ACID-BASE EQUILIBRIUM MODELING BASED ON THE BALANCE CONCEPT

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Abstract

Two approaches are applied to the clinical evaluation of acid--base equilibria: one is the traditional "Danish school" approach of Siggaard-Andersen et al., the other is the "modern" approach by Stewart and Fencl. The two theories are interlinked by what is called the balance approach, described in detail in [1]. A simulation model can be applied in order to model various pathogeneses of acid-base disorders and to monitor their manifestations from both the traditional and the modern acid-base theory aspects.

Key words

Acid-base equilibrium, Balance approach,
Danish school of acid-base equilibrium, Model, Stewart's theory

1 Introduction

Two approaches are applied to the evaluation of an acid-base equilibrium (ABE): the traditional approach of the Danish school of Astrup, Siggaard Andersen and collaborators, using BE and compensation diagrams, and Stewart's approach, sometimes referred to as "modern", based on physico-chemical calculations of acid-base and electroneutral equilibria of ions and buffers in plasma. Both theories basically target the same topic, only from different aspects [2–4]. Nevertheless, advocates of one or the other theory sometimes trigger fierce arguments. Kamel and Halperin, in their most recent monograph [5], thereby conclude that the traditional theory augmented with ion balance correction calculations is quite well suited to the evaluation of ABEs, while Stewart's approach basically brings no new contribution to the concept. By contrast, many other authors consider Stewart's approach a breakthrough and resentfully reject any criticisms. Advocates of the second approach prevail in the Czech Republic. [6–8].

Stewart published two papers [9,10] that maybe would have passed unnoticed had Mr. Vladimír Fencl, a renowned professor with Czech roots teaching at Boston University, not devoted a great effort to the promotion and an additional expansion of Stewart's ideas [11–16]. This is why any criticism of the Stewart--Fencl theory is widely perceived as blasphemy, particularly in the Czech milieu.

We have put forward a new concept, based on balances, which, as we believe, interlinks the two theories and provides an explanation of pathophysiological processes involved in ionic and acid-base equilibrium disorders [1,17].

In order to verify this theory (and to persuade clinicians) we are developing a simulator, accessible from our website, that will enable our approach to be explained interactively.

2 In which aspect is the Stewart theory wrong?

The balance concept will **enable changes in acid-base parameters and ions, which are wrongly explained by the Stewart theory and inadequately explained by the traditional theory, to be explained on a pathophysiological basis.**

The mathematical causality being mistaken for pathophysiological causality is the major **weakness of Stewart's approach** (Figure 1). Mathematical causality enables the pH and bicarbonate plasma concentration to be calculated from following input variables: partial pressure of carbon dioxide (pCO_2), the Strong Ion concentration Difference (SID) and the total non-bicarbonate buff er concentration ($[A_{tot}]$). The explanation of the pathophysiology of acid-base disorders by a mechanistic adoption of the dependences of pH and HCO_3^- on the input variables pCO_2, SID and A_{tot} is seemingly simple, but fails to explain the real causal chain of the disorders (Figure 2).

Indubitably, the changes in the SID, A_{tot} and/or pCO_2 levels will bring about changes in pH and in the bicarbonate concentration. This, however, does not imply that the body controls its pH and bicarbonates by controlling the balance of strong ions and by subsequently affecting the SID or controlling the albumin and phosphate levels and, in turn, by affecting the A_{tot} parameter. The internal environment stability control depends on the balance of various components involved in the internal environment (i.e., ECF composition). Ionic, volumetric and osmotic homeostasis of the internal environment depends on a controlled balance of various constituents (ions, water, ...). Acid--base homeostasis is no exception. Once again, the control of material (CO_2, H^+ and HCO_3^-) flow balance is involved. The CO_2, H^+ and HCO_3^- flows are interrelated due to the presence of the bicarbonate buffer system in the body fluids.

The CO_2 flow is controlled by respiration – CO_2 balance disorders bring about respiratory disorders of the acid-base equilibrium. However, remember that the CO_2 level in venous blood together with equilibrated IST depends not only on the respi.. ration-dependent arterial concentration but also on perfusion – the hypo-perfused tissues experience hypercapnic acidosis even in normal acid-base situations in arterial blood (hypercapnic hypo-perfusive tissue acidosis results in the bonding of H^+ ions to proteins in the cells with damaged performance of the enzymes). In normal situations, the metabolic H^+ formation is in equilibrium with the kidney-generated bicarbonate flow during urine acidification. H^+/HCO_3^- flow balance disorders result in metabolic acid-base equilibrium disorders.

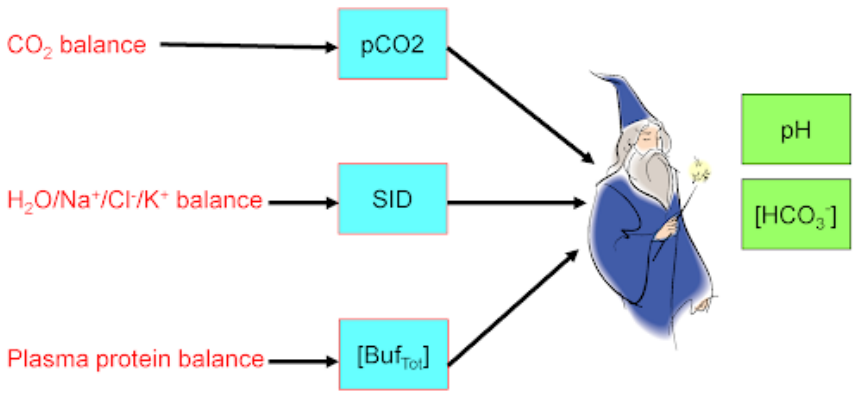

Figure 1– Stewart's approach is based on mathematical relations that can be used to calculate the pH and [HCO3-] levels from the mutually independent pCO2, SID and [A_{tot}] data.

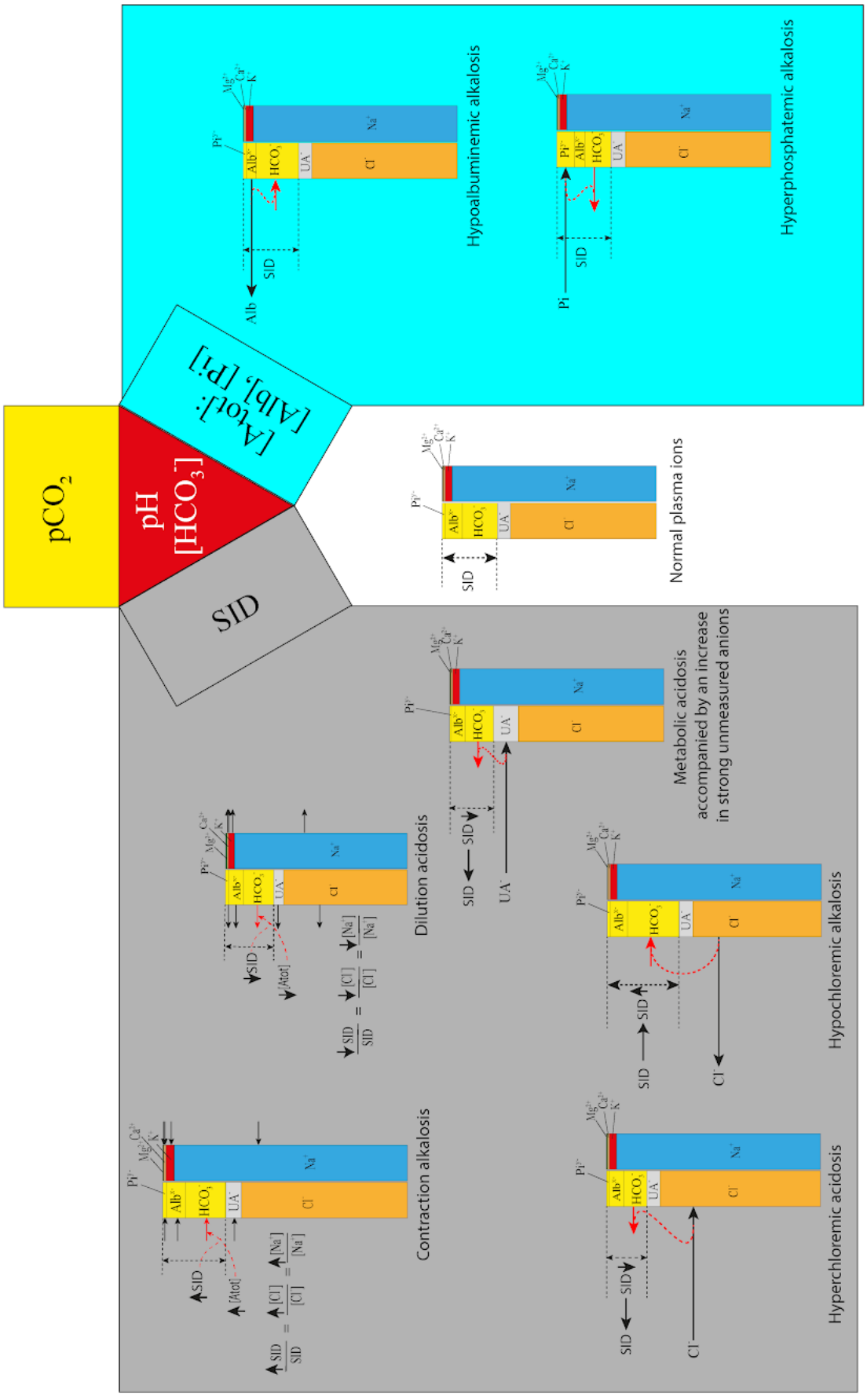

Figure 2 – Stewart's approach to metabolic acid-base disorders is based on the concept where the SID and A_{tot} changes constitute the initial pathogenetic cause, all the remaining parameters – HCO_3^- and H^+ – adapting to the actual situation. This follows from the acid-base equilibrium equations. However, from this one should not deduce that the body controls the acid-base equilibrium by controlling the SID and the non-bicarbonate buffer concentration (A_{tot}).

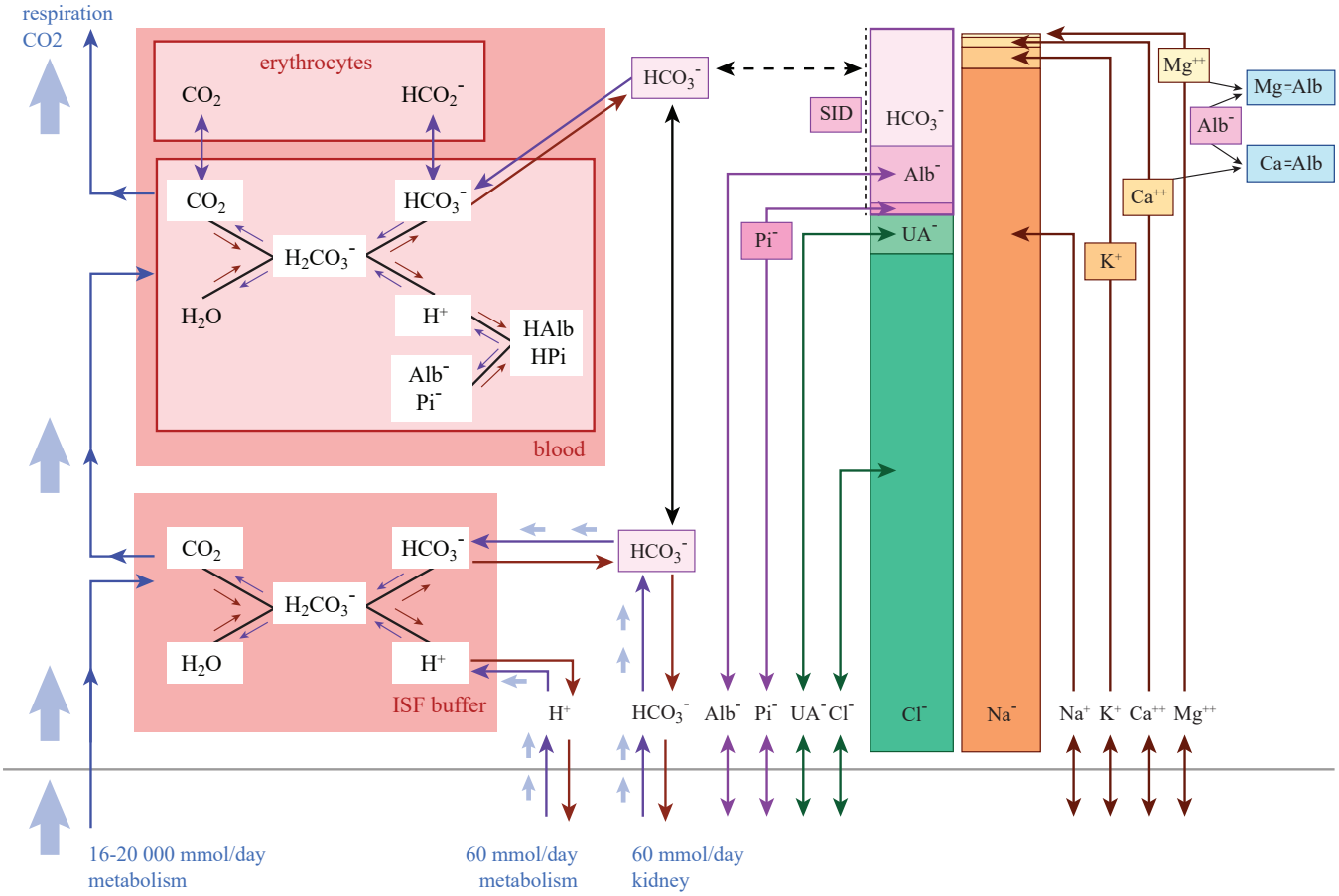

Figure 3 – Metabolic formation of carbon dioxide and strong acids must be in equilibrium with their elimination from the body. The CO2 removal is the responsibility of the respiratory system, which keeps the CO2 concentration in arterial blood constant (dependent on alveolar ventilation). The elimination of strong acids is the responsibility of the kidneys. Every eliminated hydrogen ion, which is mainly bonded to phosphates as what is called titratable acidity (TA) or is included in the ammonium ion in the urine, is comprised of one bicarbonate ion in the internal environment. At the same time, bicarbonates are also filtered from plasma to the glomerular filtrate. In normal situations, virtually all bicarbonates passing through the filter system are reabsorbed by the kidneys. The renal control of the acid-base equilibrium consists in the control of new bicarbonate formation during urine acidification (whereby the H+/HCO3- balance is affected, bringing about change in BB and BE). The respiratory acid-base equilibrium control is effected through the CO2 balance control, affecting then the pCO2 level in arterial blood. Taken from [1].

So, the body **does not control the body fluid pH or the HCO_3^- level through the SID change and the albumin level control. Instead, the body controls those parameters by controlling the flow balance of CO_2 (respiratory ABE control) and H^+ and HCO_3^- (the metabolic component of ABE control). Disorders of those balances bring about acid-base disorders. The Balance theory provides a pathophysiological explanation of the causes of the changes in the ionogram, SID and A_{tot} accompanying various acid-base disorders**.

3 In what respect is the explanation of the ABE disorder pathophysiology insufficient?

The Danish school focuses on the ABE disorder diagnosis primarily based on the **concentrations** of the buffer system components in blood (and, in turn, in the ECF) and the **concentrations** of ions in the ECF. This school inadequately describes the diagnosis of mixed disorders (particularly where the two disorders act in opposite directions) and, in particular, their causes, and fails when evaluating hemodilution and hemoconcentration states[1].

4 What does the balance theory newly contribute?

The balance concept is based on the following six principles enabling the changes in the acid-base parameters and ions to be explained on a pathophysiological basis (see [1], Section 6):

1. All **trans-membrane transports** take place in a steady state in the overall balance by an **electroneutral route**.
2. **Electroneutrality does not change during biochemical reactions** in the human body. So, for instance, the negatively charged lactate or citrate metabolizes to water and CO_2 while taking up H^+ ions, hence, like lactic or citric acid.
3. The acid-base equilibrium depends on the **balance of the CO_2, proton and bicarbonate flows interconnected via the bicarbonate buffer system**. This is the same as in the traditional theory and enables ABE disorders to be classed into respiratory disorders (CO_2 balance) and metabolic disorders (H^+/HCO_3^- balance).
4. The **plasma SID and BB levels describe the same entities, calculated in different ways**, the SID and BB (BE) level changes are identical and describe the balance of the proton and bicarbonate flows. An addition of 1 mmol/l of protons will reduce the SID and BB by 1 mmol/l, whereas an addition of 1 mmol/l of bicarbonate will increase the SID and BB by 1 mmol/l (and vice versa).
5. The bicarbonate buffer system in the body fluids captures

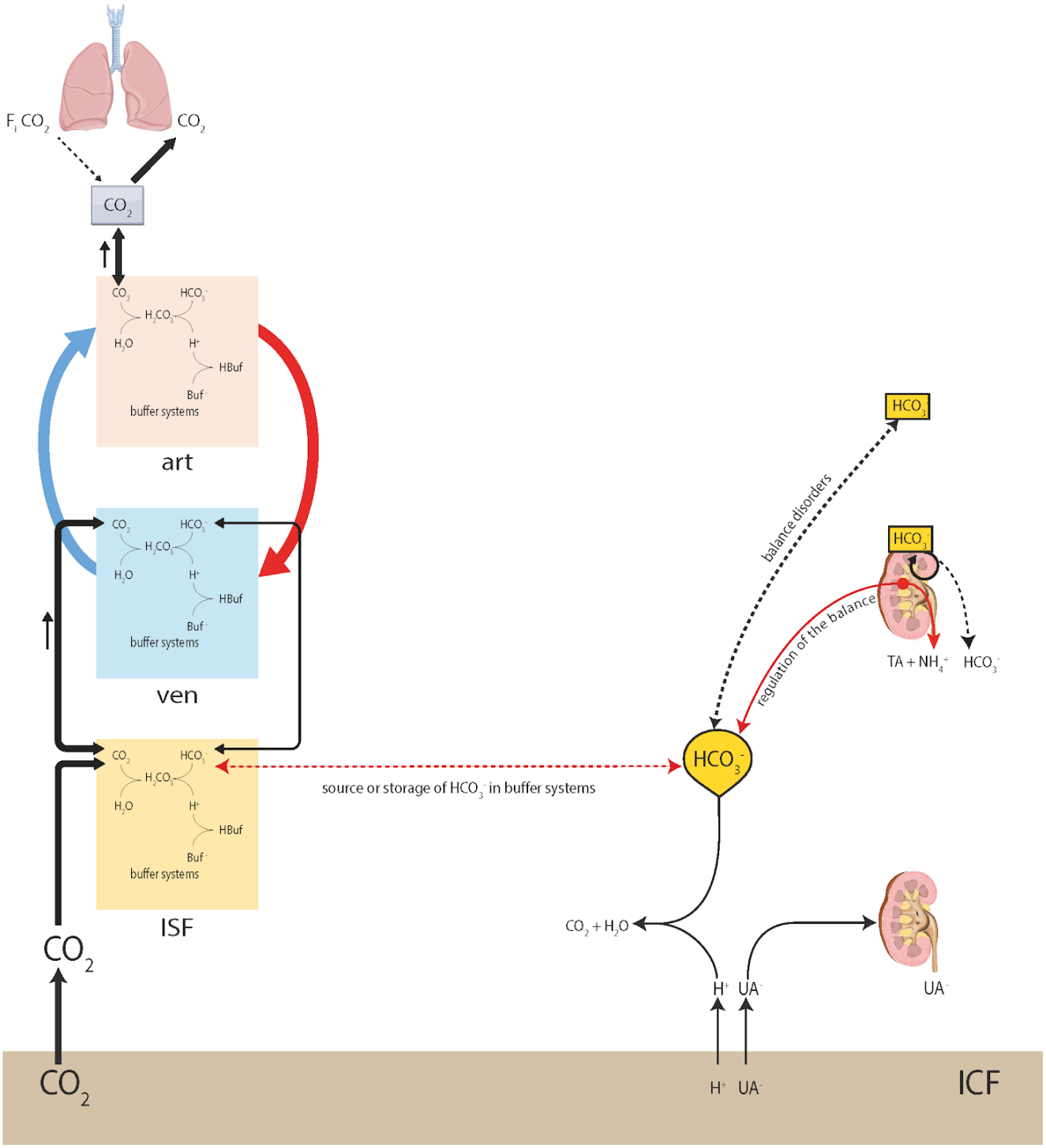

Figure 4 – Acid-base balance flows: metabolic CO2 production, respiratory elimination flow, strong acid production and excretion flow. Interlinking of those flows through the bicarbonate buffer enables the respiratory system to correct metabolic disorders of the acid-base equilibrium and the kidneys to correct respiratory disorders. Disorders of such balances result in respiratory and metabolic disorders of the acid-base equilibrium. The ubiquitous bicarbonate buffer in body fluids captures hydrogen ions from strong acids and creates a bicarbonate concentration gradient in the extracellular fluid. Since the diffusion rate depends on the concentration difference and the bicarbonate concentration is six orders of magnitude higher than the hydrogen ion concentration, the bicarbonate diffusion flows are higher than the H+ flows. The bicarbonate flows can be used to describe the metabolic balance of the acid-base equilibrium. In physiological circumstances the hydrogen ion input from the metabolic strong acid formation to the extracellular fluid is made up for by the new formation of bicarbonates created by the kidneys due to urine acidification (and all bicarbonates passing into to the glomerular filtrate are reabsorbed). If the bicarbonate flow balance is negative (metabolic acidosis), the missing bicarbonates are provided by the buffer systems, whereas in the opposite situation (metabolic alkalosis), the excess bicarbonates are accumulated by the buffer systems (with the appropriate acid-base equilibrium shifts, manifested, among other things, by adequate changes in the BB and SID values). So the buffer systems fulfill their buffering function with respect to nonequilibrium bicarbonate flows leading to acid-base equilibrium disorders, and H+/HCO3- balance disorders result in metabolic acid-base equilibrium disorders. Taken from [1].

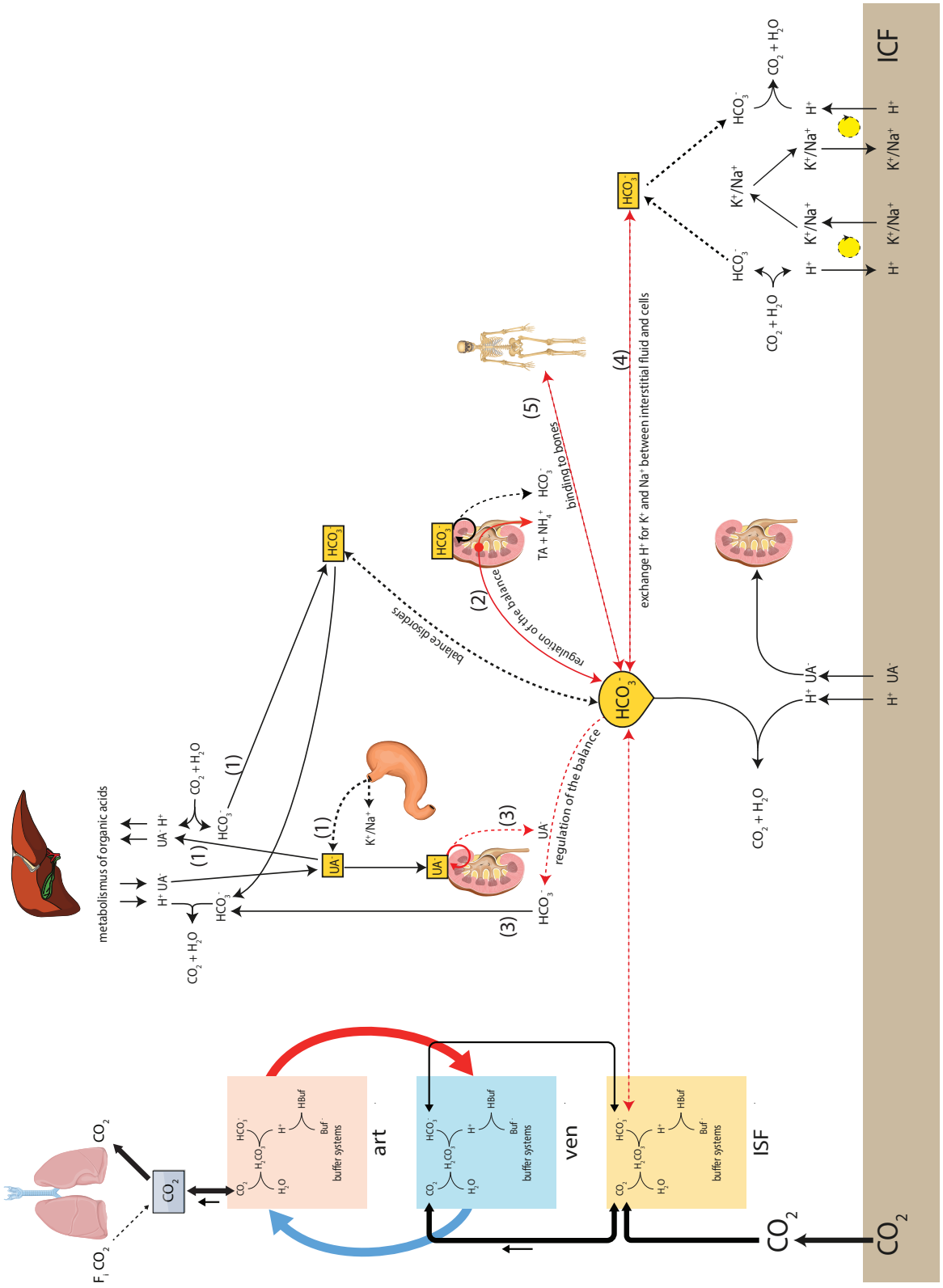

Figure 5 – Acid-base balance control flows. Strong acid formation (60-70 mmol/day) depends on the diet (increases with protein intake). Salts of organic acids (potassium citrate, etc.) in fruit and vegetables have an acidification effect because the organic acids are metabolized as acids (together with the hydrogen ion), and the bicarbonate ion created on the absorption of the organic acid alkalinizes the internal environment (1). In bicarbonate balance disorder circumstances the kidneys increase or decrease urine acidification, associated with new formation of bicarbonates, thereby attempting to re-balance the disturbed balance (2). The kidney response to alkalemia consists not only in urine acidification reduction followed by bicarbonate generation reduction. The pH increase also results in reduced reabsorption of the organic acid anions (3), and the hydrogen ion retained by the ECF acidifies the internal environment. The cells (4) that can absorb large quantities of hydrogen ions in exchange for potassium and sodium ions during acidemia represent a next control mechanism. Inside the cells the hydrogen ions are buffered by the intracellular buffers. The reverse is true of alkalemias. The basic bone material also functions as a binding site for H+ ions and bicarbonates during long-term acid-base balance disorders (5). Taken from [1]

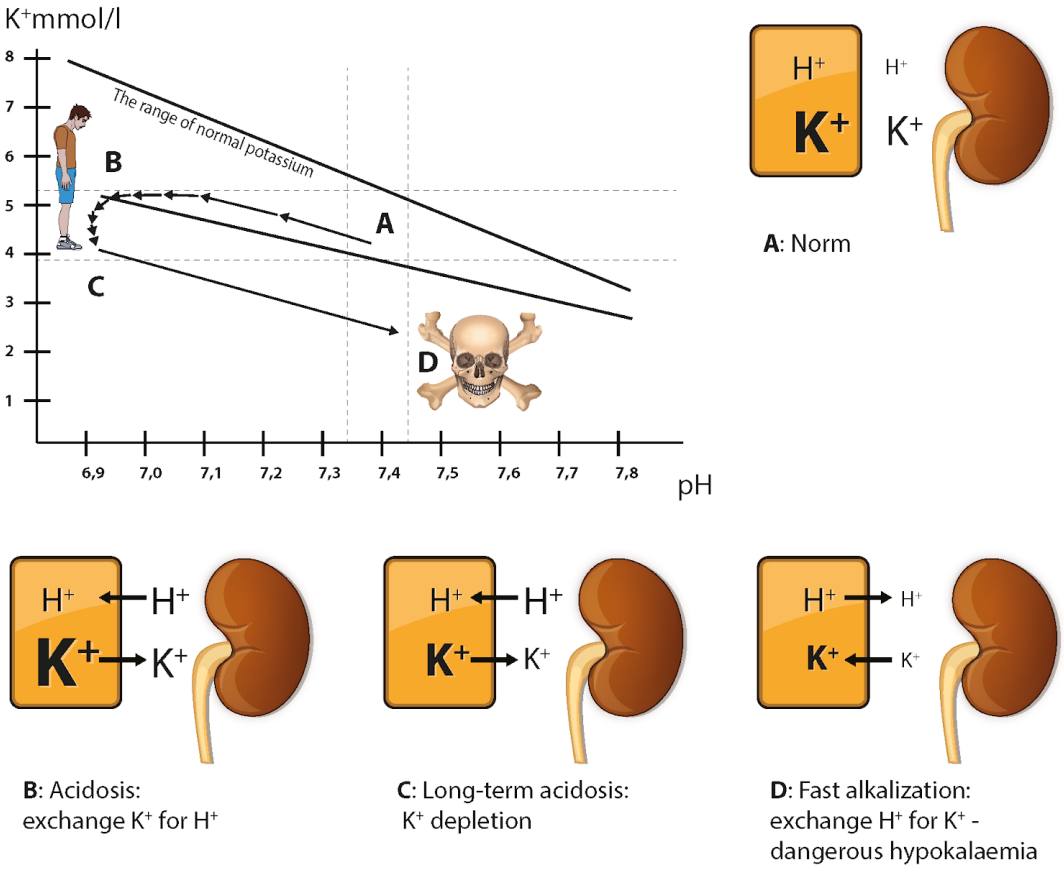

Figure 6 – Relation between kalemia and pH. H+ ions enter the cells in exchange for K+ ions during acidemias. So, the normal kalemia level depends on pH. Long-term acidemias are associated with potassium being washed out of the cells, which may result in potassium depletion. On fast alkalinization during long-term acidemias, the cells start reabsorbing potassium rapidly but, since a large potassium fraction has been excreted from the body, fast alkalinization may result in life-threatening hypokalemia. Taken from [1].

and releases protons. Therefore, **proton flows are equivalent to bicarbonate flows**.

6. The **buffer systems are "storerooms" for situations involving bicarbonate flow disbalances** with appropriate changes in the acid-base equilibrium.

The balance theory is NOT based on evaluation of the bicarbonate concentration in the ECF, as it might seem at the first glance. What interests us is the **balance** of the H^+/HCO_3^- flows and **electroneutrally interlinked flows** of the remaining ions. The hydrogen and bicarbonate ion flows are interlinked via the bicarbonate system, which is ubiquitous in the body fluids. The diffusion flow rate depends on the concentration gradient. The proton concentration gradient is many orders of magnitude lower than the bicarbonate concentration gradient, and as such the proton diffusion flows are lower than the bicarbonate diffusion flows. Owing to this, the **acid-base metabolic balance can be described in terms of the bicarbonate flow balance**. A negative bicarbonate balance characterizes metabolic acidosis, whereas a positive balance characterizes metabolic alkalosis – in this, our theory agrees with the traditional Danish ABE school.

The **buffer systems are true buffers (dampeners) of variations in the acid-base balances of the H^+/HCO_3^- flows during metabolic acid-base equilibrium disorders**. When the bicarbonate balance is negative/positive (metabolic acidosis/alkalosis), the buffer systems provide/accumulate bicarbonates, and the subsequent change in the equilibrium within the buffer systems result in pH changes (see Figures 3-7 taken from ref. [1]).

Not only the concentrations of the components but also the total amount plays a crucial role in the balance concept.

Both the traditional and the Stewart ABE theories primarily focus on the concentrations of the substances, which sometimes leads to incorrect conclusions. Not only the concentrations but also the total amount of the buffer bases (particularly bicarbonates in the ECF) is of importance with respect to the performance of the buffer systems as H^+/HCO_3^- flow balance variation buffers during metabolic ABE disorders. As, e.g., Halperin and Kamel point to [5,18], ECF volume reduction will be accompanied by a reduction in the total amount of bicarbonates, which are able, through H^+ bonding to dampen the H^+/HCO_3^- balance fluctuations during metabolic acidoses. With the ECF volume reduced, the bicarbonate concentration decrease – or the BE (or SID) decrease – may not match the severity of the metabolic acidosis.

Furthermore, Kamel and Halperin [5] point to the role of bicarbonate reserves in the ECF in the prevention of the hydrogen ion bonding to brain tissue proteins during metabolic acidoses. Bicarbonates in the ECF, particularly of the muscle tissue, bind the hydrogen ion load during acidoses, while the brain tissue, which contains relatively small amounts of HCO_3^- but is subject to large blood flows, only binds a minimal quantity of hydrogen ions. Whenever the volume is endangered (effective arterial blood volume is reduced), pCO_2 increases particularly in the

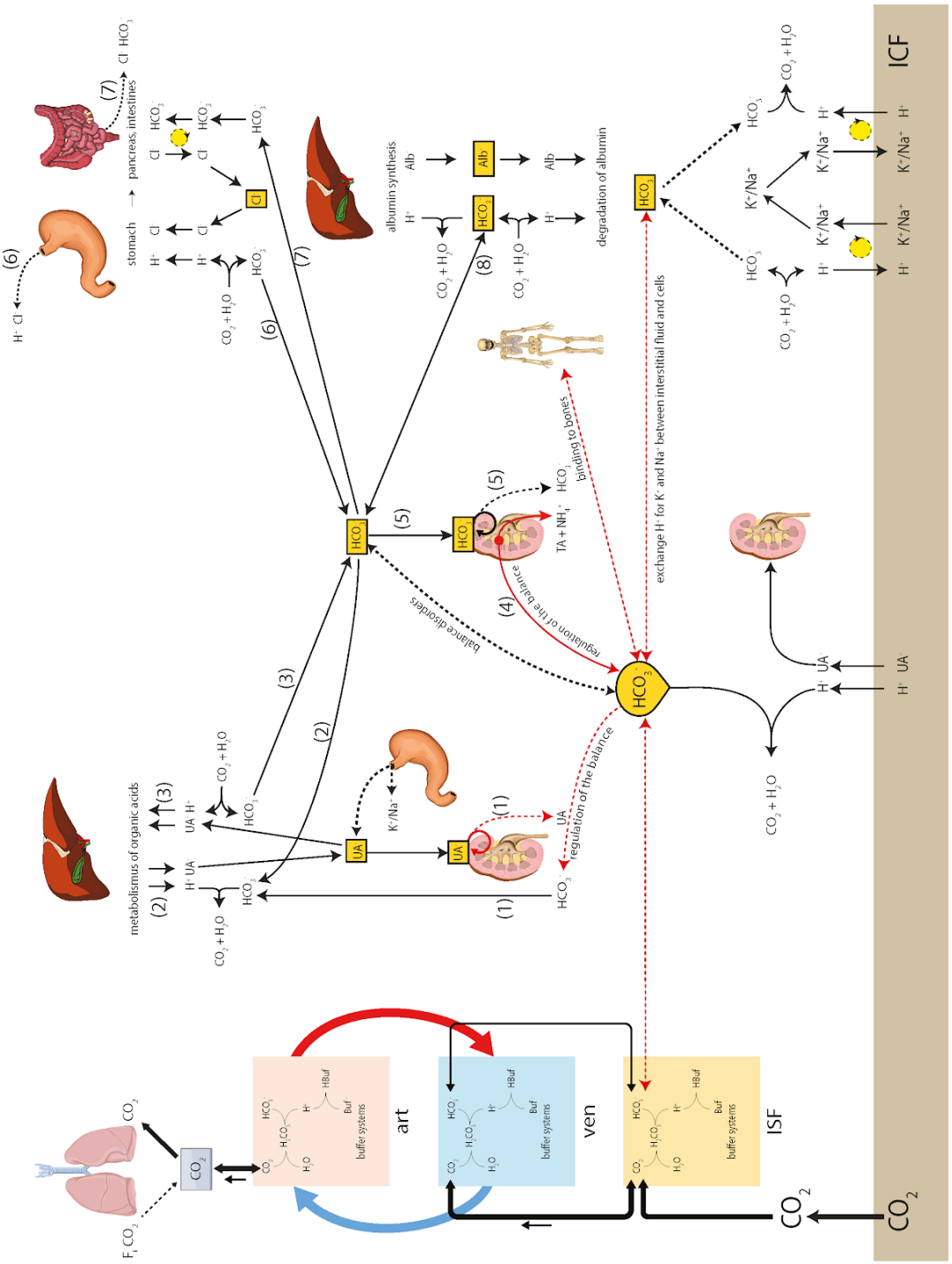

Figure 7 – Acid-base balance disorders. Organic acids are formed and metabolized. Normally their formation and metabolic degradation are in equilibrium, the majority of the organic acids is reabsorbed by the kidneys. Reduction in the reabsorption of the organic acid anions is a controlling response to alkalinization of the internal environment (1). In pathological circumstances (e.g. during lactate acidosis, ketoacidosis and the like) the formation of organic acids is enhanced, whereby the balance is shifted towards metabolic acidosis (2). On the contrary, fast metabolic consumption of organic acid anions (lactate, keto substances, ...) takes place together with the hydrogen ion (organic acid anions are metabolized electroneutrally as acids), which brings about a balance shift to the alkaline side due to a sudden bicarbonate intake (3) (this is why anions of certain organic acids are sometimes referred to as potential bicarbonates). Urine acidification disorders during a renal failure (4) or bicarbonate reabsorption disorders (5) result in metabolic acidosis. Hydrochloric acid is secerned into the gastric juice, bicarbonates are secerned and chlorides reabsorbed in the pancreas and intestines, bicarbonates and chlorides in the gastrointestinal tract are well-balanced during a time unit (the internal environment is alkalinized slightly on the food intake – this is referred to as an alkalinization wave, the acid-base balance is re-established after the food has passed into the intestines). Bicarbonate retention and chloride loss on vomiting result in hypochloremic alkalosis (6) whereas bicarbonate loss and chloride retention on diarrhea result in hyperchloremic acidosis (8). The negatively charged albumin is formed and reabsorbed together with the hydrogen ion (during which bicarbonates are used up or generated). If the albumin creation and degradation processes are well-balanced, no balance disorders take place (8). If the albumin degradation rate prevails over the formation rate (and the bicarbonate formation rate prevails over the bicarbonate use rate), the albumin level decreases and bicarbonates are retained, which results in hypoalbuminemic alkalosis. Taken from [1].

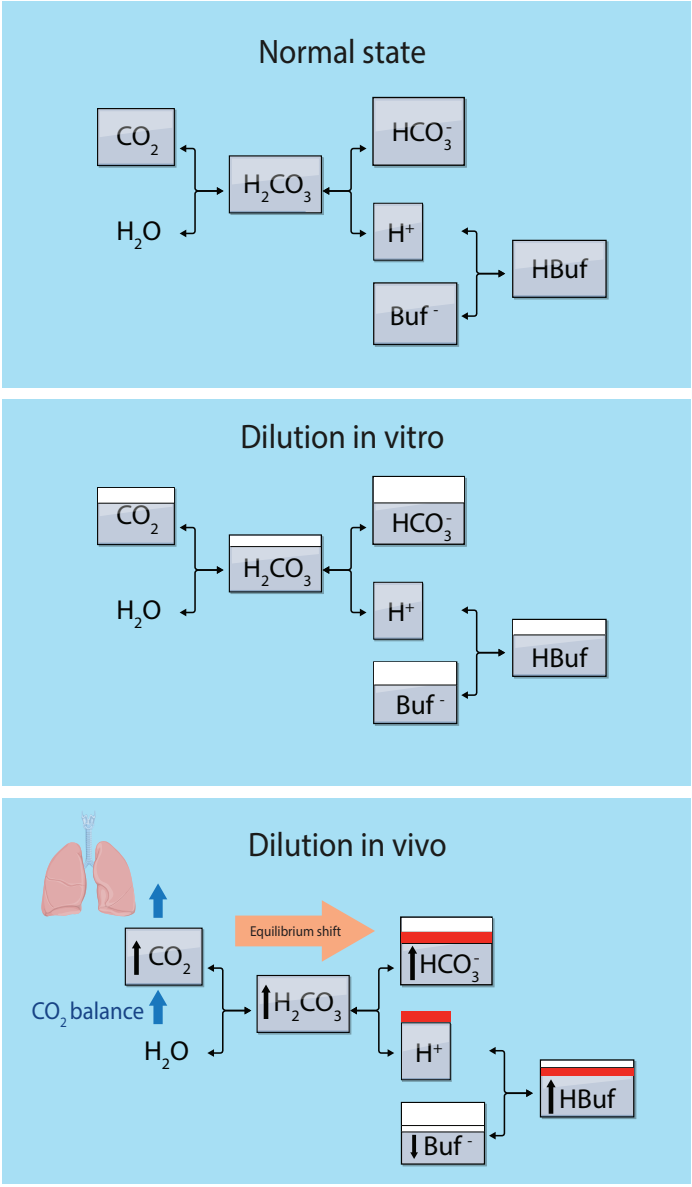

Figure 8 – Pathogenesis of dilution acidosis. The buffering capacity is reduced on buffer dilution, the pH, however, does not change. Since a constant weak acid level is maintained by respiration, the reaction equilibrium is shifted to the right side and acidification results. Taken from [1].

muscle tissue, and the brain tissue is threatened by H^+ bonding to proteins. A difference > 6 mmHg in the pCO_2 levels between arterial blood and a brachial vein indicates endangered volume.

Balance theory provides a different explanation of metabolic disorders of the acid-base equilibrium.

5 Dilution acidosis and contraction alkalosis according to the balance principle

A number of authors, such as [19] (and also Kazda in the Czech Republic [20]), explain dilution acidosis occurring after adding saline in terms of SID being reduced as a result of excess chloride and bicarbonate vanishing due to electroneutrality. However, bicarbonate in the buffer reaction only vanishes through binding with H^+, and this is released from the non-bicarbonate AH buffers – whereby the negative charge of A- increases – so that electroneutrality does not change in the buffer reactions and hence, this explanation is wrong.

The true cause of dilution acidosis / contraction alkalosis has nothing to do with chloride: it is related to the dilution/concentration of the buffers, the concentration of the weak acid (CO_2 and H_2CO_3) not being changed as indicated in Figure 8 [1].

Buffers as "chemical engines" maintain a constant pH, which is dependent on the weak acid [HA] to its conjugated base [A^-] concentration ratio: $[H^+] = Ka\ [HA]/[A^-]$ (Ka is the dissociation constant). The concentrations of the weak acid and its conjugated base change identically on dilution or concentration – their concentration ratio remains constant and hence, so does the pH. In blood buffering systems, however, the CO_2 concentration and hence, the weak acid (H_2CO_3) concentration in arterial blood (and also in venous blood and in the tissues if the flow rate does not change) are constant, whereby the equilibrium in the buffer systems shifts to the right (acid) side on dilution or to the left (alkaline) side on concentration.

If saline (NaCl) is added to the plasma, then the initiating cause of dilution does not rest in the fact that chloride increases relatively to Na^+: the decisive phenomenon is the dilution of the buffers (including the conjugated bases, giving rise to SID decrease), while neither CO_2 nor H_2CO_3 is diluted. This gives rise to a shift of equilibria within the plasma buffer system – to a HCO_3^- concentration decrease and a matching non-bicarbonate base concentration increase (without any change in the SID, reduced by dilution, or BE), and pH decrease. The dilution effect manifests itself in the same way on the dilution of crystalloids (without changing the Na^+/Cl^- concentration ratio).

We implemented the Watson model [21] as a teaching aid as a part of our Atlas of Physiology and Pathophysiology [22] (*http://www.physiome.cz/atlas/acidobaze/02/ABR_v_plazme1_2.html*), enabling the plasma dilution (or concentration) simulation experiment to be interactively replayed (see Figure 9).

In contrast to what occurs in the plasma model, the pH changes occurring on dilution or hemoconcentration are dampened by engaging intracellular buffers [23,24] and by the response of the kidneys.

The pathogenetic explanation of dilution acidosis is presented in Figure 10, while the pathogenetic explanation of contraction alkalosis disorders is shown in Figure 11.

6 Pathogenesis of hyperchloremic acidosis and hypochloremic alkalosis

The pathogenetic causes of hyperchloremic alkalosis are shown in Figure 12. According to Stewart, the bicarbonate concentration and pH adapt to the SID and pCO_2. In the balance approach the bicarbonate level is determined by the bicarbonate loss/supply balance, and by the appropriate equilibrium in the buffer system. 1 mmol/l of bicarbonate removal does not imply bicarbonate level reduction by 1 mmol: the reduction will be somewhat smaller because the non-bicarbonate base levels will also be lowered. 1 mmol/l of bicarbonate removal, however, will reduce the SID by 1 mmol.

In Stewart's concept, hypochloremic alkalosis is a result of SID lowering owing to the relative chloride concentration increase. Bicarbonate will adapt to that and will lower its concentration. In the balance concept, the basic cause is bicarbonate accumulation accompanied by an equimolar chloride loss (see Figure 13).

7 Pathogenesis of metabolic acidosis accompanied by an increase in strong unmeasured anions

According to Stewart, the pathogenetic cause of acidosis accompanied by an increase in the strong unmeasured anions rests in the lowering of the SID: the bicarbonate level will respond by decreasing, whereupon the pH will decrease as well. In balance theory this phenomenon basically results from the retention of the strong dissociated acids by the ECF. Hydrogen

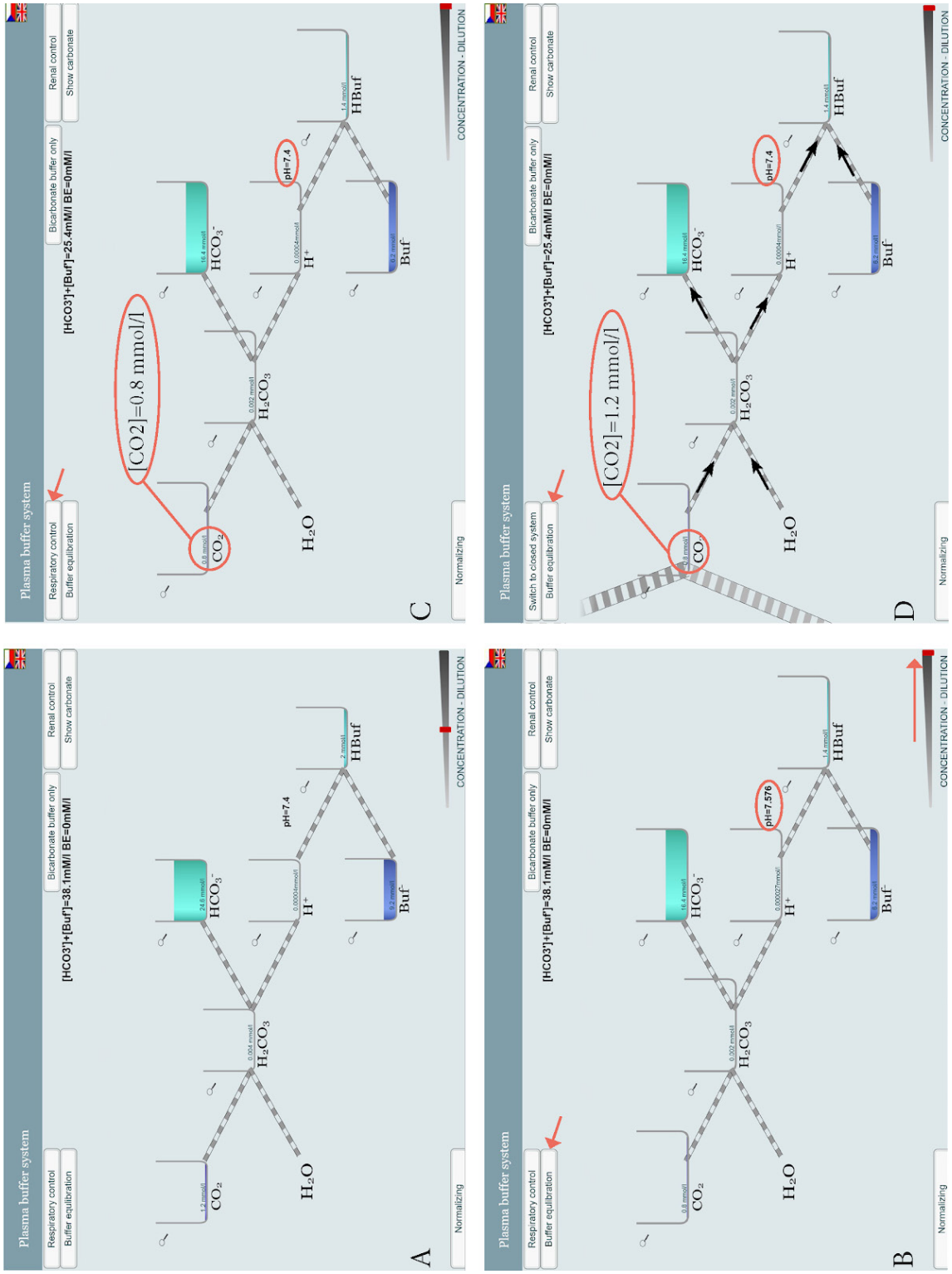

Figure 9 – Plasma dilution simulation. From the initial condition (A) move the "concentration - dilution slider" to the left side: all the buffer components (including H+) will be diluted (B). A new buffer component equilibrium will be established upon pressing the "Buffer equilibration" button and the concentration of H+ will return to its initial level (C). This is so because the latter is determined by the weak acid-to-its conjugated base concentration ratio, and dilution reduces the concentrations of the weak acids (HBuf- and H2CO3) and of the conjugated bases (HCO3- and Buf-) to the same extent. Only the buffering capacity is reduced, but the pH remains constant on dilution (this is why buffers are routinely used to maintain constant pH levels during various chemical analyses). Note that the CO2 concentration was also reduced, from the initial 1.2 mmol/l to 0.8 mmol/l in this case. This applies when a plasma solution is diluted in anaerobic conditions under paraffin in a test tube – the pH will not change. In the body, however, the CO2 concentration in arterial blood is held constant by respiration. Press the "Respiration control" button to switch to the constant CO2 level mode. Push that button once more to keep pCO2 at 40 torr. Partial pressure of CO2 in arterial blood is held constant by respiration. Press the "Buffer equilibration" button. An increase from 0.8 mmol/l to 1.2 mmol/l will shift the equilibrium to the right side, the H+ ion concentration will increase and pH will decrease (D).

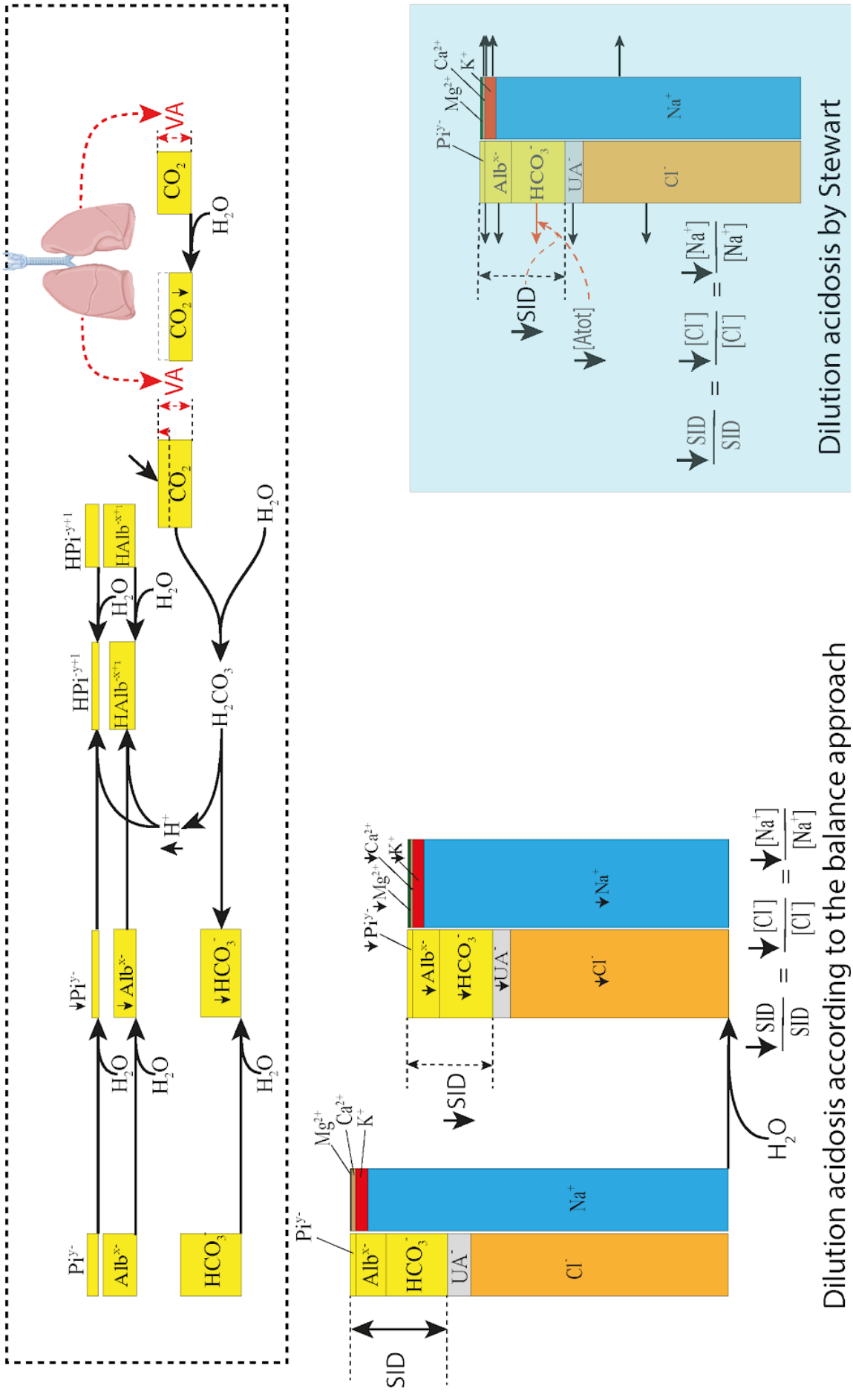

Figure 10 – Pathogenetic causes of dilution acidosis. The pH level in buffer systems is determined by the concentration ratio of the conjugated buffering bases and weak acids. This implies that the buffer capacity in vitro is reduced if the buffer is diluted while the pH remains unchanged because both concentrations – of the conjugated buffer base and of the weak acid – are lowered equally. This, however, is not true of plasma and blood buffering systems in vivo: the CO2/H2CO3 concentration in arterial blood is controlled by ventilation – kept at a constant level dependent on alveolar ventilation (VA), and the equilibrium in a buffer system is shifted and the H+ ion concentration is increased. This is a graphic explanation of the causes of changes in the HCO3- and H+ concentrations, explained by Stewart's concept only as a consequence of the lowering SID and Atot (at a constant pCO2). The basis is the same. It can be demonstrated on the equations deriving the final equation for the dependence of pH on pCO2 , SID and Atot that if the pCO2 level is reduced by the same dilution patterns as the SID and Atot dilution, the pH does not change.

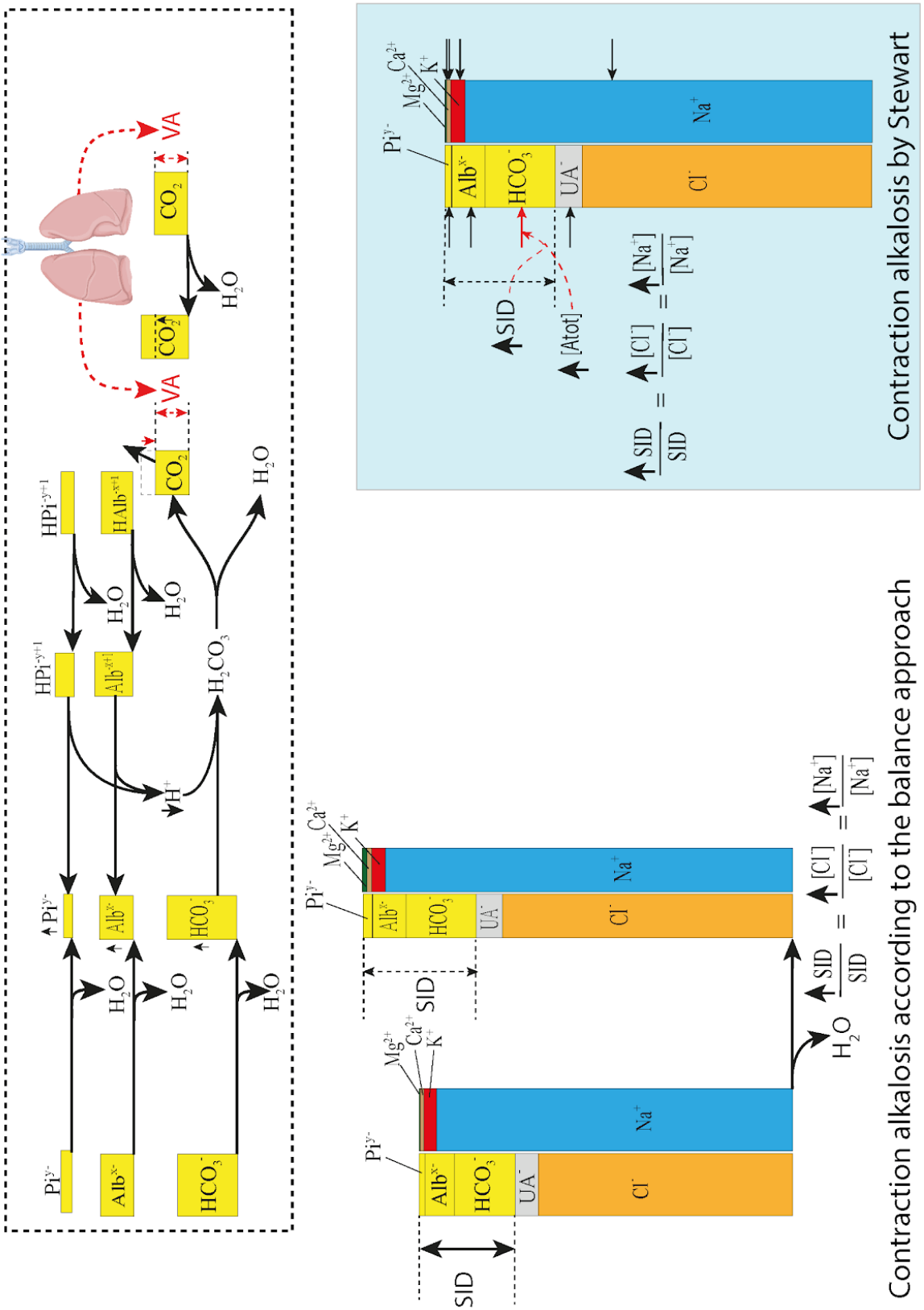

Figure 11 – Pathogenetic causes of contraction alkalosis. Contraction alkalosis is due to concentration increase of the buffer system components except CO2 and H2CO3 , whose concentrations in arterial blood are determined by alveolar ventilation. Similar to the pathogenesis of dilution alkalosis, the CO2 and H2CO3, level, independent of the buffer component concentration increase, brings about chemical equilibrium shift and the H+ concentration decrease. Stewart's concept of contraction alkalosis without presenting a detailed explanation of the causes interprets the pH and HCO3- concentration changes in terms of the increased SID and Atot.

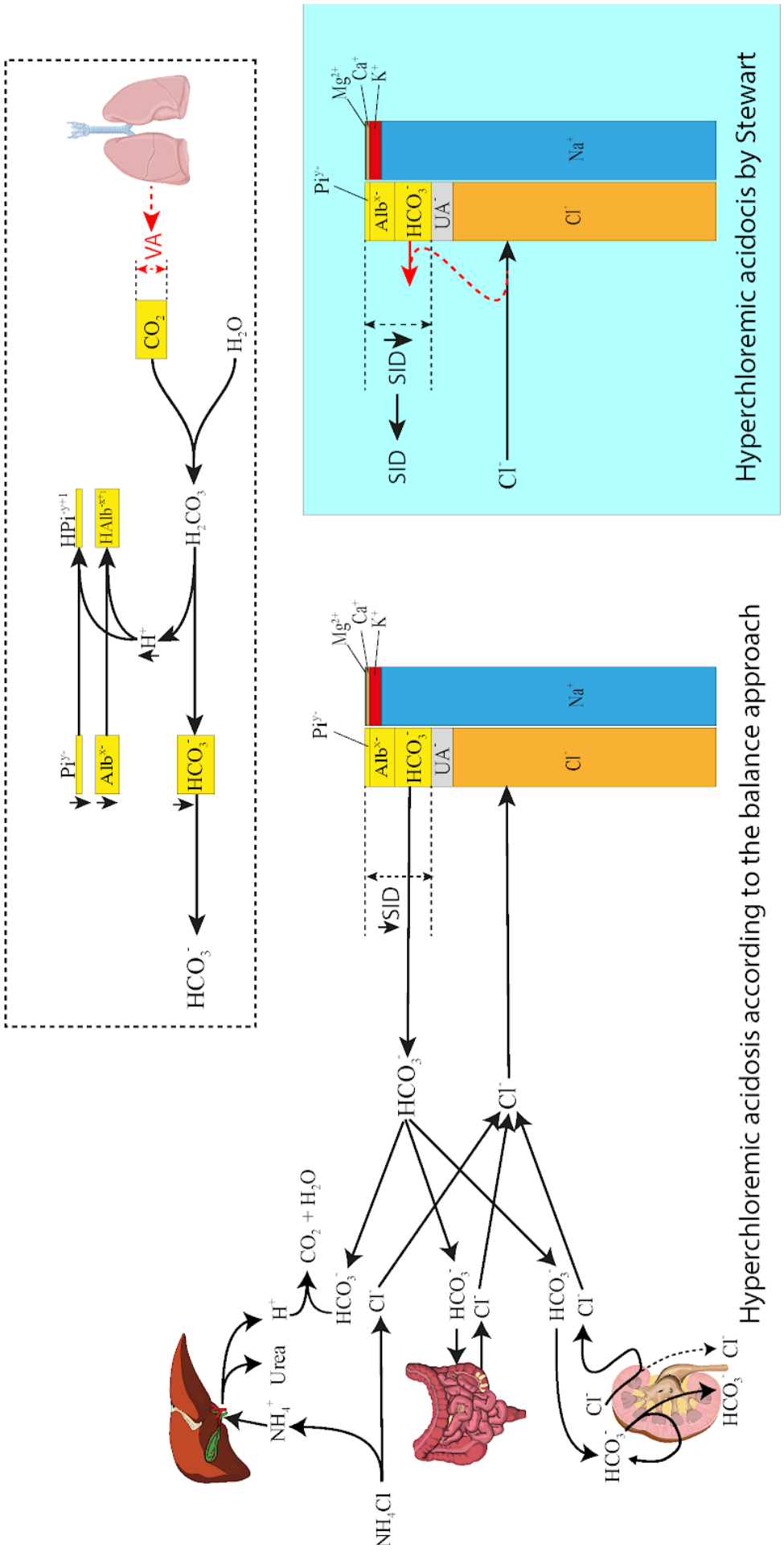

Figure 12 – Pathogenetic causes of hyperchloremic acidosis. The basic cause is the bicarbonate loss, accompanied by equimolar accumulation of chlorides, e.g., on the administration of NH4Cl, bicarbonate loss and chloride accumulation during diarrhea, and decrease in the bicarbonate resorption and increase in the chloride resorption during renal proximal tubular acidosis. A bicarbonate loss will induce bicarbonate concentration decrease and shifts in the acid-base buffering systems resulting in pH decrease and reduction of all the buffering bases and, in turn, decrease in SID. The SID decrease is a consequence of the equimolar loss of bicarbonates and retention of chlorides. In this the present concept differs from Stewart's concept where the SID decrease is one of the initial causes.

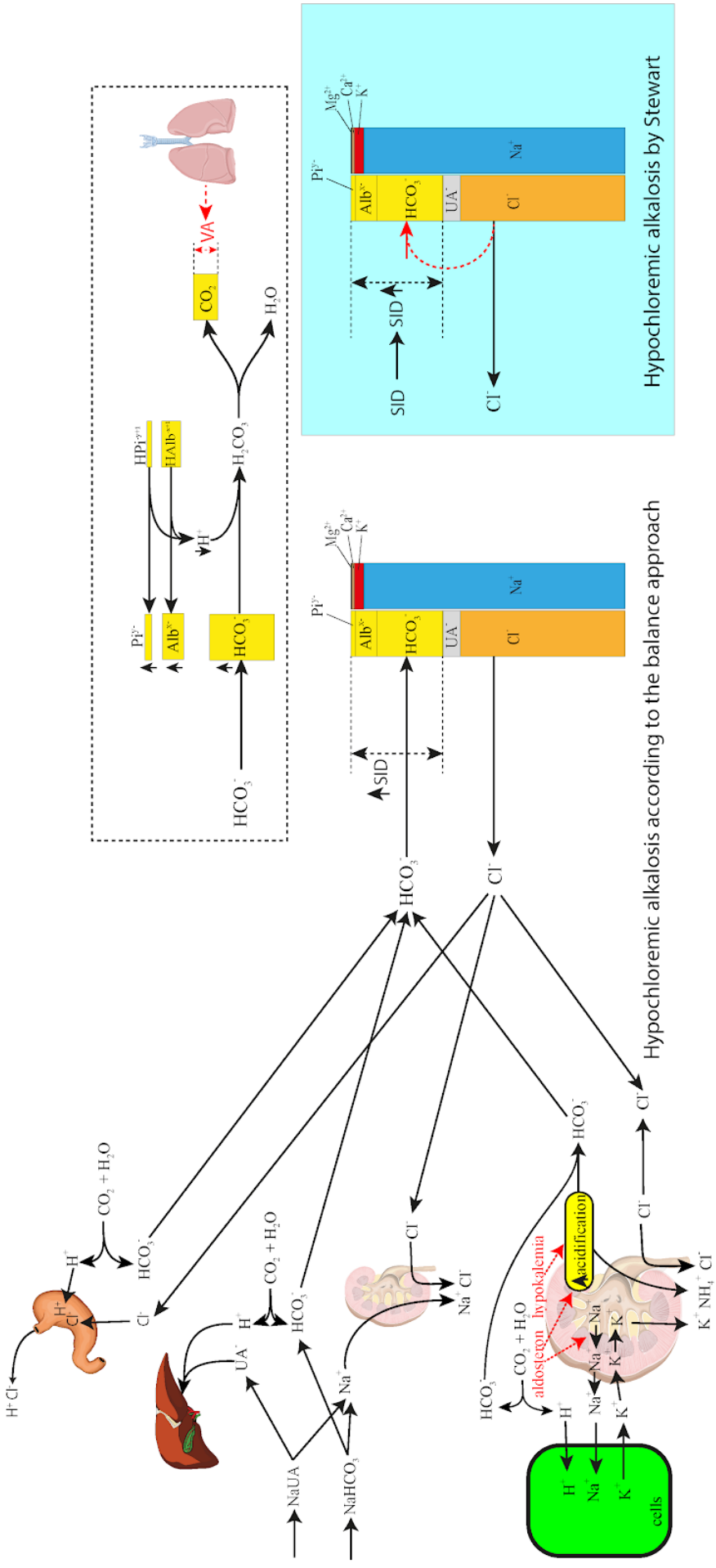

Figure 13 – Pathogenetic causes of hypochloremic alkalosis. The basic cause is accumulation of bicarbonates accompanied by an equimolar loss of chlorides. This can be induced, e.g., by vomiting or by the administration of infusions or drugs during which sodium intake exceeds chloride intake (this includes, e.g., NaHCO3, Na lactate, Na acetate, sodium salts of medicinal products, or administration of blood products with sodium citrate). Organic anions (UA- in the figure) are metabolized with hydrogen ions, excess sodium is excreted along with chloride ions by the kidneys. Hypochloremic alkalosis is a result of primary or secondary aldosteronism. Bicarbonate accumulation means bicarbonate concentration increase and shifts in the acid-base buffering systems bringing about increase of the pH and of all the buffering bases and hence, increase in the SID as well. In this, the present concept differs from Stewart's concept where the SID increase is one of the initial causes..

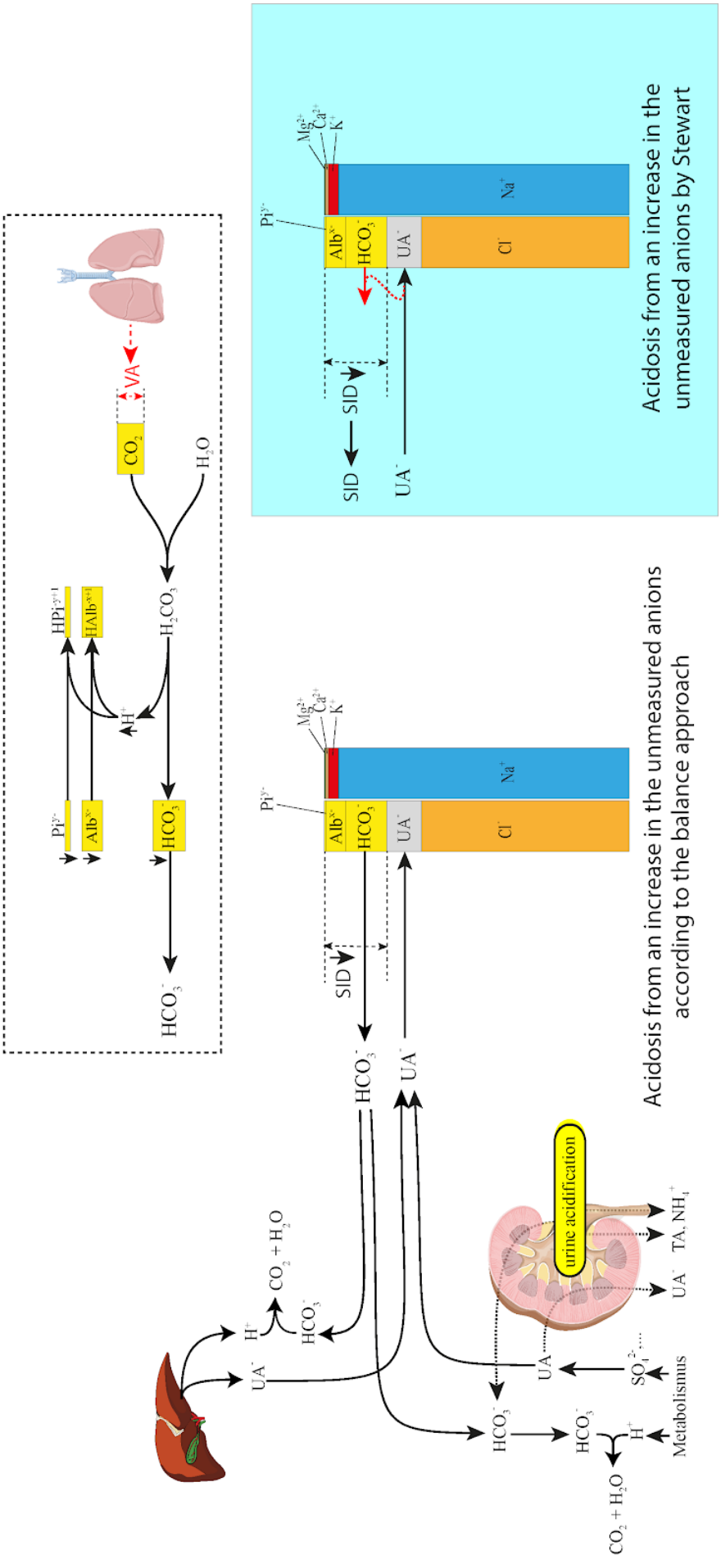

Figure 14 – Pathogenetic causes of acidosis from an increase in the unmeasured anions – this group includes anions of strong acids such as SO_4^{2-}, as well as anions of organic acids (lactate, keto--compounds, ...) and of acids emerging from metabolization of exogenic substances. Anion retention is accompanied by an equimolar loss of bicarbonates releasing hydrogen ions from the acids retained. This can be due, among other things, to the retention of endogenic anions, such as sulfates in renal insufficiency conditions, where the kidneys fail to form sufficient amounts of bicarbonates releasing hydrogen ions during the acidification processes. Bicarbonate loss brings about an equilibrium shift in the acid-base buffer systems resulting in a decrease of the pH and of the concentrations of all the buffering bases and hence, decrease in the SID as well. In this, the present explanation of the pathogenesis differs from Stewart's concept where the SID decrease is one of the initial causes.

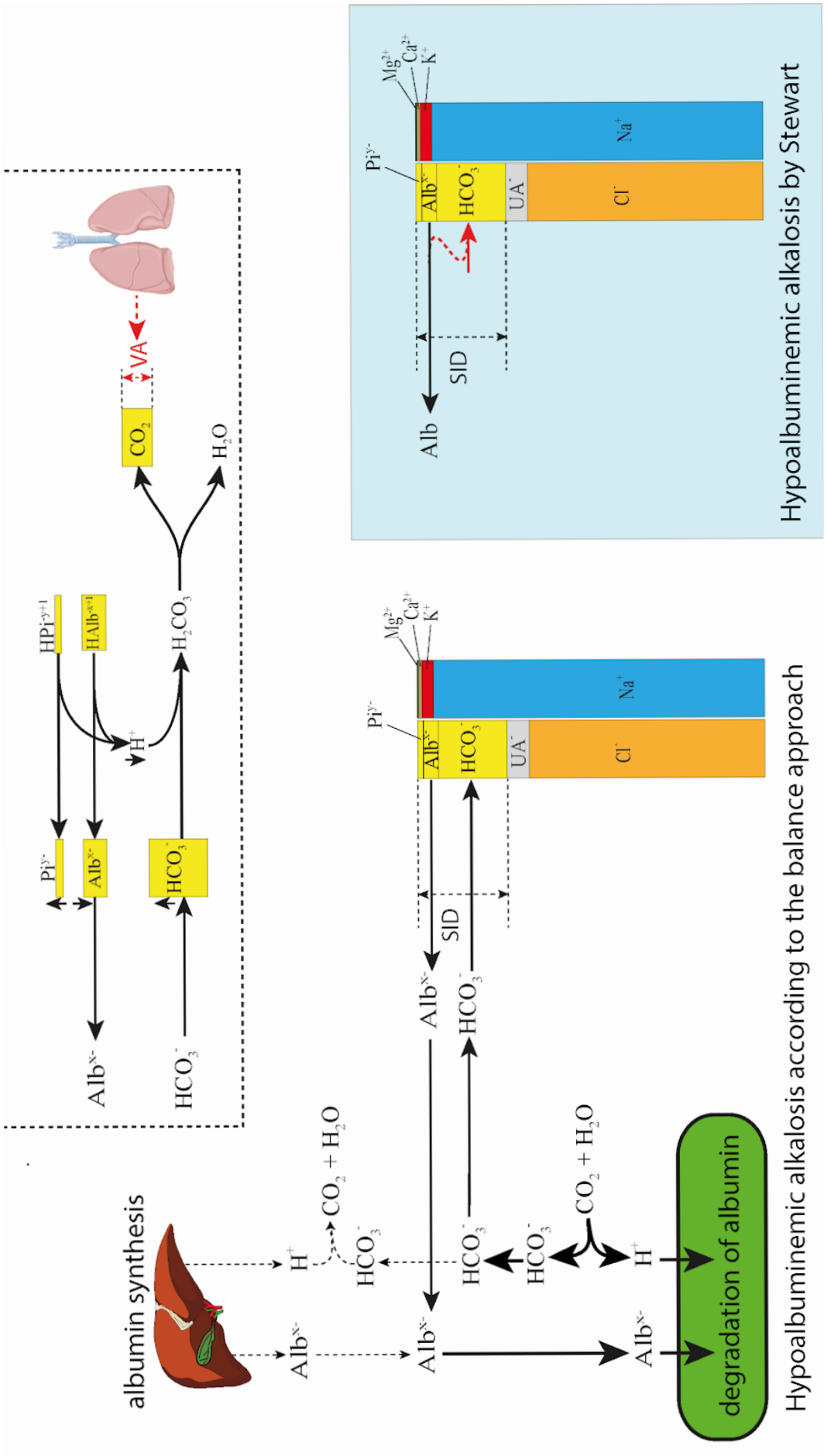

Figure 15 – Pathogenetic causes of hypoalbuminemic alkalosis. The cause of hypoalbuminemic alkalosis is a negative albumin formation/degradation balance. The formation of albumin as a negatively charged protein is accompanied by the release of hydrogen ions (and adequate consumption of bicarbonates). Conversely, albumin catabolism is accompanied by the consumption of hydrogen ions and formation of bicarbonates. A negative albumin balance, where use is lower than formation, is accompanied by a negative bicarbonate balance, the albumin decrease being matched by an equivalent intake of bicarbonates. As a result, the pH is shifted, while the SID remains unchanged and the albumin level decreases. In this, the present concept differs from Stewart's concept where an albumin level decrease at a constant SID is the initiating event.

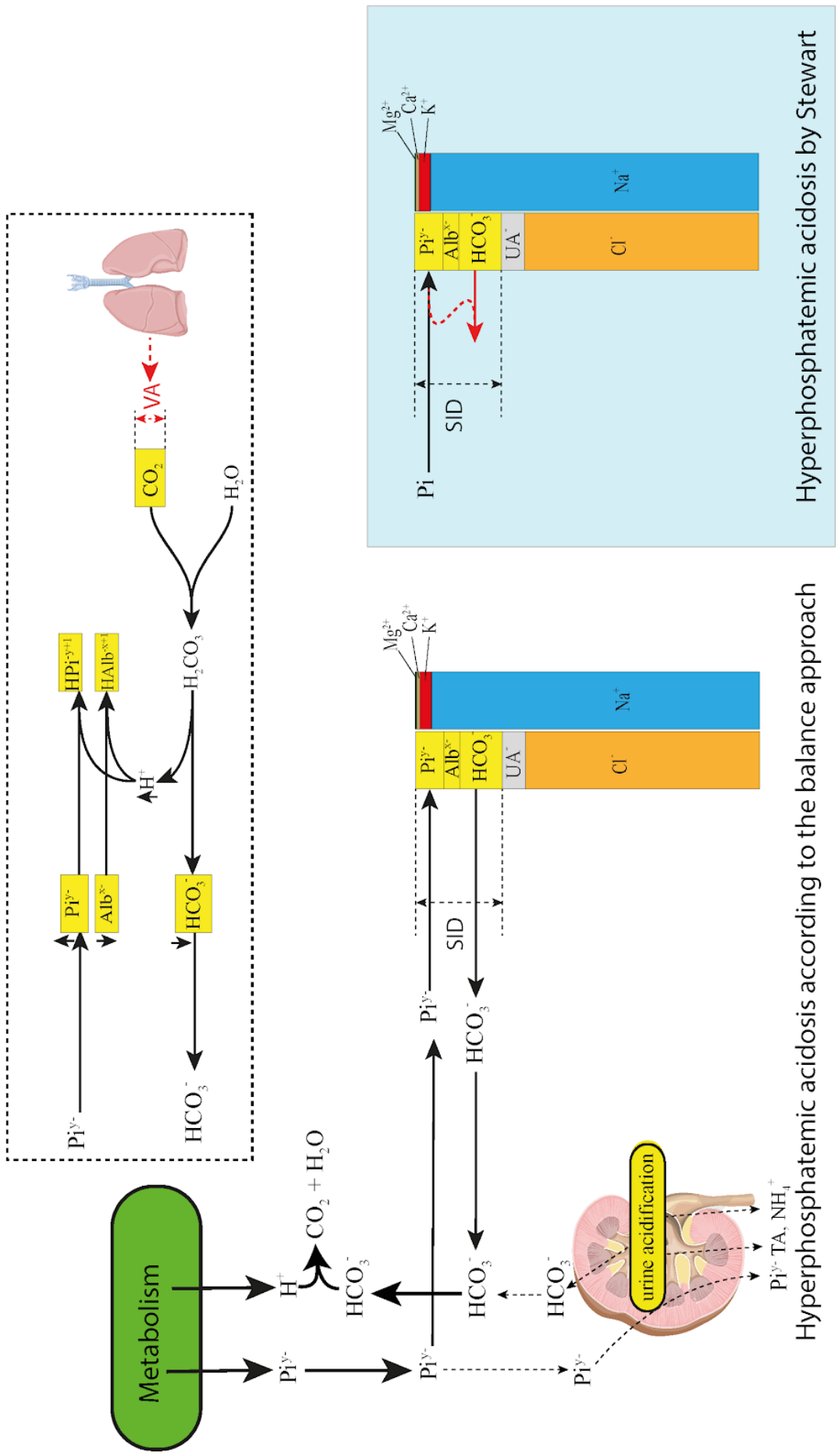

Figure 16 – Pathogenetic causes of hyperphosphatemic acidosis. Hyperphosphatemic acidosis is due to the accumulation of hydrogen ions accompanying accumulation of phosphates during severe renal failure. The accumulated hydrogen ions are released by bicarbonates, and thus a phosphate increase is accompanied by equivalent consumption of bicarbonates, the SID remaining constant. This results in a shift in the buffer systems and, in turn, an increase in the concentration of hydrogen ions. In this, the present concept differs from Stewart's concept where a phosphate increase at a constant SID is the initiating event.

ions bind immediately to bicarbonate, thereby reducing the concentration of the latter. So, retention of strong acid anions is accompanied by an equimolar loss of bicarbonates that release hydrogen ions from the retained acids (Figure 14).

8 Pathogenesis of hypoalbuminemic alkalosis

Albumin is a negatively charged protein. Albumin synthesis and degradation are electroneutral processes. While synthesized, albumin is accompanied by hydrogen ions (and adequate consumption of bicarbonates). During catabolism, albumin is degraded by an electroneutral route in the metabolism along with the hydrogen ions (the consumption of hydrogen ions is accompanied by formation of bicarbonates). Normally, the albumin synthesis/degradation rates are in equilibrium and the balance of the bicarbonates and of the negatively charged albumin anions is not disturbed. The pathogenetic cause of hypoalbuminemic alkalosis is a negative albumin formation/degradation balance (e.g. on an increase in the catabolism of albumin as a rapid aminoacid source during major surgical procedures). This results in a pH shift to the alkaline side, while the SID value remains unchanged and the albumin level decreases. In this respect the explanation in balance theory differs from that in Stewart's concept, where the albumin level decrease while the SID value is constant is the initiating event (Figure 15).

9 Pathogenesis of hyperphosphatemic alkalosis

Hyperphosphatemic alkalosis is due to accumulation of phosphates together with hydrogen ions. Hydrogen ions are released by bicarbonates, and thus a growth of phosphates is accompanied by an equimolar consumption of bicarbonates, the SID remaining unchanged (see Figure 16).

10 Why create acid-base equilibrium models according to the balance approach?

We see the major balance concept contribution in the causal explanation of the interlinking between the acid-base disorders and ion and volume disorders, and in the understanding of internal environment disorders from the integrative physiology aspect. We agree that a clinician needs a phenomenological description of the actual acid-base equilibrium for the diagnosis and selection of appropriate therapy. Stewart's approach offers a fairly simple and practically applicable, although pathophysiologically incomplete explanation of acid-base disorders by using 3 independent variables. The balance concept enables you to understand the pathogenetic causes of the phenomena described by Stewart's method.

It is particularly combined disorders that require the interrelations and disorders of the volume and reserves (not only concentrations) of the components to be considered, and this cannot be done without the balance concept.

Where new views upon the diagnosis are to be used and calculations applying mathematical models to patient data are to be made, you cannot do without the balance method.

A number of rather complex acid-base equilibrium models have been published [25–30] However, they are actually too complex to find application in the clinical practice and are unable to serve as a guide for selecting the best treatment method against acid-base equilibrium disorders. Such complex models are sometimes only created as scientific outcomes to be cited in other papers. Sometimes the authors claim to have created something useful for clinicians, but this is hardly more than just a statement.

We do not wish to set up models to augment the number of papers in scientific journals and to be cited in later papers, but to make a real contribution for clinical doctors:

- To use the models as simulators enabling the pathogenesis of the most diverse internal environment disorders to be incrementally monitored and to enable clinicians, by looking "under the bonnet", to understand what is actually going on during the development of a pathogenesis. So, our efforts also include the development of a model fitted with a convenient user interface for presentation on a website.
- The creation of models as tools for diagnosis and for corrective therapy calculations. We feel that a wealth of hitherto unused information is not only hidden in the clinically measured data, but also in the dynamics of responses to the initiating events, such as reactions to infusions.

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