Acid-base chemistry and its disturbances

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System of the presentation

- Difficult subject?
- Gradual steps → good understanding, building on what I already know
- Active learning:
  - Slide with questions to solve – give it time, try to find solutions by yourself
  - Minimum time is below
  - Answers – mostly next slide
- Why active learning?
  - Greater joy and interest (in the end)
  - Deeper knowledge
  - Remembering longer

➔The extra effort pays off

Acid-base Chemistry and Physiology Refresher *(hopefully)*

Hydrogen ions

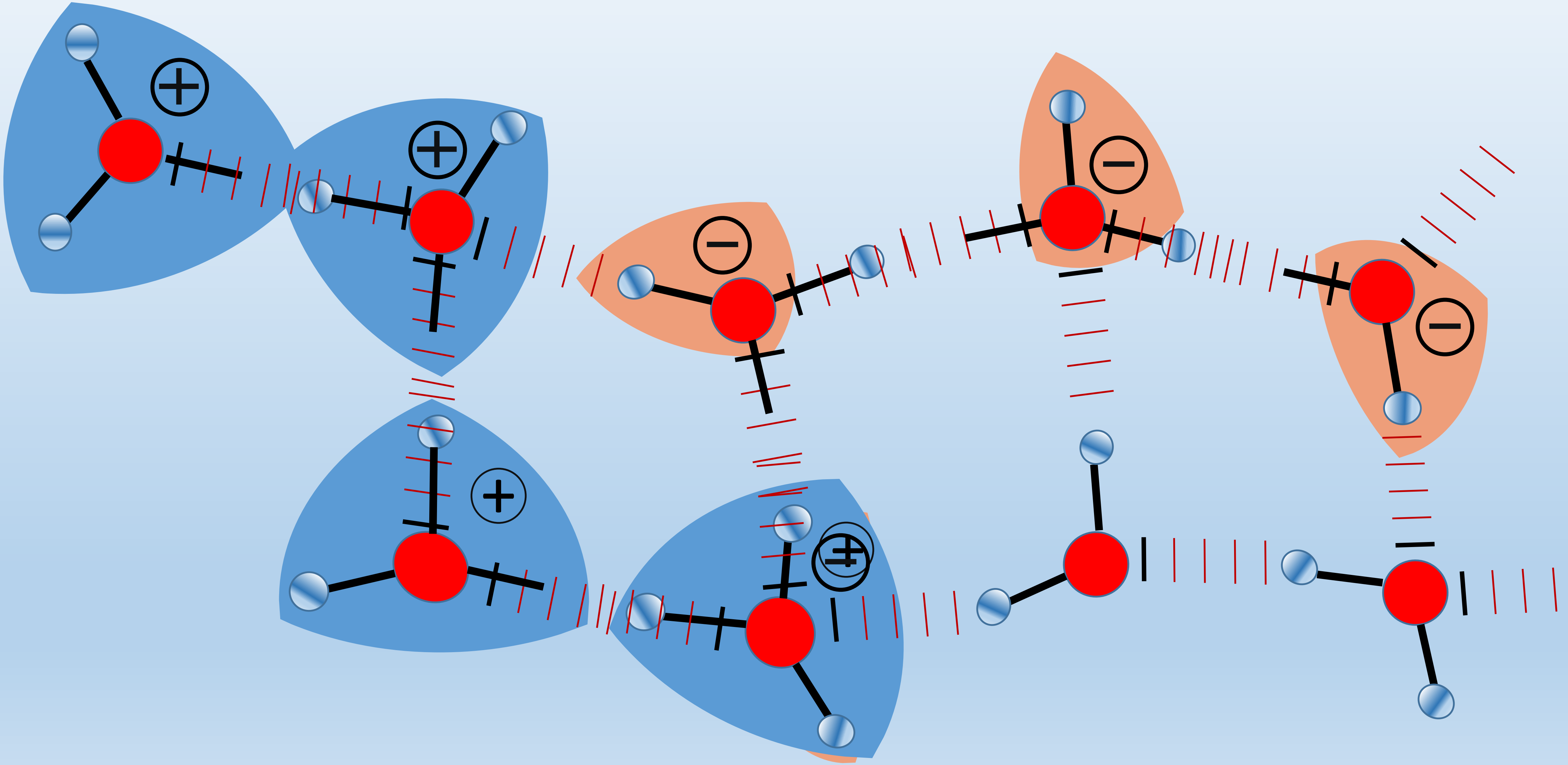
- Is the concentration of hydrogen ions in extracellular fluid (ICF) small, large, huge or minuscule?
- Why is maintaining H^+ concentration within narrow limits much more important than maintaining strict concentrations of let's say iodine or zink[1]?
- Is it more accurate to speak of H_3O^+ or H^+? Why?
- What is a hydrogen bond (H bond)?
- Is there more H_3O^+ or OH^- in plasma under physiological conditions?
- Minimum time: 2 min

1.Hint: Focus on properties of certain biomolecules as well as properties of water itself.

Hydrogen ions

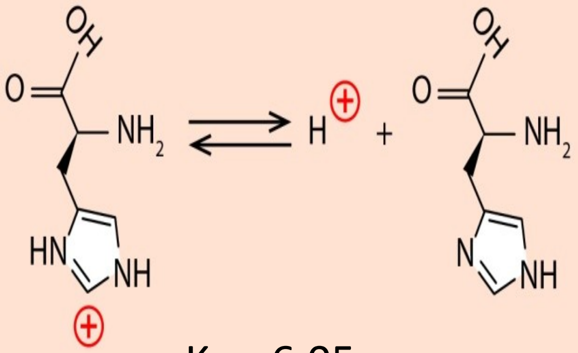
- Concentration of H^+ = $[H^+]$ ~ **1 000 000x** << $[Na^+]$ – minuscule
- Maintaining pH within tight limits is important because of very large reactivity of H^+ and its effect on the conformation of many macromolecules, especially proteins.
- Hydrogen bond – special type of weak chemical bond created by H^+; it binds H_20 molecules together →liquefaction of water
- $pH_{plasma,Norm} \approx 7{,}4 > 7{,}0$ → alkaline pH → $[OH^-] > [H3O^+]$

Dynamics of H_3O^+ and OH^- movement in water



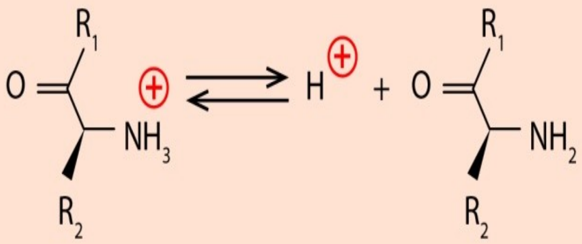
Amino-acid charge and protein conformation

Histidine side chain



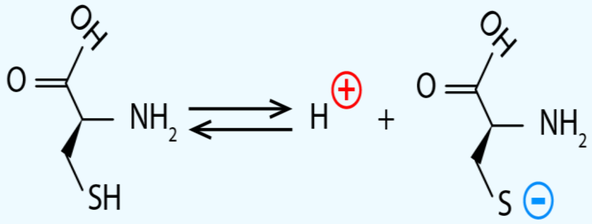
pK_A = 6,05

Amino terminus



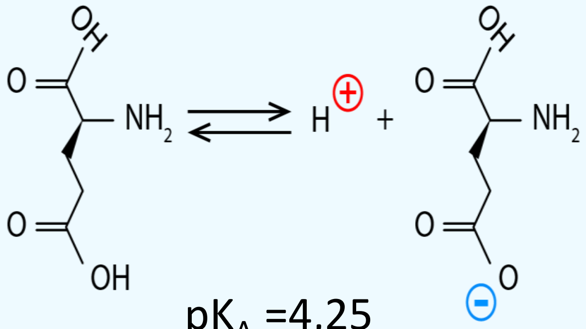
pK_A = 9,2

Cysteine:

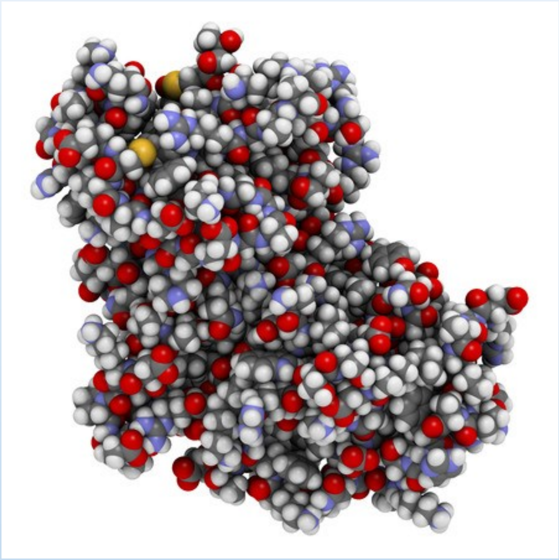


pK_A = 8,2

Glutamic acid:



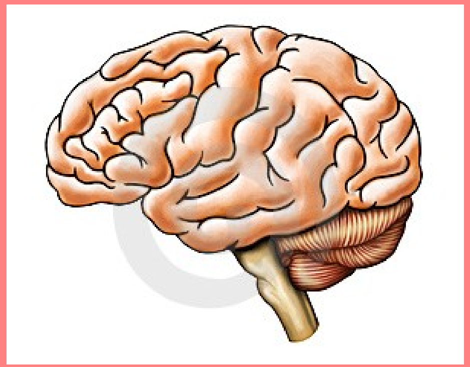
pK_A =4,25

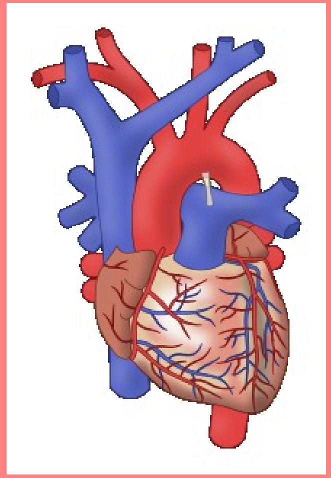


Conformation change

Dysfunction

Crucial organs:





pH definition and its consequences

- Would you remember how pH is defined?
- And what are rules of calculating with logarithms? E.g. log(A x B) =
- Try to figure out what these rules imply for the pH behavior: For instance, when H^+ concentration (denoted as $[H^+]$) increases two times, how does pH change?[1]
- How does pH change, when the H^+ concentration decreases 10x?
- *For straight-A students: How does pH change, when $[OH^-]$ increases 2x?*

- Minimum time: 3 minutes or until completion of all tasks.

- 1) You might find it helpful to know that $\log_{10}(2) = 0.3$

pH definition and its consequences - solution

- $pH = -\log_{10}([H^+])$
- $\log(AB) = \log(A) + \log(B)$
- H^+ concentration increasing twice: $[H^+]_{New} = 2[H^+]_{Old}$
- From the pH definition and the logarithm calculation rules:

$pH_{New} = -\log([H^+]_{New}) = -\log(2 \times [H^+]_{Old}) = -\log(2) + (-\log([H^+]_{Old}) =$
$= -0,3 + pH_{Old}$

➔Therefore: If H^+ concentration doubles: $pH_{New} = pH_{Old} – 0,3$

- When $[H^+]_{New} = 1/10 \times [H^+]_{Old}$: $pH_{New} = -\log(1/10) + (-\log([H^+]_{Old})=$
$= +1 + pH_{Old}$. If $[H^+]$ decreases ten times, pH goes up by 1.

Buffers

- What are buffers and what their effects in a solution are?
- How do buffers influence pH change, when acid or base is added?
- What does pK_a of a simple buffer denote?
- For straight-A students: Can you write down the mass action equation of a simple buffer?
- Which pH does render a single substance buffer most effective?

- Minimum time: 3 minutes

Buffers – Solution 1

- Buffers inhibit the pH change by binding the extra H^+ when their concentration increases (when pH falls) and releasing H^+ when $[H^+]$ decreases (pH goes up).
- They are crucial for stabilizing pH within certain range!
- Hydrogen ion and buffer react according to the formula:
- $HB \rightleftharpoons H^+ + B^-$ or:

  $HB^+ \rightleftharpoons H^+ + B$

- Reaction equilibrium concentrations can be expressed by the well-known mass action formula:

$$K_A = \frac{[H^+] * [B_i^-]}{[HB_i]}$$

- This can be expressed in the logarithmic form as well:

$$pH = pK_A + \log_{10}\frac{[B_i^-]}{[HB_i]}$$

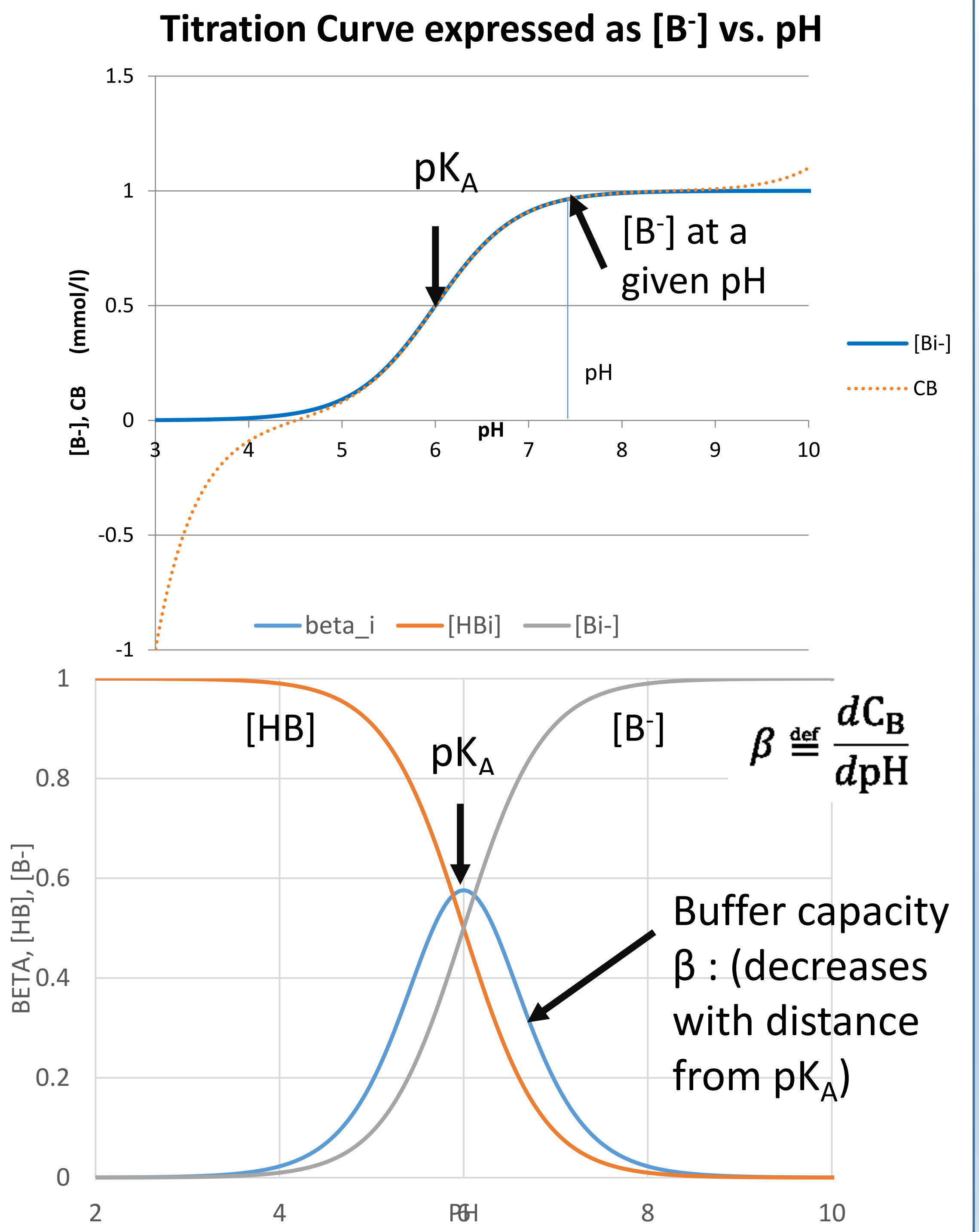
- $[HB]$ and $[B^-]$ are in 1:1 ratio, when $pH = pK_A$

(prove this using the previous relationship)

Buffers – Solution 2

- Single-substance buffer is most effective when the pH coincides with its pK_A .
- Efficiency of a buffer at a given pH can be measured by its buffer capacity β.
- When pH and pK_A fall far, the efficiency of the buffer is constrained by the buffer component that is low in concentration.
- For instance, at acidic pH, there is ↓$[B^-]$,
- At alkalic pH, there is ↓[HB]

- *For straight-A students: How does the $[B^-]/[HB]$ ratio change when acid is added at pH far from its pK_A? Does it change a lot or a bit?*



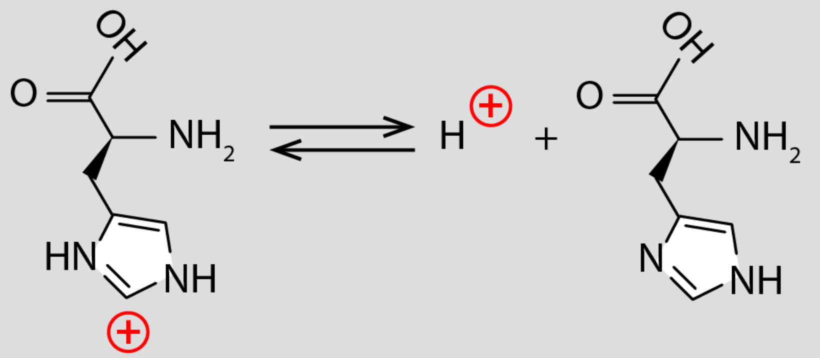
Protein Buffers

- Principal buffers in blood are:
  - **Hemoglobin!**
  - Albumin, and other proteins of blood plasma

- Key buffer residues are histidine side chains.
- pK_A's of individual histidine side chains differ significantly (influence of surrounding aminoacids)

Consequence: Virtually **linear** protein **titration curve. Buffer capacity** is almost constant over a wide range of pH.

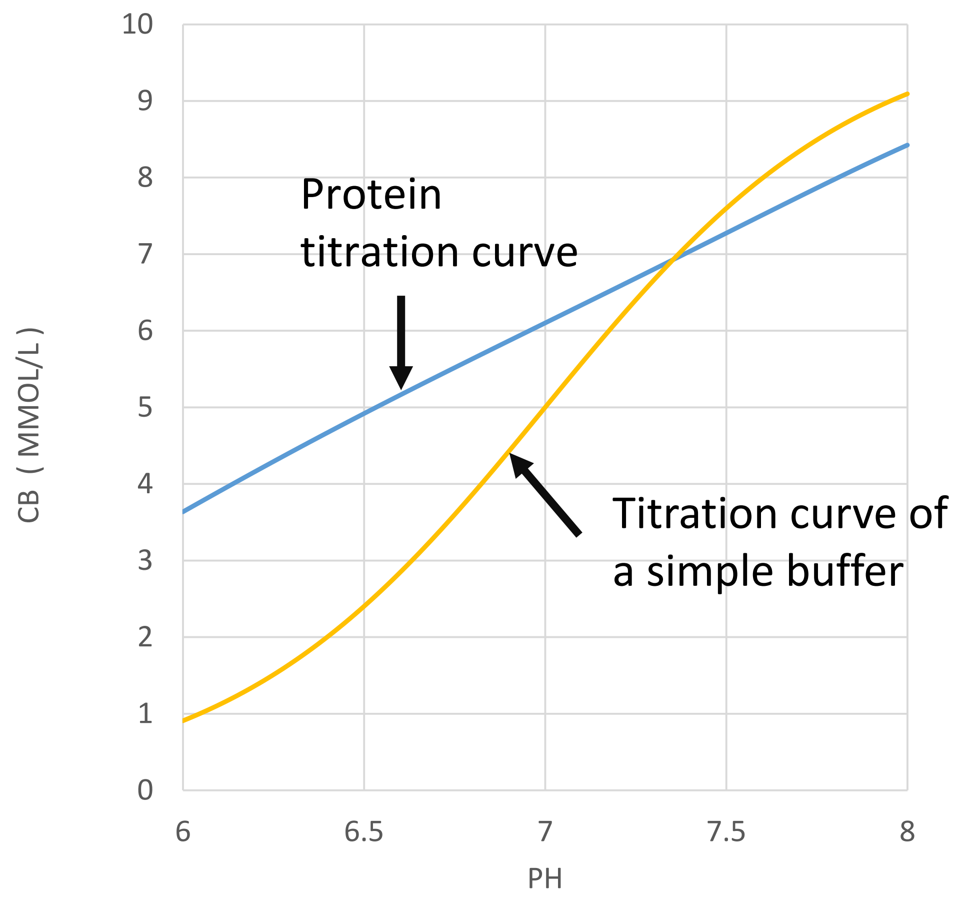
Histidine side chain



Tab: pK_A … ins in the albumin molecule (ordered)

pK_9	pK_{15}	pK_{10}	pK_{13}	pK_{11}	pK_8	pK_{12}	pK_7	pK_5	pK_3	pK_1	pK_2	pK_{14}	pK_{16}	pK_6	pK_4
4.85	5.2	5.75	5.82	6.17	6.35	6.73	6.75	7.01	7.10	7.12	7.22	7.3	7.3	7.31	7.49

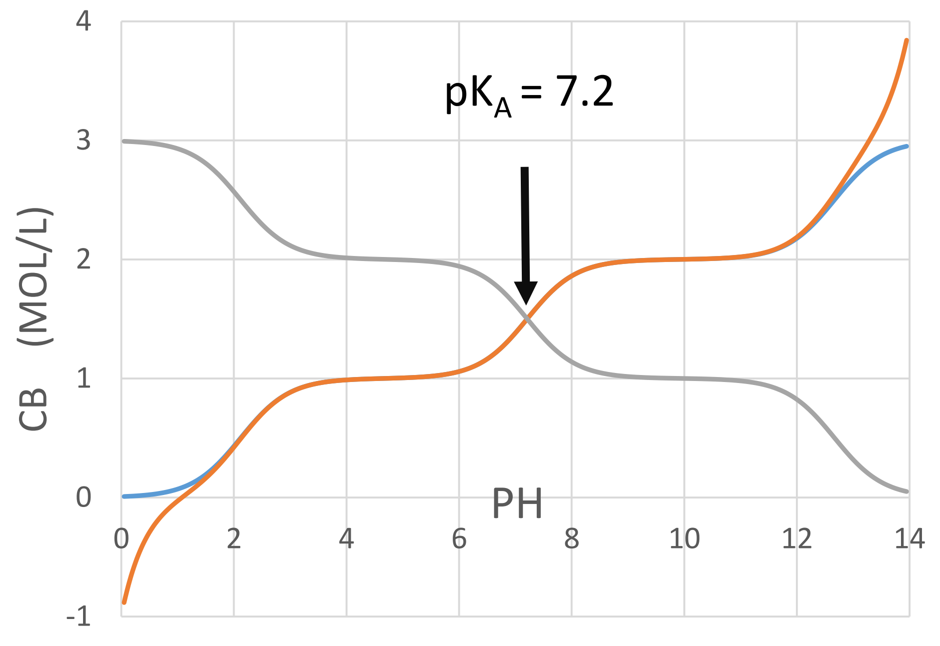
Protein Buffers

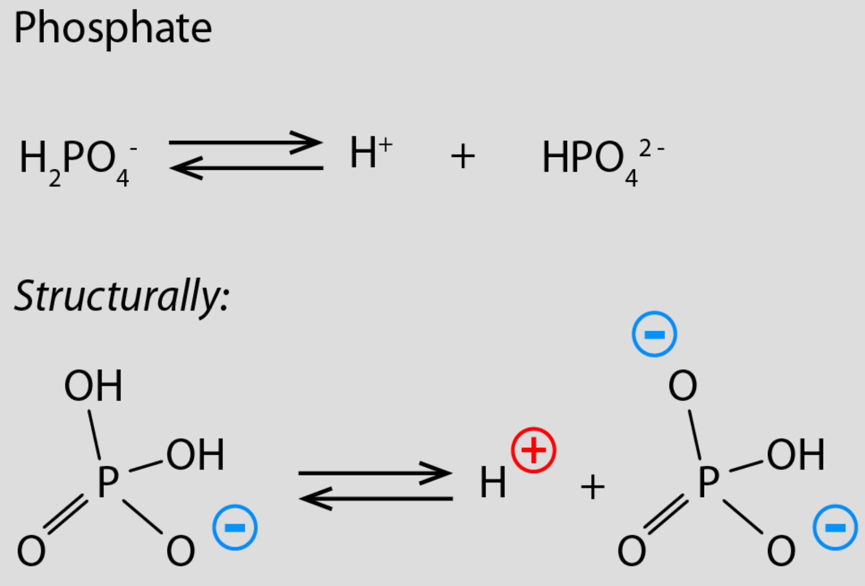


Phosphate Buffer

- Principal intracellular buffer
- Incl. phosphate residues of DNA

- The 2nd dissociation step is important, having $pK_A = 7.2$





Bicarbonate Buffer

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

Catalyzed by Carboanhydrase – present in stomach, kidneys and erythrocytes.

Equilibrium (mass action) expressed by the **Henderson-Hasselbalch equation:**

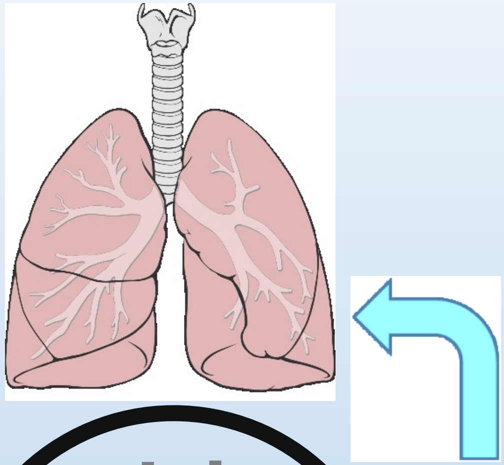
$$pH = pK_A + log\frac{[HCO_3^-]}{s * pCO_2}$$

Substituting numerical values (for pCO_2 in kPa) :

$$pH = 6{,}1 + log\frac{[HCO_3^-]}{0{,}22 * pCO_2}$$

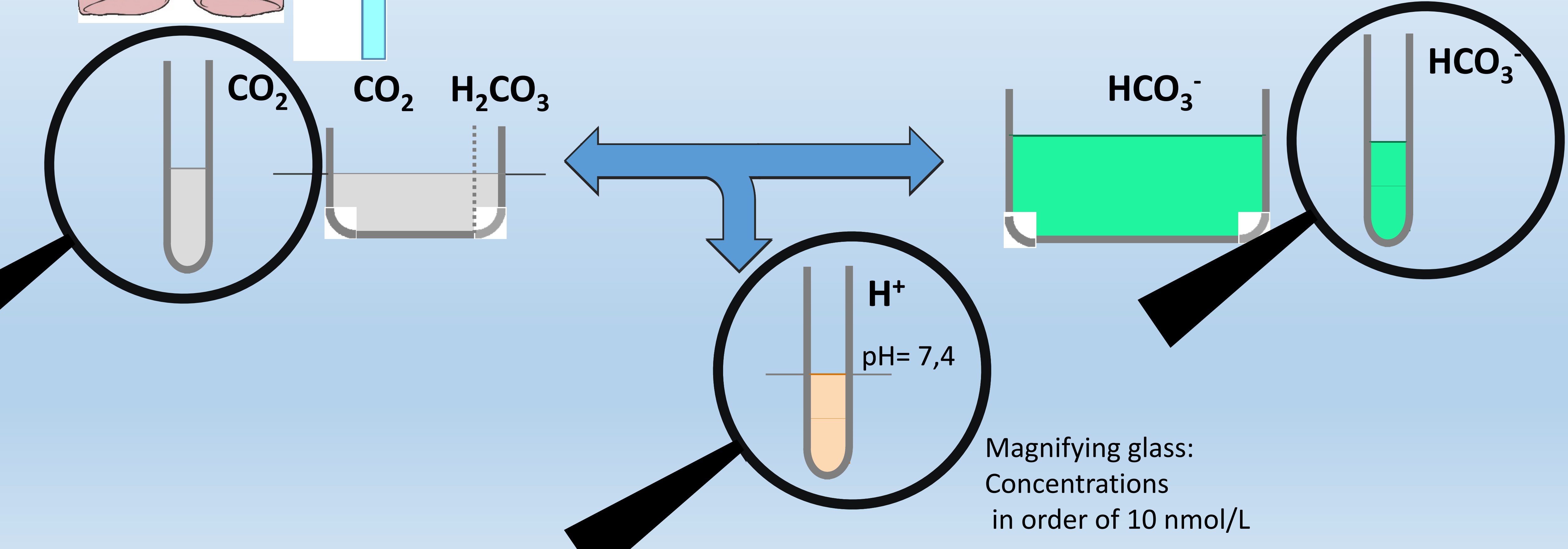
Question for straight-A students: pK_A of the bicarbonate buffer is 6.1. This is quite off the physiological pH = 7.4. Does this lower the buffer capacity of bicarbonate buffer?

Bicarbonate Buffer



Possible depiction of reaction equilibria (as described by Henderson-Hasselbalch equation):

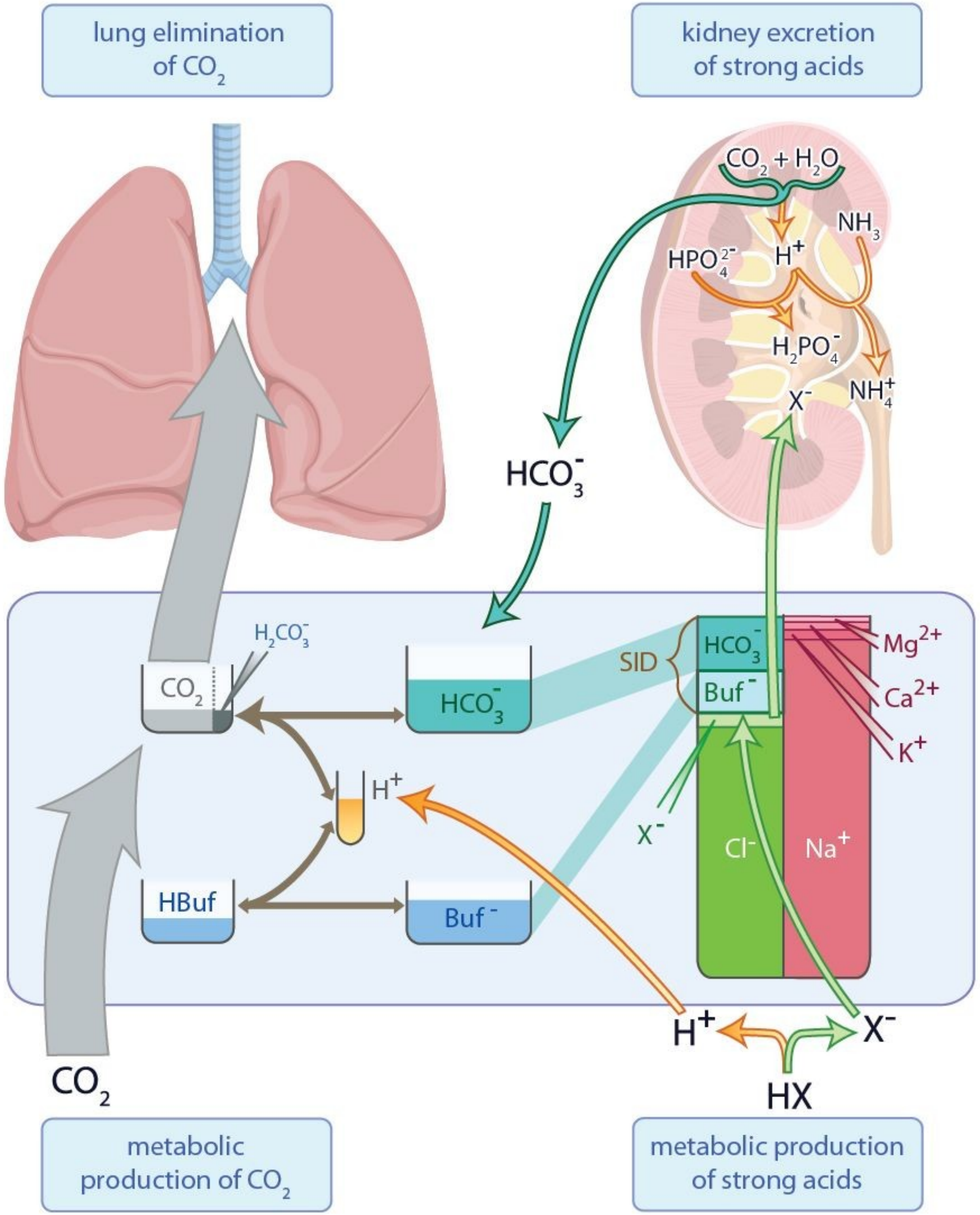
$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$



Magnifying glass:
Concentrations
in order of 10 nmol/L

Metabolism and the System of Regulating Acid-base Status

- The biggest turnover is in the system of CO_2
  - Thus pCO_2 can be easily regulated. CO_2 behaves as an open system
- Other flows and the relationship with concentrations of other ions (electro-neutrality) are depicted in the figure:



Bicarbonate Buffer

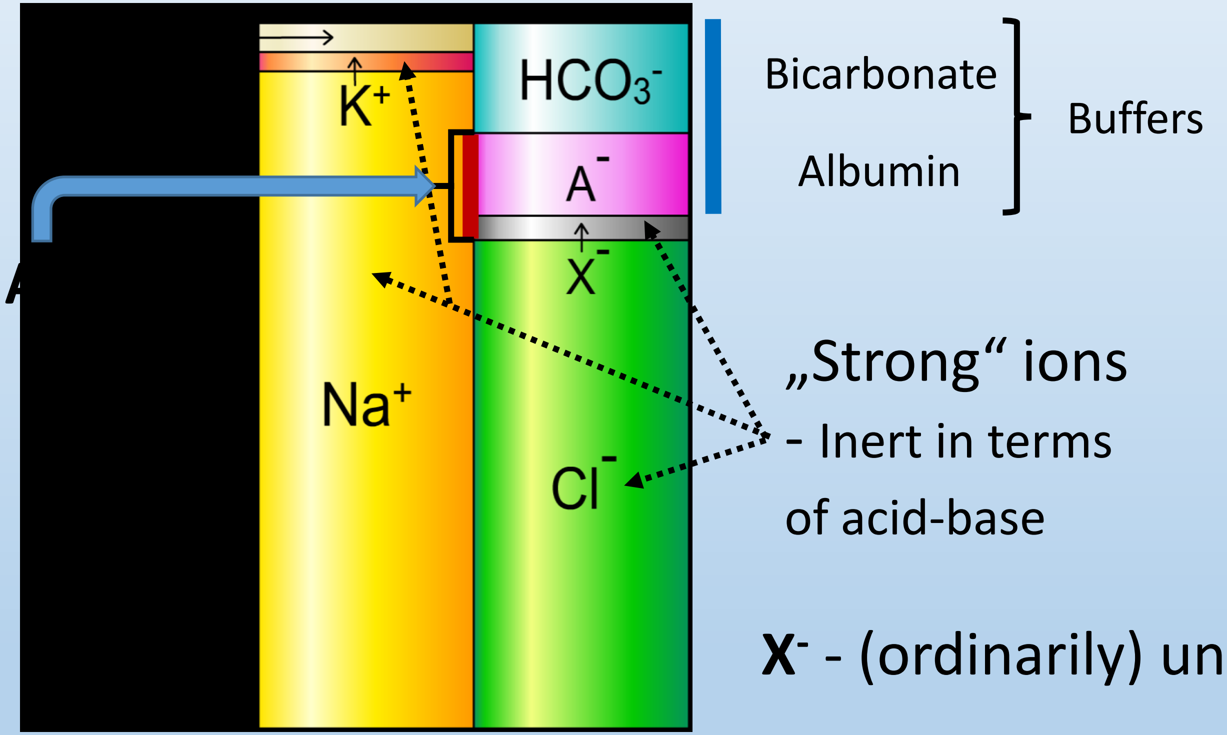
- It is the **principal buffer in terms of longer-term regulation** of H^+ balance in the body.
- Lungs – regulate pCO_2
- Kidneys – regulate the level of HCO_3^- in blood plasma and excretion of H^+

	Primary Disturbance	When H+ = 40 nmol/L	Compensation
Respiratory Acidosis	↑pCO_2	Reacts to the right -↑H^+	Kidneys - ↑HCO_3^-, ↑BE
Metabolic Acidosis	↓HCO_3^- (or ↑↑↑H^+)	Reacts to the right when primary cause ↓HCO_3^- (Reacts to the left when primary cause ↑↑↑H^+) –end result - ↑H^+	Lungs - ↓pCO_2
Respiratory Alkalosis	↓pCO_2	Reacts to the left - ↓H^+	Kidneys - ↓HCO_3^-, ↓BE
Metabolic Alkalosis	↑HCO_3^-	Reacts to the left -↓H^+	Lungs - ↑pCO_2

Base Excess - BE

- Base Excess – a very precise measure of metabolic disturbances (and metabolic compensations)
- Underlying logic: Lungs regulate pCO_2 . This regulation does not influence the total concentration of base forms of buffers.
- By definition: When pH = 7,4 (norm) and pCO_2 = 5,3 kPa (norm), then BE = 0 mmol/L
- Now, when we add 10mmol/L of acids, part of this amount reacts away with bicarbonate and part with the B- form of nonbicarbonate buffers – BE decreases to -10 mmol/L
- Conversely, taking away 15 mmol/L of acids (H^+) when BE =0 increases both the level of bicarbonate and the B- of non-bicarbonate buffers – BE increases to +15 mmol/L
- The value of BE is independent of subsequent changes in pCO_2

System of Buffers and Electroneutrality



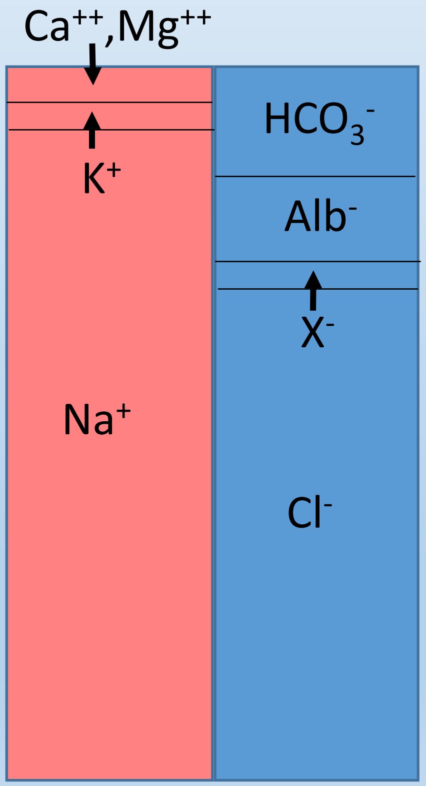
Electroneutrality:
When buffer concentration changes – the concentration of strong ions has to change as well

X$^-$ - (ordinarily) unmeasured ions –e.g. **lactate, keto**$^-$**,** SO_4^{2-}

AG = Anion gap = $Na^+ + K^+ - Cl^- - HCO_3^-$

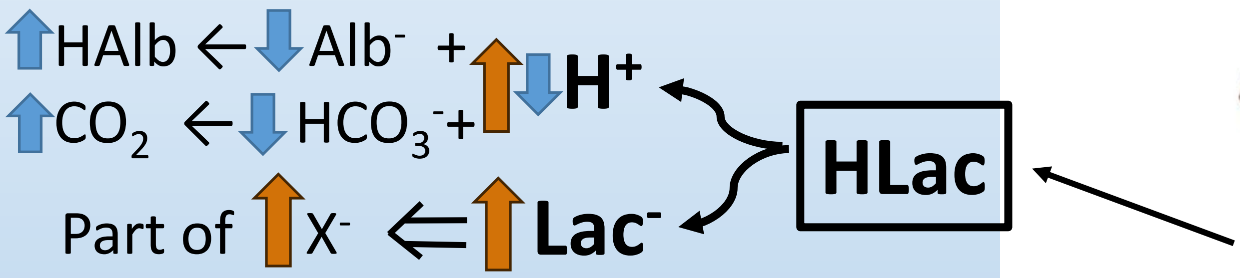
Parameter used in differential diagnosis of metabolic acidoses

System of Buffers and Electroneutrality 2 – Example



Runner in High Tatras:

Production of **lactic acid** in muscles

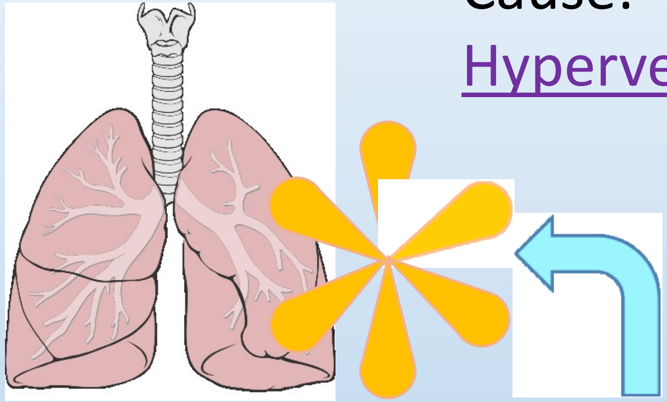


Acid-base Balance Disturbances

= Pathophysiology of ABB

Respiratory Disturbances and their Compensation

Respiratory Alkalosis and its Compensation



Cause:

Hyperventilation

Kidney (metabolic) compensation:

Takes 2- 3 days to develop

Kidneys excrete less H^+ and more bicarb.

= less bicarbonate returns to blood

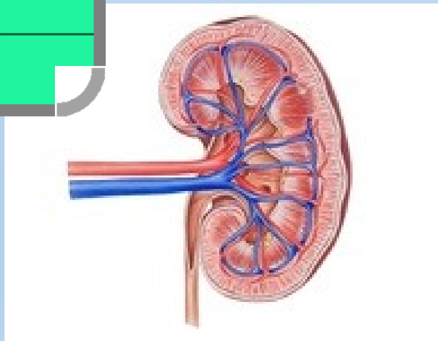
CO_2 **H_2CO_3**

5,3 kPa

⇓

2,7 kPa

HCO_3^-



H^+

pH = 7,4 ⇔ 40 nmol/l

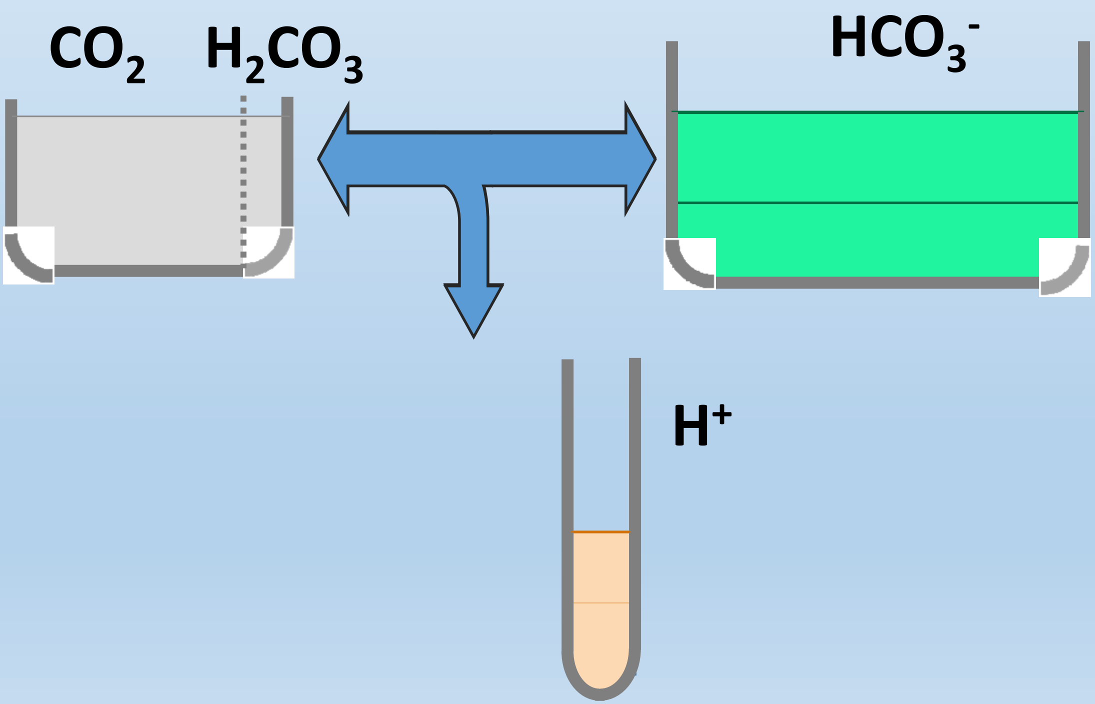
↓ ↓

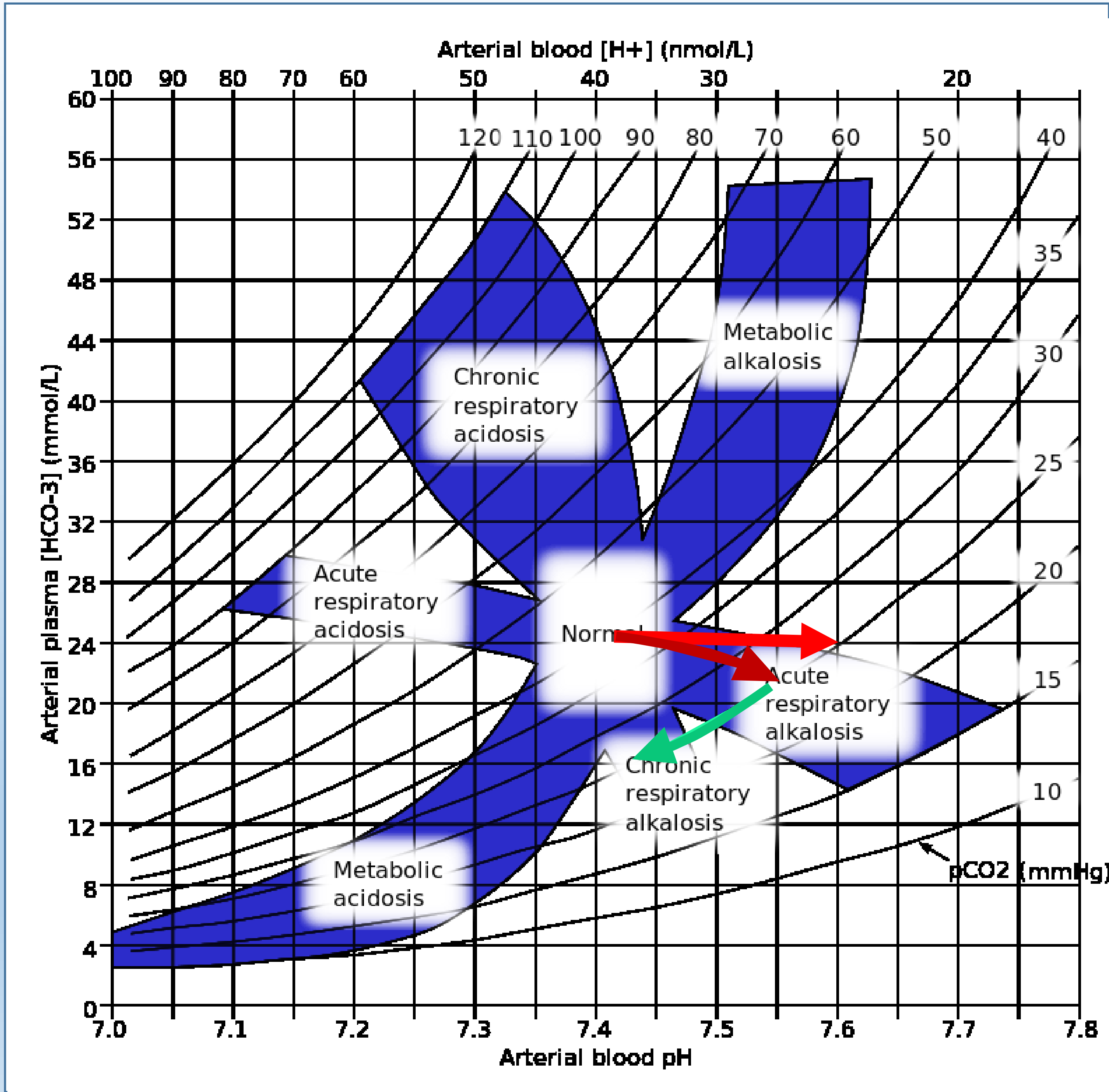
Alkalosis: **pH = 7,7** ⇔ 20 nmol/l

pH= 7,4

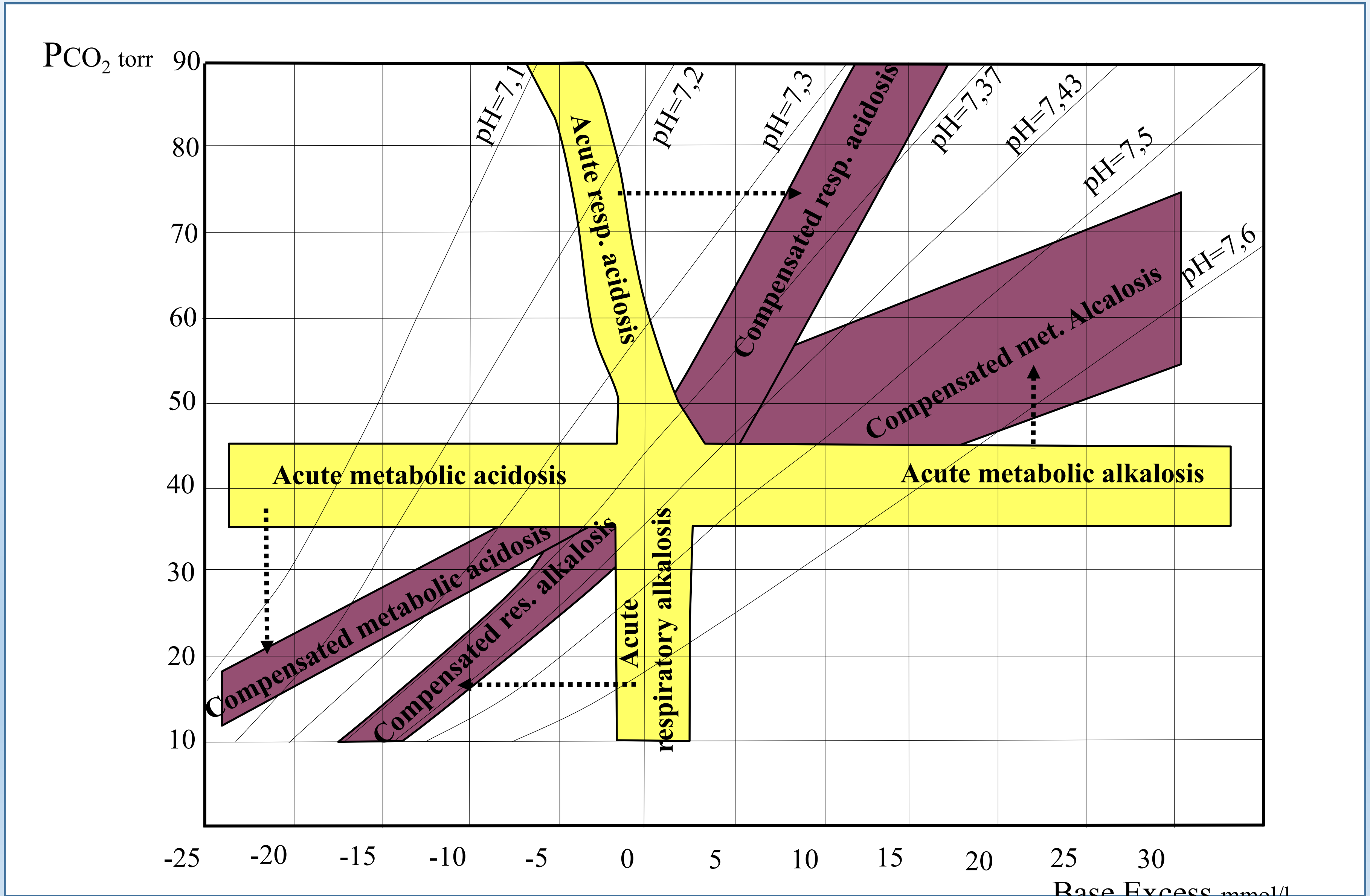
Thanks to the **compensation** the $[H^+]$ and pH return closer to norm

Compensation Diagrams

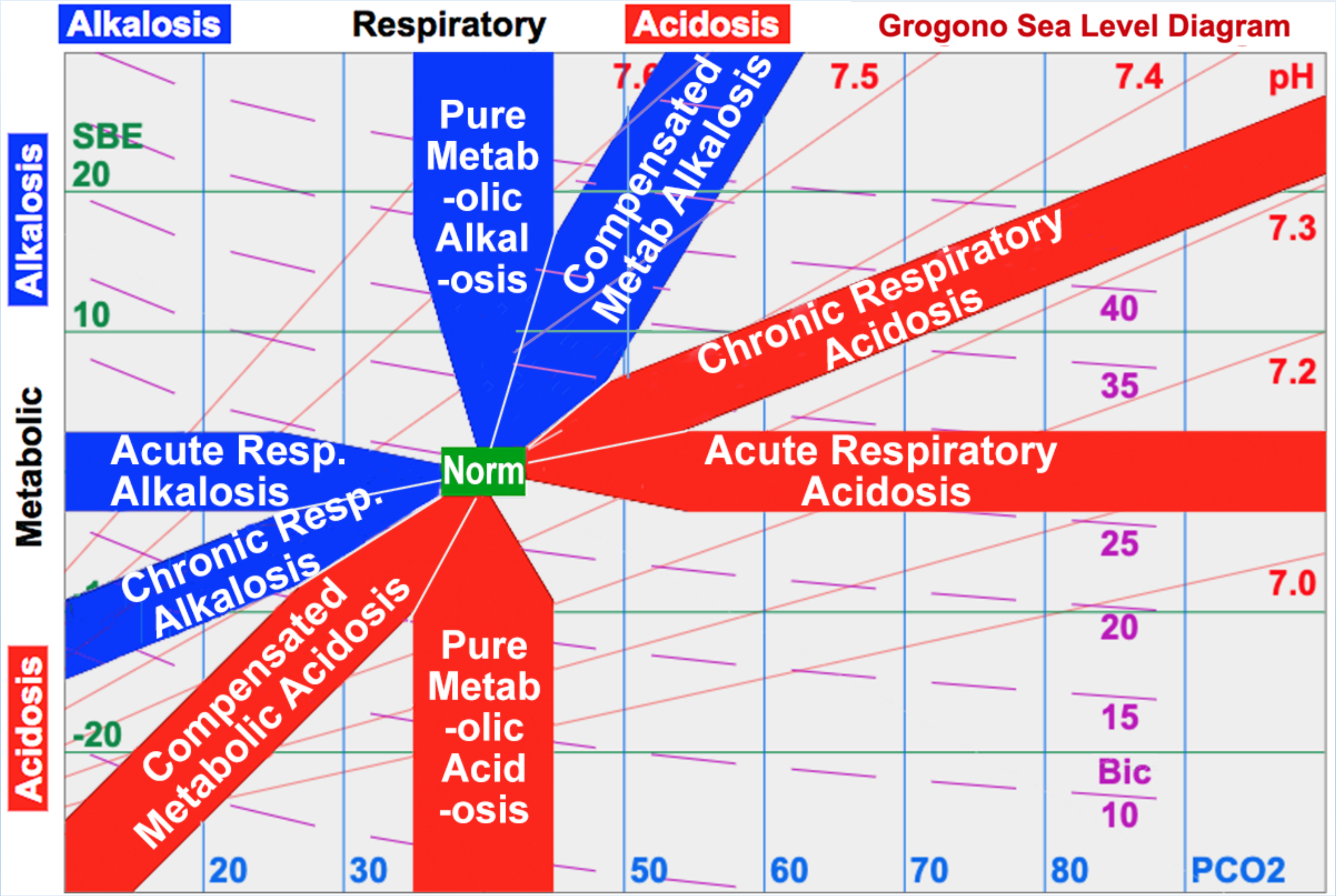




Compensation Diagrams 2



Compensation Diagram pCO_2 vs BE – Different



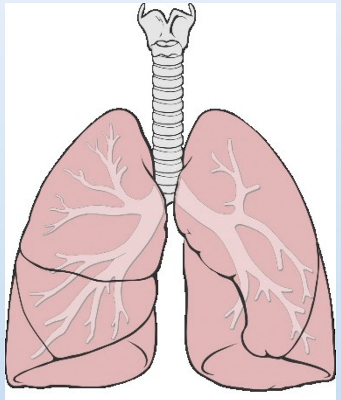
"Boston" Rules for Diagnosing ABB Disturbances

Alternative to the compensation diagrams - however, you have to remember them ☹

For straight-A students - optional: This is for pCO_2 expressed in mmHg – convert to a version in kPa (pCO_2 40 mmHg = 5,3 kPa)

Metabolic	Acidosis		$(pCO_2)_{EXPECTED} = 1.5 * [HCO_3^-] + 8$ or $\Delta pCO_2 = 1.2 * \Delta[HCO_3^-]$
	Alkalosis		$(pCO_2)_{EXPECTED} = 0.7 * [HCO_3^-] + 20$ or $\Delta pCO_2 = 0.6 * \Delta[HCO_3^-]$
Respiratory	Acidosis	Acute	$[HCO_3^-]_{EXPECTED} = 24 + 1\left(\frac{pCO_2 - 40}{10}\right)$
		Chronic	$[HCO_3^-]_{EXPECTED} = 24 + 3.5\left(\frac{pCO_2 - 40}{10}\right)$
	Alkalosis	Acute	$[HCO_3^-]_{EXPECTED} = 24 + 2\left(\frac{pCO_2 - 40}{10}\right)$
		Chronic	$[HCO_3^-]_{EXPECTED} = 24 + 5\left(\frac{pCO_2 - 40}{10}\right)$

Respiratory Acidosis and its Compensation



Cause: **Hypoventilation**

Part of global respiratory insufficiency (insufficiency type II)

Kidney (metabolic) compensation:

Takes 2- 3 days to develop

Kidneys excrete **more H^+** = returning **more bicarbonate into blood**

HCO_3^-

CO_2 **H_2CO_3**

10,6 kPa

↑

5,3 kPa

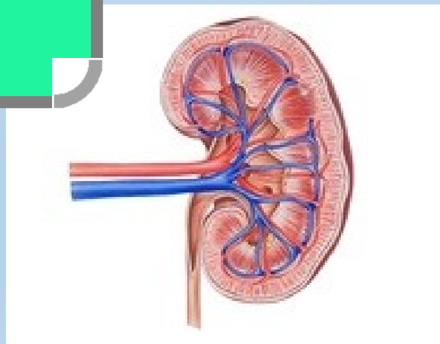
H^+

Acidosis: **pH = 7,7** ⇔ 80 nmol/l

↑ ↑

pH = 7,4 ⇔ 40 nmol/l

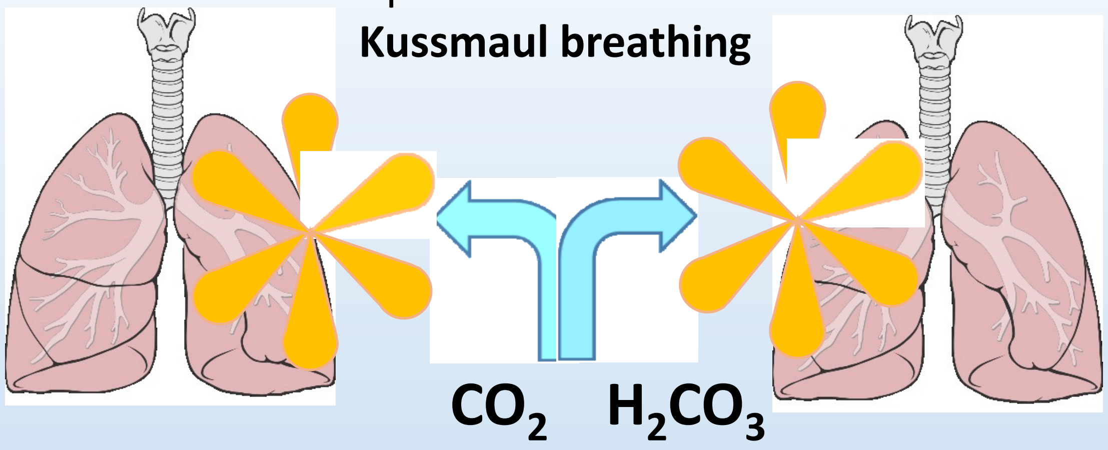
Thanks to the **compensation** the $[H^+]$ and pH return closer to norm



Metabolic Disturbances and their Compensation

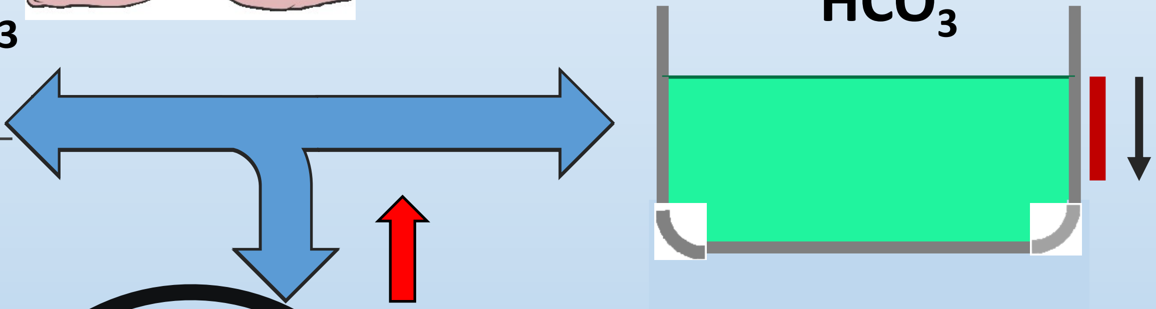
Metabolic Acidosis 1 + Compensation

Hyperventilation as a compensation of acidosis: **Kussmaul breathing**



↑ AG = $Na^+ + K^+ - Cl^-$ - ↓HCO_3^-

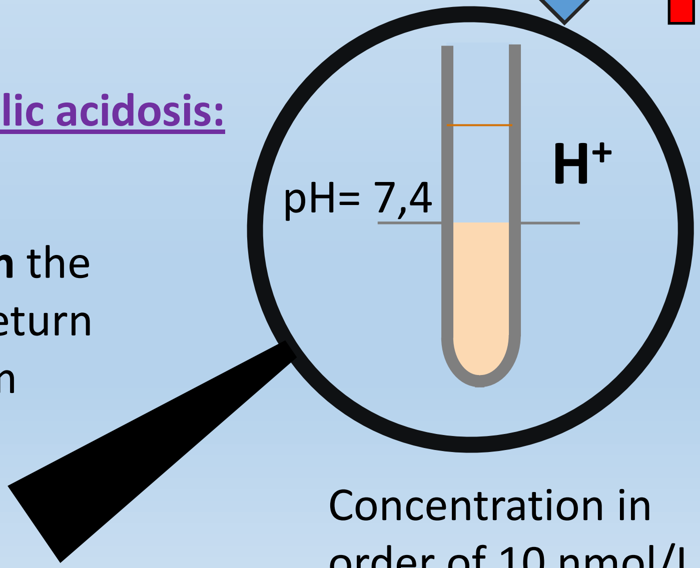
(does not include X^-)



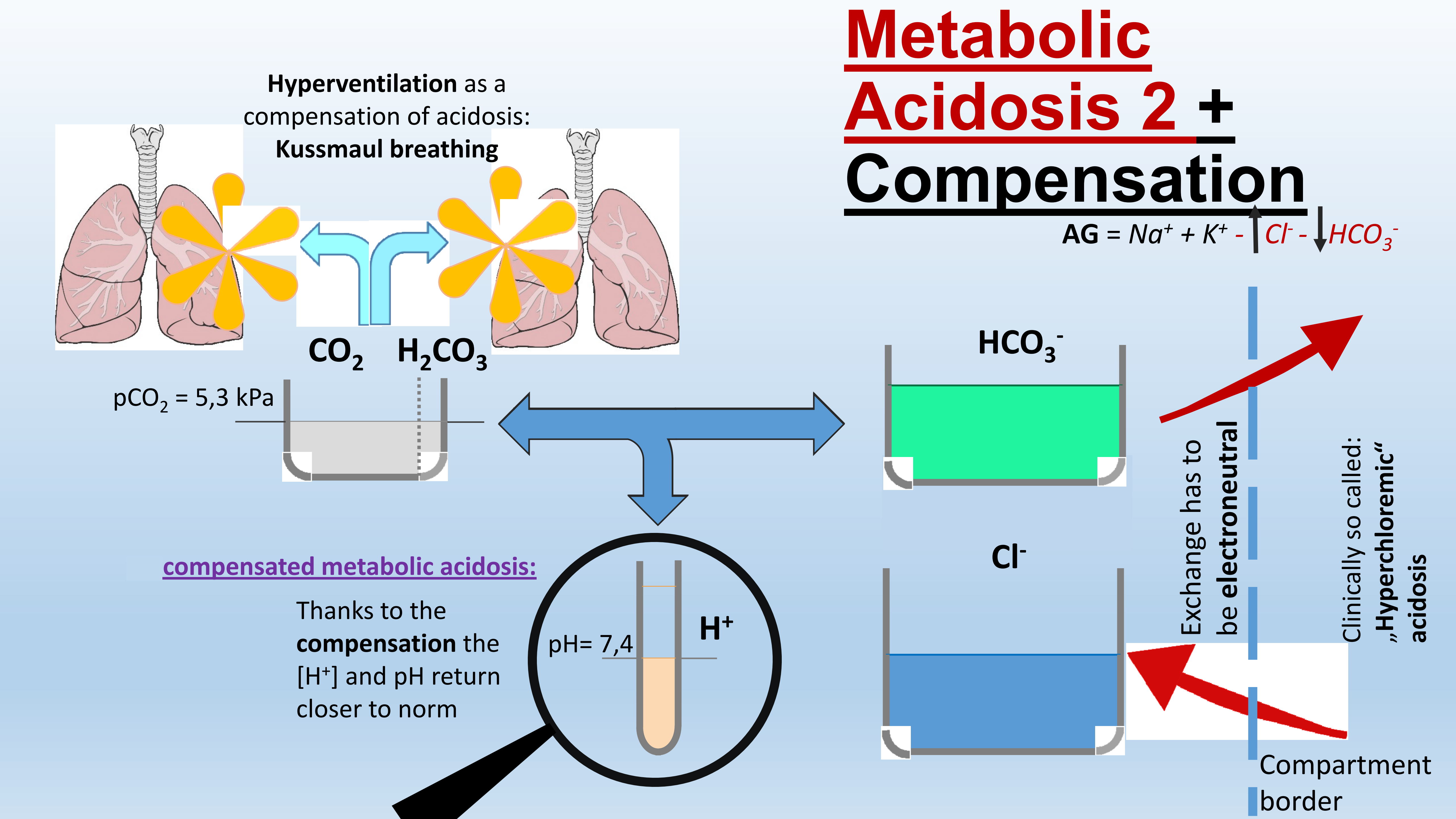
➔ ↑AG is equivalent to ↑***X^-***

<u>**compensated metabolic acidosis:**</u>

Thanks to the **compensation** the [H^+] and pH return closer to norm



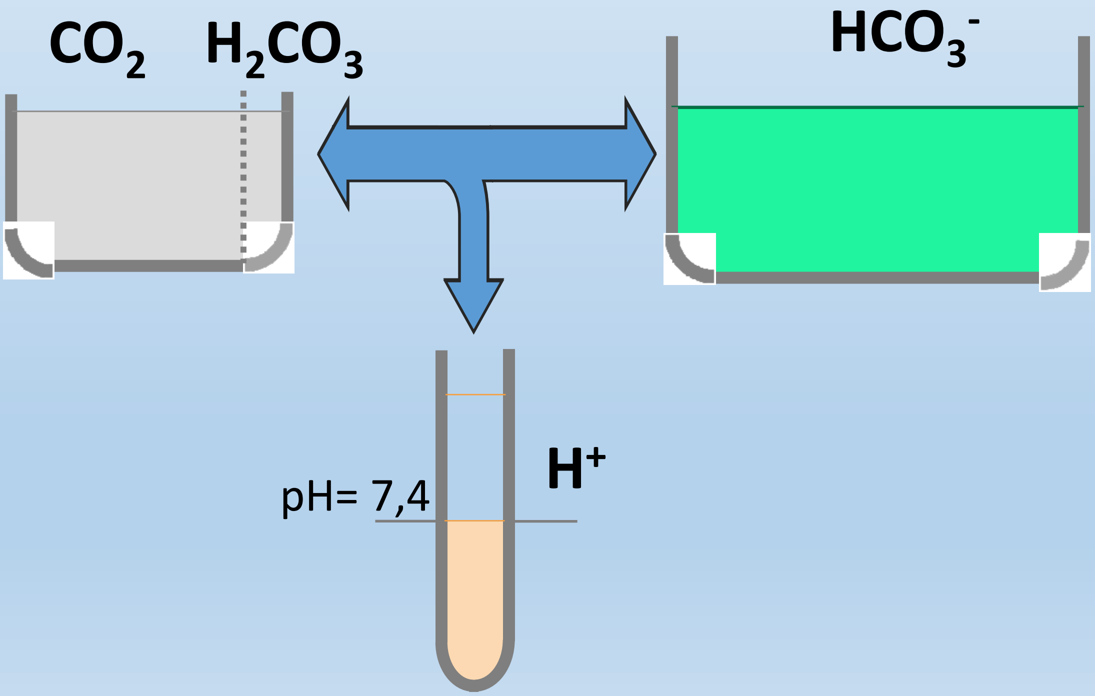
Concentration in order of 10 nmol/L

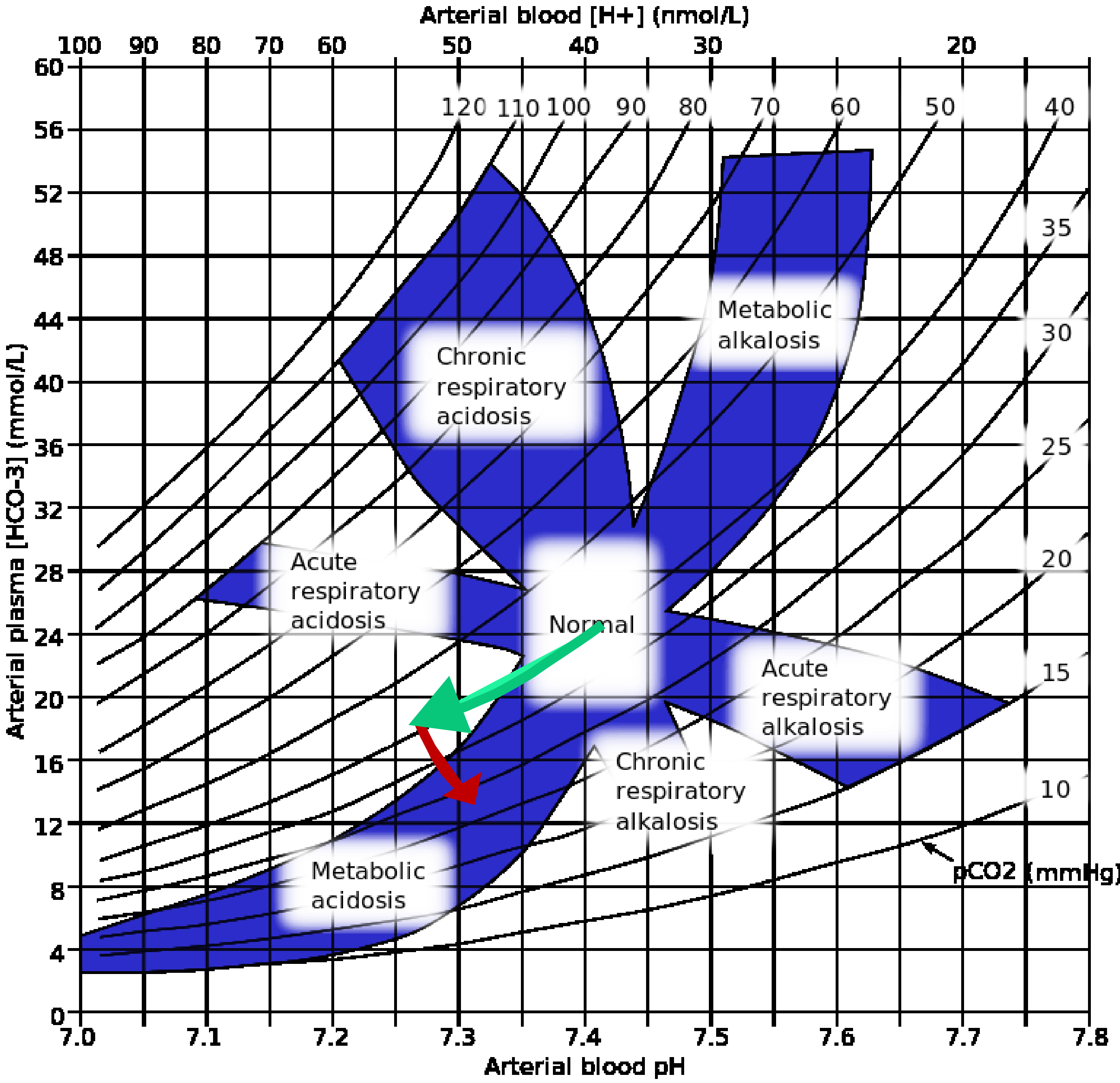


Metabolic Acidosis 2 + Compensation
AG = Na+ + K+ - ↑Cl- - ↓HCO3-
Hyperventilation as a compensation of acidosis: Kussmaul breathing
CO2
H2CO3
pCO2 = 5,3 kPa
HCO3-
Cl-
Exchange has to be electroneutral
Clinically so called: „Hyperchloremic“ acidosis
Compartment border
compensated metabolic acidosis:
Thanks to the compensation the [H+] and pH return closer to norm
pH= 7,4
H+

Metabolic Acidosis- Compensation Diagrams

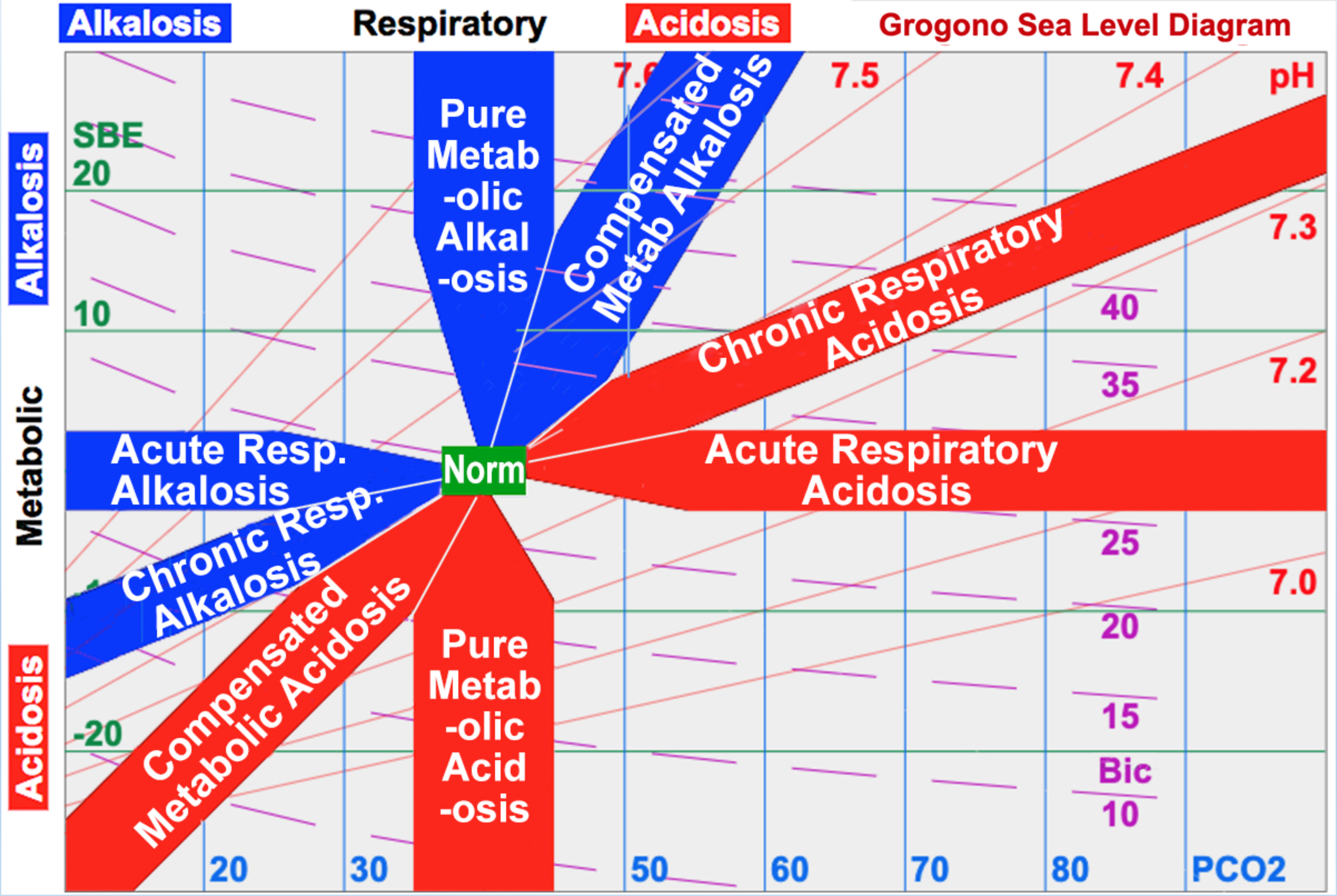
Respiratory compensation generally develops faster than the metabolic disturbance itself, thus the division into acute and chronic disturbances is missing in diagrams focused more clinically.





Metabolic Acidosis – Compensation Diagrams

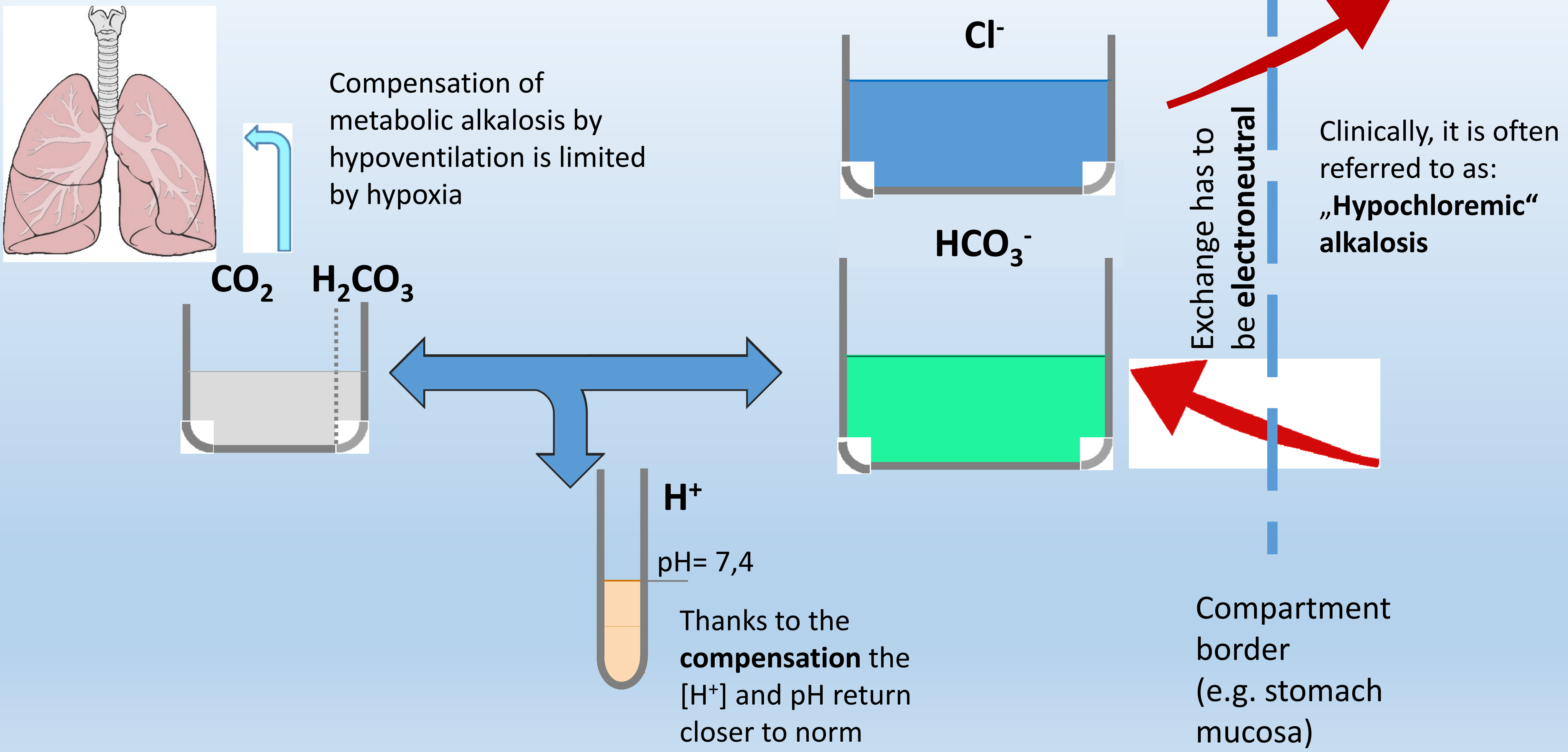
Try to draw the beakers using your memory only and add corresponding arrows illustrating acute and chronic metabolic acidosis into the diagram (full respiratory compensation develops in about 10 h)



Exercise – Metabolic Alkalosis

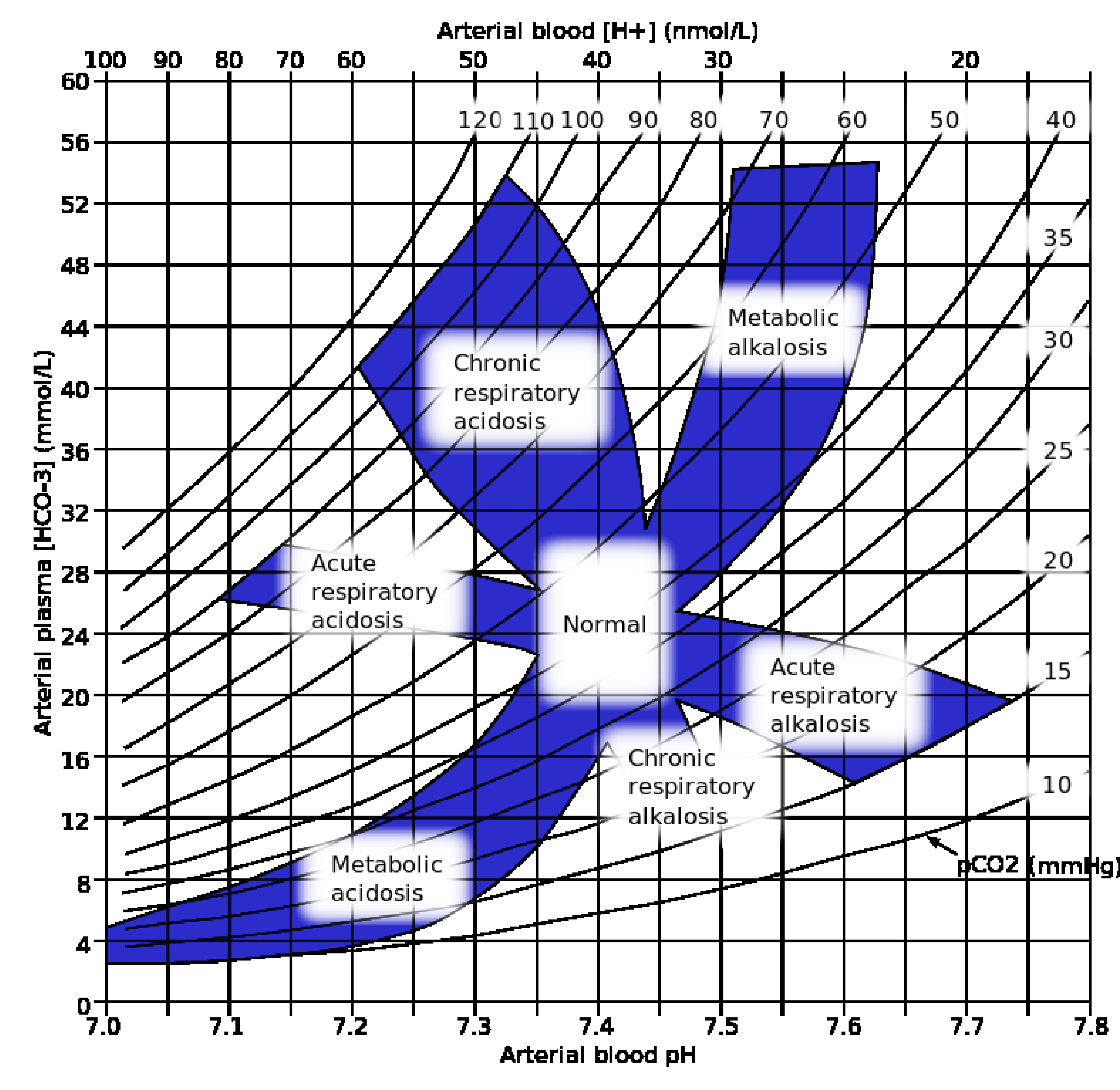
- Try to derive the beaker chart of metabolic alkalosis and its compensation by yourself. (result can be checked on the next slide)

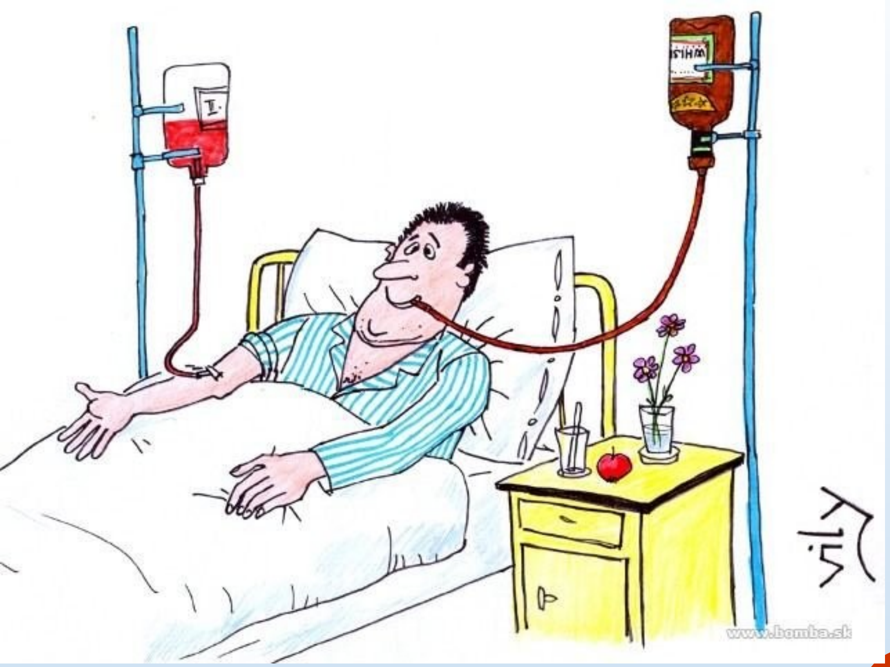
Metabolic Alkalosis + Compensation



Compensation of metabolic alkalosis

- Try do deduce the beakers and the arrows in the compensation diagram yourself.
- Min 2 minutes





Clinical Examples of ABB Disturbances

What is Taken and Assessed?

- Blood Gases Measurement in Arterial Blood (so called „Astrup“)
- Serum electrolytes
- Concentrations of buffers (e.g. hemoglobin) and other parameters

Blood Gases Measurement – „Astrup“

Assessed by the machine (sensors = selective electrodes):

pH = 7,4 ± 0,04

pCO_2 = 5,3 kPa

pO_2 = 13,3 kPa

- Calculated by the machine:
- $[HCO_3^-]$ = 24 mmol/l
  - *calculated using HH equation*
- BE = 0 mEq/l
  - *Base Excess, Hb concentration is needed for the calculation.*

Case Study No. 1

- 38 yo female, DM 1st type
- Chills and fever lasting several days
- She has not felt well --> not eaten much → not taken much insulin
- During admission day: Abdominal cramps, vomited several times
- Physical exam: BF 30 min^{-1}, HF 112 min^{-1}, BP 110/70 lying and 100/60 standing, 37 °C,
- Dry mucosae and fruity breath odor

Lab:

pH	7.20
pO2	12.8 kPa
pCO2	2.8 kPa
HCO3-	8 mEq/L
Glc	15 mmol/L
Na+	148 mEq/L
K+	5.5 mEq/L
Cl-	110 mEq/L

Positive aceton in urine

What acid base disturbance do we deal with? Is it a compensated disturbance?

What else could be said about her hydration and ion concentrations?

Possible Causes of Metabolic Acidosis

A) Loss of bicarbonates due to increased acid buffering

- Ketoacidosis
  - Diabetic
  - Alcohol
  - Starving
- Lactic Acidosis
  - Enormous physical strain
  - Circulatory shock / systemic ischemia
- Allogenic substances
  - Salicylate poisoning

AG (anion gap) is increased!: Anion of the buffered away acid accumulates in the body.

B) Loss of bicarbonates into the third space/out of body

- Through intestines
  - Diarrhea
  - Fistulas and stomias
- Through kidneys (loss of regulation)
  - So called Renal tubular acidoses
  - Renal failure (can have ↑AG)

The difference in common strong ions reflects ↓ HCO_3^-

E.g. ↑ Cl^- (instead of the bicarbonate)- so called „hyperchloremic acidoses“

(Or there can be e.g. ↓ Na^+ or..)

AG (anion gap) is normal!

Case Study No. 2

- You examine a 20 YO student at the hospital admission.
- Cannot concentrate and even could not move her fingers for a brief moment (which scared her). Still feels strange pins and needles in her fingers.
- She has not been seriously ill until now, no medication
- Physical examination – normal
- SA: She has split with her boyfriend recently, had been together for 4 years. Difficult to go thru.
- Lab: pH = 7.49
    - pO_2 = 13.4 kPa
    - pCO_2 = 4.1 kPa
    - HCO_3^- = 22 mmol/L
    - BE = -1 mmol/l

What acid-base disturbance this is?
What kind of acute problem do we see here?
What would be your advise her?

Possible Causes of Respiratory Alkalosis

Hyperventilation

- A) At hypoxemia
  - High altitude disease
  - Right-left pulmonary shunting
    - And ventilation-perfusion dysbalance similar to shunt
  - With artificial ventilation
- B) Respiratory center irritation
  - Trauma, inflammation, salicylates.
- C) Panic attack

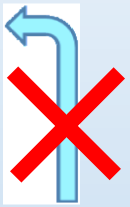
Case study No. 3

- 68 year old male comes to your ambulance.
- History of chronic bronchitis and pulmonary emphysema.
- Mild dyspnea, COVID antigen test negative
- Lab: pH = 7.31
    - pO_2 = 8.0 kPa
    - pCO_2 = 10.6 kPa
    - HCO_3^- = 38 mmol/L
    - BE = 12 mmol/L

What kind of acid-base disturbance do we deal with?
It this an acute a chronic problem?

Possible Causes of Respiratory Acidosis

- Decreased alveolar ventilation
    - A) Respiratory center depression
        - Drugs, medicaments (e.g. opioids)
        - Damage or ischemia:
            - Trauma
            - Stroke
            - Tumor
            - Cerebral edema / increased intracranial pressure
    - B) Nerve or muscle disease
        - Myasthenia gravis
        - Polyradiculoneuritis
        - Serious obesity/ Pickwickian syndrome



- C) Lung disease
    - Restrictive diseases
        - ARDS
        - Pulmonary fibroses
    - Obstructive diseases
        - Astma
        - Tumor
        - Foreign body
    - Increase in dead space
        - Pulmonary embolism
        - Pulmonary emphysema
    - Trauma, pneumothorax, serial rib fractures

- Increased pCO_2 in the inspired air

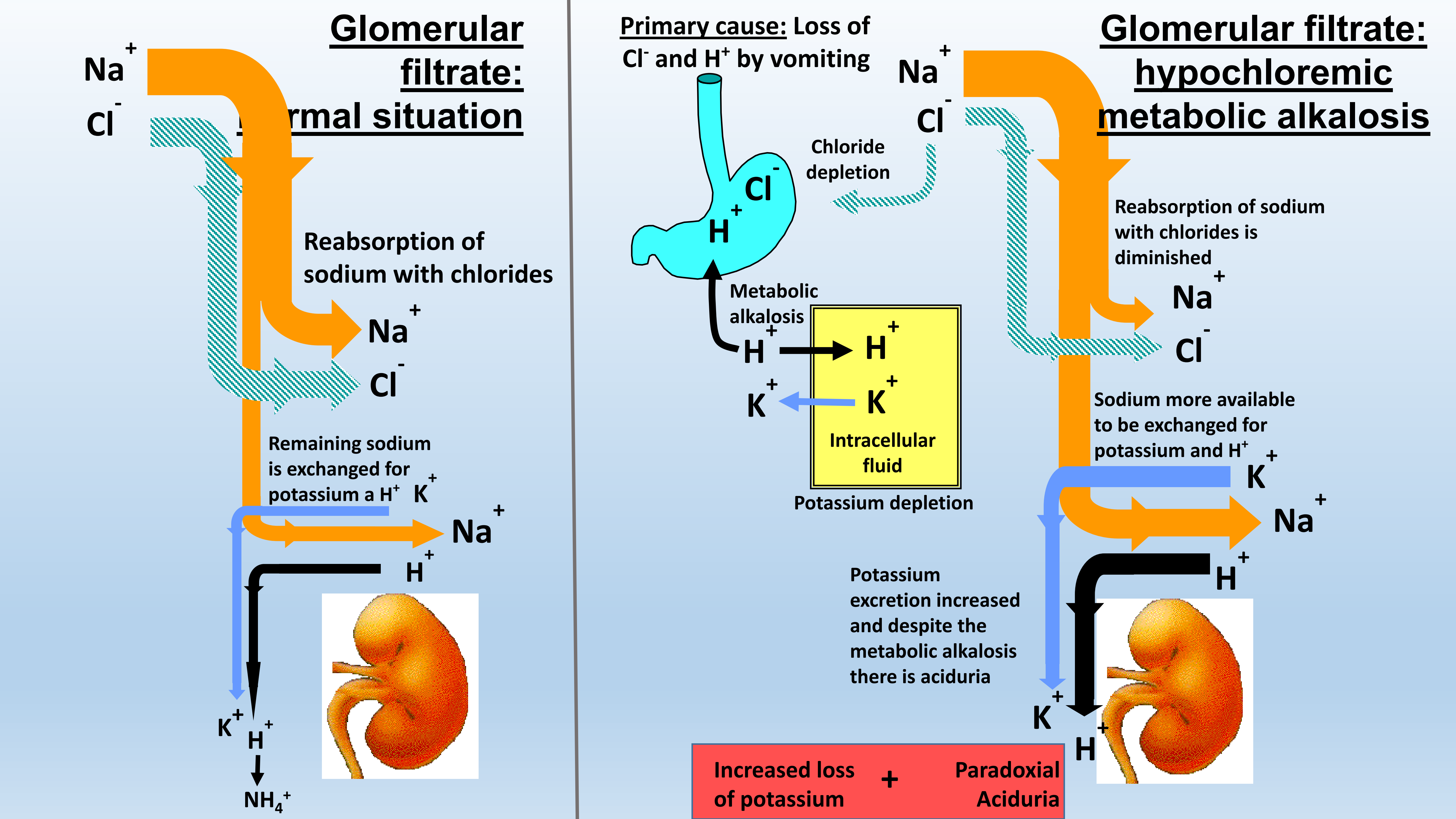
Possible Causes of Metabolic Alkalosis

- Loss of acid by vomiting

  ↑ HCO_3^- produced by stomach into the blood (when H^+ is secreted into the lumen).
- Increased renal HCO_3^- production/ increased urine H^+ secretion
  - Hyperaldosteronism
  - So called Bartter syndrome
- Liver failure (↓production of urea from NH_4^+ - the reaction would be acidifying)
- Non-adequate infusion of bicarbonates/ Ringer lactate.

Pathogenesis of Paradoxical Aciduria and Loss of K^+ after Severe Vomiting

- Clinacally important!
- After profuse vomiting, **hyperchloremic metabolic acidosis** develops
- Under normal circumstances, kidneys should regulate and produce only slightly acidic or alkaline urine.
- Instead, kidneys can worsen the alkalosis
- See next slide:



Glomerular filtrate:
rmal situation
Na^+
Cl^-
Reabsorption of sodium with chlorides
Na^+
Cl^-
Remaining sodium is exchanged for potassium a H^+
K^+
Na^+
H^+
K^+
H^+
NH_4^+
Primary cause: Loss of Cl^- and H^+ by vomiting
Cl^-
H^+
Chloride depletion
Metabolic alkalosis
H^+
H^+
K^+
K^+
Intracellular fluid
Potassium depletion
Glomerular filtrate: hypochloremic metabolic alkalosis
Na^+
Cl^-
Reabsorption of sodium with chlorides is diminished
Na^+
Cl^-
Sodium more available to be exchanged for potassium and H^+
K^+
Na^+
H^+
Potassium excretion increased and despite the metabolic alkalosis there is aciduria
K^+
H^+
Increased loss of potassium + Paradoxial Aciduria

Summary

1. Physiology and chemistry
   H+, pH, buffers, buffers incorporated into metabolism, HH equation, electroneutrality
2. Disturbances divided into respiratory and metabolic
3. Clinical examples and causes

	Primary disturbance	Compensation
Respiratory acidosis	↑pCO_2	Renal - ↑HCO_3^-, ↑BE
Metabolic acidosis	↓HCO_3^-	Pulmonary - ↓pCO_2
Respiratory alkalosis	↓pCO_2	Renal - ↓HCO_3^-, ↓BE
Metabolic alkalosis	↑HCO_3^-	Pulmonary - ↑pCO_2

Thank you for your attention