Recent Advance

Interpretation of arterial blood gases

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Abstract

Measuring arterial blood gas is routinely performed in critically ill patients, and may unravel severe life-threatening acid-base disorders or hypoxemia. It provides the vital information about ventilation, oxygenation, and acid-base status in such persons. These three processes are intimately related to each other in achieving normal oxygenation and acid-balance in the body.

The interpretation of arterial blood gas requires a reasonable understanding of respiratory physiology and acid-base balance in the body. Hence, in the following section, first the role of alveolar ventilation, oxygenation, and the maintenance of acid-base homeostasis have been discussed. This is followed by a step-wise approach to analyze the acid-base disorders, if present.

The Arterial blood gas (ABG) measurement is performed in most patients admitted to intensive care units. It provides vital information about adequacy of oxygenation and acid-base homeostasis. Adequate ventilation is important not only for normal arterial oxygen tension (PaO_2), but also for the normal arterial CO_2 tension ($PaCO_2$). The measurement of pH states whether an acidemia (low pH) or alkalemia (high pH) is present.

The body is continuously producing acids as a byproduct of metabolism. About 1 mEq/Kg body weight of "fixed" or "non-volatile" acids (sulfuric acid, phosphoric acids, and other organic acids) are formed daily from the metabolism of dietary proteins (Kurtz et al, 1983) which are excreted through the kidneys. In addition, the body also produces CO_2 through the oxidative metabolism, which is eliminated by the lungs.

Thus, it is important that the arterial blood gases and pH are maintained within a narrow normal range. This is achieved by the close interaction of three basic processes, namely ventilation, oxygenation, and acid-base homeostasis. Before attempting to interpret the ABG, it is important to understand the role they play in maintaining the ABG values within the normal range.

1. Alveolar ventilation

The body produces about 15,000 to 20,000 mmol of CO_2 per day. About 90% of CO_2 is carried in the blood as HCO_3, about 5% as dissolved form, and the remaining CO_2 in the combination with hemoglobin. The CO_2 is ultimately carried to the lungs from where it is excreted. The measurement of $PaCO_2$ reflects the ratio of metabolic CO_2 production to alveolar ventilation. The relationship of CO_2 and VCO_2 is shown by the $PaCO_2$ equation

$$\mathbf{PaCO_2 = VCO_2 \times 0.863 \ / VA}$$

(where $PaCO_2$ is the partial pressure of dissolved CO_2 in blood, VCO_2 is the amount of CO_2 produced per minute, VA is alveolar ventilation (i.e. minute ventilation - dead space ventilation).

Thus, in case of alveolar hypoventilation due to any cause or ventilation/perfusion [V/Q] imbalance, the $PaCO_2$ increases (hypercapnia), whereas in hyperventilation its value decreases (hypocapnia). An elevated $PaCO_2$ value also lowers the PaO_2 by decreasing the partial pressure of oxygen in alveolar air (PAO_2) (as explained in alveolar gas equation later), and lowers the pH.

2. Oxygenation

The maintenance of normal partial pressure of oxygen in arterial blood (PaO_2) is vital for survival. This is achieved by diffusion of oxygen across the alveolar membrane:

(a) The diffusion of oxygen across the alveoli

The rate of diffusion of O_2 across the alveoli depends upon the partial pressure of oxygen in the alveolar air (PAO_2). The PAO_2 is always higher than the arterial PO_2 (PaO_2), This difference of partial pressure of oxygen between alveoli and arterial blood is denoted as PAO_2-PaO_2, or simply as $P(A\text{-}a)O_2$, and this is the driving pressure for diffusion of oxygen across the alveolar membrane. The relationship between PaO_2 and PAO_2 is derived from the simplified alveolar air equation as shown below.

$$\mathbf{PAO_2 = PIO_2 - 1.2\ (PaCO_2)}$$

(Where PAO_2 is the average alveolar PO_2; PIO_2 is the partial pressure of inspired oxygen in trachea. In this equation, the multiplication factor "1.2" is dropped when FIO_2 exceeds 60%).

$$\mathbf{PIO_2 = FIO_2\ (PB - 47)}$$

(Where FIO_2 is the fraction of inspired oxygen and PB is the barometric pressure of 760 mm Hg; and water vapor pressure at normal body temperature is 47).

The normal $P(A\text{-}a)O_2$ difference is due to a normal amount of ventilation/perfusion (V/Q) imbalance in the human lung which happens due to the gravity-related blood flow changes within the lungs. The normal value of $P(A\text{-}a)O_2$ ranges between 5 to 10 mm Hg in a person breathing room air, although it tends to increase with age, and a value even as high as 20 mm Hg is considered normal in an 80 yr old person.

It is easy to understand that hypoxemia can occur either due to alveolar hypoventilation or ventilation/perfusion

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(V/Q) mismatch in the lung. The increased V/Q mismatch is the commonest cause of hypoxemia in ICUs. Hypoventilation accounts for hypoxemia in cases in whom either the respiratory centre is severe depressed or the respiratory pump failure is present. Rarely, it may be due to low PAO_2 as at high-altitude.

Hypoxemia should always be interpreted on the basis of the $P(A\text{-}a)O_2$ value. The increased $P(A\text{-}a)O_2$ value is seen in conditions as in pneumonia, atelectasis, asthma, interstitial lung disease or pulmonary edema. The increased $P(A\text{-}a)O_2$ is also seen in right-to-left cardiac shunts.

Hypoxemia associated with normal $P(A\text{-}a)O_2$ is seen in hypoventilation such as drug overdose, coma, CNS depression, and sufficient respiratory muscle weakness due to any cause.

(b) The oxygen content of the blood

The oxygen is carried in the blood in two forms, the combined form with hemoglobin, and as a dissolved gas in the plasma. Most of the oxygen is carried in a chemically combined form with hemoglobin, whereas the dissolved form constitutes a very minute amount of the total oxygen content of the blood. One gram of hemoglobin, when fully saturated, combines with 1.34 ml of oxygen. Thus, a person with hemoglobin of 15 gm% will carry 15 x 1.34 = 20.1 ml of oxygen as carbamino compounds, whereas it will contain only 0.3 ml of oxygen in dissolved form, when the hemoglobin is fully saturated. The oxygen content can be measured directly or calculated by the oxygen content equation as shown here:

$$\mathbf{CaO_2 = (Hb \times 1.34 \times SaO_2) + (.003 \times PaO_2)}$$

(where Hb is in gm%; SaO_2 is percent saturation of hemoglobin with oxygen; and .003 is the solubility coefficient of oxygen in the plasma)

Here, it is also important to understand the oxyhemoglobin desaturation curve. As per this curve, at PaO_2 of 60 mm Hg, the hemoglobin is 90% saturated, and the oxygen content of blood is very close to normal values. Thus in critically ill patients, one should not try to achieve a higher $SaO_2 > 92\%$, if a patient needs an $FIO_2 > 0.6$ for a prolonged period.

3. Acid-base balance

The blood pH is maintained within a normal range through the interaction of blood buffers, lungs, and kidneys. The buffer systems include both bases and acids in the blood, which act instantaneously to prevent the change in pH. The lungs take few minutes, whereas the kidneys take a much longer time, usually 3 to 5 days to bring pH to normal.

The pH primarily depends upon the ratio of HCO_3^- to $H2CO_3$ as shown in the Henderson-Hasselbalch equation,

$$\mathbf{pH = pK + \log (HCO_3^-/.03 \times PaCO_2)}$$

(where the value of the constant pK is 6.4).

The acid-base disorders are primarily classified into metabolic and respiratory disorders, which are further sub-classified as acidosis or alkalosis depending upon whether $PaCO_2$ or HCO^-_3 is primarily affected. Acidemia is said to be present when the blood pH is less than 7.35, whereas, in alkalemia the pH is more than 7.45. The underlying processes causing acidemia and alkalemia are known as acidosis or alkalosis, respectively. It should be remembered that two or more acid-base disturbances can concurrently exit, for example, respiratory acidosis with metabolic alkalosis, or metabolic acidosis or alkalosis with another metabolic or respiratory disturbance.

(a) Respiratory acidosis

In respiratory acidosis, the increase in the $PaCO_2$ causes a fall in pH. Hypercapnia results when the $PaCO_2$ is more than 45 mm Hg, and is seen when the CO_2 excretion by lungs lags behind CO_2 production, resulting in positive CO_2 balance (Adrouge and Madias, 1998). It is mainly caused by hypoventilation or a severely low V/Q mismatch.

The CO_2 molecule is more lipid soluble than H^+, hence respiratory acid-base changes (acidosis or alkalosis) equilibrate across cell membrane far more rapidly than do primary metabolic acid-base changes (Laffey and Kavannah, 2009). Moreover, higher the base-line $PaCO_2$, the greater will be the rise in its value for a given fall in alveolar ventilation even when CO_2 production remains unchanged.

In acute hypercapnia, the plasma HCO_3^- concentration rises mainly by the HCO_3^+-Cl^- shift in the RBCs, and it increases by 1 mEq/L for each 10 mm Hg rise in $PaCO_2$. However, in chronic respiratory acidosis, the increase in plasma HCO_3^- is due to renal compensatory mechanism, and the rise is much higher (see table no. 1).

(b) Respiratory alkalosis

$PaCO_2$ represents the balance between the production and elimination of CO_2, and is maintained within a narrow physiologic range (Laffey and Kavanagh, 2009). A decrease in $PaCO_2$ increases the blood pH as defined by Handerson-Hasselbalch equation. Hypocapnia occurs when $PaCO_2$ is less than 35 mm of Hg, and it primarily reflects the rate of elimination of CO_2. Thus, the principal physiologic causes of hypocapnia, including pregnancy are related to hyperventilation (Lafey and Kavanagh, 2009). However, a temporary induction of hypocapnia is a potential life-saving strategy adopted in severe intracranial hypertension or neonatal pulmonary artery hypertension.

Hyperventilation is the main mechanism causing hypocapnia, as commonly seen in asthma, interstitial lung disease, or pulmonary edema. It is also a physiological response in metabolic acidosis of any cause contributing to

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a low $PaCO_2$ as discussed later in this article. Some drugs, particularly salicylates, xanthines, progesterone and beta-2 agonists cause hyperventilation by stimulating the respiratory centre. Moreover, hyperventilation is also commonly seen in fever, sepsis, and late stages of pregnancy. Some CNS conditions, particularly infections and tumors, may cause hypeventilation.

In respiratory alkalosis, there is a CO_2 wash out due to hyperventilation resulting in a low $PaCO_2$. Hence to maintain pH, the kidneys excrete more HCO_3. However, the renal compensation is a slow process and takes a few days to minimize the pH changes. The blood pH rarely exceed 7.55 in most cases of respiratory alkalosis, however marked alkalemia can be observed with inappropriately set ventilators, some psychiatric conditions, and some lesions of CNS (Adrogue and Madias, 1998).

(c) Metabolic acidosis

The metabolic acidosis results from either loss of bicarbonate or addition of strong acid(s) in the extracellular fluids. When an acid enters the plasma, it is neutralized by the blood buffers, including bicarbonate, and this results in a fall in serum HCO^-_3 concentration and pH. An arterial pH < 6.8 is often associated with death, although, lower pH values than this have been reported in few patients who survived.

The acute metabolic acidosis leads to hyperventilation which decreases the CO_2 level within a short time and brings pH towards normal. However, the $PaCO_2$ level usually does not fall lower than 10 mm Hg, even in severely acidotic patients (Fulop, 1998).

A complete understanding of acidosis will require the calculation of anion gap (AG). The metabolic acidosis is classified as increased anion gap acidosis, or a normal anionic gap (hyperchloremic) acidosis.

(i) Anion gap (AG)

The AG is the difference between the plasma concentration of major cations and anions. Conventionally, it is calculated as the difference between Na^+ and the sum of (Cl^- + HCO^-_3). The normal value of AG is 8 -14 mEq/L.

$$\textbf{Anion gap (AG)} = Na^+ - (Cl^- + HCO_3^-)$$

As the total number of cations in the plasma is always equal to that of anions to maintain the electroneutrality, the AG represents the unmeasured anions in the plasma (Emmett and Narins, 1977), and it primarily includes albumin, phosphate, sulfate, and organic acids (Rastegar, 2007). Most of the normal AG is due to albumin, and the normal AG will be smaller in hypoalbuminemia. As each gram% of albumin contributes 2.5 mEq/L to the AG, it should be corrected for the serum albumin concentration (Figge and Jabor, 1998). A low anion gap is also seen in halide (Bromide or iodide) intoxication, and multiple myeloma with cationic IgG paraproteinemia.

An increased AG almost always indicates metabolic acidosis. The most common cause of increased AG acidosis is due to addition of strong acids into the plasma, as in diabetic ketoacidosis, lactic acidosis, or alcoholic acidosis. Poisoning with salicylates, ethylene glycol, methanol, formaldehyde, or paraldehyde also causes increased AG acidosis. However, salicylate stimulates respiratory centre causing hyperventilation, thus respiratory alkalosis gets superadded to the primary metabolic acidosis. In chronic renal failure, the excretion of acids through kidneys is reduced causing an increase in AG. However, an increased AG may sometimes also be seen in alkalemia because of an increase in the net ionic charge on plasma proteins, and in dehydration because of increased serum protein concentration.

The hyperchloremic acidosis is caused by renal tubular acidosis or loss of HCO^-_3 from the gastrointestinal tract. Here, the Cl^- ions replace the HCO^-_3 ions lost in buffering H^+ ions to maintain electroneutrality. Renal causes for this condition include renal tubular acidosis type I, II, and IV, and chronic renal failure with GFR > 15-20 ml/min. The extra-renal causes for normal AG acidosis include diarrhea, pancreatic, and biliary fistulas.

(ii) Osmolar Gap

In some conditions of increased AG metabolic acidosis, the estimation of osmolar gap may uncover the presence of osmotically active substances. However, it should be used cautiously because osmolar gap have poor positive predictive value and negative predictive value, and are not considered good screening tests for toxic alcohol poisoning. In patients with excessively elevated osmolar gap, the presence of toxic alcohols should be confirmed by the laboratory methods.

The osmolar gap is defined as the difference between the measured osmolality and the calculated osmolarity. The osmolality is measured in the laboratory, whereas the calculated osmolarity uses the concentrations of sodium, glucose and blood urea nitrogen.

$$\textbf{Osmolar gap} = \textbf{measured osmolality} - \textbf{calculated osmolarity}$$
$$\textbf{Calculated osmolarity} = 2[Na^+] + \textbf{glucose}/18 + \textbf{BUN}/2.8)$$

The normal osmolar gap is less than 10. An increased osmolar gap indicates the presence of unmeasured osmoles, as seen in poisoning with methanol, ethylene glycol, paraldehyde, and isopropyl alcohol. Although mannitol increases serum osmolarity transiently, it does not have any effect on metabolic homeostasis.

(iii) The Delta Ratio ($\Delta AG/\Delta HCO^-_3$)Gap

The delta ratio may help in the assessment of increased AG metabolic acidosis to determine if a mixed acid-base disturbance is present. It is defined as the ratio of increased AG to increased bicarbonate concentration.

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Delta ratio = Δ Anion gap/ Δ HCO^-_3

(where Δ Anion gap is the difference between the measured AG and the normal AG, and ΔHCO^-_3 is the difference between the normal bicarbonate and the measured bicarbonate).

When a strong acid is added to plasma, it is neutralized by both bicarbonate and non-bicarbonate buffers present in extra- and intracellular compartments, resulting in a fall in serum HCO_3^- and a rise in the anion gap (Rastegar, 2007). However, most of the excess anions remain in the extracellualr fluids. Hence the increase in AG usually exceeds the fall in plasma HCO^-_3.

A delta ratio between 1 to 2 is seen in pure AG metabolic acidosis, however, in diabetic ketoacidosis, the excess ketones are excreted in the urine lowering the AG, and decreasing the effect of intracellular buffering, thus the delta ratio is close to 1:1. In lactic acidosis an average delta ratio is around 1.6. A delta ratio < 1 is seen in both high AG and normal AG metabolic acidosis. A delta ratio < 0.4 is usually seen in hyperchloremic acidosis. A delta ratio > 2 is seen in high AG metabolic acidosis with a concurrent metabolic alkalosis or a pre-existing compensated respiratory acidosis.

(d) Metabolic alkalosis

Metabolic alkalosis is common in hospitalized patients (Hodgkin et al, 1980). It occurs when there is a net accumulation of base within or the loss of acid from the plasma, which manifests with an increase in the blood pH and plasma bicarbonate. The metabolic alkalosis has a depressant effect on respiratory centre causing hypoventilation and a resultant increase in $PaCO_2$. Normally $PaCO_2$ increases by 0.5 to 0.7 mm Hg for every 1 mEq/L rise in plasma bicarbonate concentration (Javaheri and Kazemi, 1987). However, $PaCO_2$ rarely increases more than 60 mm Hg purely as a compensatory mechanism even in a severe metabolic alkalosis.

It is commonly caused whenever excessive chloride ions are lost from the gut, kidney, or skin, such as in vomiting, diuretic therapy, and nasogastric suctioning (Galla, 2000). It is also commonly caused by conditions where potassium is depleted in the body, as in primary or secondary mineralocorticoid excess. Chronic milk-alkali syndrome is now rarely a cause of metabolic alkalosis. The drugs, penicillin, carbenicillin, and ampicillin have also been implicated for this disturbnance. It is also seen after the successful treatment of ketoacidosis or lactic acidosis, as these anions are later metabolized to bicarbonate (Galla, 2000).

Compensation in acid-base disorders

As stressed earlier, the pH is maintained within a narrow range under physiologic conditions. According to the Henderson-Hasselbalch equation, the pH mainly depends upon the ratio of HCO^-_3/ H_2CO_3. Hence, an increase in HCO^-_3 is accompanied by a corresponding increase in $PaCO_2$ (H_2CO_3) value, and vice versa. The respiratory compensation for metabolic derangements is rapid, but the kidneys take about 3 to 5 days to compensate for respiratory disturbances. The table no. 1 shows the corresponding compensatory changes in various types of acid-base disorders.

Steps for interpretation of ABGs

A clinical history and physical examination is important before attempting to interpret the arterial blood gas (ABG) for acid-base balance. The three important values in an ABG, namely pH, $PaCO_2$, and HCO^-_3 will indicate the likely acid-base disorders, if present. One must also calculate the likely compensatory changes expected in the patient as shown in Table no. 1. If the compensatory changes are beyond the expected range, an additional acid-base disorder should be suspected. A systemic approach while interpreting ABG is necessary to unravel the acid-base disorders. And finally, PaO_2 will identify hypoxemic state, if present, and in a patient receiving mechanical ventilator, it is vital to check PaO_2 to check the adequacy of ventilator settings.

(1) First, look at the arterial pH. It will suggest whether an academia (pH < 7.35) or alkalemia (pH > 7.45) is present. However, in the presence of mixed acid-base disorder, the pH may be normal, e.g. a patient with COPD with respiratory acidosis may also develop metabolic alkalosis

Table no. 1. Compensatory changes in acid-base imbalances

Primary acid-base disorder	*Compensatory changes*
Acute respiratory acidosis	For every 10 mm Hg rise in $PaCO_2$, the HCO_3^- increases by 1 mEq/L
Chronic respiratory acidosis	For every 10 mm Hg rise in $PaCO_2$, the HCO_3^- increases by 3.5 mEq/L
Acute respiratory alkalosis	For every 10 mm Hg fall in $PaCO_2$, the HCO_3^- decreases by 2 mEq/L
Chronic respiratory alkalosis	For every 10 mm Hg fall in $PaCO_2$, the HCO_3^- decreases by 5 mEq/L
Metabolic acidosis	For each 1 mEq/L fall in HCO_3^-, the $PaCO_2$ decreases by 1.2 mm Hg, *or* $PaCO_2 = HCO_3^- + 15$, *or* $PaCO_2 = 1.5\ (HCO_3^-) + 8$ (Winter's formula)
Metabolic alkalosis	For each 1 mEq/L HCO_3^- increase, the $PaCO_2$ increases by 0.7 mm Hg

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due to diuretic use, and as a result may have a lesser fall in pH than expected.

(2) Next, check the $PaCO_2$ and HCO^-_3 values, and determine if the disturbance is respiratory or metabolic. A low HCO^-_3 will suggest metabolic acidosis, whereas a high $PaCO_2$ will indicate the presence of respiratory acidosis. In other words, in primary respiratory disturbances the pH and $PaCO_2$ change in opposite directions, whereas in metabolic disturbances they change in the same direction.

(3) Next, check the level of compensation as shown in the Table no. 1. and determine if the compensation is appropriate for the primary disturbance. If it is not so, it is likely that more than one acid-base disturbance is present. Remember that body can not overcompensate in order to normalize the pH. A normal pH in a patient with acid-base disorder usually indicates a mixed disorder.

(4) Calculate the anion gap (AG), if metabolic acidosis is suspected. Make for if albuminemia is present as discussed earlier. An AG more than 20 mEq/l strongly indicates an anion gap metabolic acidosis. Sometimes an increased AG may be the only clue to a metabolic acidosis. If the cause of increased AG is not obvious (for example absence of lactic acidosis, diabetic ketoacidosis, or renal impairment) and the ingestion of some toxic material is suspected, calculate the osmolar gap as discussed earlier.

(5) In presence of increased AG, calculate the delta ratio ($\Delta AG/\Delta HCO^-_3$). In an uncomplicated AG metabolic acidosis, it is between 1 and 2. A value of delta ratio outside this range suggests the presence of another metabolic disturbance. The delta ratio < 1 indicates the presence of a simultaneous non-AG metabolic acidosis, whereas a delta raio > 2 indicates the presence of a metabolic alkalosis too.

(6) Finally check the PaO_2 in relation to the inspired oxygen concentration (FIO_2) as discussed in alveolar air equation. In acute lung injury (ALI) the ratio PaO_2/FIO_2 < 300, and in ARDS it is < 200.

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