6. DISORDERS OF THE SALT- AND WATER-BALANCE AND THE ACID-BASE EQUILIBRIUM

In order to secure the normal function of cells, tissues and organ systems it is not enough to provide them with nutrients and oxygen continuously and to remove their waste-products, but it is of basic importance to maintain the stability of the size of water-compartments, the stability of their osmotic pressure and pH is also required. The size of the water-compartment decreases somewhat with increasing age and the distribution of the water-spaces (water compartments) also changes. However, under physiological conditions both the osmotic pressure and pH remain stable.

Management of salt- and water-balance involves partly the regulation of various volumes in the body (volume regulation) partly that of the osmotic pressure (osmoregulation). The two regulations theoretically (and for didactic reasons) may be separated, however, in practice they exist only in combined forms. In the pH regulation several organ functions have a contributory role.

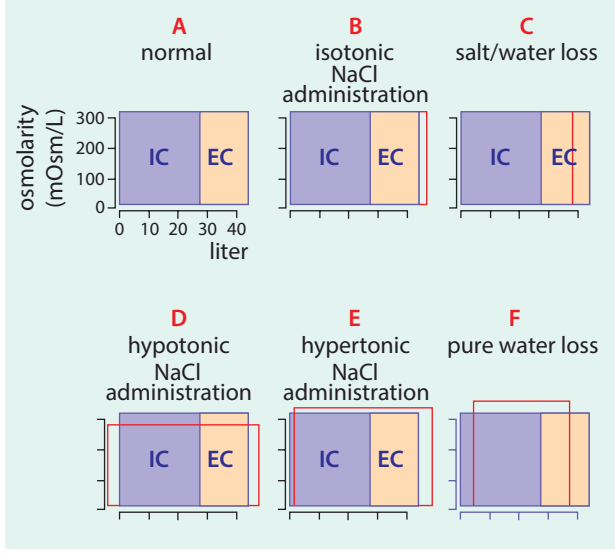

Fig. 6.1.: Changes of the extra- and intacellular volume and osmotic pressure. **A**: normal state, **B**: isotonic NaCl solution increases mainly the ECV, C: after proportionate loss of salt and water the ECV decreases, **D**: hypotonic NaCl solution increases both ECV and ICV (more the ECV), the osmotic pressure decreases in both compartments, **E**: after hypertonic NaCl the ECV increases, the ICV decreases, the osmotic pressure increases in both compartments, **F**: loss of pure water is followed by proportionate decrease of volume and increase of osmotic pressure in both compartments.

6.1. DISORDERS OF SALT- AND WATER-BALANCE

6.1.1. DISTRIBUTION AND CHARACTERISTICS OF WATER-SPACES

In young adult ca. 60% of body weight is water. About 2/3 of this is deposited intracellularly (IC), the rest is extracellular (EC) water. The EC water can be further divided as intravascular space (about 3 liters of plasma), all the rest is interstitial fluid (Fig. 6.1.). The distribution of water-spaces depends on age: in neonates the EC (mainly the interstitial) portion is much greater, at old age the total water-space and the EC volume decrease, particularly the interstitial volume. The size of the water-spaces can be measured by administering known amounts of substances that distribute evenly in the given water-space and their concentration can be measured.

The composition of the water-spaces is very different: in the EC space the dominant cation is Na^+, dominant anion is Cl^-, in contrast to the IC space where the dominant cation is K^+ with a lot of phosphate and protein anions. The pH value is also slightly different in various water-spaces: in the IC space it is slightly lower (ca. 7.2). Regarding the osmotic pressure there is no difference between the water-spaces. Regulation of volume always has a priority, even if it means sacrificing the osmoregulation, the pH- or K-balance.

Regarding the volume regulation, there are three possibilities: the EC volume is normal, higher than normal, or lower than normal. The same possibilities are valid also for the osmoregulation. From the combination of all these 9 variants can be seen (Fig. 6.2.), only one of them (N°5) is normal.

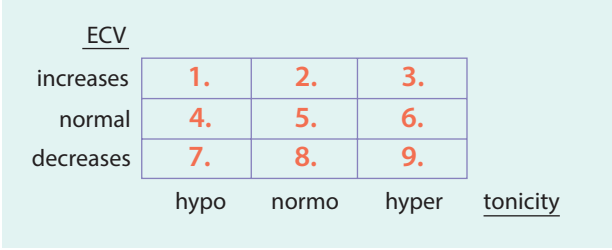

Fig. 6.2.: Changes of the ECV and the effective osmotic pressure (tonicity) result in 9 variants: only #5 is normal. Excess of ECV (#1-3 variants, hypervolemia and edema forms) or its loss (#7-9 hypovolemia and exsiccosis) may be accompanied by hypo-, normo- or hypertonicity depending on whether a high ECV is caused by excess water, excess isotonic fluid or excess salt. Low ECV may be due to loss of salt, proportionate loss of salt and water, or water only. It follows that the effects of ECV and tonicity changes are mixed. States of hypo- and hypertonicity may appear without ECV change (#4 and #6).

6.1.2. VOLUME REGULATION AND ITS DISORDERS

Although the "volume" expression suggests fluid volume, the main target of this regulation is the retention or excretion of salt: it is only followed by the retention or excretion of water – this is how the volume changes (diuretics are in fact saluretics, this is how they decrease the EC volume). Volume regulation is directed primarily to the plasma-space, and due to a balance between plasma and interstitial spaces it also affects the whole EC volume. Although there is certain regulation for the IC volume, little is known about its mechanisms (products of IC metabolic processes and mechanisms as a consequence of osmotic changes may be in the background).

Stretch sensitive receptors can be found both at the high- and low-pressure parts of the vascular system (aortic arch, carotid sinus, vs. the atria, big veins, pulmonary vessels), which influence the rise or fall of renal salt-excretion with concomitant increase or decrease of water excretion. The salt content of the body significantly modifies the EC volume (ECV), but the ECV only, since the bulk of salt content of the body is contained almost exclusively in the ECV. Increased salt retention is performed by the help of aldosterone (RAAS), while for higher salt excretion the endogenous natriuretic factors (ANP and BNP /atrial and brain natriuretic peptides/, the renal PGE_2, PGI_2, kinins, renomedullary lipids and other natriuretic factors) are used. In all cases the salt is followed by proportional retention or excretion of water. By the help of these mechanisms the plasma volume and together with it the connected interstitial volume can increase or decrease. The distribution within the ECV may change independent of the size of ECV, due to the transcapillary fluid exchange by the local Starling forces: the plasma and interstitial volumes do not change necessarily by the same degree or even in the same direction. At higher external pressure (e.g. immersion, swimming) the interstitial hydrostatic pressure increases, salt and water enters the plasma space, this activates the natriuretic mechanisms and soon enhanced diuresis starts. (After swimming the opposite happens and the low plasma volume induces thirst).

Decreased pressure in the renal artery or decreased renal perfusion activates renin-secretion in the juxtaglomerular apparatus of the kidney. Low arterial pressure and fall of blood volume indirectly, by enhancing the sympathetic activity, also increase the secretion of renin. Renin, as an enzyme, splits liver derived angiotensinogen to decapeptide angiotensin I which is transformed by ACE enzyme to octapeptide angiotensin II. Angiotensin II has a vasoconstrictor effect and induces water-intake and also enhances the aldosterone secretion to increase tubular salt and water reabsorption and H^+-, K^+-excretion. Hyperkalemia may directly stimulate aldosterone secretion. The RAAS effects are antagonized at different points by natriuretic factors: e.g. ANP inhibits renin secretion, the production and effect of angiotensin II and aldosterone, also the sympathetic activity; it has a vasodilatory effect and causes natriuresis directly. ANP enhances the capillary permeability, inhibits the production and action of ADH.

As compared with aldosterone and natriuretic factors, a subsidiary role is played in volume regulation by the antidiuretic hormone (ADH): severe hypovolemia (which cannot be fully compensated by aldosterone) elicits moderate increase of ADH secretion and water retention, without simultaneous retention of salt.

A significant enhancement of salt intake is normally soon followed by proportionate increase of salt excretion. In the new balance the salt content of the body (and the size of ECV) rises only moderately. By the same token, diuretics transiently increase salt excretion, but with unchanged salt intake the salt excretion is normalized still in the presence of the diuretic drug – with slightly decreased ECV. Although the changes of ECV are not too big, even less the changes of plasma volume, these changes may still be important regarding the regulation of blood pressure: the increased salt intake contributes to the development of volume-hypertension, while the diuretics have antihypertensive effect (Figs 6.3. and 6.4.).

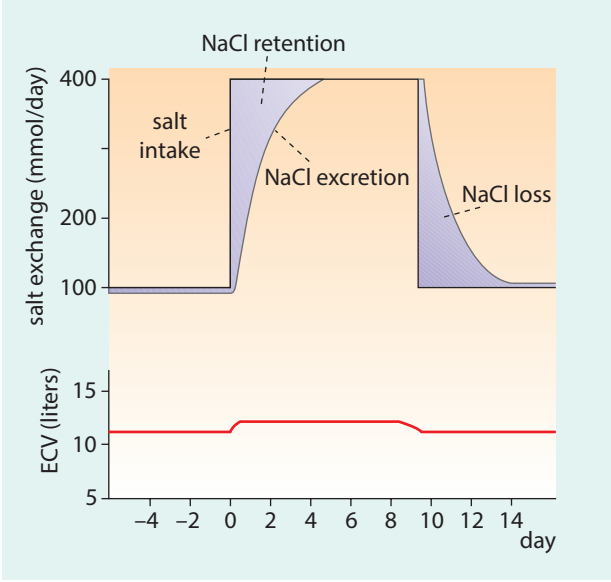

Fig. 6.3.: A rapid rise of salt intake is followed by a fast increase of salt excretion, thereby salt-retention remains moderate and causes only small rise of ECV (more plasma causes hypertension). Upon normalization of salt intake, the original balance is regained. For such adaptive changes, function of RAAS, natriuretic factors and normal kidney are necessary.

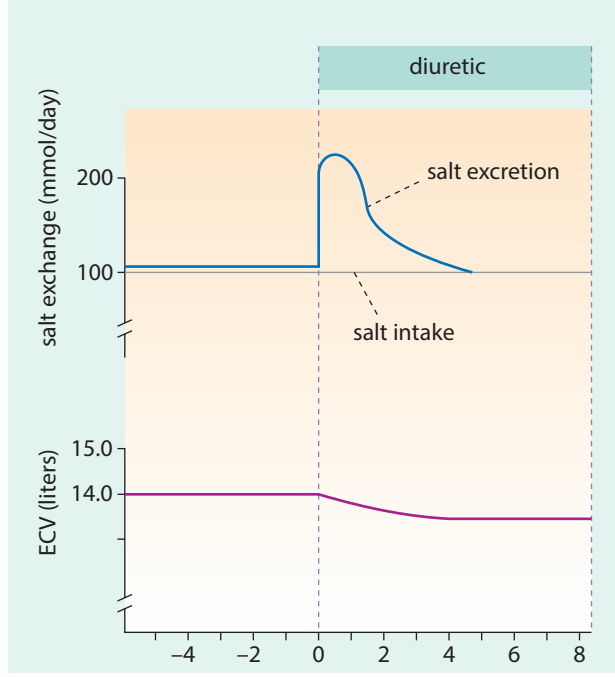

Fig. 6.4.: Salt excretion can be increased by diuretics. Although this is transient (the salt intake/excretion is soon resumed) during treatment the ECV remains slightly lower, hypertension is suppressed.

6.1.2.1. DECREASE OF EXTRACELLULAR VOLUME

Decrease of ECV due to salt- and water-loss is generally called *exsiccosis* – this refers to a simultaneous fall in plasma space (hypovolemia) and interstitial space.

The term exsiccosis is often used interchangeably with *dehydration*, although the latter word is better used for cases of pure water loss or deficit. Dehydration necessarily affects also the IC volume besides the ECV, and it also results in rise of osmotic pressure. In its consequences the symptoms of a moderate ECV decrease and an elevated osmotic pressure are mixed (the ECV decrease is smaller than during loss of similar amount of salt and water). Exsiccosis and dehydration may be really combined if the salt- and water-loss is not proportionate, but more water than salt is lost (e.g. sweating, exhaled vapor).

Most important causes of exsiccoses

1. gastrointestinal salt- and water-loss (e.g. vomiting, diarrhea, biliary or pancreatic drainage)
2. renal salt- and water-loss (e.g. diabetes, renal polyuria, diuretics, Addison disease)
3. fluid loss through the skin (sweating, burnings) or by respiration
4. fluid loss into the "third" water space (ascites, fluid accumulation in gut in ileus, /ch. 7.2.2.2./, quickly developing edema, big hematoma e.g. fracture of femur).

Hypovolemia may develop not only in exsiccosis, but also in cases of rise in interstitial fluid: e.g. hypoproteinemic edema, or other cases of abnormal fluid exchange at the capillary level (e.g. severe cardiogenic congestion, anaphylaxis) (ch. 6.1.2.2.).

Consequences of exsiccoses

Symptoms of decreased interstitial fluid are easily noticeable: the turgor decreases (wrinkled skin, dry tongue, soft eyebulbs, in babies subsiding fontanel), but these consequences are probably of smaller importance. Very important are, however, the hypovolemic circulatory disorders, with hypotension (particularly postural hypotension, fainting tendency, weakness, tachycardia), hemoconcentration, decreased tissue perfusion, tissue hypoxia, oliguria (even in cases of primary polyuria without proportional fluid intake), prerenal azotemia (ch. 5.5.3.1.), extrarenal uremia. In most severe cases hypovolemic shock develops (ch. 2.2.2.6.). In case of exsiccosis sweating decreases, leading to hyperthermia in a warm environment (ch. 8.5.2.2.).

The consequences of exsiccosis are particularly severe in babies and seniors. In babies and small children, the ECV and its dynamics are relatively high, thus, as compared with their body weights the daily fluid-in-

take and fluid-loss are great. Thus, the ECV may easily decrease and the exsiccosis strongly affects the total water and total Na content, leaving hardly any room for compensation of plasma loss. In seniors the interstitial water is already smaller and binds more strongly to the connective tissue, not allowing water replacement from the interstitium to the plasma. On top of these the feeling of thirst in seniors is insufficient, therefore exsiccosis develops easily and even moderate exsiccosis may cause severe hypovolemia. Combined changes of ECV and osmotic pressure will be dealt with in ch. 6.1.3.

The possible compensation of hypovolemia is the enhanced activity of RAAS (except: Addison disease and renal tubular acidosis /RTA/ type IV). In case of more pronounced volume reduction additionally the ADH activity is also increased (except: diabetes insipidus). The defective compensation of volume by RAAS necessarily leads to ADH activation, but with this hyponatremia and decreased osmotic pressure also develop.

6.1.2.2. INCREASE OF EXTRACELLULAR VOLUME

Most important causes of elevated extracellular volume

1. enhanced fluid intake (e.g. giving too much water to drink to elderly person or baby, intravenous infusion)
2. decreased water excreting capacity (e.g. severe renal failure)
3. renal fluid retention due to mineralocorticoid- or ADH-hyperfunction (e.g. primary and certain secondary forms of hyperaldosteronism /e.g. anaphylaxis, nephrotic syndrome/, Cushing syndrome)

Consequences of elevated extracellular volume

Depending on the localization of the excess fluid, the high ECV may mean generalized *edema* (excess in the interstitium), or the excess remains intravascularly – in this case the hypervolemia causes *hypertension:* e.g. Conn syndrome, partly in Cushing disease and in chronic renal failure (for the mechanism see ch. 2.3.2.1. and 5.5.2.). At the level of capillaries, the fluid exchange (Starling forces: the relationship of intracapillary and pericapillary hydrostatic and oncotic pressures) determines that which of the two possibilities prevails. For edema formation this is the level for outward movement of fluid. There is no edema without appropriate changes of the Starling forces. In Conn syndrome the salt and water excess remains in the vascular space, since the precapillary vasoconstriction does not allow any marked change in hydrostatic pressure at capillary level. It leads to hypervolemia and hypertension, although due to natriuretic factors and escape mechanism the hypervolemia is moderate. Such hypervolemia may cause moderate hemodilution and decreased hematocrit value, but no edema.

The extra- and intravascular fluid volumes may change in opposite directions: e.g. in hypoproteinemia (protein-calorie malnutrition ch. 9.1.1.1., nephrotic syndrome ch. 5.5.3.5., liver cirrhosis ch. 7.6.1.7.) the ***low oncotic pressure*** allows outward flow of fluid from capillaries into the interstitium, but this leads to decrease in plasma volume, which compensatorily evokes secondary hyperaldosteronism. Similarly, hypovolemia follows portal hypertension and cardiogenic edema: this develops by the ***high hydrostatic pressure*** due to venous congestion.

On capillary level the outflow or inflow of fluid is not precisely equal. However, in case of slightly higher outward movement interstitial edema develops only at occlusion of lymph vessels (lymphedema, ch. 2.5.). In other cases, the ***dynamic disorder of lymphatic flow*** cannot carry away the larger fluid excess filtered from the capillaries.

The last mechanism of edema formation is the ***enhanced capillary permeability*** (e.g. in inflammation).

Edema may appear in various forms, depending on the localization of salt- and water-excess and the character of edema. In cardiogenic edema the venous congestion and the increased capillary hydrostatic pressure causes salt and water (but no macromolecule) outflow to the interstitium. This ”free” fluid can be mobilized within the interstitium, for pressure it moves away and it takes time that the fluid returns (pitting edema). It is localized mainly at the deepest points of the interstitial tissue. In contrast to this, occlusion of the lymphatic vessels usually causes non-generalized, but regional edema. It is rubbery edema: besides salt and water, water-binding macromolecules (proteins) also accumulate, they do not move freely between the interstitial fibers. Similar edema may develop due to protein extravasation when the capillary permeability is elevated (e.g. allergic, angioneurotic edemas, mainly in interstitial tissue of loose connective tissue /ocular, labial, laryngeal edemas/). Rigid edema develops in hypothyroidism (myxedema): mucopolysaccharides accumulate and bind water in the interstitium.

At clinical manifestation of edema about 1.5 liters of interstitial fluid accumulates (characteristically in

the legs /anasarca/ or in the sacral region in bedridden patients). When a drug has to be applied according to the body weight, this water excess has to be accounted for. By increasing the distance between cells and capillaries, edema inhibits the optimal oxygen and nutrient supply for the cells, it inhibits the wound healing process, enhances the tendency for local infections, in extreme cases it may cause necrotizing edematous vesicles mainly in the skin.

Edemas of special location may be of particular importance. Such is, e.g. the pulmonary edema (e.g. acute heart failure, inhalation of toxic gases), when due to the enhanced permeability of pulmonary capillaries protein-rich fluid leaves the capillaries, apart from the interstitium it gets also into the alveolar space, causing severe acute global respiratory failure (i.e. not simply interstitial accumulation of salt and water). Similarly, special is the cerebral edema which causes life-threatening increase of the intracranial pressure. In fact, this is not a real edema: the excess fluid is located not so much interstitially, rather within the brain cells, cf. ch. 2.6.2.4.). Edema of special location is the ascites and any other circumscribed fluid accumulation. Some local edemas may have serious consequences simply by their localization (e.g. laryngeal edema).

Whatever is the origin of a generalized edema, the interstitium receives fluid from the plasma space. For the compensation of the decreasing plasma volume secondary hyperaldosteronism can be expected, with all of its consequences (e.g. potassium loss). The only exception is the „overfilling" of the end-stage renal failure patient, when the plasma space increases and there is no hyperaldosteronism.

6.1.3. OSMOREGULATION AND ITS DISORDERS

The osmotic pressure is similar in all water-spaces: normally 280-300 mOsm/kg. Although the osmotically active substances may not be able to move between the water-spaces, the free movement of water secures that the osmotic pressure is similar everywhere. Osmoregulation is not directed for the regulation of the quantity of osmotically active substances (these substances are bound to certain water spaces, thereby their regulation may refer to the size of the given water-space and not to the osmotic pressure in this space). Osmoregulation can be performed more easily by the influence on quantity of water amount. It is also important that the osmoregulation always refers to the whole water space, since the freely moving water establishes a similar osmotic pressure in all water spaces. Osmoreceptors sensing high osmotic pressure (mainly in the hypothalamus and the liver: they sense their own stretch) will shrink due to water-loss and enhance the ADH secretion from the posterior lobe of the hypophysis. Thereby the water intake (thirst) increases, and the simultaneously increased water reabsorption collaborates. (ADH produces concentrated urine by increasing the water permeability of collecting ducts by the help of aquaporin channels). Low osmotic pressure acts in the opposite way: the water intake decreases, large volume of diluted urine is emptied – in the background stands the decreasing ADH production. Increase of the osmotic pressure and the amount of renally filtered osmotically active substances (e.g. glucose) does not result in little and concentrated urine, but, independent of presence of ADH, in osmotic diuresis and salt- and water-loss.

Apart from serving osmoregulatory mechanisms, ADH-production may also change by non-specific ways (ch. 10.2.). It may increase, e.g. in states of marked hypovolemia, in severe stress situations (surgery), in cases of pain, nausea, in influence by nicotine-, morphine- or chronic alcohol-intake, but ADH-producing tumors are also known. Independently of osmoregulation, the effect of ADH may decrease e.g. in acute alcohol intoxication and its production/action decreases in states with elevated levels of N-containing waste-products.

From the point of view of osmoregulation, the decisive factor is the effective osmotic pressure (*tonicity*) of the plasma. Those substances which cannot freely enter the cells (e.g. Na, glucose) increase the effective osmotic pressure (tonicity) of the plasma, therefore water leaves the cells until equalization of intracellular/extracellular osmotic pressures. Therefore, the volume of the cells also changes. Those substances that can freely enter the cells (e.g. urea, ethanol, methanol, ethylene glycol) do not induce water movement or change in cellular volume, and, although they increase the absolute osmotic pressure, they do not alter the tonicity. These substances do not influence significantly the production or action of ADH.

The osmotic pressure of the plasma can be calculated by the formula of [2xNa + urea + glucose], but the real osmotic pressure is higher by about 10 units due to the presence of non-measured osmotically active substances (osmotic gap). Higher *osmotic gap* suggests that the amount of such non-measured osmotically active

substances (mannitol, alcohol, ethylene glycol, ketone bodies, lactate, etc.) is markedly increased.

In the ECV the se-Na level is the most important factor of osmotic pressure, the significance of other ions and glucose is much smaller. In the abnormal rise of osmotic pressure – beside Na – other substances (glucose, urea, ketone bodies, lactate, ethylene glycol, mannitol, sorbitol, X-ray contrast substances, etc.) may play a role, while the abnormal decrease of osmotic pressure always means hyponatremia. Abnormalities of osmotic pressure will be detailed at the chapter about disorders of Na-metabolism, in forms of hyponatremia and hypernatremia. The causes of such disorders are summarized together with the disorders of ECV in Table 6.1.

6.1.4. DISORDERS OF SODIUM BALANCE

The Na^+-metabolism is strongly connected with volume regulation and osmoregulation. The normal plasma-Na level is 135-145 mmol/l, it is the same in the interstitium, but much lower in the IC volume. Ac-

Table 6.1.

Combined changes of the extracellular volume and the osmotic pressure

	Hypotonicity	Normotonicity	Hypertonicity
ECV	Netto water excess: Enhanced water intake: – Too much water to old, or baby – Psychiatric patient – Hypoosmolar irrigation Low water-excreting capacity: – In severe renal failure even moderate water intake – SIADH (ADH)* – Edemas** (severe forms) (cardial, portal, adjoining hypertension, hypalbuminemia) – Glucose infusion, mainly in surgical patients***	Isotonic fluid excess: – Renal salt/water retention – Physiological NaCl- infusion – High salt-intake in healthy adults – Early, milder forms of edema	Netto salt excess: – Conn-syndrome – Cushing-syndrome – Extreme salt intake, e.g. in small children (by mistake, instead of sugar), in oligo-anuric patient (the EC Na-concentration depends on intake) – Hypertonic $NaHCO_3$ –infusion e.g. in severe lactic acidosis after standstill of heart
ECV norm.	– Salt-deprivation – Sweating + water replacement (sweet refreshments!)	NORMAL STATE	– Increased salt intake (eventual) (transient, the osmoregulation quickly corrects it)
ECV^-	Salt loss exceeds water loss: – Addison-disease (aldosterone, ADH) – Overdose of diuretics with low salt intake – Salt-losing kidney**** – RTA IV. (aldosterone effect) – Ileus – Early phase of cystic fibrosis diarrhea (thick secretum)	Proportionate salt/water loss: – Burns – Bleedings – Vomiting, diarrhea – Renal loss (e.g. asthenuric polyuria)	Water loss dominates: Decreased water intake: e.g. elderly, baby Increased loss of hypotonic fluid or water: – Perspiration insensibe (heavy exercise in hot environment) – Diabetes insipidus (ADH) – Diabetic osmotic diuresis – Sweating

* SIADH (=Syndrome of Inappropriate ADH secretion) non-physiologically high ADH-secretion, possible causes: surgery, stress, fear, pain, stroke, local inflammation, adenoma, tumors, congenital disorder.

** In states of edema the effective circulating volume decreases, this is compensated by secondary hyperaldosteronism. However, the renal salt/water retention will increase mainly the size of the edema or ascites. At earlier/milder stages there is normotonicity, later in more severe edema the decrease of circulating blood volume enhances ADH secretion, thus, hypotonicity develops although in the ECV the total amount of Na is high.

*** The 5%-os glucose infusion osmotically physiological, but after glucose utilization only water remains in the ECV. This is often applied in postoperative states, when the ADH is also elevated – together lead to hypotonicity and hypervolemia.

**** Salt-losing kidney may develop e.g. in diabetes mellitus, chronic renal failure, in primary tubular damage (hypoxia, ATN), aged kidney, acutely in BNP overproduction due to diffuse brain damage (cerebral salt-wasting syndrome).

cordingly, the bulk of the body Na-content is deposited mainly in the EC space. Increasing or decreasing the Na-reabsorption also means increase or decrease of ECV, without alteration of plasma Na-concentration – these have been mentioned in the chapter on regulation of volume (ch. 6.1.2.). However, the Na-concentration may change in the ECV: its increase or decrease means hypertonicity or hypotonicity, respectively – these have been dealt with at the disorders of osmoregulation (ch. 6.1.3.).

6.1.4.1. HYPONATREMIA

Causes of hyponatremia

Hyponatremia may induce *hypoosmolarity*, if lasting salt loss is not replaced: e.g. salt-losing kidney; overdose of diuretics; in Addison disease persistent salt- and water-loss and decreased plasma volume due to aldosterone deficiency; repeated (but not single, eventual) vomiting, diarrhea cases (without full normalization of the volume by RAAS). The volume is partly compensated by the hypovolemia-induced increase of ADH secretion and water retention. Hyponatremia may develop in cases of salt restriction or if salt- and water-loss is replaced by water only or by sweet refreshments (e.g. in case of work in a hot environment: normovolemic hypotonicity). Further, it may develop in cases of ECV rise, like when too much water or glucose infusion is given to failing patient, or in cases of psychogenic polydypsia, then in cases when the water intake exceeds the water excreting capacity („water intoxication"), particularly if the renal water-excreting capacity is limited (hyposthenuria). Such limitation is common in elderly patients and in chronic renal failure. Hyponatremia develops when severe edema causes hypovolemia and induces ADH secretion (e.g. compensation of chronic heart failure; ch. 2.1.). Hyponatremia may be the consequence of primary ADH-overproduction (SIADH syndrome; ch. 10.2.4.) or situations accompanied by high vasopressin (ADH) levels (barbiturate overdose, side effects of certain drugs in elderly, operations), particularly if glucose infusion is also given.

Consequences of hyponatremia

In the IC space deviations of the osmotic pressure in any direction from the normal lead to non-specific inhibition of cellular enzymes, since the osmotic pressure influences the structure and the optimal activity of the enzymes. Altered activity of IC enzymes and the imbalance between various enzymes necessarily results in disorder of the metabolism and function of the cell.

Hyponatremia causes cellular swelling, and in moderate forms it causes muscle cramps (e.g. calf cramps that improve for salt replacement; ch. 8.5.2.2.). In more severe forms cellular brain edema develops, thereby the intracranial pressure increases with the consequent symptoms of dizziness, headache, nausea, vomiting, anorexia, hypodypsia, dysphagia, incoordinated movements, disorders of vision and consciousness (e.g. hallucinations with disorientation), epileptiform seizures and finally coma (ch. 8.5.2.3.). The objective symptoms are rise of blood pressure, bradycardia, papilledema, irregular breathing. In most severe forms the cerebellar tonsils get wedged into the foramen magnum, cause medullary compression and the consequent respiratory and circulatory failure leads to death.

It had been an ancient Chinese torture to make the accused person to drink huge amounts of water (it was given through a funnel). In Europe similar method was used at witch-hunts: in water intoxication the hallucinating disoriented „witch" confessed any sin she was accused with.

The possible compensation of hypoosmolarity is suppression of ADH (except in SIADH), the increase of aldosterone (except in Addison disease) and in addition the development of „salt-hunger".

Pseudohyponatremia (hyponatremia with hypertonicity): Hypertonicity is accompanied by a relative decrease of plasma Na^+-concentration, if the tonicity increases because of acute excess of glucose, mannitol, or other substance. The consequences correspond to the picture of hypernatremia and high ECV. In contrast to this in chronic glucose overload (diabetes mellitus) leads to osmotic diuresis, the consequence is significant water loss and smaller but pronounced salt loss. These overcompensate the glucose-induced ECV rise and lead to exsiccosis, the plasma Na-concentration may even rise. Upon normalizing the blood glucose (without fluid and salt replacement) pseudohyponatremia, dramatic exsiccosis and shock may develop.

Pseudohyponatremia may also develop without elevated/unchanged tonicity e.g. in case of hyperlipidemia or hyperproteinemia (hyponatremia with normotonicity), since the accumulating lipid or protein components do not influence significantly the osmotic pressure, but bind water.

6.1.4.2. HYPERNATREMIA

Causes of hypernatremia

– purely water loss (diabetes insipidus, respiratory water loss), or loss of hypoosmolar fluid (sweating) without replacement; lasting water deprivation also causes higher osmotic pressure (hypovolemic hypertonicity),

– enhanced salt consumption only temporarily increases the osmotic pressure (with normovolemia), since the osmoregulation quickly normalizes the situation (except in rare cases of hyposensitivity of osmoreceptors),
– long-term elevated salt retention, e.g. Conn syndrome and Cushing disease/syndrome (ch. 10.8.3. and 10.8.4.) (hypervolemic hypertonicity).

Consequences of hypernatremia
Quickly developing hypernatremia and hypertonicity would lead to shrinkage of brain cells and the whole brain, causing damage of bridging veins and subdural hematoma. The brain cells can adapt to slower changes of tonicity: osmotically active substances („idiogenic osmoles") accumulate IC. The price of this compensation is a non-specific inhibition of the enzyme functions. The clinical consequences: dizziness, anorexia, lethargy or irritability, seizures, finally coma. Fast correction of tonicity is prohibited, since the elimination of the idiogenic osmoles needs time, and fast decrease of EC tonicity would lead to cellular swelling and brain edema. Treatment should happen with slow infusion of isotonic (not hypotonic!) saline. In other tissues such adaptation is less important.

Adaptive answer for hypernatremia may be ADH release (except in diabetes insipidus), increasing the feeling of thirst, in some cases decreasing the secretion of aldosterone (except in Conn and Cushing syndromes).

6.1.5. DISORDERS OF POTASSIUM BALANCE

The K^+ content of the human body is 2500-4500 mmol. About 98% of this is located IC. In the IC space the K-concentration is 140-160 mmol/l, while in the ECV it is 3.5-5.5 mmol/l, i.e. the K-content of the plasma is only a small fraction of the K-content of the body. The plasma K^+-level depends on its distribution within the body between the EC and IC spaces (*internal K-balance*), and on the *external K-balance,* i.e. on the ratio between the intake and output of K. In general, the disorders of K-balance can be divided as disorders of the internal or those of the external K-balance.

6.1.5.1. REGULATORY FACTORS OF INTERNAL POTASSIUM BALANCE

1. The pH-state
In the course of elevation of H^+-concentration in the ECV, H^+-ions enter the cells. In order to maintain electrical balance cations of single positive charge (mainly K^+) leave the cells. Thus, acidosis is coupled with hyperkalemia, alkalosis with hypokalemia. Mainly the pronounced and long-lasting metabolic changes lead to shifts in K^+-levels. If the metabolic acidosis is due to accumulation of organic acids (e.g. lactate, ketoacids) the EC hyperkalemia may be rather moderate, since the cells can take up the organic anion to secure electric balance, and there is little need for outward move of K^+.

2. EC hypertonicity
If substances which cannot get freely through the cell membranes (e.g. glucose, Na^+) accumulate in the EC space, hypertonicity develops. The EC hypertonicity induces outward movement of water from the cells. Although a little K^+ moves together with the water (solvent drag), the IC K^+-concentration relatively increases. The number of IC ions does not change much, rather the decreased IC water explains the increase in concentration. The rising IC K^+ concentration induces further, significant K^+-efflux. The EC hypotonicity has no direct effect on se-K^+-level.

3. Insulin
Upon the effect of insulin, the Na^+/K^+-ATPase activity increases, K^+ enters the cells. In case of insulin deficiency EC hyperkalemia might be expected, however this is mitigated by the K^+-loss due to osmotic diuresis.

4. Catecholamines
The β_2-adrenergic effect enhances the secretion of insulin and the Na^+/K^+-ATPase activity of the cell membrane, thereby K^+ moves into the cells. In contrast, the α-adrenergic activity decreases the K^+-uptake of cells.

5. Mineralocorticoids
The mineralocorticoids (e.g. aldosterone) regulate mainly the external K^+-balance, but possibly contribute also to the maintenance of internal K^+-balance.

6. Physical activity
Upon the effect of moderate or intensive physical activity K^+ leaves the muscle cells and causes transient hyperkalemia. The practical importance of this is that repeated strong clenching of the fist during blood sampling increases the K^+-concentration of the sample (false value is measured!).

6.1.5.2. REGULATORY FACTORS OF EXTERNAL POTASSIUM BALANCE

The daily K^+ intake by the food is ca. 40-120 mmol (average 80 mmol). About 90 % of this is absorbed in the gastrointestinal (GI) tract. This exogenous K^+ gets into the EC compartment, and this is also the place of K^+ loss. In case of K^+-loss, the loss from the plasma relatively exceeds the K^+-loss of the whole body, although altogether more K^+ is lost from the IC compartment. The K^+-loss happens via the kidneys (90 %), smaller part (10 %) via the GI tract.

1. K^+-intake
Intravenous K^+-administration may even cause hyperkalemia with lethal consequences! Intravenously K^+ may be given only in infusion, in small concentration, slowly and with continuous monitoring!

Moderately large oral K^+-intake in healthy persons does not cause hyperkalemia, because the renal and GI excretion proportionally increases. The risk may be greater in case of using K^+-sparing medications by hypertensive patients. In end-stage renal failure or in acute renal failure (GFR < 5ml/min) very moderate K^+-intake (e.g. consuming a few bananas) may result in very severe hyperkalemia.

2. Mineralocorticoids (MC)
Aldosterone (and MC-s of smaller importance, e.g. 11-deoxycorticosterone /DOC/) enhances the Na^+/K^+- and Na^+/H^+-exchange in the distal tubules and collecting ducts of the kidney. Salt and water retention with K^+- and H^+-loss follows. Aldosterone enhances the Na^+/K^+-ATPase activity at the interstitial (basolateral) surface of the epithelial cells of the distal tubules. Consequently, the K^+ concentration within the epithelial cell increases, and this enhances the Na^+/K^+-exchange at the apical (luminal) side. It is likely that the K^+-excretion in the distal tubules is also influenced by other mechanisms, because a single mechanism may not be able to explain the flexibility of the regulation of K^+-excretion. While there is an „escape" mechanism for Na^+-reabsorption, there is no such mechanism for K^+-excretion (cf. natriuretic hormones, ch. 2.3.2.1. and 10.8.3.).

3. Measure of glomerular filtration (Na^+-intake and distal tubular flow)
Increased filtration enhances K^+-excretion. In these cases, the GFR increases, more water and Na^+ gets into the distal tubules, and this enhances the Na^+/K^+-exchange. Faster flow (e.g. osmotic diuresis) inhibits the reabsorption of K^+-ions. Anions that cannot be reabsorbed in the distal tubules increase the electric gradient between the tubular cell and the lumen, and this also enhances the K^+-excretion. Such negatively charged ion may be the bicarbonate (RTA II), penicillin derivatives, or the toluene.

4. The pH-state
In acidosis the renal K^+-excretion decreases, in alkalosis it increases.

5. Gastrointestinal excretion
At normal K^+-intake 10% of it is excreted by the feces. In severe renal failure the high aldosterone secretion is able to increase the K^+-excretion also in the gut, therefore in such cases (after absorbing practically all the consumed K^+ in the small bowel) even 50-60% of the intake can be secreted via the GI tract.

6.1.5.3. HYPOKALEMIA

Most important causes

Disorders of the internal K^+-balance:
1. Metabolic alkalosis
2. Insulin treatment in diabetic coma, or in acute hyperinsulinemia for other reasons.
3. Applying β_2-adrenergic agonist, or stress-induced increase of endogenous activity.
4. Effect of α-adrenergic antagonist
5. Anabolic states e.g. B_{12}- and folic acid-treatment after pernicious anemia, treatment of severe neutropenia by granulocyte-macrophage colony-stimulating factor (GM-CSF), or in parenteral nutrition after cachexia-inducing disease.
6. Hypokalemic periodic paralysis: inherited metabolic disorder, with repeated transient hypokalemia and muscle weakness.

Disorders of external K^+-balance:

1. *Low K^+-intake*
Hypokalemia may develop in long-term starvation, in anorexia nervosa, in chronic alcoholism, in senile monotonous food intake.

In South-America the traditional clay-consumption decreases the absorption of potassium and iron from the gut (dry clay-cubes are sold in the marketplac-

es). Decreased intake may accelerate the hypokalemia caused by enhanced K^+-excretion.

2. *Enhanced renal K^+-excretion*

- in osmotic diuresis (e.g. diabetic glucose- and ketonuria; hypercalcemic polyuria; in early phase of renal failure the accumulation of N-containing products may inhibit the reabsorption of water, Na^+ and K^+)
- in pathological states with mineralocorticoid (MC) hyperfunction, like Conn syndrome, secondary hyperaldosteronism (with hyperreninemia, narrowing of the renal artery, decreased blood volume and edema), hyperplasia of the zona glomerulosa, 11-β-hydroxylase deficiency (one form of congenital adrenal hyperplasia, with glucocorticoid deficiency and MC excess, in which large amount of 11-deoxycorticosterone /DOC/ is produced), Bartter syndrome (tubular Na^+-, K^+-, Cl^--loss, with consequent hyperaldosteronism), 11-β-HSD-deficiency (lack of 11-β-hydroxysteroid-dehydrogenase enzyme which should deactivate cortisol in the kidney – its lack makes possible the cortisol action on MC receptors, therefore despite normal se-MC and -cortisol levels the MC-activity appears to be higher = "apparent aldosterone excess"), Cushing disease and syndrome, or exogenous glucocorticoid effect (it causes MC-effect by spillover mechanism)
- in diuretic treatment (this is the most frequent cause, in extreme cases 2 mmol/l se-K level is possible!)

  About 30% of the population receives diuretics due to hypertension or heart failure. Most diuretic drug inhibits reabsorption of K^+. The repeated decrease of ECV induces secondary hyperaldosteronism, which also decreases the K^+-level. Replacement of K is necessary in the form of enterosolvent capsules. (Unpleasant side effects of gastric soluble capsules may decrease patient adherence to medication regimen.) The only exceptions are the spironolactone derivatives – these are aldosterone antagonists therefore do not cause hypokalemia (= K-sparing diuretics).
- in renal tubular acidosis (RTA) types I and II (ch. 6.2.2.1.), the cause of hypokalemia is secondary hyperaldosteronism due to loss of Na^+ and water.

3. *K^+-loss through the GI tract*

– During vomiting some K^+ is lost directly by the gastric juice, more by the hypovolemia-induced secondary hyperaldosteronism, and the metabolic alkalosis due to HCl-loss is also coupled with hypokalemia tendency.

- During diarrhea a lot of K^+ is lost directly with the bowel juice. This is combined with the hypovolemia-induced secondary hyperaldosteronism and lots of desquamating mucosal cells are lost (these have IC K^+ – normally this K^+ should be regained). The K^+-loss may be extreme: in the body of babies who died due to E. coli induced diarrhea the K^+-content was 40% below the normal amount.
- Ileus may be cause or consequence of hypokalemia. In ileus the secretory activity in the occluded gut section is high, this accumulated fluid of the 3rd water space is unavailable for the ECV. The K^+-content of the fluid is high, which cannot be reabsorbed (it may be lost by vomiting or suction). The K^+-content of necrotized desquamating mucosa cells is added. Besides the ECV decreases and induces secondary hyperaldosteronism with further K^+-loss. The hypokalemia-induced muscle weakness (also in the gut) and a paralytic component is added to the obstructive ileus.

4. *Extreme sweating*

The direct K^+-loss is minimal, but the falling ECV induces secondary hyperaldosteronism and hypokalemia.

Consequences of hypokalemia

- In hypokalemia metabolic alkalosis develops.
- The membrane potential increase (more negative than normally, Fig 6.5.). It is more difficult to reach the threshold potential for muscle action. Muscle weakness (!!) postural hypotension, in more severe cases paralysis, due to weak respiratory muscles hypoventilation, in the GI tract meteorism, paralytic ileus, in the excretory system bladder atonia may develop.
- Tendency for toxicity of digitalis.
- Slow repolarization of myocardium, due to short absolute refractory period tendency for extrasystolia, arrhythmia, in most severe cases ventricular fibrillation may develop. Diastolic arrest of ventricular function is also possible.
- Characteristic ECG changes: prolonged PR (PQ), ST-segment depression, flat T wave, longer QT-time with a tendency for the development of "torsade de pointes", or ventricular fibrillation, sudden cardiac death. High U-wave may be seen

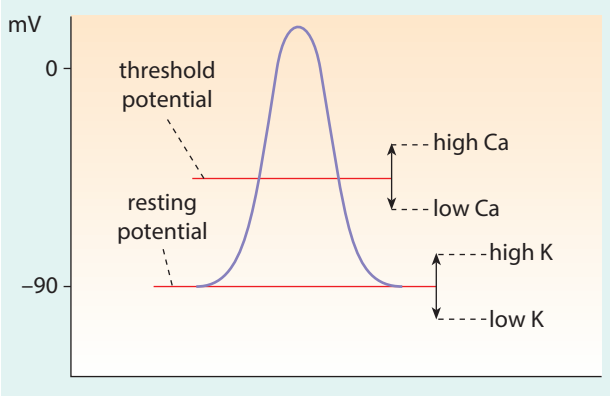

Fig. 6.5.: The excitability of cells may be influenced by EC K- and Ca-levels, by shifting the resting potential or the threshold potential for activation.

- Together with the T-wave the QT-time looks even longer.
- In the kidney it has an ADH-antagonist effect, with polyuria.

6.1.5.4. Hyperkalemia

Most important causes

Disorders of the internal K^+-balance:

1. Metabolic acidosis e.g. renal failure, diabetic ketoacidosis.
2. EC hypertonicity e.g. water deprivation or hyperglycemia.
3. Insulin deficiency (1DM, due to osmotic diuresis the K^+-loss limits the hyperkalemia).
4. Medications, e.g. digitalis, or depolarizing muscle relaxants (succinylcholin). The digitalis type drugs are positive inotropic substances, they increase the myocardial contractility, inhibit the Na^+/K^+-ATPase activity of cells, thereby producing EC hyperkalemia.
5. Massive cell necrosis (cytostatic treatment of tumors or in hemolytic anemia: from the necrotizing cells a lot of K^+ is released).
6. Hyperkalemic periodic paralysis is an inherited metabolic disorder of unknown origin: eventually fast release of K^+ from the IC space.

Disorders of external K^+-balance:

1. *Increased K^+-intake*

Intravenous K^+-administration may easily cause lethal hyperkalemia. Moderately high oral K^+-intake causes no hyperkalemia in heathy persons, but even moderate oral excess induces fatal hyperkalemia in patients with severe acute or chronic renal failure.

2. *Decreased K^+-excretion*
   - low GFR (<5 ml/min) in acute or chronic renal failure
   - hypoaldosteronism, e.g. Addison disease (generalized adrenal cortex deficiency with low aldosterone level), or 21-β- hydroxylase deficiency (one form of adrenogenital syndrome)
   - RTA IV (its most frequent causes are diabetic nephropathy, hypertensive glomerulosclerosis, congenital tubular defect; the mechanism resembling the consequences of mineralocorticoid-deficiency)
   - drug effects: e.g. ACE-inhibitors (decreased angiotensinogen II production and aldosterone secretion), spironolactone derivatives (competitive aldosterone antagonists), non-steroid antiinflammatory drugs (NSAID – they inhibit renin synthesis, decrease renal blood perfusion and the production of natriuretic renal PG-s), heparin (its lasting administration inhibits aldosterone synthesis)
   - special states: zona glomerulosa is insensitive to hyperkalemia, or tubular epithelial cells are insensitive to aldosterone ("end-organ resistance").

Consequences of hyperkalemia

- In hyperkalemia the resting membrane potential shifts towards depolarization (Fig. 6.5.). This state, on the long run, results in decreased excitability of cells. Reflex abnormalities, often ascending muscle weakness, flaccid paralysis of the leg may develop, since it is difficult to re-excite the excited muscles.
- In the myocardium faster action potentials and fast repolarization are characteristic, with slow conduction. These increase the danger of extrasystolia. Hyperkalemia may evoke ventricular fibrillation or flutter. Se-K level as high as 7 mmol/l is so dangerous that in renal failure it means an indication of hemodialysis.
- Hyperkalemia causes respiratory depression, what makes narcosis dangerous.
- Characteristic ECG disorders: conduction difficulties in the atria, long PR interval, P wave is flat (or disappears), the QRS (moderately) widened, ST depression may be observed. An early sign may be that the *T wave is symmetrical positive, high, peaked*, the QT time is shortened.

The se-K^+ level and the K^+-content of the body do not necessarily change in the same direction. There are situations with severe K^+-depletion in the body without simultaneous hypokalemia, e.g. in severe heart failure, in the early stages of diuretic treatment normokalemia may be maintained for long, despite definite K^+-loss. In diabetic ketoacidosis hyperkalemia is possible in plasma despite severe K^+-depletion of the body, while for insulin treatment the K^+ moves into the cells and the se-K^+ shows life-threatening low levels.

6.2. DISORDERS OF ACID-BASE BALANCE

6.2.1. REGULATION OF ACID-BASE BALANCE

In normal arterial plasma the H^+ concentration is 40 nmol/liter (4×10^{-8} mol/liter), thus the blood pH is 7.35-7.42. The IC pH is lower (about 7.2), with significant differences within the cell. Survival limits of plasma pH are 6.8 or 7.8 (adaptation is needed more often for acidic loads).

In the everyday practice, only the blood pH can be measured, although the IC events are more important and the IC pH-changes do not run necessarily parallel with the EC ones. In general, treatments of blood pH restore H^+-concentration in the interstitium, as well as in the IC compartment.

In order to secure pH-stability it is necessary that the organism fends off the acute influencing effects by the help of buffer systems, while on the long run the influencing factors must be eliminated, mainly by the help of respiration and the kidney.

6.2.1.1. BUFFER SYSTEMS

Buffer systems of the body are mixtures of solutions of weak acid (only partially dissociates) and its salt, the pH of which hardly changes upon addition of stronger acid or alkali. The essence of buffer action can be demonstrated by the example of carbonic-acid/bicarbonate ($H_2CO_3/Na^+HCO_3^-$) buffer system (equation 6.1.):

$$\begin{matrix}100\ H^+Cl^- \\ + \\ 1000\ Na^+HCO_3^-\end{matrix} \rightarrow \begin{matrix}100\ Na^+Cl^- \\ 900\ Na^+HCO_3^- \\ 5\ H^+HCO_3^- \\ 95\ (H_2CO_3 \leftrightarrow H_2O + CO_2)\end{matrix}$$

6.1. equation

Accordingly: upon addition of 100 H^+ to the system, 95 H^+ seem absorbed and only 5 H^+ will elevate the concentration in the mixture, i.e. the pH does not change *proportionately* with the primary influence. In presence of sufficient amount of carbonic acid an alkali load is followed by buffering in the opposite direction (instead of H^+ absorption, OH^- is neutralized by the dissociation of carbonic acid). Buffer capacity depends on the concentration of individual components.

Buffer systems of the plasma (blood):

a) carbonic-acid bicarbonate buffer system (H_2CO_3/$NaHCO_3$)
b) phosphate buffer (Na_2HPO_4/NaH_2PO_4)
c) buffer effect of plasma proteins
d) buffer effect of hemoglobin (Hb^-/HHb)

System a) is the most important. Plasma concentration of carbonic acid ($H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$, together) is 1.2 mmol/liter (if p_aCO_2 = 40 mmHg and the solubility factor of CO_2 = 0.03 mmol/liter/mmHg). The bicarbonate concentration (simplified for practice: $Na^+HCO_3^-$) is 24 mmol/liter. Stability of the 1:20 ratio between the two components is decisive, since the pH of buffer systems is determined by the ratio of concentrations of their components. According to the Henderson-Hasselbach equation, in the plasma at pH 7.4 (equation 6.2.):

$$pH = pK + lg\left[\frac{Na^+HCO_3^-}{H_2CO_3}\right]$$

$$7.4 = 6.1 + lg\left[\frac{24}{1.2}\right] = 6.1 + lg\left[\frac{20}{1}\right]$$

6.2. equation

The pK dissociation constant shows the pH value at which the dissociation of the weak acid is 50%. The buffer system is most effective at the pH near the pK value. In this system, it is 6.1, i.e. the system offers most effective defense at acidic loads. Further advantage of this buffer system is that both components are present in relatively high amounts in plasma, and their quantities can be altered independently by the respiration ($H_2O + CO_2 \leftrightarrow H_2CO_3$), or the kidney ($Na^+HCO_3^-$). The former is called *respiratory*, the latter one as *metabolic component*; the disorders of their primary changes are called *respiratory* or *metabolic* acidosis/alkalosis.

The b-c-d) buffer systems are in interaction with system a). During acute accumulation of carbonic acid, these buffers absorb H^+ (exchanged for Na^+ as cation), thereby they become unavailable for further buffering, but the amount of sodium bicarbonate increases proportionately and the stability of 1:20 ratio is secured (e.g. by H^+-uptake Na_2HPO_4 is transformed to NaH_2PO_4, which is not suitable for further similar buffering, but the released Na^+ will increase the sodium bicarbonate level). At acute decrease of carbonic acid, the shift between the buffers happens in the opposite direction. It is true, however, for both cases, that the sum of bicarbonate and those b-d) buffer-anions that are suitable for further buffering (buffer base = BB) is unchanged (equation 6.3.). This is in contrast to the metabolic disorders, in which primarily the buffer base is altered. In metabolic acidosis BB falls, since the strong acid draws Na^+ and decreases bicarbonate without significantly modifying the b-d type buffers. In metabolic alkalosis, due to opposite changes, the BB increases.

Besides buffers of the EC compartment, the *IC and bone buffers* are important, mainly in buffering metabolic disorders. About 60% of acidic loads are buffered this way, and about 1/3 of alkaline loads.

Intracellular buffer mechanisms:

1. physico-chemical methods (similar as in the plasma, but due to the dissimilar ion-composition, the participants are different: mainly proteins and additionally phosphate are important instead of bicarbonate, the dominant cation is K^+)
2. biochemical methods (e.g. organic acids can be transformed to neutral glucose, or the opposite process may happen)
3. organellar mechanisms (vesicles of high H^+-concentration can be formed or eliminated).

In the *bone tissue, interstitial buffering* is also possible by H^+-uptake or release of the matrix, which is replaced by Ca^{2+}. In chronic acidosis, osteomalacia may be the consequence of such buffering.

Within the cells the pH is about 7.2 – lower than in the EC compartment – the compensation is faster, more complete. Shifts are manifested later, except if the disorder originates inside the cell, e.g. IC accumulation of organic acids due to metabolic defect of the cell. Due to the efficient IC buffer mechanisms, the IC pH is relatively stable, but *cell functions may be altered without a pH-shift*, since the price of this stability is that the charge, conformation and function of IC proteins (e.g. H^+-binding enzymes) are altered, causing non-specific inhibition of enzymes.

6.2.1.2. ROLE OF RESPIRATON IN pH REGULATION

On the one hand, a role for respiration can be demonstrated as cause of respiratory pH-disorders (primary decrease or increase of CO_2-elimination). On the other hand, a role is obvious as a compensatory mechanism of metabolic disorders (altered CO_2-elimination to regulate pH). At rest, daily 15 000-20 000 mmol CO_2 is eliminated by respiration – a total blockade of this would push pH below 7.0 within 20 min. Normal respiratory system would be able to eliminate more CO_2 than the possible CO_2-production at maximal efforts. This also means that CO_2 accumulates only if the respiratory functions are insufficient.

It is necessary to increase ventilation and CO_2-elimination at high and to decrease them at low metabolic rate. CO_2-elimination exceeding the actual need in primary hyperventilation causes hypocapnia and respiratory alkalosis, insufficient CO_2-elimination leads to hypercapnia and respiratory acidosis. CO_2-elimination may increase as a compensation in metabolic acidosis (for partial compensation of 1 mmol/liter fall in bicarbonate the pCO_2 decreases by 1.0-1.3 mmHg), while in metabolic alkalosis the CO_2-elimination decreases in a compensatory way (a rise of 1 mmol/liter bicarbonate is compensated by 0.4-0.7 mmHg rise in pCO_2). The latter mechanism is usually not complete, because the concomitant hypoxia inhibits the fall in respiration. The respiratory compensation of metabolic disorders starts quickly, but its maximum is reached only with about 12-h latency. In any form of shift in CO_2-level, the vasomotor consequences (e.g. brain circulation) of hypercapnia/hypocapnia must be taken into account.

$$\uparrow CO_2 + H_2O \rightleftharpoons \uparrow H_2CO_3 \rightleftharpoons H^+ + \underline{HCO_3^-}\uparrow$$
$$HBuffer \rightleftharpoons H^+ + \underline{HBufferanion^-}\downarrow \quad (HPO_4^{2-} / Protein^- / Hb^-)$$
$$\Big\} \underline{BB\ unchanged}$$

6.3. equation

6.2.1.3. ROLE OF THE KIDNEY IN pH REGULATION

During the metabolism, many acids are produced that are stronger than carbonic acid. Minimum an acid equivalent of daily 35 mmol H^+ must be removed by the kidneys. Healthy kidneys are able to excrete even 2-3-times larger amounts. The H^+ transported by different ways to the tubular lumen is exchanged by filtered Na^+, which is reabsorbed to increase plasma bicarbonate by various mechanisms (Fig. 6.6):

1. regaining the filtered bicarbonate
2. increasing the titratable acidity of the urine (to pH 4.4.); the H^+ gradient is large: the H^+ concentration is 1000-fold higher than in the filtrate and 800-fold exceeds the IC H^+ concentration in tubular cells.
3. the excreted H^+, if combined with NH_3 (from glutamine) in the lumen (= NH_4^+) makes possible the excretion of anions of strong acids without further acidification of the urin.

All three mechanisms allow re-entry of $Na^+HCO_3^-$ into the circulation: regained bicarbonate + regenerated bicarbonate (produced in loco via mechanisms *2)* and *3)*). Other tubular transport mechanisms (Na^+/K^+ exchange, NaCl transport, etc.) are of lesser importance as regards pH regulation. The direct source of excreted H^+ is carbonic acid from CO_2 of tubular cell metabolism. This H^+ is exchanged for filtered Na^+ of the lumen. The HCO_3^- of this carbonic acid is absorbed with the filtered Na^+ at the basolateral membrane as reabsorbed or regained bicarbonate. Lasting acid excess enhances tubular metabolism and increases Na^+/H^+ exchange, but the tubular adaptation needs time.

Acid overproduction (e.g. diabetic ketoacidosis) enhances bicarbonate reabsorption, but also the titratable acidity of the urine. In this case the source of Na^+ is a filtered salt /e.g. Na-lactate/ of a slightly stronger acid than carbonic acid, the anion of this salt produces free weak acid with the H^+, as a result pH decreases in the lumen. After maximal acidification importance of the ammonia secretion increases. (In addition, aldosterone enhances H^+-excretion.)

In presence of excess alkali, these mechanisms are stopped, and the normally filtered bicarbonate is emp-

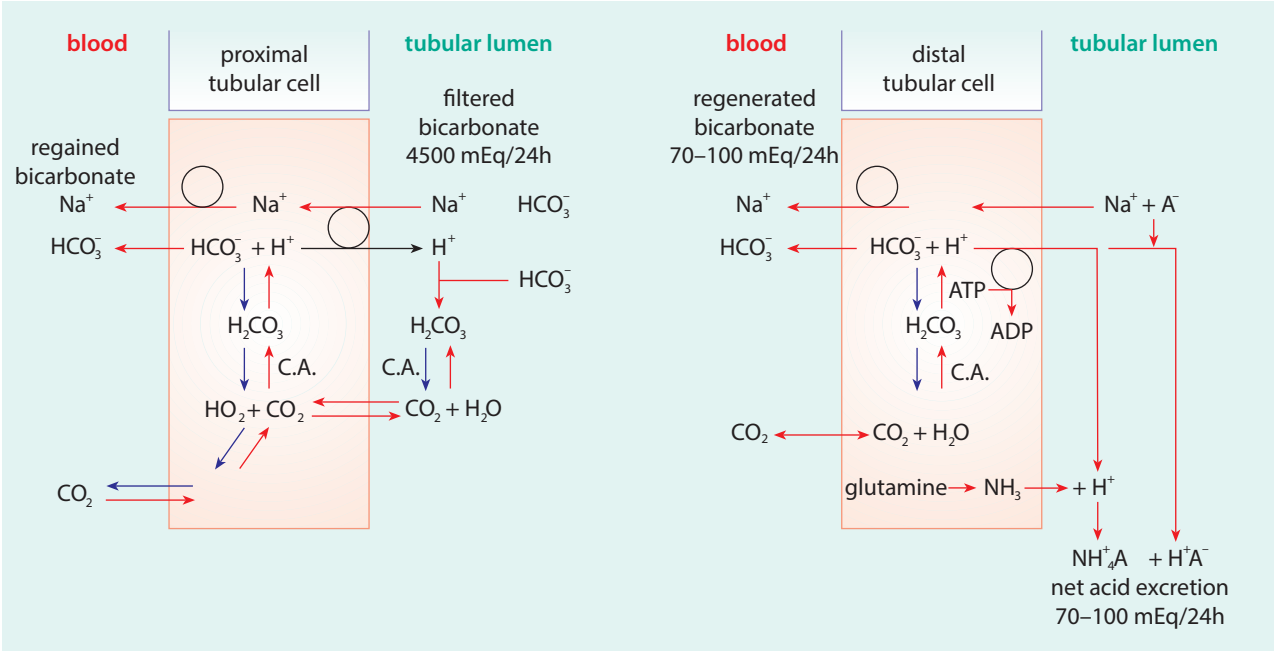

Fig. 6.6.: The role of tubular cells in pH-regulation: The tubular cell metabolism produces CO_2. This, within the cells, with water forms carbonic acid by carboanhydrase enzyme, and dissociates to H^+ and bicarbonate anion. The H^+ is exchanged for Na^+ from the lumen. The Na^+ with the bicarbonate anion is absorbed to circulation at the contraluminal side of the cell. In the proximal tubule this leads to disappearance of 85-90% of filtered Na-bicarbonate = **"regained" bicarbonate.** In the lumen carbonic acid is produced, it dissociates to water (lost by urine) and CO_2 (diffuses to circulation, lost by respiration). (1. mechanism). In distal tubules similar Na^+/H^+ exchange takes place, but the Na^+ is combined with the anion (A^-) of the salt of a somewhat stronger acid, from the free acid H^+ dissociates and the acidity of the urine increases, urine pH decreases (2. mechanism). The H^+ from further Na^+/H^+ exchange is bound by ammonia produced by the distal cell, the produced ammonium-ion can bind further anions of strong acids, without further acidification of the urine. (3. mechanism). By mechanisms 2 and 3 Na-bicarbonate is absorbed (as in the proximal tubules): this is not filtered, but locally produced form = **"regenerated" bicarbonate**. Irrespective of the way how Na-bicarbonate is absorbed, it can participate pH regulation – simultaneously the excess acid is excreted. These tubular processes are enhanced by plasma acidosis and decrease se-level of K^+ or Cl^- ions.

tied by the urine. Besides, further decrease of plasma bicarbonate can be reached by the help of the collecting tubules, where the so-called intercalated cells exchange the Cl^- of the filtrate for secreted bicarbonate.

Changes of renal bicarbonate reabsorption may participate in the compensation of respiratory processes, but this compensation is a slow process (Fig. 6.8.), often too slow for compensation of respiratory disorders.

6.2.2. DISORDERS OF pH REGULATION

The disorders are classified according to the *primary* change in the 1.2:24 ratio of carbonic acid:bicarbonate (Fig. 6.7.).

The primary disorder is usually followed by ***compensation***. First step of this is a re-arrangement between the buffer systems, which is soon exhausted. Cellular buffering is slower, although it starts soon, but its maximum is reached in 6-8-h. Even slower is the respiratory compensation, while an increase in renal acid-excretion is marked only after 24-h and reaches its maximum after about 72-h (Fig. 6.8.).

In case of full compensation, the normal carbonic-acid/bicarbonate ratio of 1/20 is restored and the pH is normal. However, without enough time or capacity,

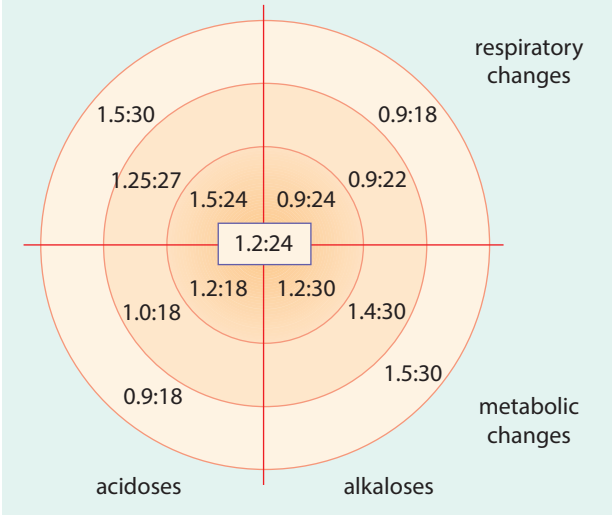

Fig. 6.7.: The rectangle in the middle indicates the normal situation, where the carbonic-acid:bicarbonate ratio is 1.2:24 (1:20). The innermost circle refers to primary, non-compensated changes – classification of regulatory disorders happens according to this. In respiratory abnormalities primarily the CO_2, in metabolic ones the bicarbonate changes. In acidosis the 1:20 ratio is shifted for carbonic acid (rise of carbonic acid or fall of bicarbonate), in alkalosis the opposite happens. Thus, the 4 principal disorders: respiratory acidosis, respiratory alkalosis, metabolic acidosis, metabolic alkalosis. The middle circle shows the phase of partial compensation, while the outer circle the full compensation, when the 1:20 ratio is re-established at various absolute amounts of carbonic acid and bicarbonate.

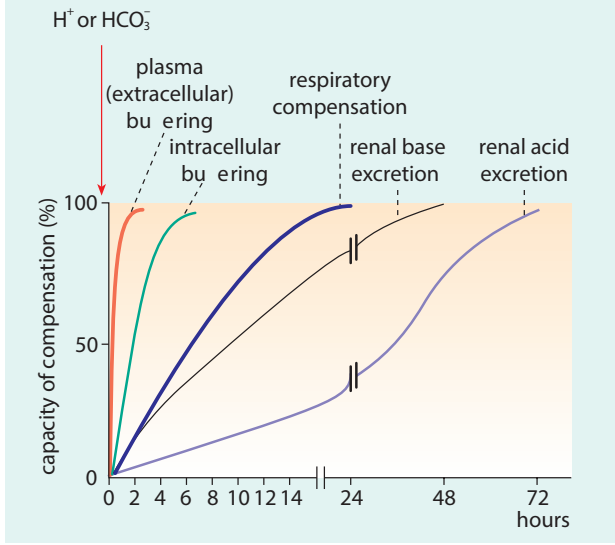

Fig. 6.8.: Speed of compensation of pH-disorders by various mechanisms. Very fast are the plasma and intracellular buffers, while the renal compensation starts later and reaches its maximum very late.

the compensation remains partial, the pH is shifted. Shifted pH may be called acidemia or alkalemia. In the diagnosis of simple, and not fully compensated pH disorders, the data on actual pH, actual pCO_2 and actual bicarbonate may be sufficient.

Full compensation means that the levels of carbonic acid and bicarbonate change proportionally. For example, proportionately low carbonic acid and bicarbonate levels may occur in renally compensated respiratory alkalosis as well as in respiratory compensation of metabolic acidosis. Apart from differences in the clinical symptoms, knowledge of further **parameters of acid-base balance** may help in the diagnosis and in establishing a therapy (especially in case of mixed acid-base disorders). The most important parameters:

- *buffer base* (BB, normal value 46-48 mmol/liter): Sum of bicarbonate and other plasma buffer anions that are suitable for further buffering.
- *base excess* (BE, normally 0 ± 2.5 mmol/liter): Deviation of actual BB from the normal value. It shows numerically that how much acid or base would be needed in metabolic disorders to normalize BB.
- *standard bicarbonate* (normally 24 mmol/liter): It is the measured bicarbonate level after standardization in vitro (equilibration at 38 °C, 40 mmHg pCO_2). In acute respiratory disorders, a compensatory adjustment of bicarbonate to pCO_2 utilizes only redistribution between plasma buffers and, with standardization of pCO_2, the bicarbonate

level normalizes. In other cases, like metabolic or chronic respiratory disorders, the standard bicarbonate is abnormal, as are BB and BE.

The parameters can be established by the help of *nomograms*. Most accurate is the Siggaard-Andersen nomogram, but recently various simplified nomograms are used.

6.2.2.1. METABOLIC ACIDOSIS

Parameters of pH in metabolic acidosis: primary disorder is a fall in HCO_3^-, therefore the pH, the actual and standard HCO_3^-, the BB, the BE and the pCO_2 all decrease. The fall in pCO_2 is already a step to compensation.

FORMS OF METABOLIC ACIDOSIS

The main causes of metabolic acidosis are grouped by their influence on the anion gap in plasma. Anion gap is the concentration difference between the routinely measured cations and the measured anions. This represents the difference between the unmeasured anions and the (very low amount of) unmeasured cations, since the total number of cations should be equal to the total number of anions in the blood.

I. High anion gap metabolic acidosis

Anion-gap = $[Na^+] - ([Cl^-] + [HCO_3^-]) = 140 - (105 + 24) = 11$ mmol/liter. (Because potassium concentrations are very low, omission of potassium has become widely accepted.) Anion gap indicates the amount of other, not routinely measured anions (lactate, phosphate, sulfate, etc.). The anion-gap increases if acids (stronger than carbonic acid) accumulate: their dissociation increases the anion gap, while buffering their H^+ leads to decrease of HCO_3^-. (HCl is an exception: it causes hyperchloremic metabolic acidosis with normal anion gap). Such acids:

- may be produced in the body (overproduction of acids from metabolism, e.g. lactate)
- may be of exogenous origin (extrinsic load)
- may accumulate in the body because of poor excretion in renal failure

II. Hyperchloremic metabolic acidosis with unchanged anion gap

It may be caused by HCl accumulation or loss of HCO_3^-; when the HCO_3^- level decreases, the renal Cl^- reabsorption increases and se-Cl^- rises in a compensatory way.

CAUSES OF METABOLIC ACIDOSIS

I. High anion gap metabolic acidosis

1. Acid overproduction (intrinsic load):

Ketoacidosis from ketone bodies (aceto-acetic acid, β-OH-butyric acid /acetone is not acid/): in type-1 diabetes mellitus (in type-2 diabetes only rarely, lipolysis leads to hepatic steatosis and moderate ketoacidosis), in starvation and in chronic alcoholism (due to malnutrition).

Lactic acidosis: serum lactate level may rise from the normal 1 mmol/liter to 5-10 mmol/liter. Two types are known:

Type-A develops due to higher lactate production. It is a result of extensive tissue hypoxia (anaerobic glycolysis), with decreased activity of pyruvate dehydrogenase and pyruvate carboxylase. Circulatory shock is the most frequent of serious forms, but it may occur in less severe forms in hypoxemic hypoxia (respiratory or heart failure), anemic hypoxia, in type-2 diabetes and during physical exercise exceeding the anaerobic threshold. (Beyond the point of anaerobic glycolysis in the muscle, exhaustion starts and no lasting further work is possible. The level of anaerobic threshold depends on training state. Athletes, like long-distance runners reach anaerobic threshold at higher percentage of their maximal oxygen consumption; while with sedentary lifestyle at lower oxygen consumption, i.e. they reach anaerobic threshold at low work load.)

Type-B lactic acidosis: utilization of lactic acid for gluconeogenesis (production of glucose from pyruvic acid) in the liver or the kidney is impaired. Possible causes: hepatic cirrhosis, severe chronic renal failure, ketone bodies (these inhibit hepatic uptake of lactate), medications (e.g. biguanide oral antidiabetics inhibit gluconeogenesis), sorbitol, fructose, xylose (in artificial sweeteners: fructose-1-phosphate inhibits gluconeogenesis). In insulin-like growth factor (IGF)-producing malignant tumors (mainly hemopoietic ones) lactate increases because of the enhanced glycolysis and inhibited gluconeogenesis. Other tumors have high metabolic rate, the relative hypoperfusion and hypoxia lead to lactic acidosis.

2. Extrinsic acidic load (toxicoses):

In *salicylate toxicosis* acidic metabolites are produced (smaller doses cause respiratory alkalosis by enhancing ventilation).

In *ethylene-glycol*-induced toxicosis (antifreeze) glycolic acid is produced.

In *methano*l intoxication formic acid is produced.

Paraldehyde (toxic barbiturate-type drugs) is transformed to acetic acid.

In the last three processes the toxin is metabolized by the alcohol dehydrogenase enzyme, the activity of which decreases NAD/NADH ratio: with a rise of NADH, the pyruvate is transformed to lactate rather than used in gluconeogenesis. Accordingly, all three toxicoses may worsen lactic acidosis. Due to high number of the osmotically active particles, in these cases the plasma osmotic pressure is higher than expected on the basis of the tonicity (or calculated on basis of se-Na + se-glucose + BUN), i.e. the osmotic gap is high.

3. Decreased renal excretion of acids:

In *severe chronic renal failure* (GFR < 25 ml/min) even the normally produced acidic metabolites cannot be excreted, since the tubular H^+-pump activity decreases (the urinary acidification is smaller), the bicarbonate reabsorption decreases and the NH_3-production is low; the anion gap is high due to phosphate and sulfate retention;

In *severe form of certain acute tubular nephropathies*, e.g. *rhabdomyolysis* (massive muscle damage e.g. in trauma, cramps, overdose of cocaine or other drugs, side effects of certain cholesterol decreasing drugs): high phosphate and myoglobin release from the muscles causes renal damage and decreased renal excretion of acids.

II. Hyperchloremic metabolic acidosis with unchanged anion gap

Hypo-, hyper- and normokalemic forms are known.

1. Hypokalemic metabolic acidosis:

Diarrhea causes direct loss of NaCl, water, K^+ and a lot of HCO_3^- with the intestinal fluid. Further K^+ is lost with the desquamating cells. The developing hypovolemia (reduction in circulating blood volume) activates RAAS (secondary hyperaldosteronism), the aldosterone enhances K^+ and H^+ excretion and contributes to K^+-loss.

Pancreatic fistula is a less frequent case, but it acts similarly.

Renal tubular acidosis I (RTA-I) – distal, classic form: It develops mainly on genetic basis, but acquired forms are also known. Due to impaired H^+ excretion in the distal tubules, the urinary acidification (to normal pH 4.4) cannot take place, inducing metabolic acidosis. Bicarbonate regeneration in the distal tubules (which would account for 15% of bicarbonate reabsorption) is impaired, but the excreted HCO_3^-in the urine is less than 10% of the filtered amount. Bicarbonate loss is combined with loss of Na^+ and water. The decreasing ECV activates RAAS, which contributes to K^+-loss, hypokalemia and enhances Cl^- reabsorption.

In RTA-I less citrate is emptied by the urine. Normally 40% of the excreted Ca^{2+} would be emptied as a citrate complex (it has higher solubility). Without citrate, the Ca^{2+} precipitates in the tubules, Ca-phosphate stones are formed, in the parenchyma nephrocalcinosis develops. Due to chronic acidemia (bone buffering and Ca mobilization from bone) rachitis, growth retardation may develop in children, while in adults osteomalacia with bone pains.

RTA-II (proximal): Regain of bicarbonate in proximal tubules (which would account for 85% of bicarbonate reabsorption) cannot take place, because of impaired Na^+/H^+ exchange. Distal tubules cannot compensate for the bicarbonate loss (although some urinary acidification is possible, which is better than in RTA-I), water is also lost, moderate acidemia and hypovolemia develop. Due to decreased ECV, activation of RAAS leads to hypokalemia. The symptoms may develop following administration of carboanhydrase inhibitory diuretics, and RTA-II may be part of *Fanconi syndrome* (combined defect of proximal tubules affecting reabsorption of glucose, phosphate, amino acids, and causing hypoglycemia and osteomalacia). Since the citrate excretion is normal, in RTA-II renal stones and nephrocalcinosis do not develop, the bone metabolism is normal (except in Fanconi syndrome).

RTA III: It is a mild form, a mixture of the former two types. The production of NH_3 is disturbed. It may occur in interstitial nephritis.

2. Hyperkalemic metabolic acidosis:

Hypoaldosteronism: Addison disease or other adrenal insufficiency; adrenocortical syndromes with cortisol and mineralocorticoid deficiency (21-β-hydroxylase deficiency); aldosterone-antagonist diuretics (spironolactones)

Interstitial nephritis

Hydronephrosis

RTA-IV: It is a congenital or acquired (due to diabetic nephropathy, hypertensive glomerulosclerosis, chronic tubulointerstitial kidney diseases, etc.) disorder of the distal tubules. Aldosterone resistance is a congenital tu-

bular defect, in acquired forms low levels of renin and aldosterone (inability of their activation) may explain the disorder. The juxtaglomerular apparatus produces renin, the basal renin secretion is normal, but it but cannot be increased. In RTA-IV the Na^+/K^+ and Na^+/H^+ exchanges are abnormal, the defective K^+ excretion leads to hyperkalemia, and by inhibiting the NH_3-production, this enhances the problem of H^+-excretion.

3. Normokalemic metabolic acidosis:
Dilution acidosis: This is a minor pH-disorder. Due to excessive NaCl-infusion in the large ECV the proportion of Cl^- (relatively acidotic) anion is relative high as compared with the unchanged HCO_3^- (more basic anion). Later the bicarbonate decreases in absolute terms, since the intercalated cells of the distal nephron parts reabsorb more Cl^- from the Cl-rich filtrate and secrete more HCO_3^-.

NH_4Cl-treatment (used in alkalosis for acidification of the plasma)

Lys-, Arg-HCl infusion: in parenteral nutrition amino acids are given in acidic hydrolysates, and their metabolism releases Cl^-.

CONSEQUENCES OF METABOLIC ACIDOSIS

1. Hyperkalemia due to internal and external K^+ balance: H^+ enters the cells and K^+ leaves them, while in the kidney Na^+/H^+ exchange is preferred (for promoting acid excretion) to Na^+/K^+ exchange, therefore K^+ is retained. Hyperkalemia leads to cardiac consequences (ventricular fibrillation), while in the cells buffering inhibits cell functions.
2. The ionized form of se-Ca^{2+} increases, the protein-bound form decreases.
3. Myocardial contractility decreases (inhibition of K^+-channels).
4. The catecholamine sensitivity of smooth muscle increases, the sympathetic activation by stress is greater, and the vasoconstrictor tone is increased (although the local effect of acidosis would be vasodilation). The reflex hypertension contributes to an enhancement of preload and afterload.
5. The vascular permeability increases.
   #3-5 consequences predispose to heart failure and clinically manifest pulmonary edema.
6. The respiratory compensation (Kussmaul breathing) causes hypocapnia, cerebral vasoconstriction and brain hypoxia.
7. In lasting metabolic acidosis, the bone mineralization is poor, and osteomalacia may develop.
8. Insulin resistance develops: glycolysis, Na^+/K^+-ATPase disorder, and hyperglycemia are common.
9. Cell proliferation is suppressed, there is a greater tendency for apoptosis.

TREATMENT OF METABOLIC ACIDOSIS

Below pH 7.1 infusion of $NaHCO_3$ is necessary. Not earlier, because it may easily turn into metabolic alkalosis and concomitant tissue hypoxia. The other danger of infusion is a too big volume load, particularly in renal forms of acidosis.

6.2.2.2. METABOLIC ALKALOSIS

The pH parameters of metabolic alkalosis: primary disorder is the elevated HCO_3^-, and pH, actual and standard bicarbonate, BB, BE and the pCO_2 are also elevated. The rise of pCO_2 is already a step of compensation.

FORMS AND CAUSES OF METABOLIC ALKALOSIS

Hypo-, hyper- and normovolemic forms are known.

1. Hypovolemic metabolic alkalosis
Vomiting: Due to loss of gastric acid, the HCO_3^- concentration increases both in the blood (alkalosis) and in the glomerular filtrate. If the excess bicarbonate exceeds the reabsorption capacity of proximal tubules, more Na^+ and HCO_3^- reach the distal parts. Here the Na^+ reabsorption increases by enhanced exchange of Na^+/H^+ and Na^+/K^+. The resultant hypokalemia induces K^+ outflow from cells together with H^+ influx. In the tubular cells, the high H^+ level enhances H^+ excretion to urine and simultaneously the bicarbonate reabsorption increases (paradox aciduria, Fig. 6.6.). Vomiting also causes Na^+- and water-loss, and the decreasing ECV activates the RAAS, which sustains Na^+/K^+ and Na^+/H^+ exchange and bicarbonate reabsorption in the distal tubules. The hypokalemia and alkalosis become self-sustaining. Vomiting also results in Cl^--loss: less Cl^- is filtered, less can be reabsorbed (the intercalated cells cannot secrete HCO_3^- instead of Cl^-). Further complication is that in the respiratory compensation of metabolic alkalosis the pCO_2 increases, and the high CO_2 availability also increases HCO_3^- reabsorption in the tubules.

Metabolic alkalosis may develop in the course of *repeated removal of gastric acid* to prevent aspiration in comatose patient at intensive therapy unit.

Cl^--losing diarrhea in newborns causes metabolic alkalosis.

Cl-deficient baby-food may cause moderate alkalosis or deterioration of other Cl-losing state.

Frequent cause of metabolic alkalosis is *diuretic treatment* with drugs that inhibit Na^+-, K^+- and Cl^--reabsorption in the ascending limb of the loop of Henle (e.g. Furosemide).

In patients with *chronic edema* and secondary hyperaldosteronism diuretics may induce hypokalemia and consequent alkalosis.

Cl^--losing kidney: it is a rare tubular disorder.

Contraction alkalosis: an ECV fall can suppress the ratio of Cl^-/HCO_3^-, i.e. the relatively acidotic Cl^- anion decreases in comparison with the relatively more basic HCO_3^- anion. This may happen e.g. in sweating, or in the course of diuretic treatment.

If Cl^- content of the glomerular filtrate is low, the HCO_3^- excretion decreases in the distal nephron parts (instead of NaCl, $NaHCO_3$ is reabsorbed). HCO_3^- retention may cause moderate alkalosis, or it may aggravate the pre-existing one (cf. vomiting). The hypovolemic metabolic alkalosis is salt-sensitive: infusion of physiological saline may improve it by normalizing ECV and Cl^- level.

2. Hypervolemic metabolic alkalosis

Primary hyperaldosteronism, or high mineralocorticoid activity:

- Conn syndrome (primary hyperaldosteronism, aldosterone-producing adrenal adenoma),
- hyperreninemia (Wilms tumor, clear cell renal cell carcinoma or other kidney tumors),
- 11-β-hydroxylase deficiency: a form of congenital adrenal hyperplasia with glucocorticoid deficit and great excess of mineralocorticoid effects particularly due to 11-deoxy-corticosterone (DOC),
- 11-β HSD deficiency: a lack of cortisol-action neutralizing 11-β–OH-steroid dehydrogenase enzyme in the kidney enables cortisol to act on renal mineralocorticoid receptors, therefore high mineralocorticoid activity („apparent mineralocorticoid excess") is seen with a normal levels of mineralocorticoids and cortisol,
- spillover mechanism (hormones of similar structure can bind to the receptors and enhanced hormone activity may develop): excess cortisol can stimulate the mineralocorticoid receptors in Cushing disease (ACTH-producing pituitary adenoma), Cushing syndrome (adrenal glucocorticoid-producing adenoma), or during treatment with exogenous steroids.

Hypoparathyroidism: while PTH inhibits HCO_3^- reabsorption, in its absence enhanced reabsorption leads to alkalosis,

Bicarbonate intake: milk-alkali syndrome (ulcer patients were advised to consume lots of cold milk and bicarbonate – it often led to alkalosis and hypercalcemia) or too big bicarbonate infusion in diabetic ketoacidosis (at pH >7.0 infusion should be stopped).

3. Normovolemic metabolic alkalosis

Secondary hyperaldosteronism in chronic cardiac, hypoproteinemic edema, or in portal hypertension with edema and ascites.

Posthypercapnic alkalosis: following chronic respiratory acidosis a too fast increase of ventilation may wash out the CO_2-excess, but the accumulated HCO_3^- cannot be excreted so quickly, causing transient alkalosis.

Hypokalemia promotes H^+ entry to the cells (in exchange K^+ leaves the cell – internal balance, ch. 6.1.5.1.), while in the distal tubules Na^+/H^+ exchange is emphasized (external balance, ch. 6.1.5.2.). Both processes cause alkalosis. Hypokalemia and alkalosis exhibit a vicious circle (ch. 7.2.1.2., hypokalemic alkalosis in vomiting).

CONSEQUENCES OF METABOLIC ALKALOSIS

In contrast to the good compensation of metabolic acidosis by Kussmaul breathing, the respiratory compensation of metabolic alkalosis is limited, since the ventilation cannot be decreased too much due to the simultaneously induced hypoxia.

1. Hypokalemia: It may lead to serious arrhythmias, even to lethal ventricular fibrillation.
2. Hypocalcemia: The ionized Ca^{2+} falls in the plasma, since the buffering plasma proteins (while release H^+) bind Ca^{2+}. Meanwhile the proteins suffer conformation changes and their functions (e.g. enzyme functions) decrease. Hypocalcemia enhances neuromuscular excitability, the most severe consequence of which is tetany (ascending tonic-clonic spasms) affecting the laryngeal (but not the respiratory!) muscles. Laryngospasm may be lethal. Due to compensatory mechanisms in slowly developing chronic alkalosis, a manifest tetany is rare.
3. The oxygen-dissociation curve of Hb is shifted to left, thereby the oxygen-binding capacity of Hb increases but the diffusion is worse and tissue oxygenation is difficult.

4. An increase of the parasympathetic tone decreases blood pressure and heart rate.
5. Due to the high insulin efficacy, glycolysis is enhanced and gluconeogenesis is decreased, causing a tendency for hypoglycemia.
6. Alkalosis promotes cell proliferation.

TREATMENT OF METABOLIC ALKALOSIS

At pH >7.5 NH_4Cl, acids, if necessary K and spironolactone treatment is advised.

6.2.2.3. RESPIRATORY ACIDOSIS

Usual pH parameters in respiratory acidosis: primary disorder is the elevated pCO_2, as an acute (minutes to 12-h) consequence the pH decreases (this is often non-compensated because of the slow character of renal compensation); due to shift between EC buffers, the actual HCO_3^- increases, but the standard HCO_3^- and BB do not change, BE = 0 ± 2.5 mmol/l. In chronic cases (after days) the pH may even return to normal, while not only the actual but also the standard HCO_3^-, BB and BE increase (resembling metabolic alkalosis).

CAUSES OF RESPIRATORY ACIDOSIS

It may be caused by any pathological condition, which can induce acute or chronic respiratory failure with hypoxia and hypercapnia. (Causes: see respiratory failure, ch. 3.1.2.4.1. and 3.6.1.)

CONSEQUENCES OF RESPIRATORY ACIDOSIS

1. Hypercapnia induces cerebral vasodilation, high intracranial pressure and headache. Irritability and/or somnolence may join. Acute extreme pCO_2-rise may lead to CO_2-narcosis and coma.
2. Chronic (even very high) pCO_2-elevation is better tolerated. However, the central CO_2-sensitivity decreases and respiration is controlled by hypoxia (SAS is frequent). In severe chronic respiratory acidosis, the consequences are similar as those in metabolic acidosis.

TREATMENT OF RESPIRATORY ACIDOSIS

It is necessary to increase ventilation to suppress pCO_2. Since in chronic cases, the renal HCO_3^- retention is pronounced and the standard HCO_3^- is high, too fast decrease of pCO_2 may induce transient metabolic alkalosis.

6.2.2.4. RESPIRATORY ALKALOSIS

Usual pH parameters in respiratory alkalosis: the primary disturbance is the fall in pCO_2, acutely (minutes to 12-h) the pH rises (practically not compensated), due to a shift between the EC buffers the actual HCO_3^- decreases, while the standard HCO_3^- and BB, BE do not change. In chronic cases (days) with full renal compensation, the pH may be even normal, while not only the actual but also the standard HCO_3^-, BB and BE are lowered.

CAUSES OF RESPIRATORY ALKALOSIS

Any form of acute or chronic alveolar hyperventilation: the ventilation exceeds the actual metabolic need and CO_2 is washed out. (Causes: see hyperventilation, ch. 3.1.2.4.2.)

CONSEQUENCES OF RESPIRATORY ALKALOSIS

1. By hypocapnia, cerebral vasoconstriction develops and the brain hypoperfusion causes dizziness, fainting, loss of consciousness. In chronic cases psychosomatic type of symptoms may be characteristic.
2. The ionized Ca^{2+} of blood decreases, this enhances neuromuscular excitability, and a tendency for tetany may occur (although it rarely causes laryngospasm). Probably moderate Ca-deficiency due to latent hypoparathyroidism explains tetany in these cases (instead of syncope as in other cases).
3. The dissociation curve of Hb is shifted to the left, the oxygen-binding capacity of Hb is elevated, but the tissue oxygenation is worsened.
4. Other consequences mentioned at metabolic alkalosis may also occur.

TREATMENT OF RESPIRATORY ALKALOSIS

Re-breathing of CO_2 (breathing into and back from a sack), or in case of tetany, i.v. Ca-administration is life-saving, in worst case, conicotomy is needed..

6.2.2.5. MIXED ACID-BASE DISORDERS

Combined disorders occur rather frequently. Respiratory plus metabolic acidosis is observed together e.g. in pulmonary edema with depression of respiration and circulation. Respiratory plus metabolic alkalosis is seen e.g. in liver failure treated with diuretics or in ICU pa-

tients with artificial ventilation and nasogastric suction of gastric juice. Respiratory acidosis plus metabolic alkalosis may appear together in chronic pulmonary patients treated with diuretics. Respiratory alkalosis and metabolic acidosis may be combined in septic shock, sepsis with renal failure, in liver failure (hepatorenal syndrome) or in salicylate intoxication. Components of metabolic acidosis and alkalosis may complicate ileus, vomiting in renal failure, or lactic acidosis in shock. The mixed disturbances may compensate each other, and the pH is not necessarily abnormal. In other cases, however, one disorder may become manifest by the other abnormality.

6.3. SALT AND WATER vs. ACID-BASE DISORDERS IN THE ELDERLY

6.3.1. SALT- AND WATER-BALANCE AT OLD AGE

Elderly persons are exposed to the dangers of either *exsiccosis* or *over-watering*. The spontaneous drinking decreases due to diminished feeling of thirst. Water deprivation is followed by slow and incomplete water intake as compared with the young counterparts. Wrinkling of skin is also well-known – not so much the esthetical points are important, rather the fact that the water-binding capacity of the subcutaneous connective tissue decreases: in the young, this water may be enough to replace the lost plasma volume from the interstitium. In seniors this is hardly possible, the plasma volume quickly decreases, with all of its consequences. Lack of water, any form of salt- and water-loss may lead to severe *hypovolemia*, often to *hypertonicity*, which correspond to the frequent occurrence of *orthostatic hypotension* with accompanying muscle weakness and disorientation. In contrast, salt- and/or water-load easily result in hypervolemia, *sudden rise of blood pressure* or, occasionally, to hypotonicity and *pitting edema*. In the background stand the altered *renal structure and perfusion*, together with the *weakening effects of regulatory hormones* of salt- and water-balance.

With aging the number of functioning nephrons progressively decreases. By age 80-y the GFR decreases to half the normal (the glomeruli are more sclerotic, the basement membrane thickens and its structure changes, in the capillary loops fibrin-deposits can be demonstrated) – these may result in increased permeability and proteinuria. The decrease in the number of intact tubules leads to *hyposthenuria* (ch. 5.3.2.); ADH does not cause sufficient concentrating of the urine, while the maximal dilution is also absent even in lack of ADH ("salt-wasting kidney"). The excretory functions are further deteriorated due to the frequent decrease of renal perfusion (redistribution due to cardiac causes, exsiccoses, etc.). The dose of drugs excreted by the kidney has to be adjusted (decreased).

The capacity of regulatory systems is also limited. Similar hypovolemia induces smaller activation of RAAS in old than in young persons, the effects of angiotensin and aldosterone are weaker (in old animals the intracerebroventricularly applied angiotensin II also causes smaller water intake than in young ones). A decreased plasma volume evokes ADH production and consequent hypotonicity without actually fully normalizing the volume. The basal ADH production may even be enhanced, but its renal effect is weaker (less nephrons, poorly functioning receptors), and its dypsogenic effect is also decreased. Upon salt- and water-intake the inactivation of RAAS and induction of natriuretic factor effect are delayed (the atriopeptin level is high, but its efficacy is decreased). The old patient cannot defend the effects of either enhanced salt intake or enhanced water intake.

At hospital admissions in 1.1% of patients above 60-y exhibited >148 mmol/l se-Na, suggesting insufficient water intake: at such se-Na levels the excess mortality was ca. 40%. The water supply is often deficient even in hospitals. Contrary to this, salt intake easily causes hypernatremia (the salt-losing capacity is limited in elderly) – this may evoke hypertensive crisis, therefore it should be avoided. On the other hand, at ICU admissions of seniors the se-Na concentration was lower than 130 mmol/l in 11.3% of the patients (in those transferred from chronic health care institutions this was 22%, and in 4.5% the se-Na was below 125 mmol/l). In disabled, old patients particularly in those with heart failure (ch. 2.1.), diuretics (= saluretics!) are often used, and while drinking is usually provided (often by sweet juices, glucose is converted into carbon dioxide and water), it is done without salt replacement. Although in young persons the salt restriction is generally advised, in old ones this is not so clear – eventually a simple saline infusion is very effective: the dizzy, taint, anorexic patient with hypodipsia and nausea becomes interested, his/her general condition improves, starts eating and drinking. The importance of hypotonicity is emphasized by the observation that in hyponatremic patients the all-cause mortality was 7-8-times higher than in normonatremic ones.

6.3.2. DISORDERS OF ACID-BASE BALANCE AT OLD AGE

Physiological ageing has no effect on the normal value of pH, but its regulation exhibits significant age-dependent changes. The most frequent causes of pH-changes and age-related characteristics of their compensatory possibilities are to be detailed.

In seniors the most frequent causes of *metabolic acidosis* are diabetic ketoacidosis, lactic acidosis (e.g. hypoperfusion of some tissues in chronic heart failure, or anemia due to decreased erythropoietin synthesis), salicylate intoxication (e.g. much NSAID for arthritis), diarrhea, RTA (e.g. in diabetic nephropathy). In the background of *metabolic alkalosis* mostly vomiting, secondary hyperaldosteronism due to edemas in chronic congestive heart failure and hypokalemia are the main causative factors, which are exaggerated by diuretic treatment.

Both the respiratory and renal compensation of metabolic type pH-disorders becomes lessened with increasing age. It is more difficult to compensate metabolic acidosis by hyperventilation, since the regulation of respiration becomes less sensitive to CO_2 or H^+ increase as well as to hypoxia. The aging kidney reacts more slowly to acidic burden, therefore the pH normalization is more difficult. In RTA (that may accompany tubular degeneration) the urinary pH does not decrease below pH 5.5, despite immense EC academia.

The most frequent cause of *respiratory acidosis* in the elderly is the alveolar hypoventilation due to disorder of regulation of respiration: the respiratory center is less sensitive to hypercapnia, similarly the chemoreceptors to hypoxia (by age 70-y the responsivity decrease to about half of normal, the plasma O_2-tension decreases by 0.3% yearly), and the patients often use ventilation-depressing medications. A tendency for respiratory acidosis may be caused by the decrease of vital capacity and FEV_1, worsening of the volume or distensibility of thorax (e.g. kyphoscoliosis), and decrease of diffusion surface (emphysema-like changes). The function of respiratory muscles may be abnormal in various neuromuscular disorders. All these are aggravated by the fact that the chronic bronchitis is more frequent (longer effect of air-polluting agents, smoking), and the mucociliary clearance decreases. Causes of *respiratory alkalosis*: hypoxias, sepsis, pulmonary microembolism, heart- and liver-failure, mild salicylate toxicosis (NSAID), frequent states of anxiety.

The respiratory disorders may be complicated by the decreased renal compensatory capacity. In older patients, oxygen therapy and assisted respiration may be more frequent.

In old patients the *mixed acid-base disorders* are more frequent, e.g. in acute respiratory insufficiency, pneumonia, heart failure respiratory and metabolic acidosis are more frequent, in severe heart failure the decreased tissue perfusion leads to lactate acidosis, while diuretic treatment pushes the balance towards metabolic alkalosis.

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