Ho Medical
ANAESTHESIA

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Acid-Base Physiology

1990 Write short notes on buffers.

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1. A buffer is a solution which has the ability to minimised changes in pH when an acid or base is added to it. It usually consists of a weak acid and its conjugate base. In the body, the buffer binds H^+ ions reversibly to minimise change in pH:

$$\mathbf{Buffer} + \mathbf{H}^+ \Leftrightarrow \mathbf{H.Buffer}$$

2. Effectiveness of a buffer:
    a. Amount of buffer present
    b. pKa of buffer (pH when 50% of acid is dissociated): buffers are most effective in pH solutions ± 1 of their pKa.
    c. Open (physiological) or closed (chemical) system.

3. Buffers in the body:

Buffer	Equation	pKa
Extracellular		
Bicarbonate	$H^+ + HCO_3^- \Leftrightarrow H_2CO_3 \Leftrightarrow H_2O + CO_2$	6.1
Haemoglobin	$H^+ + Hb \Leftrightarrow H.Hb$	6.8
Protein	$H^+ + protein^- \Leftrightarrow H.protein$	2/9
Intracellular		
Protein	$H^+ + protein^- \Leftrightarrow H.protein$	2/9
Phosphate	$H^+ + HPO_4^{2-} \Leftrightarrow H_2PO_4^-$	6.8
Renal Tubules		
Ammonia	$H^+ + NH_3 \Leftrightarrow NH_4^+$	
Bicarbonate	$H^+ + CO_3^- \Leftrightarrow H_2O + CO_2$	6.1
Phosphate	$H^+ + HPO_4^{2-} \Leftrightarrow H_2PO_4^-$	6.8

4. Bicarbonate System:
    a. Weak acid (carbonic acid) + bicarbonate salt (ECF – sodium, ICF – potassium, magnesium)
    b. Adding:
        i. Strong acid → buffering by HCO_3^- → H_sCO_3 → $H_2O + CO_2$ → CO_2 excreted from ECF by the lungs.
        ii. Strong base → buffering by H_2CO_3 → HCO_3^- → excreted by kidney.
    c. Despite pKa 6.1, it is an effective buffering system because it is an open system → CO_2 is regulated by the pulmonary system, while HCO_3^- is regulated by renal system. It can only buffer metabolic acids (not carbonic acid).

5. Haemoglobin: see notes below

6. Proteins:
    a. Amino (pKa 9) and carboxyl (pKa 2) and imidazole (pKa 6.8) side chains can buffer H^+ ions. Not very significant in ECF
    b. More important in ICF as proteins are higher in concentration and the more acidic environment improves buffering ability.

7. Phosphate:

a. Low ECF concentration → not significant as ECF buffer
b. Significant contribution to ICF and renal DCT buffering due to higher concentrations and more acidic conditions

EXTRA NOTES:

8. Acid load in the body:

Acid	**Amount/day**	**Mechanism**
Carbon dioxide	15000mmol	CO_2 produced by decarboxylation reactions of Krebs cycle → carbonic acid. Most excreted by lungs.
Sulphuric acid	45	Metabolism of sulphur containing amino acids
Hydrochloric acid	12	Metabolism of lysine, arginine and histidine.
Phosphoric acid	13	Metabolism of phosphoroproteins
Lactic acid	1500	Anaerobic metabolism of glucose in RBCs, skin, skeletal muscle. Most metabolised by liver → HCO_3^-
Ketones		Metabolism of TGs during fasting
Total	50-100mmol Net	

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Physiol-10B15/03A9/92 Discuss the role of haemoglobin as a buffer.

1. A buffer is a solution which has the ability to minimised changes in pH when an acid or base is added to it. It usually consists of a weak acid, its salt and its conjugate base. In the body, the buffer binds H^+ ions reversibly to minimise change in pH:

$$\mathbf{Buffer} + \mathbf{H^+} \Leftrightarrow \mathbf{H.Buffer}$$

2. Haemoglobin is a metalloprotein present within erythrocytes (intracellularly). It is the most important extracellular buffer for CO_2 produced by aerobic metabolism, due to its unique properties and accounts for 90% buffering of carbonic acid. This is important because the bicarbonate system cannot buffer carbonic acid from CO_2 as they form part of the same weak acid-conjugate base pair. Hb is present in RBCs with a potassium salt:

$$\mathbf{H^+ + KHb \Leftrightarrow HHb + K^+}$$
$$\mathbf{H_2CO_3 + KHb \Leftrightarrow HHb + HCO_3^-}$$

3. Properties of the Hb buffer:
    a. Present in large concentrations – 150g/L
    b. Structure: metalloprotein (65000 Da) containing 4 polypeptide Haeme-globin chains.
        i. Each Hb molecule contains 38 histidine residues (with imidazole side-chain) which buffer H^+ (pKa 6.8).

$$\mathbf{Imidazole^- + H^+ \Leftrightarrow Imidazole.H}$$

    c. pKa 6.8 is similar to intracellular pKa which ↑ buffering capacity.
    d. Deoxy-Hb is a better buffer than oxy-Hb (Haldane-effect):
        i. Deoxy-Hb (pKa 8.2) is a weaker acid, and dissociated more than oxy-Hb (pKa 6.6).
        ii. 1 mmol oxyHb → DeoxyHb allows ↑0.7mmol H^+ buffering → 0.7mmol CO_2 enters system without change in pH.
        iii. Venous blood has ↑buffering capacity compared to O_2 blood, thus pH venous is only slightly reduced compared to ↑pCO_2 → carried as bicarbonate and carbamino compounds which contribute to H^+ load.

4. Chemical Hb buffering: the properties of CO_2 as a volatile acid contribute to Hb buffering
    a. CO_2 rapidly diffuses across the red cell membrane
    b. RBCs contain carbonic anhydrase which catalyses:

$$\mathbf{H_2O + CO_2 \Leftrightarrow H^+ + HCO_3^-}$$

    c. Hb buffers the H^+ and favours formation of HCO_3^- → diffuses down concentration gradient out of cell.
    d. Thus, the presence of acid in the ECF leads to maintenance of concentration gradient and ongoing diffusion of HCO_3^- out of the cell → 30% Haldane effect.

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EXTRA-NOTES

5. Carbamino compounds: produced by the reaction of CO_2 with terminal amine groups of each Hb chain → carbamic acid. This has a low pKa such that at plasma and intracellular pH, the acid is mostly dissociated:

   $R\text{-}NH\text{-}COOH \Leftrightarrow R\text{-}NH\text{-}COO^- + H^+$

   Thus, the carriage of CO_2 by Hb as carbamino compounds actually adds H^+ to the intracellular system. This requires buffering. Carbamino compounds do NOT contribute to Hb as a buffer.

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Physiol-06B15/98B5 Explain how a metabolic acidosis develops in hypovolaemic shock. Describe the consequences of this metabolic acidosis for the body.

1. Metabolic Acidosis is the pathological process resulting in a decrease in pH primarily through depletion of HCO_3^-. Hypovolaemic shock is the pathological reduction in intravascular volume leading to inadequate perfusion to meet the metabolic demands of tissues.

2. Shock:
    a. Inadequate delivery of O_2 to tissues:
        i. The lack of O_2 does not allow removal of the end-products of glycolysis and the citric acid cycle → build-up of pyruvate and NADH/$FADH_2$.
        ii. Shift to anaerobic glycolysis: pyruvic acid converted to lactic acid which diffuses out of cells to ↓pyruvic acid concentration → allows glycolysis to continue.

$$\mathbf{pyruvate + NADH + H^+ \leftrightharpoons lactic\ acid + NAD^+}$$

        iii. Energy inefficient – produces 2ATP for every pyruvate converted.
    b. Inadequate removal of lactate via the Cori cycle:
        i. Under normal circumstances, lactate produced by anaerobic metabolism (RBCs, kidney etc) is cycled in the liver and reconverted to pyruvate → glucose (gluconeogenesis).
        ii. Shock: exhausted pathways for this conversion, and low hepatic blood flow → accumulation of lactate → metabolic acidosis

3. Consequences of metabolic acidosis:
    a. Respiratory:
        i. Ventilation:
            1. Sensors: peripheral chemoreceptors detect ↓pH
            2. Controller: activated by chemoreceptors in ↑ ventilation
            3. Effectors: muscles of respiration ↑RR, TV → ↑MV → ↓pCO_2 (respiratory compensation). ↓pH 1 → ↑MV 3L/min
        ii. HbO_2 dissociation curve: R shift → ↑offloading O_2 to peripheral tissues
    b. Cardiovascular:
        i. Direct negative inotrope: inhibits slow Ca^{2+} influx, and release from SR.
        ii. Tachycardia due to catecholamine release
        iii. Vessels: ↓SVR (metabolic autoregulation), ↑PVR. This is offset by hypovolaemic ↑SVR (local, neural and hormonal autoregulation).
        iv. Impaired response to catecholamines when pH < 7.2
        v. Arrhythmogenicity:
            1. Hyperkalaemia: K exchanged with H into ECF. pH ↓0.1 → ↑K 0.6mmol/L
            2. ↑ free Ca^{2+} via dissociation from albumin (H^+ competes for binding sites on albumin).
    c. CNS: neuronal dysfunction → impaired consciousness.
    d. GIT: ↓ GI motility.
    e. Renal: correction (delayed)
        i. ↑reabsorption of HCO_3^-
        ii. ↑excretion H^+ as titratable acid and ammonium

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Physiol-07A11/05A15 Discuss how the body handles a metabolic acidosis.

1. Metabolic Acidosis is the pathological process resulting in a decrease in pH primarily through depletion of HCO_3^-. The body's responses can be classified into rapidity of activation. Its overall aim is to shift pH back to normal (ECH 7.4, ICF 6.8) as this is required for normal cell homeostasis.

2. Buffering: the body contains several buffer systems consisting of a weak acid and its conjugate base. Buffers minimise the change in pH when a strong acid or base is added. This occurs in minutes – hours.

Buffer	**Equation**	**pKa**	**Description**
Extracellular: pH range 7.36-7.44			
Bicarbonate	$H^+ + CO_3^- \Leftrightarrow H_2O + CO_2$	6.1	Most important ECF buffer. Open system (mechanisms to change pCO_2 and HCO_3^-) ↑effectiveness In metabolic acidosis, relative ↓HCO_3^- → bicarbonate not as effective.
Haemoglobin	$H^+ + Hb \Leftrightarrow H.Hb$	6.8	Imidazole residues of histidine groups (38 / Hb molecule). Favours formation of HCO_3^- (via carbonic anhydrase inside RBC).
Protein	$H^+ + protein^- \Leftrightarrow H.protein$		Less important in ECF due to low concentration
Intracellular: pH lower range 6.8-7.1			
Protein	$H^+ + protein^- \Leftrightarrow H.protein$		
Phosphate	$H^+ + HPO_4^{2-} \Leftrightarrow H_2PO_4^-$	6.8	
Bone			
Ca-bicarbonate	Exchange of ECF H^+ for ICF Na^+/Ca^{2+}		Over time, high acidity demineralises bone and releases alkaline compounds $CaCO_3$, $CaHPO_4$.

3. Compensation: the respiratory system responds to metabolic acidosis by ↑ CO_2 excretion to restore the $[HCO_3^-]/PaCO_2$ ratio. CO_2 can be considered as a volatile acid and alterations in body pH occur quickly because CO_2 crosses cell membranes easily.
    a. Sensor: peripheral chemoreceptors in carotid/aortic bodies detect ↓pH → stimulation medulla via the vagus and glossopharyngeal nerves.
    Central chemoreceptors have a delayed response due to the diffusion of HCO_3^- across the BBB, thus lowering brain ECF pH.
    b. Controller: respiratory centre in the medulla
    c. Effector:
        i. Change ventilation causes change pCO_2: ↑RR / TV → ↑MV → ↓pCO_2

$$\mathbf{P_aCO_2 = k.\frac{\dot{V}CO_2}{\dot{V}_A}}$$

        ii. Change pCO_2 causes change pH:

$$\mathbf{pH = pKa + \log_{10}\frac{HCO_3^-}{0.03\ x\ pCO_2}}$$

    There is *no direct excretion of metabolic acids* and thus this mechanism is limited in dealing with fixed metabolic acidosis.

4. Correction: the renal system responds to metabolic acidosis by ↑ the reabsorption of HCO_3^-, and ↑ the net excretion of H^+ as titratable acids. This is the only way of excreting fixed acids.

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a. Reabsorption of HCO_3^- and Secretion of H^+ from PCT: high capacity, low gradient (secretes 4320mmol H^+, limiting pH 7.0). Energy from Na-K ATPase.
   i. Tubular cell: $H_2O + CO_2 \rightarrow H^+ + HCO_3^-$
   ii. H^+ excreted with Na^+ counter-transport
   iii. Lumen: $H^+ + HCO_3^-$ (filtered from glomerulus) $\rightarrow H_2O + CO_2$
   iv. CO_2 reabsorbed into PCT $\rightarrow$ combines OH^- $\rightarrow$ HCO_3^- $\rightarrow$ reabsorbed into blood.
   v. HCO_3^- thus reabsorbed indirectly. This occurs 80% PCT, 10% TALH, 10% DCT/CD.
   vi. H^+ reforms H_2O which is excreted in the urine. Thus, overall *no H^+ is excreted in the PCT*.

b. Secretion of H^+ from DCT: low capacity, high gradient (secretes 70mmol H^+, limiting pH 4.4).
   i. Intercalated cells: $H_2O + CO_2 \rightarrow H^+ + HCO_3^-$
   ii. H^+ secreted by *H/K-ATPase pump*
   iii. Lumen: $H^+ + HCO_3^-$ (filtered from glomerulus) $\rightarrow H_2O + CO_2$
   iv. Cl^- passively secreted as HCO_3^- is reabsorbed.
   v. Can concentrate urine to pH 4.4 (1000-fold H^+ concentration)
   vi. Pump activated by aldosterone $\rightarrow$ $\uparrow H^+$ secretion and K reabsorption.

c. Secretion of H^+ as titratable acid: H^+ excreted to filtered buffers in the urine. Measured by the amount of alkali required to titrate urine to pH 7.4. This allows secreted of extra H^+ after all HCO_3^- is reabsorbed.

   $H^+ + HPO_4^{2-} \Leftrightarrow H_2PO_4^-$ (DCT)

   i. H^+ is trapped by the phosphate buffer and unable to combine with HCO_3^- to form $H_2O + CO_2$.
   ii. Exhausted pH 4.4

d. Secretion of NH_4^+ from PCT/DCT: accounts for 75% of excretion of metabolic acids in body (50mmol/day).

   $H^+ + NH_3 \Leftrightarrow NH_4^+$

   i. PCT/TALH/DCT: **glutamine $\rightarrow$ $NH_4^+ + HCO_3^-$**
   NH_4 secreted into lumen in exchange for Na, whilst HCO_3^- reabsorbed into blood.
   $NH_3 + H^+ \Leftrightarrow NH_4^+$ (pKa = 9.2, thus most present as NH_4^+ in PCT)
   ii. Cycling of NH_4^+: Reabsorption of ammonium on ALH $\rightarrow$ medulla interstitium (facilitated by low urine pH). High acid load (low urine pH) $\rightarrow$ $\uparrow NH_4^+$ transfer from interstitium $\rightarrow$ lumen $\rightarrow$ excretion in urine.
   iii. Older theory: NH_3 is soluble to cell membranes and diffuses into the lumen to absorb H^+ $\rightarrow$ thus H^+ secreted as ammonium.
   iv. HCO_3^- is also reabsorbed in this way.
   v. During metabolic acidosis, the liver $\uparrow$production of glutamine $\rightarrow$ $\uparrow$ available pool of ammonium.

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1995 Explain how a metabolic alkalosis develops in an adult patient with a small bowel obstruction and nasogastric losses in excess of 1000ml per day for 5 days. Give a brief account of the physiological principles determining fluid replacement.

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1. The body maintains HCO_3^- at a relatively stable level of 24mmol/L. It does so through:
    a. Reabsorption of nearly all filtered bicarbonate
    b. Excretion of fixed acid paired with regeneration of bicarbonate.

    If the plasma bicarbonate exceeds 24mmol/L, this is normally promptly excreted by rapid renal excretion of excess bicarbonate.

2. Maintenance of alkalosis: requires impairment of bicarbonate excretion.
    a. Chloride depletion: the kidney reabsorbs anions with Na/K reabsorption to maintain electrical neutrality. The depletion of Cl → ↑HCO_3^- reabsorbed as this is the only other main ECF anion.
    b. Potassium depletion: ↑ HCO_3^- reabsorption in PCT/DCT in the presence of ↓K.
        i. ↑aldosterone → ↑Na reabsorption, ↑H/K excretion
        ii. ↓K → cells exchange H/K → ↓ECF H^+.

3. Vomiting and nasogastric loss is an important clinical cause of metabolic acidosis through the loss of H^+ ions in the acid juice. Gastric juice pH 1.4 → [H^+] concentration 0.04mol/L. Thus, over 5 days 0.04mmol H^+ and Cl^- are lost. Thus, this causes a Hypochloraemic metabolic alkalosis.
    a. Depletion of H^+ → ↑HCO_3^- by bicarbonate buffering
    b. Depletion of Cl^- → ↑HCO_3^- by renal reabsorption to maintain electrical neutrality.
    c. Depletion of ECF volume → ↑fluid, Na reabsorption in kidney → coupled to ↑HCO_3^- reabsorption.

4. Fluid replacement therapy: aimed at restoring H, Cl and volume.
    a. Chloride replacement: the most important fluid therapy and allows correction even if H and fluid depletion are untreated. Usually this is given in the form of normal saline infusions which contain 150mmol Cl^-.
    b. HCl infusion: can be given if rapid correction of acid-base status and Cl is required. This must be done through a central line in ICU.
        i. Cl^- is rapidly replaced
        ii. H^+ consumed excess HCO_3^- from the bicarbonate buffering system.
    c. Carbonic anhydrase inhibitors: inhibits the conversion of $H_2O + CO_2$ → HCO_3^- and H^+ in PCT → inhibits reabsorption of HCO_3^-. Can be used where fluid overload is a problem.

EXTRA NOTES:

5. Effects of metabolic alkalosis:

System	Effect
CVS	↓ contractility arrhythmias
Resp	Impaired O_2 unloading (shift Hb-O_2 curve left) Compensatory hypoventilation → atelectasis, hypoxaemia, V/Q mismatch
CNS	↓ CBF Confusion, mental obtundation
NMJ	NMJ excitability

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6. Body response:
    a. Compensation: respiratory hypoventilation due to peripheral chemoreceptors → ↑pCO_2. This response is somewhat variable due to concomitant hypoxaemia, pain and pulmonary congestion.

$$\textbf{Expected } \mathbf{pCO_2} = \mathbf{0.7\ x\ HCO_3^-} + \mathbf{20}$$

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Physiol-95A6 Describe the effects of intravenously administered sodium bicarbonate (8.4%) 100ml used in asystolic cardiac arrest in a 70 kg man.

1. A sodium bicarbonate infusion is commonly administered as part of ALS in cardiac arrest. The physiological handling of bicarbonate by the body has much to do with this.

2. 8.4% of 100mL sodium bicarbonate contains 8.4g of sodium bicarbonate is 100mLs water. As $NaHCO_3$ has MW 84g and it dissociates into Na^+ + HCO_3^-, the osmolality is 2 Osmoles (2000mosm) per kilogram and 200mosm in the solution.

3. The normal 70kg male has fluid distribution as follows:
    a. TBW 42L (60% weight)
    b. ICF 23L (55% TBW)
    c. ECF 19L (45% TBW)
    d. Interstitial fluid 8.4 L (20% TBW)
    e. Plasma fluid 3.2L (7.5% TBW)
    f. Other slowly exchangeable ECF (dense CT, TCF, bone water) 7.4L (17.5%)

4. Distribution: The high Na^+ content restricts distribution to the ECF

Dimension	Distribution
Osmolality	Total osmolality before = 285mosm/L $\textbf{Total osm after} = \frac{(\textbf{285 x 34.6 + 200})}{\textbf{34.7}} = \frac{\textbf{290mosm}}{\textbf{L}} (\uparrow \textbf{1.8}\%)$ Plasma tonicity ↑ > 1-2% → activation of osmoreceptors → release ADH → ↓urine output.
Water	Hyperosmolality draws water out of ICF → ECF by osmosis $\textbf{Total volume ECF} = \frac{\textbf{285 x 11.6 + 200}}{\textbf{290}} = \textbf{12.1L} (\uparrow \textbf{4}\%)$
Sodium	Hypernatraemia occurs from administration of Na+, partly controlled by osmosis
Bicarbonate	HCO_3^- before = 24mmol/L x 11.6 = 278.4mosm HCO_3^- after = 378.4mosm [HCO_3^-] after = 378.4/12.1 = 31.2mosm/L ↑HCO_3^- will cause metabolic alkalosis When HCO_3^- > 27mmol/L → rapid excretion in urine
K	H moves out of cells in exchange for K → hypokalaemia This stabilises cardiac membrane by reducing resting membrane potential.
Oncotic Pressure	Decreases due to ↑ECF volume → ↓ water reabsorption in PCT (glomerulotubular imbalance) → ↑ urine flow.
pH	Assuming intubated patient with pCO_2 = 40mmHg $\textbf{pH} = \textbf{pKa} + \log_{10} \frac{\textbf{HCO}_3^-}{\textbf{0.03 x pCO}_2}$ pH = 7.51

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MAKE-UP Describe the effects of intravenously administered 1N Hydrochloric Acid 100mls.

1. 1N Hydrochloric acid 100mLs contains 100mmol H^+. This is sufficient to cause a metabolic acidosis. The body's defence involves buffering, compensation, and correction.

2. Effects on the body:
    a. Shift of Hb-O_2 dissociation curve to the right → assists with O_2 unloading
    b. Anion gap unchanged → Hyperchloraemic metabolic acidosis
    c. No direct effects on CNs as metabolic acids to not cross BBB
    d. Hyperkalaemia: exchange of H/K

3. Buffering:
    a. Bicarbonate system: $H^+ + CO_3^- \Leftrightarrow H_2O + CO_2$
    b. Total bicarbonate load = 24 mmol/L x 19L = 456mmol
    c. After acid infusion, $[HCO_3^-]$ = 356/19 = 18.7mmol/L

$$\mathbf{pH = pKa + \log_{10} \frac{HCO_3^-}{0.03 \times pCO_2}}$$
$$\mathbf{pH = 7.29}$$

    d. Hypocapnoea causes intracellular alkalosis → general depressant effect on cell activity
    e. ↓pCO_2 → ↓H^+ ECF near central chemoreceptors (CO_2 diffuses across BBB and produces $H^+ + HCO_3^-$) → inhibits ventilatory response initially. Bicarbonate slowly equilibrates across BBB into ECF → ↑H^+ → removal of central inhibition after 12-24 hours.

4. Compensation: ↓pH will stimulate peripheral chemoreceptors to ↑ ventilation → ↓pCO_2 which returns HCO_3:pCO_2 ratio to normal. This returns pH towards normal. This response occurs within minutes but takes 12-24 hours to reach maximum value.

$$\mathbf{Expected\ pCO_2 = 1.5 \times HCO_3^- + 8}$$
pCO_2 = 36mmHg

5. Correction:
    a. Excretion of excess Cl^- → equivalent reabsorption of HCO_3^-
    b. Takes days

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MAKE-UP: Rules for interpreting an ABG

1. Respiratory Acidosis:
    a. Acute - ↑10mmHg CO_2 → ↑1mmol HCO_3^-
    b. Chronic - ↑10mmHg CO_2 → ↑4mmol HCO_3^-

2. Respiratory Alkalosis:
    a. Acute - ↓10mmHg CO_2 → ↓2mmol HCO_3^-
    b. Chronic - ↑10mmHg CO_2 → ↓5mmol HCO_3^-

3. Metabolic Acidosis:
    a. Expected $CO_2 = 1.5[HCO_3^-] + 8mmHg$

4. Metabolic Alkalosis:
    a. Expected $CO_2 = 0.7[HCO_3^-] + 20mmHg$