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Acid base balance disturbances

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The importance of hydrogen Ion concentration in he body

Hydrogen ion concentration has a widespread effect on the function of the body's enzyme systems. The hydrogen ion is highly reactive and will combine with bases or negatively charged ions at very low concentrations. Proteins contain many negatively charged and basic groups within their structure. Thus, a change in pH will alter the degree ionization of a protein, which may in turn affect its functioning. At more extreme hydrogen ion concentrations a protein's structure may be completely disrupted (the protein is then said to be denatured).

The importance of hydrogen ion concentration

- Enzymes function optimally over a very narrow range of hydrogen ion concentrations. For most enzymes this optimum pH is close to the physiological range for plasma (pH= 7.35 to 7.45, or [H+]= 35 to 45nmol/l).
- Although most enzymes function optimally around physiological pH it should be noted that a few enzymes function best at a much higher hydrogen ion concentration (ie: at a lower pH). The most notable of these enzymes is pepsin, which works best in the acid environment of the stomach - optimum pH 1.5-3 or [H^+]= 3-30 million nanomol/l.

Production of hydrogen ions

- The processes of metabolism generate hydrogen ions. Small amounts (40-80mmol/24h) are formed from the oxidation of amino acids and the anaerobic metabolism of glucose to lactic and pyruvic acid. Far more acid is produced as a result of carbon dioxide (CO_2) release from oxidative (aerobic) metabolism - 15,000mmol/24h (15x103 mmol/24h). Although CO_2 does not contain hydrogen ions it rapidly reacts with water to form carbonic acid (H_2CO3), which further dissociates into hydrogen and bicarbonate ions ($HCO3^-$).
- This reaction is shown below:

$$\mathbf{CO_2 + H_20 <= H_2CO3 => HCO3^- + H^+}$$

- This reaction occurs throughout the body and in certain circumstances is speeded up by the enzyme carbonic anhydrase. Carbonic acid is a weak acid and with bicarbonate, its conjugate base, forms the most important buffering system in the body.
- Acids or bases may also be ingested, however, it is uncommon for these to make a significant contribution to the body's hydrogen ion concentration, other than in deliberate overdose.

Control of hydrogen ion concentration

With hydrogen ion concentration being so critical to enzyme function, the body has sophisticated mechanisms for ensuring pH remains in the normal range. Three systems are involved: blood and tissue buffering, excretion of CO_2 by the lungs and the renal excretion of H^+ and regeneration of $HCO3^-$.

1. Buffers

As we have seen, buffers are able to limit changes in hydrogen ion concentration. This prevents the large quantities of hydrogen ions produced by metabolism resulting in dangerous changes in blood or tissue pH.

- **a) Bicarbonate**
  This is the most important buffer system in the body. Although bicarbonate is not an efficient buffer at physiological pH its efficiency is improved because CO_2 is removed by the lungs and bicarbonate regenerated by the kidney. There are other buffers that act in a similar way to bicarbonate, for example: hydrogen phosphate ($HPO3^{2-}$), however, these are present in smaller concentrations in tissues and plasma.
- **b) Proteins**
  Many proteins, and notably albumin, contain weak acidic and basic groups within their structure. Therefore, plasma and other proteins form important buffering systems. Intracellular proteins limit pH changes within cells, whilst the protein matrix of bone can buffer large amounts of hydrogen ions in patients with chronic acidosis.

Control of hydrogen ion concentration

- **c) Haemoglobin**
  Haemoglobin (Hb) is not only important in the carriage of oxygen to the tissues but also in the transport of CO_2 and in buffering hydrogen ions *(The physiology of oxygen delivery, Update in anaesthesia 1999; 10:8-14)*.

✓Haemoglobin binds both CO2 and H+ and so is a powerful buffer. Deoxygenated haemoglobin has the strongest affinity for both CO2 and H+; thus, its buffering effect is strongest in the tissues. Little CO2 is produced in red cells and so the CO2 produced by the tissues passes easily into the cell down a concentration gradient. Carbon dioxide then either combines directly with haemoglobin or combines with water to form carbonic acid. The CO2 that binds directly with haemoglobin combines reversibly with terminal amine groups on the haemoglobin molecule to form carbaminohaemoglobin. In the lungs the CO_2 is released and passes down its concentration gradient into the alveoli.

✓The buffering of hydrogen ions formed from carbonic acid is more complicated.In the tissues, dissolved CO_2 passes into the red blood cell down its concentration gradient where it combines with water to form carbonic acid. This reaction is catalysed by the enzyme carbonic anhydrase. Carbonic acid then dissociates into bicarbonate and hydrogen ions. The hydrogen ions bind to reduced haemoglobin to form HHb. Bicarbonate ions ($HCO3^-$) generated by this process pass back into the plasma in exchange for chloride ions (Cl^-). This ensures that there is no net loss or gain of negative ions by the red cell. In the lungs this process is reversed and hydrogen ions bound to haemoglobin recombine with bicarbonate to form CO_2 which passes into the alveoli. In addition, reduced Hb is reformed to return to the tissues.

Buffers concentration and its proportion on the whole buffer capacity of extracellular space in healthy person		
	Concentration (mM, mean)	**Buffer capacity (mM to pH unit)**
Bicarbonate	24 (67%)	50 (82%) during constant p_aCO_2
Other buffers	12 (33%)	11 (18%)
Hemoglobin	7	9
Plasma proteins	4	2
Phosphates	1	0.4
All	36 (100%)	61 (100%)

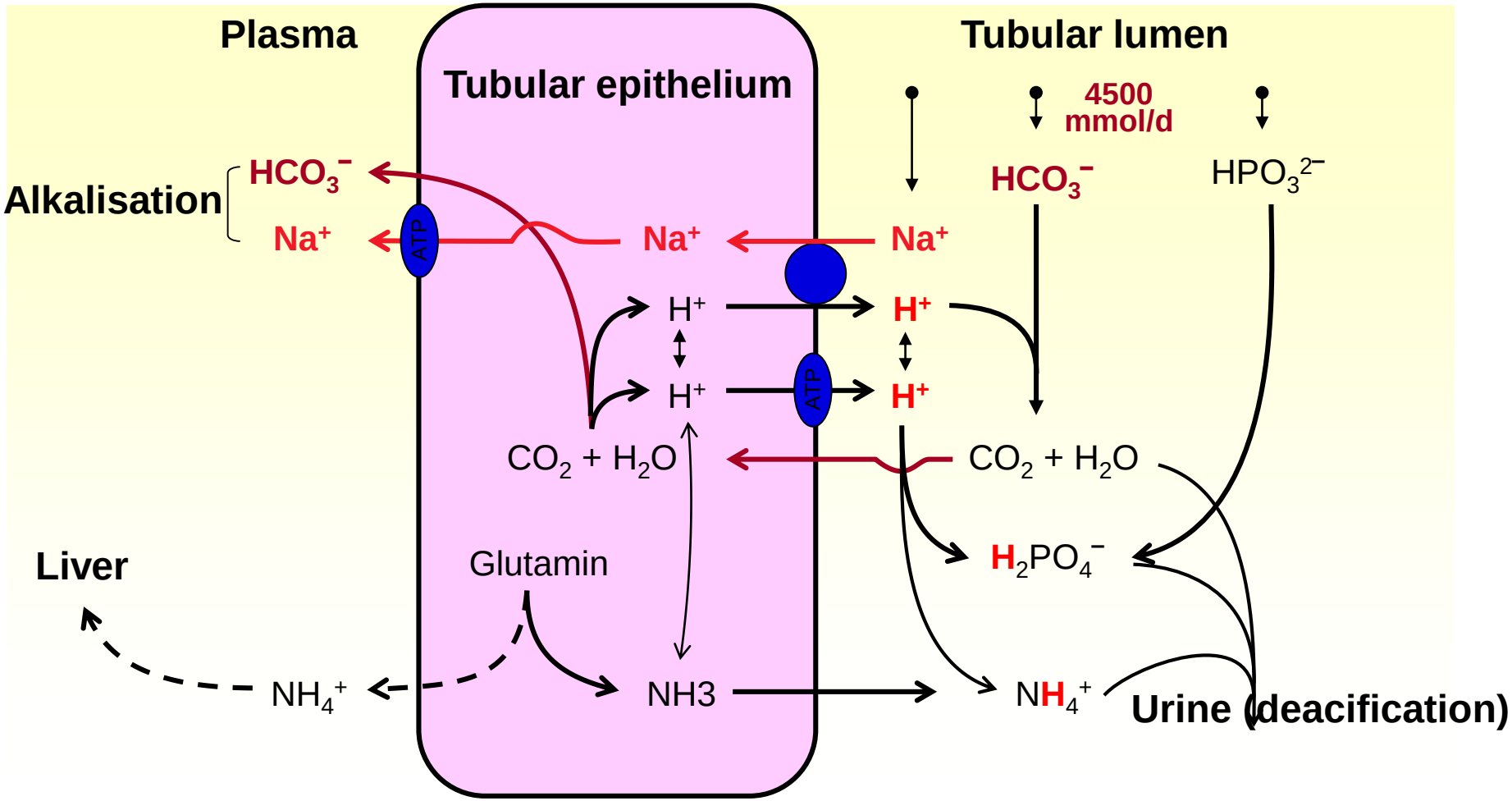
2. Carbon Dioxide Elimination

- CO_2 is responsible for the majority of hydrogen ions produced by mefabolism. Therefore, the respiratory system forms the single most important organ system involved in the control of hydrogen ions. From respiratory physiology it should be remembered that the arterial partial pressure of CO_2 (p_aCO_2) is inversely proportional to alveolar ventilation (ie: if alveolar ventilation falls the p_aCO_2 rises). Therefore, relatively small changes in ventilation can have a profound effect on hydrogen ion concentration and pH. An acute rise in pCO_2 of 1 kPa results in a 5.5nmol/l rise in the hydrogen ion concentrafion (resulting in a fall in plasma pH from 7.4 to 7.34).
- The importance of p_aCO_2 and hydrogen ion concentration is underlined by the fact that the control of ventilation is brought about by the effect of CO_2 on cerebrospinal fluid (CSF) pH.

3. Excretion of hydrogen ions in the kidneys

- Hydrogen ions are actively secreted in the proximal and distal tubules, but the maximum urinary [H+] is around 0.025mmol/l (pH 4.6). Therefore, in order to excrete the 30-40mmol of H+ required per day, a urine volume of 1200 litres would have to be produced. However, buffering of hydrogen ions also occurs in the urine. This allows the excretion of these large quantities of H+ without requiring such huge urine volumes. Hydrogen ion secretion occurs against a steep concentration gradient, 40nmol/l in plasma against up to 25000nmol/l (25x103nmol/l) in urine. Therefore, hydrogen ion secretion is an active process and requires energy in the form of ATP.
- The predominant buffers in the urine are phosphate ($HPO4^{2-}$) and ammonia (NH3). Phosphate is freely filtered by the glomerulus and passes down the tubule where it combines with H^+ to form H_2PO4^-. Hydrogen ions are secreted in exchange for sodium ions; the energy for this exchange comes from the sodium-potassium ATPase that maintains the concentration gradient for sodium.

H^+ elimination by kidneys



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Electrolytes

- **Sodium/Potassium:** sodium reabsorption and hydrogen ion excretion are interlinked. Sodium reabsorption is controlled by the action of aldosterone on ion exchange proteins in the distal tubule. These ion exchange proteins exchange sodium for hydrogen or potassium ions. Thus, changes in aldosterone secretion may result in altered acid secretion.
- **Chloride:** The number of positive and negative ions in the plasma must balance at all times. Aside from the plasma proteins, bicarbonate and chloride are the two most abundant negative ions (anions) in the plasma. In order to maintain electrical neutrality any change in chloride must be accompanied by the opposite change in bicarbonate concentration. Therefore, the chloride concentation may influence acid base balance.

Definition of ABB disturbances

- according to the type
- according to the stage of compexity
- according to the compensation state

ABB disturbances according to type

Acidosis (↓pH)

- respiratory (base problem at the level of respiration)
- metabolic (base problem at the level of GIT and/or kidneys)

Alkalosis (↑pH)

- respiratory (base problem at the level of respiration)
- metabolic (base problem at the level of GIT and/or kidneys)

ABB disturbances according to stage of complexity

Acidosis (⬇pH)

- simple
- mixed (more disturbances at the same time; in the same or opposite direction)
- combined (mixed disturbance with dysregulation of electrolytes and other ABB parameters)

Alkalosis (⬆pH)

- simple
- mixed (more disturbances at the same time; in the same or opposite direction)
- combined (mixed disturbance with dysregulation of electrolytes and other ABB parameters)

Compensation

The systems controlling acid base balance are interlinked.

- Rapid chemical buffering: this occurs almost instantly but buffers are rapidly exhausted, requiring the elimination of hydrogen ions to remain effective.
- Respiratory compensation: the respiratory centre in the brainstem responds rapidly to changes in CSF pH. Thus, a change in plasma pH or p_aCO_2 results in a change in ventilation within minutes.
- Renal compensation: the kidneys respond to disturbances in acid base balance by altering the amount of bicarbonate reabsorbed and hydrogen ions excreted. However, it may take up to several days for bicarbonate concentration to reach a new equilibrium.These compensatory mechanisms are efficient and often return the plasma pH to near normal. However, it is uncommon for complete compensation to occur and over compensation does not occur.

Compensatory mechanisms of ABB

Respiratory

- Rapid changes are buffered locally by buffer systems
- Respiration disturbances are compensated metabolically

Metabolic

- Rapid changes are buffered locally by buffer systems
- Metabolic disturbances are compensated respirationally and later metabolically

ABB disturbances according to state of compensation

Acidosis

- compensated (pH 7. 35 - 7. 45)
- decompensated (↓pH)
- non-compensated (↓pH)
- partly compensated (↓pH)
- overcompensated (↑pH)

Alkalosis

- compensated (pH 7. 35 – 7. 45)
- decompensated (↑pH)
- non-compensated (↑pH)
- partly compensated (↑pH)
- overcompensated (↓pH)

ABB disturbances – compensation explication

- compensated = normal pH, shifts in pCO_2, SB, AB, BE values and oth.
- partly compensated = abnormal pH, shifts in other ABB parameters, state of ABB is going better (trend to pH compensation can be observed)
- decompensated = abnormal pH, shifts in other ABR parameters, state of ABB is going worse
- non-compensated = abnormal pH, other ABB parameters shifts don´t reflect presence of compensatory mechanisms (severe states)
- overcompensated – usually iatrogenic, non-adequate treatment (too quick and/or too intensive – it is necessary to give sufficient time for participation of gentle buffer controlling mechanisms).

Respiratory acidosis

This results when the PaCO2 is above the upper limit of normal, >6kPa (45mmHg).

- Respiratory acidosis is most commonly due to decreased alveolar ventilation causing decreased excretion of CO2.
- Less commonly it is due to excessive production of CO_2 by aerobic metabolism.
- a) Inadequate CO_2 excretion: the causes of decreased alveolar ventilation are numerous. Many of the causes of decreased alveolar ventilation are of interest to theanaesthetist and many are under our control.
- b) Excess CO_2 production: respiratory acidosis is rarely caused by excess production of CO_2. This may occur in syndromes such as malignant hyperpyrexia, though a metabolic acidosis usually predominates. More commonly, modest overproduction of CO_2 in the face of moderately depressed ventilation may result in acidosis. For example, in patients with severe lung disease a pyrexia or high carbohydrate diet may result in respiratory acidosis.

Causes of respiration acidosis

Central	Brain injury: CMP, trauma Drugs: anesthethics, opioids Sleep apnoe
Airways obstruction	Foreign body
Lung diseases	CHOPN, asthma, pneumothorax
Thorax	Deformities: skoliosis High state of diaphragm: obesity, pregnancy, ascites Muscle weakness: muscle relaxantia, myastenia gravis, electrolyte disturbances
Peripheral neurological diseases	Nerve injury: spinal chord trauma, n. frenicus Neuropathies: poliomyelitis, low motor neuron disease Drugs: epidural local anesthesia

Respiratory alkalosis

Results from the excessive excretion of CO_2, and occurs when the p_aCO_2 is less than 4.5kPa (34mmHg).

- This is commonly seen in hyperventilation due to anxiety states. In more serious disease states, such as severe asthma or moderate pulmonary embolism, respiratory alkalosis may occur. Here hypoxia, due to ventilation perfusion (V/Q) abnormalities, causes hyperventilation (in the spontaneously breathing patient). As V/Q abnormalities have little effect on the excretion of CO_2 the patients tend to have a low arterial partial pressure of oxygen (p_aO_2) and low p_aCO_2.

Metabolic acidosis

May result from either an excess of acid or reduced buffering capacity due to a low concentration of bicarbonate. Excess acid may occur due increased production of organic acids or, more rarely, ingestion of acidic compounds.

a) Excess H+ production: this is perhaps the commonest cause of metabolic acidosis and results from the excessive production of organic acids (usually lactic or pyruvic acid) as a result of anaerobic metabolism. This may result from local or global tissue hypoxia. Tissue hypoxia may occur in the following situations:

- Reduced arterial oxygen content: for example anaemia or reduced PaO2.
- Hypoperfusion: this may be local or global. Any cause of reduced cardiac output may result in metabolic acidosis (eg: hypovolaemia, cardiogenic shock etc). Similarly, local hypoperfusion in conditions such as ischaemic bowel or an ischaemic limb may cause acidosis.
- Reduced ability to use oxygen as a substrate. In conditions such as severe sepsis and cyanide poisoning anaerobic metabolism occurs as a result of mitochondrial dysfunction.
- Another form of metabolic acidosis is diabetic ketoacidosis. Cells are unable to use glucose to produce energy due to the lack of insulin. Fats form the major source of energy and result in the production of ketone bodies (aceto- acetate and 3-hydroxybutyrate) from acetyl coenzyme A. Hydrogen ions are released during the production of ketones resulting in the metabolic acidosis often observed.

b) Ingestion of acids: this is an uncommon cause of metabolic acidosis and is usually the result of poisoning with agents such as ethylene glycol (antifreeze) or ammonium chloride.

Metabolic acidosis

c) Inadequate excretion of +: this results from renal tubular dysfunction and usually occurs in conjunction with inadequate reabsorption of bicarbonate. Any form of renal failure may result in metabolic acidosis. There are also specific disorders of renal hydrogen ion excretion known as the renal tubular acidoses.
Some endocrine disturbance may also result in inadequate H+ excretion e.g. hypoaldosteronism. Aldosterone regulates sodium reabsorption in the distal renal tubule. As sodium reabsorption and H+ excretion are linked, a lack of aldosterone (eg: Addison's disease) tends to result in reduced sodium reabsorption and, therefore, reduced ability to excrete H+ into the tubule resulting in reduced H+ loss. The potassium sparing diuretics may have a similar effect as they act as aldostrone antagonists.

d) Excessive loss of bicarbonate: gastro- intestinal secretions are high in sodium bicarbonate. The loss of small bowel contents or excessive diarrhoea results in the loss of large amounts of bicarbonate resulting in metabolic acidosis. This may be seen in such conditions as Cholera or Crohn's disease.

Metabolic alkalosis

May result from the excessive loss of hydrogen ions, the excessive reabsorption of bicarbonate or the ingestion of alkalis.

- **a) Excess H+ loss:** gastric secretions contain large quantities of hydrogen ions. Loss of gastric secretions, therefore, results in a metabolic alkalosis. This occurs in prolonged vomiting for example, pyloric stenosis or anorexia nervosa.
- **b) Excessive reabsorption of bicarbonate:** as discussed earlier bicarbonate and chloride concentrations are linked. If chloride concentration falls or chloride losses are excessive then bicarbonate will be reabsorbed to maintain electrical neutrality. Chloride may be lost from the gastro-intestinal tract, therefore, in prolonged vomiting it is not only the loss of hydrogen ions that results in the alkalosis but also chloride losses resulting bicarbonate reabsorption. Chloride losses may also occur in the kidney usually as a result of diuretic drugs. The thiazide and loop diuretics a common cause of a metabolic alkalosis. These drugs cause increased loss of chloride in the urine resulting in excessive bicarbonate reabsorption.
- **c) Ingestion of alkalis:** alkaline antacids when taken in excess may result in mild metabolic alkalosis. This is an uncommon cause of metabolic alkalosis.

Metabolic acidosis

Aniont gap

- Na^+ (140) + K^+(5) = Cl^- (105)+HCO_3^-(25) + Gap
- Gap increases in metabolic acidosis, when some special movement of ions is realised in extracellulart fluid.

Metabolic acidosis
Aniont gap < 8 mmol/l

- Hypoalbuminemia (decrease of unmeasured anions)
- Multiple myeloma(increase of IgG paraproteins as unmeasured cations)
- Increase of unmeasured cations (↑K+, ↑Ca++, ↑Mg++, Li+ poisoning)

Metabolic acidosis
Aniont gap >12 mmol/l

Presence of unmeasured metabolic anions

- Diabetic ketoacidosis
- Alcoholic ketoacidosis
- Lactate acidosis
- Starvation
- Kindney insufficiency

Presence of drugs and/or metabolic anions (poisoning by salicylates, methanol and ethylen glycol

Metabolic acidosis
Aniont gap 8-12 mmol/l

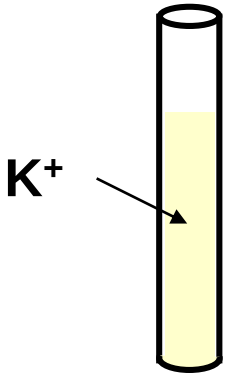
Loss of bicarbonates

- Diarrhea
- Loss of pancreatic juice
- Ileostomy

Chlorides retention

- Renal tubular acidosis
- Parenteraů nutrition (arginin and lysin)

pH and plasma K^+ concentration



pH	Normální hodnoty K^+ (mmol/l)
6,8	6,5 – 8,0
7,1	5,5 – 6,5
7,3	5,2
7,4	**4,5**
7,7	3,5

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Hyperkalemia

- Plasmatic concentration > 5.2 mmol / l (normal interval: 3.7-5.2 mmol / l).
- Hyperkalemia above 7.2 mmol / l can cause diastolic cardiac arrest.
- *Symptoms*: nausea, irregular heart rate, without symptoms

Causes of hyperkalemia	Causes of hypokalemia
High-kalium load due to special diet: too much bananas, tomatos, oranges, salt substituents or parenteral administration	Low-kalium diet
Diminished kalium excretion (low concentration of hormones)	Alkolosis
Acidosis	Hypomagnesemia
Excessive endogeneous kalium load (trauma, injuries, burns, tumors)	Increased kalium excretion (usually associated with water loss: vomiting, diarrhea, medications like laxatives, loop diuretics or high concentration of hormones)
Genetic defects in ion channels	

Alkalosis and ions homeostasis

- Alkalosis, especially chronic , can be associated with decrease K^+ ions in the body.
- Vomiting and some diuretics can cause hypochloremic alkalosis leading to severe K^+ depletion.
- During K^+ depletion „paradox aciduria“ can occur in urine when kidney tries to replace K^+ excretion by H^+ excretion.

Alkalosis and ions homeostasis

- Alkalosis causes dissociation of H^+ ions from proteins.
- Therefore, Ca^{2+} are bound on free negative groups of the proteins. It is leading to acute critical decrease of ionised calcium level.
- This is leading to tetany and seizures which could be fatal.

Base ABR parameters

- pH
- pCO_2
- pO_2
- The base excess (BE): is defined as the amount of acid (in mmol) required to restore 1 litre of blood to its normal pH, at a pCO_2 of 5.3kPa (40mmHg). During the calculation any change in pH due to the PCO_2 of the sample is eliminated, therefore, the base excess reflects only the metabolic component of any disturbance of acid base balance. If there is a metabolic alkalosis then acid would have to be added to return the blood pH to normal, therefore, the base excess will be positive. However, if there is a metabolic acidosis, acid would need to be subtracted to return blood pH to normal, therefore, the base excess is negative.
- The actual bicarbonate – bicarbonate concentration at actual pCO_2
- The standard bicarbonate: this is similar to the base excess. It is defined as the calculated bicarbonate concentration of the sample corrected to a pCO_2 of 5.3kPa (40mmHg). Again abnormal values for the standard bicarbonate are only due the metabolic component of an acid base disturbance. A raised standard bicarbonate concentration indicates a metabolic alkalosis whilst a low value indicates a metabolic acidosis.

Interpretation of results:

- First examine the pH; as discussed earlier a high pH indicates alkalemia, whilst a low pH acidemia.
- Next look at the pCO_2 and decide whether it accounts for the change in pH. If the pCO_2 does account for the pH then the disturbance is a primary respiratory acid base disturbance.
- Now look at the base excess or standard bicarbonates) to assess any metabolic component of the disturbance.
- Finally, one needs to decide if any compensation for the acid base disturbance has happened. Compensation has occurred if there is a change in the pCO_2 or base excess in the opposite direction from that which would be expected from the pH.
- For example in respiratory compensation for a metabolic acidosis the pCO_2 will be low. A low pCO_2 alone causes an alkalaemia (high pH). The body is therefore using this mechanism to try to bring the low pH caused by the metabolic acidosis back towards normal.
- By now the complexity of acid base disturbance should be clear!! As in many complex concepts examples may clarify matters.

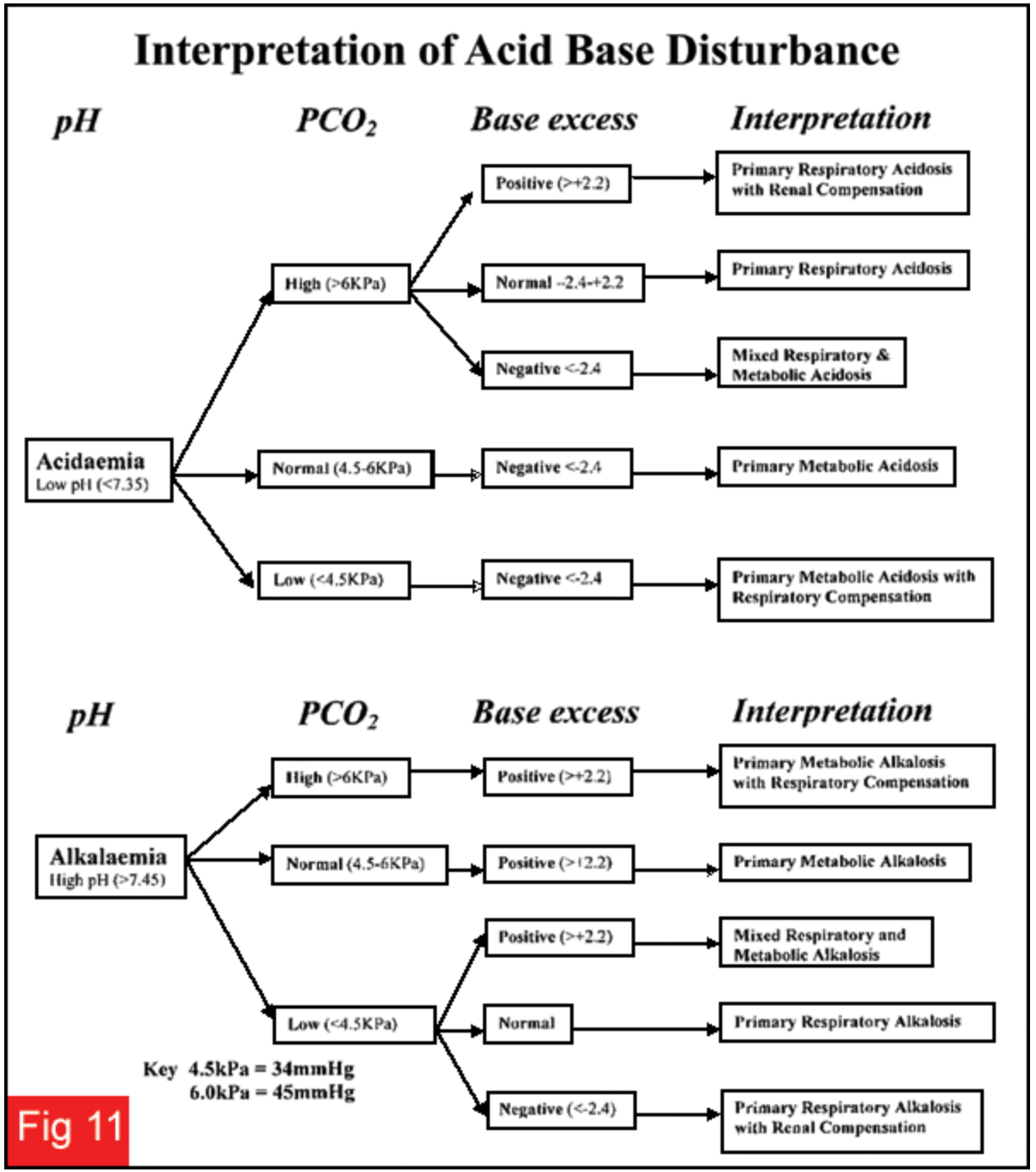
Interpretation of Acid Base Disturbance
pH
PCO2
Base excess
Interpretation
Acidaemia
Low pH (<7.35)
High (>6KPa)
Positive (>+2.2)
Primary Respiratory Acidosis with Renal Compensation
Normal –2.4-+2.2
Primary Respiratory Acidosis
Negative <-2.4
Mixed Respiratory & Metabolic Acidosis
Normal (4.5-6KPa)
Negative <-2.4
Primary Metabolic Acidosis
Low (<4.5KPa)
Negative <-2.4
Primary Metabolic Acidosis with Respiratory Compensation
pH
PCO2
Base excess
Interpretation
Alkalaemia
High pH (>7.45)
High (>6KPa)
Positive (>+2.2)
Primary Metabolic Alkalosis with Respiratory Compensation
Normal (4.5-6KPa)
Positive (>+2.2)
Primary Metabolic Alkalosis
Low (<4.5KPa)
Positive (>+2.2)
Mixed Respiratory and Metabolic Alkalosis
Normal
Primary Respiratory Alkalosis
Negative (<-2.4)
Primary Respiratory Alkalosis with Renal Compensation
Key 4.5kPa = 34mmHg
6.0kPa = 45mmHg

Fig 11

Interpretation of ABB disturbances in blood gas results

- In order to obtain meaningful results from any test it is important that they are interpreted in the light of the patient's condition. This requires knowledge of the patient's history and examination findings.
- The simplest blood gas machines measure the pH, pCO_2 and pO_2 of the sample. More complicated machines will also measure electrolytes and haemoglobin concentration. Most blood gas machines also give a reading for the base excess and/or standard bicarbonate. These values are used to assess the metabolic component of an acid base disturbance and are calculated from the measured values outlined above. They are of particular use when the cause of the acid base disturbance has both metabolic and respiratory components.

Examples:

Example 1: A 70 year old man is admitted to the intensive car unit with acute pancreatitis. He is hypotensive, hypoxic and in acute renal failure. He has a respiratory rate of 50 breaths per minute. The following blood gas results are obtained:

- pH 7.1
- pCO_2 3.0 kPa (22mmHg)
- BE -21.0 mmol/l

From the flow charts: firstly, he has a severe acidemia (pH 7.1). The PCO2 is low, which does not account for the change in pH (a pCO_2 of 3.0 would tend to cause alkalemia). Therefore, this cannot be a primary respirafory acidosis. The base excess of -21 confirms the diagnosis of a severe metabolic acidosis. The low pCO_2 indicates that there is a degree of respiratory compensation due to hyperventilation. These results were to be expected given the history.

Examples:

Example 2: A 6 week old male child is admitted with a few days history of projectile vomiting. The following blood gases are obtained:

- pH 7.50
- PCO2 6.5kPa (48mmHg)
- BE +11.0 mmol/L

The history points to pyloric stenosis. There is an alkalaemia, which is not explained by the PCO2. The positive base excess confirms the metabolic alkalosis. The raised PCO2 indicates that there is some respiratory compensation.

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Thank you for your attention