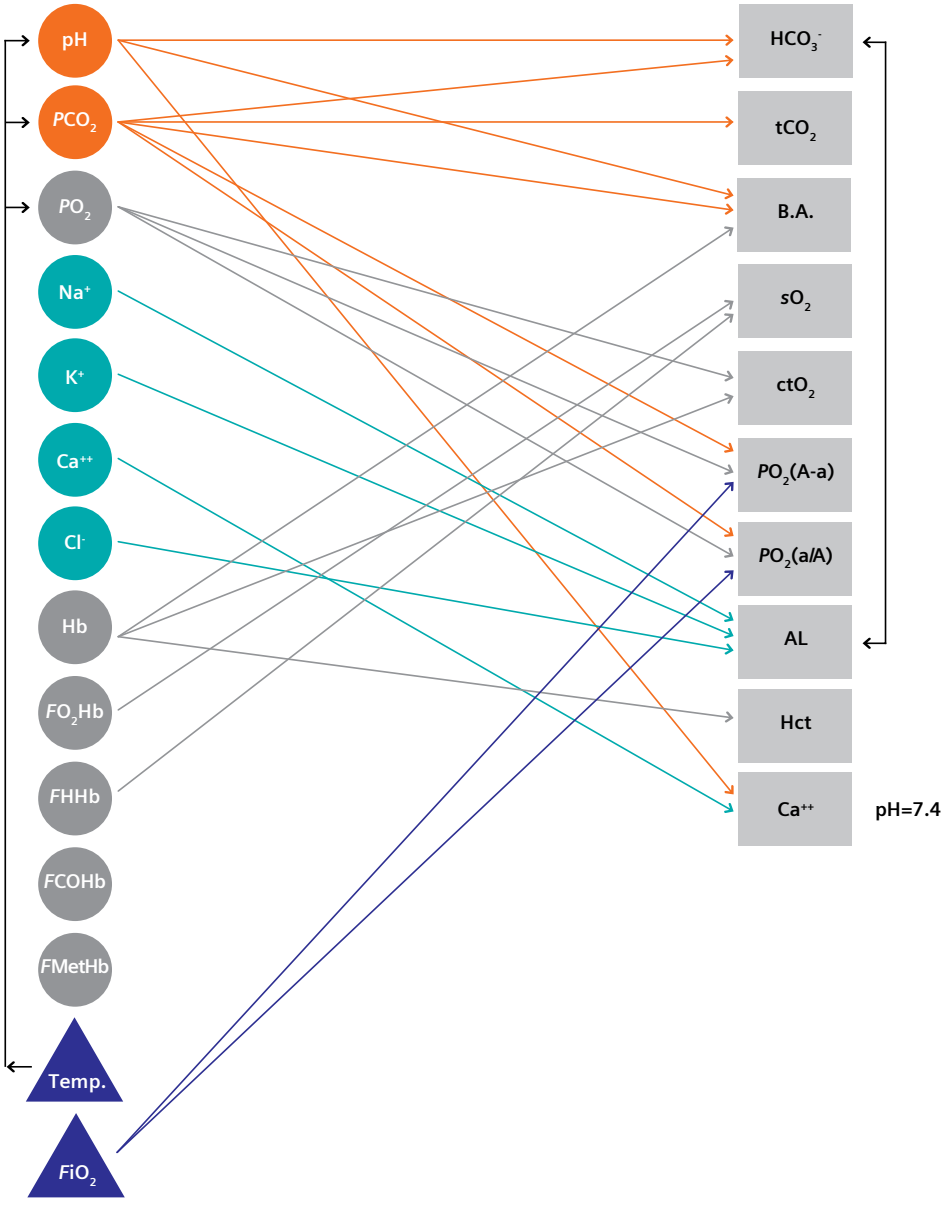
Regular values (interdependencies of the parameters)*



- measured parameters
- calculated parameters
- entered parameters

To display the parameters listed on the right side (■), the corresponding values on the left side need to be measured (●) or entered (▲).

Regular values (interdependencies of the parameters)



measured parameters

calculated parameters

entered parameters

To display the parameters listed on the right side (■), the corresponding values on the left side need to be measured (●) or entered (▲).

Appendix

Glossary

Acid	Proton donor, capable of releasing hydrogen ions in aqueous solution. The hydrogen ion concentration of a solution is always within a pH range of 10^{0} to 10^{-7}.
Acidic	pH value of <7.0.
Acidosis	Impaired acid-base metabolism due to increase of acidic metabolic products and decrease of the arterial pH to below 7.37.
Adenosine triphosphate, ATP	Energy-rich phosphate, important energy carrier of the cell.
Alkaline	pH of >7.0.
Alkalosis	Impaired acid-base metabolism with increased arterial pH to above 7.45.
Anemia	Blood deficiency with respect to the red blood count, irrespective of the leukocyte and thrombocyte count: reduced hemoglobin concentration and/or hematocrit, reduced erythrocyte count to below the age- and gender-specific reference values. Classification by pathogenesis: 1. anemia caused by excessive blood loss; 2. anemia due to reduced or ineffective erythropoiesis; 3. anemia due to excessive erythrocyte decomposition.
Anion	Negatively charged ion generated by electrolytic dissociation.
Anuria	Urine output of below 100 mL/24 hours (frequently preceded by oliguria).
Base	Proton acceptor, also referred to as lye; capable of absorbing hydrogen ions. Acid (HA) dissociates into H^{+} ions and base (A^{-}). The pH ranges from 10^{-7} to 10^{-14}.
Basic	See alkaline.
Buffer solution, buffer system, buffer mixture	Aqueous solution containing at least two electrolytes. At a certain pH, they react with only a minor change in pH to the supply of acids or bases.
Cation	Positively charged ion generated by the loss of electrons.
Cardiac	Concerning the heart.
Contusio cordis	Contusion of the heart caused by blunt chest trauma.
Chromogenic	Dye former.
Cirrhosis of the liver	Chronic liver disease; scarred connective tissue alteration of the liver due to break-up of the parenchyma.
Dehydration, dehydratization	Removal of water.
Diabetes insipidus	Reduced water absorption in the collection tubes of the kidneys and output of major hypotonic urine volume due to inadequate/absent production/secretion of the anti-diuretic hormone (ADH).
Diabetes mellitus	Impaired glucose metabolism due to relative or absolute insulin deficiency or loss of function of insulin.
Diffusion	Movement of molecules to their temperature-dependent kinetic energy along a concentration gradient (such as between alveoli and mixed-venous blood) with the objective of equalizing the concentration. Different concentrations are equalized until a balance is achieved.

Dissociation, dissociate	Dissociation of molecules in an aqueous milieu to become cations and anions.
Diuretics	Agents used to promote urinary secretion. They are divided into two groups, depending on their mechanism of action: for the promotion of salt excretion (saluretics, natriuretics) and for the promotion of water excretion.
Duodenal	The duodenum is a section of the small intestine. The gallbladder and pancreatic ducts (ductus choleductus and ductus pancreaticus) are connected to the intestine here, supplying the small intestine with digestive enzymes of the exocrinous pancreas (amylase, lipase, trypsin) in addition to bicarbonate.
Dyshemoglobins	Hemoglobin molecules that are not available for the oxygen transport due to chemical interference (COHb, MetHb, SulfHb).
Gluconeogenesis	New formation of glucose from non-sugars (amino acids, lactate, glycerine).
Glycogen	Polymer form of glucose storage.
Glycogenolysis	Decomposition of glycogen (glucose storage in the liver) to glucose.
Glycolysis	Decomposition of glucose in the organism.
Hemelytic anemia	Anemia caused by accelerated erythrocyte decomposition or shortened erythrocyte life.
Hepatic	Concerning the liver.
Hydratation, hydration, hydratization	Chemical: addition of water to a C-C double bond. Physiological: quantity and distribution of the water in the body; cp. dehydration, hyperhydration.
Hyperaldsteronism	Excess secretion of Aldosterone from the adrenal cortex; causes excess secretion of aldosterone from the adrenal cortex; causes hypernatremia, hypocalemia, hypercaliuria and metabolic alkalosis (hypochloridemia) among other things.
Hyperglycemia	Glucose content of the blood serum exceeds 10 mg/dL (6.7 mmol/L).
Hyperhydration, hyperhydratization	Excess overall water content of the body.
Hyperosmolarity	Increased osmolarity (quantity of osmotically active articles per liter of solution in mol) in the blood plasma.
Hyperoxia	Elevated partial pressure of oxygen in the blood caused by inhaling a mixture of air with elevated oxygen concentration. Prolonged exposure can lead to pulmonary fibrosis.
Hyperparathyroidism	Hyperfunction of the parathyroid glands with increased formation of Parathormone; causes hypercalcemia among other things.
Hypertonic solution	Contains a higher concentration of dissolved particles than blood plasma (s. *isotonia*).
Hypoglycemia	The glucose content of the blood serum is below the value corresponding to the respective age.
Hypopituitarism	Insufficiency of the anterior lobe of the hypophysis. Depending on the extent of destruction or displacement of the tissue, the endocrinous functions of the anterior lobe of the hypophysis are absent which affect the functions of other endocrinous organs. Besides many other effects, this results in increased glucose consumption.

Hypotonic solution	Contains a smaller concentration of dissolved particles than blood plasma (s. *isotonia*).
Hypovolemia	Reduction of the circulating blood quantity, e.g., due to severe loss of water.
Hypoxemia	Reduced oxygen concentration per volume unit of blood; classified into hypoxic hypoxemia (due to respiratory insufficiency), toxic hypoxemia (due to exposure to poison) or anemic hypoxemia (due to reduced hemoglobin concentration).
Hypoxia	A reduction of tissue oxygen, estimated based on state of oxemis (blood) and other clinical and laboratory information.
Iatrogenic	Caused by diagnostic or therapeutic exposure.
Intestinal	Concerning the gastrointestinal tract.
Ions	Electrically charged particles (cations and anions) generated by electrolytic dissociation.
Isotonia	Equality of two solutions with respect to the effective osmotic pressure. Blood plasma-related isotonic solutions contain dissolved particles at an estimated concentration of 290 mosmol/L (e.g., 0.9% aqueous NaCl solution).
Ketone bodies	Collective term for diacetic acid, βHydroxy-butyric acid and Acetone; Ketone bodies are formed as a result of increased lipolysis, as in insulin deficiency.
Ketonuria	Secretion of ketone bodies in the urine.
Malabsorption	Weak digestion, impaired resorption of nutrients in the intestine due to various causes.
Metabolites	Intermediate products of the metabolism or compounds synthesized by the organism.
Mitochondria	Cell organelles responsible for energy recovery (oxidation of nutrients).
Myocarditis	Inflammatory disease of the cardiac muscle.
Oliguria	Reduced urine secretion (less than 500 mL/24 hours); opposite to polyuria.
Osmolarity	Quantity of dissolved particles per kilogram of water.
Osmolarity	Quantity of dissolved particles per liter of water.
Osmosis	Diffusion through a permeable or semipermeable membrane.
Oxidation	Chemical process during which electrons are withdrawn from a substance (formerly: union of an element or a compound with oxygen—resulting in the reference to the term “oxide”). In contrast, oxygenation refers to the accumulation of oxygen without a change in the oxidation numbers.
Parameter	Measured quantity.
Perfusion	Pulmonary perfusion.
Permeability, permeable	Permeability of biological membranes.
pH value	The negative decadic logarithm (p) of the hydrogen ion concentration (H). A pH of 7 is referred to as neutral pH. Solutions with a pH of <7 are referred to as acids and solutions with a pH of >7 are referred to as base/lye.

pK value	The pK value represents the dissociation constant of a solution. p refers to the negative decadic logarithm and K to the ion product of the solution. If the pH and pK values are identical, the acid is 50% dissociated.
Plasma	Blood plasma: 55% of the total blood content; cell-free.
Polycythemeia rubra vera, polycythemeia	Syn.: Morbus Vaquez-Osler; irreversible proliferation of the blood-forming system with unlimited increase in the number of erythrocytes, thrombocytes and granulocytes.
Polydipsia	Increased thirst and increased fluid intake.
Polyglobulia	Increase in the number of erythrocytes.
Polyuria	Secretion of a pathologically increased urine quantity (more than 2000 mL/24 hours); opposite to oliguria.
Postprandial	After intake of food.
Protons	Hydrogen ion, H^+ ions.
Pulmonary	Concerning the lungs.
Reduction	Process in which electrons are transferred to a substance (formerly used term for oxygen withdrawal).
Renal	Concerning the kidneys.
Respiratory	Concerning the lungs.
Retina	Retina of the eye.
Thalassemia	Congenital hemeolytic form of anemia. It is genetically prevalent in ethnic groups along the Mediterranean Sea shores. The condition is characterized by a dominant congenital metabolic defect of the α- and more commonly the β-protein chains of the hemoglobin.
Tubular	Concerning the tubule (renal tubule).
Uremia	Uremia, terminal renal failure.
Ureterosigmoid–ostomy	Use of bypassed intestinal segments for urinary secretion (in this case: the sigma). The specific properties of the intestinal mucosa remain and can cause clinical symptoms, e.g., hyperchloridaemic acidosis, electrolyte shifts, dehydration.
Ventilation	Ventilation, aeration—here: ventilation of the alveoli.

Record of figures

Pre-Examination considerations

Acid-base metabolism

Oxygen status

1. Dry outside air with volume ratios and partial pressures of the gases.
   Source: Siemens Healthineers.
2. Diagram “From oxygen in the air to the mitochondria”
   Source: Siemens Healthineers. Diagram © R.F. Moran.
3. O_2 gradient between outside air and alveolar air.
   Source: Siemens Healthineers.
4. Alveolar pulmonary diffusion.
   Source: Siemens Healthineers.
5. Diagram of the hemoglobin structure.
   Source: Siemens Healthineers.
6. Physiologic hemoglobin types and hemoglobin fractions.
   Source: Siemens Healthineers.
7. Oxygen dissociation curve and diagram of the respective oxygenation steps of hemoglobin.
   Source: Siemens Healthineers.
8. Left and right shift of the oxygen dissociation curve caused by various factors.
   Source: Siemens Healthineers.
9. Structure of an amperometric cell.
   Source: Siemens Healthineers.
10. Influence of non-oxygenizeable hemoglobin fractions on the oxygen content.
    Source: Siemens Healthineers.
11. Absorption spectrums of hemoglobin fractions.
    Source: Siemens Healthineers.
12. CO-elimination.
    Source: Siemens Healthineers.
13. Relationship and dependence of the parameters PO_2, FO_2Hb and ctO_2 among one another.
    Source: modified according to Zander, R., Mertzlufft, F.O.: Der Sauerstoffstatus des arteriellen Blutes. (Oxygen status of arterial blood). Karger Verlag, Germering, 1988.
14. Parameter changes in disorders of the oxygen transport.
    Source: modified according to Zander, R., Mertzlufft, F.O.:
    Der Sauerstoffstatus des arteriellen Blutes.
    (Oxygen status of arterial blood). Karger Verlag, Germering, 1988.

Electrolytes

1. Distribution of ions in blood plasma, interstitial and intracellular fluid.
   Source: Siemens Healthineers.
2. Disorders of the water and electrolyte metabolism.
   Source: Siemens Healthineers.
3. The “sodium-potassium-pump”.
   Source: Siemens Healthineers.
4. Estimated concentrations of electrolytes in the blood plasma, interstitium and cell.
   Source: Siemens Healthineers.
5. Diagram of the measuring principle of flame atom emission spectrometry.
   Source: Siemens Healthineers.
6. Structure of a potentiometric cell.
   Source: Siemens Healthineers.
7. Calcium fractions of the serum.
   Source: Siemens Healthineers.

Metabolites

1. Energy distribution target values.
   Source: Siemens Healthineers.
2. Glucose decomposition.
   Source: Siemens Healthineers.
3. The “fate” of blood glucose in 1. healthy subjects, 2. type I diabetics,
   and 3. type II diabetics.
   Source: Siemens Healthineers.
4. Cori cycle.
   Source: Siemens Healthineers.
5. Wavelengths for total bilirubin values in neonates.
   Source: Siemens Healthineers.
6. Substances without determinable interference on the glucose values.
   Source: Siemens Healthineers.
7. Substances that affect the glucose measurement.
   Source: Siemens Healthineers.
8. Diabetic comas.
   Source: Siemens Healthineers.
9. Substances without determinable interference on the lactate value.
   Source: Siemens Healthineers.
10. Substances that affect the lactate measurement.
    Source: Siemens Healthineers.

Recommended literature (selection)

General and comprehensive

Bruhn, H. D., Fölsch, U. R.: Lehrbuch der Labormedizin (Handbook of laboratory medicine) Schattauer Verlag, Stuttgart, 1999.

Leuwer, M., Schürmeyer, T. H., Trappe, H.-J., Zuzan, O.: Checkliste Interdisziplinäre Intensivmedizin. (Checklist for interdisciplinary intensive medicine). Georg Thieme Verlag, Stuttgart, 1999.

Murphy, P.: Handbook of Critical Care. Science Press, London, 2000.

Pindur, G. und U.: Klinische Chemie und serologische Laboratoriumsdiagnostik. (Clinical chemistry and serologic laboratory diagnostics). Wissenschaftliche Verlagsgesellschaft mbH (2nd edition), Stuttgart, 1991.

Schmidt, R. F., Thews, G.: Physiologie des Menschen. (Physiology of humans). Springer Verlag (26th edition), Berlin, 1995.

Silbernagl, S., Despopoulos, A.: Taschenatlas der Physiology. (Pocket atlas of physiology). Georg Thieme Verlag (6th edition), Stuttgart, 2003.

Thomas, L.: Labor und Diagnose. (Laboratory tests and diagnosis). TH-Books Verlagsgesellschaft (5th edition), Frankfurt a. M., 1998.

Pre-Examination procedures

Bonini, P., Plebani, M., Ceriotti, F., Rubboli, F.: Errors in laboratory medicine. Clin. Chem. 48, 691–698, 2002.

Eichhorn, J. H., Moran, R. F., Cormier, A. D.: Blood Gas Pre-Analytical Considerations: Specimen Collection, Calibration and Controls. NCCLS Publications C 27-A, Villanova, 1992.

Moran, R. F., Bergkuist, C., Graham, G., Misiano, D., O'Connell, K., Sena, S.: Considerations in the simultaneous measurements of blood gases, electrolytes and related analytes in the whole blood. NCCLS Publications C46, Villanova, 1993.

Risch, A., Biedler, A., Mertzlufft, F.: Präanalytische Fehlersourcen bei der Bestimmung des arteriellen Sauerstoffpartialdrucks unter hypoxischen Bedingungen. (Pre-analytical error sources in the determination of the arterial partial pressure of oxygen under hypoxic conditions). Anaesthesist (Anaesthetist) 48, 533–537, 1999.

Risch, A., Biedler, A., Mertzlufft, F.: Auswirkung präanalytischer Fehler bei der Bestimmung des arteriellen Sauerstoffpartialdrucks auf Größe und Aussagekraft der $AaDO_2$. (Effects of pre-analytical errors in the determination of the arterial partial pressure of oxygen on the size and relevance of $AaDO_2$). Anaesthesist (Anaesthetist) 49, 29–33, 2000.

Shapiro, B. A., Harrison, R. A., Cane, R. D., Templin, R.: Clinical Applications of Blood Gases. Year Book Medical Publishers (4th edition), Chicago, 1988.

Acid-base metabolism

Davenport, H. W.: Säure-Basen-Regulation. (Acid-base regulation)
Georg Thieme Verlag, Stuttgart, 1979.

Müller-Plathe, O.: Säure-Basen-Haushalt und Blutgase.
(Acid-base metabolism and blood gases).
Georg Thieme Verlag (2nd edition), Stuttgart, 1982.

Rick, W.: Klinische Chemie und Mikroskopie. (Clinical chemistry and microscopy).
Springer Verlag (6th edition), Berlin, 1990.

Zander, R.: Anästhesiologie » Säure-Basen-Haushalt «. (Anaesthesiology » Acid-base metabolism « (Kochs, E., Krier, C., Buzello, W., Adams, H. A., editors), Georg Thieme Verlag, Stuttgart, 2001.

Oxygen status

Boemke, W., Krebs, M. O., Roussaint, R.: Die Blutgasanalyze. (Blood gas analysis).
Anaesthesist (Anaesthetist) 45, 289–310, 1996.

Gärtner, A.: Beatmungs- und Narkosetechniken. (Respiration and anaesthesia techniques).
Verlag TÜV Rheinland, 1993.

Schack, G., Hamann, H.: Blutgasanalyze. (Blood gas analysis) mta 14, 411–416, 1999.

Zander, R., Mertzlufft, F. O.: Der Sauerstoffstatus des arteriellen Blutes.
(Oxygen status of arterial blood). Karger Verlag Germering, 1988.

Zeile, G., Baake, M., Henrici, G.: Kompendium der praktischen Hämatologie.
(Compendium of practical hemeatology). GIT Verlag Ernst Giebler (2nd edition),
Darmstadt, 1983.

Electrolytes

Külpmann, W. R., Gerlach, H.: Elektrolytbestimmungen mittels ionensensitiver
Elektroden—eine Vergleichsstudie. (Electrolyte determination by means
of ion-sensitive electrodes—a comparative study). Bayer-interne Unterlagen, 1999
(Bayer-internal documents, 1999).

Külpmann, W. R., Stummvoll, H. K., Lehmann, P.: Elektrolyte: Klinik und Labor.
(Electrolytes: clinical and laboratory evaluations) Springer Verlag (2nd edition),
Vienna, 1997.

Lehrich, R. W., Moll, S., Luft, F. C.: Die Anionenlücke—ein einfaches und hilfreiches
Werkzeug in der Differentialdiagnose der metabolischen Azidose. (The anion gap—
a simple and useful tool in the differential diagnosis of metabolic acidosis).
Intensivmedizin (Intensive medicine) 36, 355–360, 1999.

Tuninger, B., Richards, P.: Wasser- und Elektrolythaushalt, Diagnostik und Therapie.
(Water and electrolyte metabolism, diagnostics and therapy). Georg Thieme Verlag
(5th edition), Stuttgart, 1985.

Metabolites

D'Orazio, P. A.: Interference by Thiocyanate on Electrochemical Biosensors for Blood Glucose. Clin. Chem. 42(7), 1124–1126, 1996.

Fogh-Anderson, N., Wimberly, P. D., Thode, J., Siggaard-Andersen, O.: Direct reading glucose electrodes detect the molarity of glucose in plasma and whole blood. Clin. Chim. Acta 189, 33–38, 1990.

Greiling, H., Gressner, A. M.: Lehrbuch der klinischen Chemie und Pathobiochemistry. (Handbook of clinical chemistry and pathobiochemistry). Schattauer Verlag (3rd edition), Stuttgart, 1995.

Krouwer, J., Maley, T. C., Moran, R. F., Rossi, D., Silvia, M.: Lactate Performance Comparison: The Ciba Corning 860 System versus Reference Methods, Reference Materials and the Ektachem 700 System. Bayerinterne Unterlagen, 1996 (Bayer-internal documents, 1996).

Mc Caffrey, R. R., D'Orazio, P. A., Mason, R. W., Maley, T. C., Edelman, P. G.: Biofunctional Membranes »Clinically Useful Biosensor Development«. (Butterfield, D. A., editors), Plenum Press, New York, 1996.

Schlebusch, H.: Dezentrale Blutglucosebestimmungen im Krankenhaus. (Regional blood glucose determinations at the hospital) DG Klinische Chemie Mitteilungen (DG notes on clinical chemistry) 27, volume 3/4, 91–103, 1996.

Zander, R.: Die klinische Bedeutung von Base Excess und Laktatkonzentration (Minisymposium). (Clinical significance of base excess and lactate concentration (mini symposium). Anästhesiol. Intensivmed. Notfallmed. Schmerzther. 37, 341–363, 2002 (Anaesthesiol. intensive and emergency medical pain management, 37, 341–363, 2002).

Regular values

Beale, R.: VO_2 und DO_2 während des kardiogenen Schocks und der Sepsis. (VO_2 and DO_2 during cardiogenic shock and sepsis) Anästhesiol. Intensivmed. Notfallmed. Schmerzther. Sonderheft 1/31, 22–25, 1996 (Anaesthesiol. intensive and emergency medical pain management, special issue 1/31, 22–25, 1996).

Wible, J. L., Petrie, R. H., Koons, A., Percz, A.: The clinical use of umbilical cord acid-base determinations in perinatal surveillance and management. Clin. Perinat. 9, 387–397, 1982.

Publication details

Publisher: Siemens Healthineers

Author: Dr. Patrizia Mikulcik

Editor: Dr. Patrizia Mikulcik
1st English edition, 2009.
This is a translation of the 3rd original.
German edition from 2007.

Co-Editor: Dr. Robert F. Moran, PhD, FCCM, FAIC, FACB, FIUPAC.

At Siemens Healthineers, our purpose is to enable healthcare providers to increase value by empowering them on their journey toward expanding precision medicine, transforming care delivery, and improving patient experience, all made possible by digitalizing healthcare.

An estimated 5 million patients globally benefit every day from our innovative technologies and services in the areas of diagnostic and therapeutic imaging, laboratory diagnostics, and molecular medicine, as well as digital health and enterprise services.

We are a leading medical technology company with over 120 years of experience and 18,000 patents globally. Through the dedication of more than 50,000 colleagues in 75 countries, we will continue to innovate and shape the future of healthcare.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

Siemens Healthineers Headquarters
Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
siemens-healthineers.com

Published by
Siemens Healthcare Diagnostics Inc.
Laboratory Diagnostics
511 Benedict Avenue
Tarrytown, NY 10591-5005
USA
Phone: +1 914-631-8000

Published by Siemens Healthcare Diagnostics Inc. · Order No. 40-20-DX-250-76 · 10-2020