Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 6 Issue 5 May 2022

Review Article

Hypertension and the Interior Ion-milieu. Can we Overcome Hypertension with Regulated Breathing?

András Sikter*

Municipal Clinic of Szentendre, Internal Medicine, Szentendre, Hungary

***Corresponding Author:** András Sikter, Municipal Clinic of Szentendre, Internal Medicine, Szentendre, Hungary.

DOI: 10.31080/ASMS.2022.06.1254

Received: March 15, 2022

Published: April 22, 2022

Abstract

The author presents a new model for age-associated diseases through a hypothesized pathogenesis of hypertension. Preservation or restoration of the constancy of each original cell-specific intracellular ion-pattern is essential for upholding cellular identity and integrity. The ageing background is intracellular acidosis: low-grade respiratory acidosis elevates the intracellular HCO_3^-/Cl^- gradient and induces metabolic syndrome, while low-grade metabolic acidosis causes exhausting buffer syndrome (EBS) with a decreased intracellular HCO_3^-/Cl^- rate. The former elicits higher aldosterone levels to restore the original ion-pattern by NHE-1 (natrium-hydrogen exchange) mechanism located in the membrane of vascular smooth muscle cells (VSMCs) and by retaining NaCl. The fault of ion-status restoration leads to Salt-sensitive hypertension through cascades of events. The ion-pattern changes in EBS elicit angiotensin II levels elevation through the renin-angiotensin system, which tries to eliminate intracellular changes via NBCn1 (natrium-bicarbonate cotransporter). However, it leads to a dead-end, and Salt-resistant hypertension develops. Hypertension occurs because restoring the original intracellular ion-pattern in VSMCs by aldosterone and angiotensin II fails. These hormonal counter-regulations lead to Na^+ retention and alkaline overcompensation in the VSMCs. There may be several explanations for the failure, but hypertension would not develop if the intracellular ion-milieu were initially neutral or slightly alkaline. Regulated breathing could overcome hypertension.

Keywords: Age-associated Diseases; Exhausting Buffer Syndrome (EBS); Hypertension; Intracellular pH Homeostasis; Metabolic Syndrome; Signalling by Intracellular Ion-pattern

Abbreviations

ATP: Adenosine-Triphosphate; CKD: Chronic Kidney Disease; Cl^-: Chloride Ion; CPAP: Continuous Positive Airway Pressure; EBS: Exhausting Buffer Syndrome; EC: Extracellular; H^+: Hydrogen Ion ("proton"); HCO_3^-: Bicarbonate Ion; $H_2PO_4^-$: Monovalent Phosphate Ion; HPO_4^{2-}: Bivalent Phosphate Ion; IC: Intracellular; K^+: Potassium Ion; Mg^{2+}: Magnesium Ion; Na^+: Sodium Ion; NaCl: Natriumchloride, (table salt); NBCn1: Natrium-Bicarbonate Cotranspoter; NHE-1: Natrium-Hydrogen Exchange; pCO_2: Partial Pressure of CO_2; $PetCO_2$: end-Tidal Pressure of CO_2; RAAS: Renin-Angiotensin-Aldosterone System; RAS: Renin-Angiotensin System; ROS: Reactive Oxygen Species; VSMCs: Vascular Smooth Muscle Cells; Zn^{2+}: Zinc Ion

Introduction

It is easy to notice a connection between Claude Bernard's eternal Milieu Intérieur theory and the Intracellular Ion-pattern as a Signalling System hypothesis. One of the main functions of ions, as charged small-molecule materials, moving between the extra- and intracellular space is to turn on or off the function of enzymes by changing their instantaneous concentration. However,

the accurate assessment of this role is impossible, as different ions sometimes affect the operation of hundreds (like Mg^{2+}) or all (like H^+) enzymes. (The need to put forward this hypothesis is also supported by the fact that there are no clinical methods for measuring intracellular ion concentrations and pH. On the other hand, if we put together all pieces of the puzzle, we can see the big picture.) The body's cells' determined physiological extra- and intracellular ion concentrations are the parts of their own identity. A durable deviation from the physiological ion levels is abnormal; it suggests a disease, but the medical practice often turns a blind eye to those. E. g., it accepts the „compensated" acid-base disturbances as being normal and such data that are not normal, e.g., physiological ranges in the blood acid-base parameters. The currently accepted physiological range of arterial pCO_2 (35-45 mmHg) is too broad and we recommend to use 38-42 instead that is currently accepted by the minority [1].

This paper wants to demonstrate through the pathogenesis of hypertension, among others, that the body insists (or would insist) on maintaining and restoring all the original extra- and intracellular ion concentrations, which can be the primary strategy for regulating the body. An alpha command for the organism is: detect the deviations from the physiological levels and restore them to the original states again and again. Unfortunately, this is often mathematically and logically impossible; the doctor can help the body create a better, more realistic environment for recovery. Hormonal restoration often leads to dead ends and dysregulation, so the non-hormonal pathways should be favoured [2].

The other issue is that, contrary to popular belief, the Second Law of Thermodynamics also applies in biology: it is called ageing. It has already been proved that ageing-associated changes in entropy can be a consequence of the Second Law of Thermodynamics, as the law is also applicable to open systems [3]. Ageing is associated with intracellular acidosis due to chronic respiratory and (or) metabolic acidosis. At the same time, the body does not tolerate even low-grade acidosis and therefore counter-regulates it, which results in age-associated disorders.

In connection with the pathogenesis of hypertension, it has been revealed that the intracellular pH and the preservation of the other ions' original concentration levels are similarly crucial for the body; therefore, it takes steps. In the end, it is difficult to decide whether the first (mildly acidic) damage of the cells or the humoral-hormonal defense against it causes more trouble. And it also turns out that Claude Bernad was right when he suggested preserving the original interior milieu status.

Homeostasis and allostatic defense often do not mean restoring the original state but stabilizing the metabolism [4]. If the stabilized form permanently differs from the original, it is pathological per se and leads to disease. The author of the present paper wants to point out how a doctor could help the regulation with simple natural tools and substances - working not against, but for it.

Role of intracellular ion-pattern in the cellular identity and integrity

The identity and integrity of the differentiated cells are paramount to maintaining health [5]. The **i**dentity of the cells depends on their genomes and particular lineage identity [6]. Each cell has its own resting intracellular ion-pattern determined by these ion concentrations together. "Intracellular ions together" is an entity that is one of the basic intracellular signalling systems [7-9]. The intracellular ion milieu represents the "software of the cell" compared to the hardware of the genome, as its current composition largely determines the biochemical processes currently taking place in the cell. It has a dual function: on the one hand, it mediates the racial and unique identities encoded in the "hardware" (genome), and on the other hand, it has to respond to changes and challenges caused by the environment. However, after performing the tasks, it should always regain its original state; otherwise, it loses its identity, and the integrity of the cell will be damaged. It is a challenging dual-task, so the cell (and organism) can often not meet challenges.

It seems impossible to remain unchanged in an ever-changing environment. Researchers of the allostasis theory believe that maintaining the internal environment and homeostasis under changing circumstances is only possible by changing the internal environment ("to maintain stability through change") [4]. Prolonged or repeated stress leads to allostatic load, overload and diseases [10]. The chronic social defeat stress model is an excellent example of allostatic load. The experimental animal model used for many years demonstrates that repeated or prolonged social defeat causes rodent cardiovascular lesions and diseases [11].

Brouillard., *et al*. described that loss causes bradypnea in the defeated individuals - which they could not interpret [11]. Sikter., *et al*. pointed out that the body induces metabolic alkalosis to compensate for chronic respiratory acidosis [2]. Most clinicians see the permanent persistence of compensated respiratory acidosis as an „acceptable compromise," even though the body's intracellular and extracellular ion composition changes fundamentally and permanently. According to the present hypothesis, this acceptance is a capital error [12]. On the one hand, intracellular acidosis does not entirely disappear, and on the other hand, the HCO_3^-/Cl^- ratio changes significantly. Third, this altered ion-milieu stabilizes, meaning the body cannot preserve its identity, which is the most significant concern. The explanation for acceptance is that most clinicians consider ions to be tertiary actors and far underestimate the importance of the stability of original ion-patterns; they allow too wide limits for normal ion concentration ranges.

Ions affect each other's concentrations in many ways, which can only be described by equations containing many unknowns, often without an excellent mathematical solution [2]. Our working hypothesis is that cells should independently restore their physiological intracellular ionic milieu, as the body's humoral and hormonal defense system usually lead to dysregulation and metabolic remodelling. Although it is essential to maintain the concentration of all ions at their physiological levels, both intra- and extracellularly, regulation prioritizes pH homeostasis, even at the expense of other ions. (This includes, but is not limited to the „compensated" acid-base disorders.) Intracellular acidosis slows down many metabolic processes, while mild alkalosis accelerates them [13]. This effect is mainly explained by reversible changes in the pH-dependent tertiary structure of proteins. The H^+ has a more substantial impact on the cytoplasm than other ions, as the pH acts on each enzyme in much the same direction, thus multiplying its effect [14].

Age-associated disorders

Ageing is an objective process that can be approached in many ways: the phenomenon of 'wear and tear', 'the accumulation of a wide variety of molecular and cellular damage over time', the biological manifestation of the Second Law of Thermodynamics, and so on [3]. The cytoplasmic mass and ATP-producing capacity of most cells are also reduced [9]. Mitochondrial dysfunction plays an essential role in developing age-related diseases [15]. One of the most critical trends in intracellular ion-patterns is intracellular acidification, which is often not observed due to the rapid hormonal counter-regulation. It is associated with lower energy levels, metabolism, reduced oxygen and energy use. One indirect evidence of this is the existence of the hibernated myocardium [16]. Research on pH homeostasis has become a popular trend today, as many have recognized that intracellular pH strongly influences almost all metabolic pathways [17].

In the case of insufficient energy supply, the body's defense system favours moderate acidosis over alkalosis because it results in a more stable metabolic balance in the short term. Proponents of the theory of „permissive hypercapnia" have consistently argued that moderate protective acidosis in acute diseases helps overcome energetic and metabolic difficulties [18]. However, acidosis regulates metabolism unfavourably in the long run. Multidirectional and intense hormonal counter-regulation of intracellular acidosis plays a prominent role in age-associated diseases [2].

Many somatic, psychic, cognitive, and neurological diseases have been associated with ageing, in which intracellular proton accumulation (= acidosis) and its counter-regulation plays an important role [2,19,20]. Cardiovascular diseases, hypertension, cancer, osteoarthritis, diabetes mellitus, osteoporosis, dementia, depression are the most common age-related diseases; they are already widespread by the age of fifty. In the following, we will focus on primary hypertension.

Sikter and Sonne's hypothesis suggests that both Salt-sensitive and Salt-resistant hypertension are preceded by low-grade intracellular acidosis of cells [21]. The RAAS responds mainly by secreting aldosterone or renin-angiotensin, respectively. It can be assumed that aldosterone regulation is partially separated from the renin-angiotensin system because it has an opposite effect on the intracellular and extracellular ratio of HCO_3^-/Cl^-, which is a crucial cornerstone in the regulation of hypertension (see later). According to the available literature, RAAS-mediated ion transport and exchange mechanisms, if worked precisely, would accurately neutralize intracellular acidosis and restore the intra- and extracellular ratio of HCO_3^-/Cl^- in any case. The facts show that counter-regulation works to restore the original ionic environment,

which would justify the intracellular ion-pattern as a signalling system hypothesis. In any case, the direction of regulation seems good [9]. However, it does not immediately answer what causes hypertension.

Salt-sensitive hypertension

As a behavioural scientist, David E. Anderson studied "inhibited breathing" and elevated $PetCO_2$ levels for fifty years as possible causes of Salt-sensitive hypertension at the University of California, San Francisco [22]. He has increasingly believed that slowed breathing as a form of behaviour may play a role in the aetiology of Salt-sensitive hypertension. He later realized that increased resting $PetCO_2$ is a direct cause of Salt-sensitive hypertension. $PetCO_2$ is also a mediator of psychosomatic pathomechanism. Anderson., *et al*. showed that African American women and men over the age of 50 had significantly higher resting $PetCO_2$ values than white-people, consistent with the fact that Salt-sensitive hypertension is much more common among them [23]. He has written more than 100 articles on the subject; Anderson., *et al*. an experimental study was recently published: human capnometric feedback training permanently reduced blood pressure in the treated group and, despite the small sample size, resulted in a significant difference from the control group [24].

According to the hypothesis, Salt-sensitive hypertension occurs when moderate respiratory acidosis induces aldosterone overproduction. It is partly by activating the renin-angiotensin system, partly differently. Aldosterone alkalizes the cytoplasm of the target cells (i.e., vascular smooth muscle cells = VSMCs, left ventricular myocardial cells, renal tubule cells) through their NHE-1 (sodium hydrogen exchange) mechanism [25]. Copious table salt intake promotes the entry of Cl^- into cells, followed by Na^+ [26]. In respiratory acidosis, the EC/IC Cl^- gradient is increased, because the compensatory increase in HCO_3^- results in a decrease in IC Cl^- levels. (Intracellularly, the HCO_3^-/Cl^- ratio increases simultaneously). In summary, increased Cl^- influx to the cytosol is a part of the restoratory motivated mechanism in Salt-sensitive hypertension, as regulation seeks to repair the original HCO_3^-/Cl^- rate, but the Na^+ follows the Cl^-. Evidence of this is that after chronic experimental hypercapnia, the body cannot restore the original ionic milieu after NaCl deprivation [27]. When NaCl was replaced with ammonium chloride after NaCl restriction, its administration did not increase blood pressure in hypertensive individuals [28]. However, maintaining normal chloride levels would also be extremely important, as low Cl^- levels increase cardiovascular risk and mortality [29]. Ionic constellation induced by low-grade chronic hypercapnia may correspond to metabolic syndrome [12].

Prolonged respiratory acidosis elevates mean $PetCO_2$ levels and causes low-grade hypercapnia with mild intracellular acidosis, elevated serum and intracellular HCO_3^- levels. The elevation of bicarbonate levels occurs at the expense of a decrease in Cl^- levels [26]. Physiological intracellular Cl^- levels are markedly lower than extracellular ones, so the percentage decrease in Cl^- levels and an increase in the EC/IC Cl^- gradient will be significant in chronic respiratory acidosis, facilitating aldosterone-modulated Cl^- influx and subsequent Na^+ entry [26]. Intracellular alkalinization plus an increase in intracellular Na^+ lead to hypertrophy of the VSMCs and hypertension [30].

Among those over fifty years of age, low-grade hypercapnia is a widespread phenomenon when the narrowed normal range of $PetCO_2$ (38-42 mmHg) is considered. The prevalence of low-grade hypercapnia may be over 50% over 50 years of age. The most common background is obstructive sleep apnea, chronic obstructive pulmonary disease or obesity hypoventilation syndrome [12]. The correlation between metabolic syndrome and hypertension is very high. There is a significant association between the "freezing" psychic response of stress and metabolic syndrome and Salt-sensitive hypertension [12,22,31]. We cannot say that all low-grade hypercapnia, metabolic syndrome, and Salt-sensitive hypertension have a psychological background; nevertheless, psychosomatic pathomechanism may undoubtedly be one of the most decisive causes. Repetitive stress and social defeat may play an essential role in low-grade hypercapnia and, consequently, hypertension [11,22,32].

Salt-resistant hypertension

It was suggested decades ago that intracellular acidosis plays an essential role in the pathophysiology of hypertension and diabetes [33]. Recently, it was shown that metabolic acidosis could trigger blood pressure elevation in an animal model [34]. Chronic kidney disease (CKD) and age-related decline in renal function lead to intra- and extracellular metabolic acidosis [35]. Due to the

lifelong consumption of acidic food, fixed acids accumulate in the cells [36]. There is also a poorly understood association between mitochondrial ageing, ROS and metabolic acidosis [15,34]. Thus, Salt-resistant "primary" hypertension is a consequence of RAS activation induced by low-grade intracellular metabolic acidosis, i.e., it is also of renal origin, caused by minimal ion and pH differences that clinicians still believe physiological. Intracellular metabolic acidosis can also be a cause and consequence of kidney damage, generating a vicious circle and exacerbating hypertension [21]. The ion-constellation induced by low-grade chronic intracellular metabolic acidosis may correspond to the exhausting buffer syndrome (EBS), named by Sikter and Sonne [37].

Angiotensin II activates the NBCn1 (sodium-bicarbonate cotransporter) in target cells, especially VSMCs, which transport sodium and bicarbonate to the cytoplasm. Here, it increases the HCO_3^-/Cl^-ratio reduced by intracellular metabolic acidosis [25]. Both aldosterone and angiotensin II regulate the acid-base balance in the target cells and the extracellular space. Both increase renal H^+ secretion, but aldosterone also increases the Cl^- reabsorption [38]; by contrast, angiotensin II is one of the most potent hormonal stimulators of renal HCO_3^- reabsorption [39]. While aldosterone increases intracellular Cl^- concentration by retaining NaCl via NHE-1 in target cells, angiotensin II decreases it through NBCn1, being Cl^- and HCO_3^- concentrations are inversely related. Aldosterone seeks to eliminate respiratory acidosis, while angiotensin II seeks to eliminate metabolic acidosis. Both NHE-1 and NBCn1 reduce H^+ and increase Na^+ levels promoting cytosolic alkalosis and Na^+/Ca^{2+} exchange in VSMCs. They enhance the contractility and hypertrophy of small arteries [25,40]. Salt-resistant hypertension is associated with angiotensin II and NCBn1, induced by intracellular metabolic acidosis.

Nephrologists believe CKD accelerates the body's ageing through metabolic acidosis [41]. The number of studies using sodium bicarbonate therapy to treat renal metabolic acidosis has increased [42,43]. Bicarbonate therapy appears to be effective even in decreasing the progression of vascular calcification [44]. The administration of bicarbonate in metabolic acidosis is a logical but double-edged sword. Counter-regulation can cause an increase in pCO_2 and intracellular acidosis: CO_2 can enter cells while HCO_3^- does not [45]. It may be the reason why there was no reduction in blood pressure due to alkalinizing therapy but a slight increase [46].

Testing the hypothesis

"Primary" hypertension can develop on at least two main pathways, which lead to Salt-sensitive and Salt-resistant hypertension. Based on the above, it seems clear that hormonal regulation responds to the putative (respiratory and metabolic) acidosis giving a specific counter-regulation, which seeks to restore the original intracellular pH and HCO_3^-/Cl^- ratio in the target cells. However, in hypertensive patients, the alkalinization does not stop after neutralization of cytoplasm. Why? There may be several possible reasons. Maybe the negative loop feedback of angiotensin II on renin does not work *in vivo* as assumed previously [47]. Perhaps the pH recovery may not be enough to stop feedback, the ratio of HCO_3^-/Cl^- should also be corrected? RAAS regulation can provide the missing Cl^- or HCO_3^- ions into the target cells by only adding excess Na^+, leading to hypertension. The increased H^+ load in RAAS-regulated target cells and the consequent increased Na^+/Ca^{2+} exchange demonstrated [26,30,40]. Possible that the Na^+ pump cannot remove excess Na^+ effectively due to a genetic or energetic defect [48]. Other reasons are also possible.

Whatever the explanation for this, the cascade mechanism leading to hypertrophy of VSMCs will not start if the IC pH is initially neutral or slightly alkalotic. (In the case the introductory statement is true, the cause of "primary" hypertension is intracellular acidosis). However, no drugs are known to stimulate respiration effectively and in a controllable manner. Capnometric feedback training could be effective in hypertension, especially in Salt-sensitive hypertension. The first pilot study has taken place, but it is time- and equipment-intensive, burdensome for both patient and therapist, and therefore unsuitable for widespread treatment, even if it might be successful [24].

Severe nocturnal obstructive sleep apnea is now routinely treated with continuous positive airway pressure (CPAP) therapy. It has been shown that CPAP treatment in obstructive sleep apnea significantly reduces serum aldosterone and angiotensin II levels and blood pressure [49,50]. We suggest lowering the average pCO_2 below 40 mmHg by CPAP - decreasing blood pressure may be more significant.

From the regulation of the body, we learn that renal function compensates for prolonged respiratory acidosis with metabolic alkalosis while altering the intra- and extracellular

ionic environment. We should look at what ions are excreted in the patients' urine during the first days of an experimental hypercapnia training. By returning lost ions orally to restore the initial ionic environment in low-grade respiratory acidosis, we can stimulate respiration and reduce $PetCO_2$. Missing ions would recover both extra- and intracellularly. The author of this article is convinced that the ratio of $H_2PO_4^-/HPO_4^{2-}$ ions administered orally affects the respiratory minute volume and $PetCO_2$. Administering an appropriate phosphate buffer composition can acidify the body, which will react with increased respiration eliminating base excess. This way, we receive a chance to restore the original acid-base and electrolyte status. The ion-combination has a physiological effect in minimal doses (below Recommended Dietary Allowance). After titrating their doses and proportions, the phosphate salts containing salt mixture can effectively eliminate low-grade respiratory acidosis [21]. While the pCO_2 level is decreasing, the intracellular ion milieu normalizes: the phosphate is transported to cells and bones where it is missing. Similarly, other cytoplasmic ions (K^+, Mg^{2+}, Zn^{2+}, etc.) also find their places, i.e., cells recover from low-grade respiratory acidosis [21].

In the case of Salt-resistant hypertension and metabolic acidosis, HCO_3^- administration may be a good initial therapy (cf.: Salt-resistant hypertension section). However, bicarbonate therapy elevates intracellular pCO_2 levels [45]. We can attribute that $NaHCO_3$ treatment does not reduce but instead raises blood pressure [46]. That is why we should supplement the bicarbonate with the described breathing-stimulate phosphate salt mixture combination in the case of metabolic acidosis and Salt-resistant hypertension. Co-administration of the two salt mixtures (using a mix of $H_2PO_4^-/HPO_4^{2-}$ and HCO_3^- salts) is recommended when metabolic and respiratory acidosis occur together. However, monitoring of ions and $PetCO_2$ is essential for testing and curing.

There is a widespread agreement on the harmful cardiovascular effects of excessive phosphate intake. At the same time, phosphate is an essential nutrient with diverse functions. Contrary to claims, its deficiency is common in humans, e.g. osteoporosis also means calcium and phosphate deficiency that we are usually unable to replace. Second, a warning from excessive phosphate intake is justified. Third, "phosphate" does not always mean the same thing. The monovalent $H_2PO_4^-$ is an H^+ donor, the divalent HPO_4^{2-} is an H^+ acceptor, the two together is a phosphate buffer. The two phosphate salts have different metabolic effects, as metabolic vs respiratory acidosis also have opposite effects on serum phosphate levels [37]. However, both chronic, low grade acidosis can cause vascular calcification [37]. Fourth, the proposed salt combination affects metabolism in small doses; the body tolerates the monovalent $H_2PO_4^-$ ion better because its administration does not increase but decreases serum phosphate levels.

Conclusions

Assembling the „puzzle pieces" draws the big picture. Claude Bernard suspected that maintaining the permanence of smaller pieces was also necessary for the identity of the entire body. As charged particles have soluble binding to executive enzymes, the ions are excellent for regulation. Phylogenesis has been experimenting for hundreds of millions of years to find the best solution for all species. Each cell has to restore the original ion-pattern repeatedly after each change; otherwise, it leads to diseases. At the same time, the regulation is highly malleable, adapting to different living conditions so that many different ion-patterns can be stable and life-saving in the short term. After prolonged existence, the body tends to accept the new ion constellation of its own, which is different from physiological: it has zero chance of functioning well in the long run.

The body puts the homeostasis of the intracellular pH ahead of other ions because of its paramount importance in regulation. Nevertheless, as age progresses, the energy levels of the body/cells show a downward trend, and the metabolism of the cells also is more stable at the pH decreased because it saves energy. Above 50 years, the prevalence of minimal-grade intracellular acidosis already is significant. The body uses hormonal/humoral defense to restore the initial pH and ion-pattern of specific tissues/cells. Nevertheless, there are theoretical and practical obstacles to perfect hormonal defense: the regulation becomes fragmented, and regulatory disturbances occur due to spillover effects.

There are two main pathways for the development of acidosis: chronic respiratory acidosis raises the intracellular HCO_3^-/Cl^- rate; this ion-pattern and metabolic constellation can correspond to the metabolic syndrome. By contrast, chronic metabolic acidosis increases intracellular Cl^- concentration decreasing the HCO_3^-/Cl^- ratio; Sikter and Sonne called this condition exhausting buffer syndrome (EBS) [37]. (Respiratory and metabolic acidosis often occur together and overlap.).

It is supposed that "primary" hypertension is triggered by intracellular acidosis. Salt-sensitive hypertension would be started by respiratory acidosis, while Salt-resistant hypertension would be inquired by the presence of intracellular metabolic acidosis. The hormonal counter-regulation protects in a targeted way. In Salt-sensitive hypertension, aldosterone attempts to neutralize the extra- and intracellular pH and restore ion constellation created by respiratory acidosis: target cells remove H^+ while retaining Cl^-. However, the Cl^- retention is followed by the Na^+, which leads to intracellular alkalosis and Ca^{2+} retention in VSMCs via a sequence of events: the hypertrophy and increased tone of the small arteries are conditions for hypertension. Angiotensin II protects in a targeted way against the ion constellation caused by metabolic acidosis, transporting HCO_3^- in the targeted VSMCs and the extracellular space. Although NBCn1 also retains the Na^+, which triggers the cascade of events described leading to increased tone and hypertrophy of the arterioles.

In principle, there may be several reasons why the renin-angiotensin-aldosterone system does not function perfectly and intracellular acidosis changes to alkalosis in target cells. If the present hypothesis is true, hypertension will not develop if a mild intracellular alkalosis existed initially. Several previous studies have shown that a sustained increase in tidal volume or a decrease in $PetCO_2$ levels lowers blood pressure. A reliable, controllable physiological respiratory enhancement method needs to be developed. Respiratory alkalinization may be helpful in the case of Salt-sensitive hypertension. By contrast, in Salt-resistant hypertension, the combined metabolic and respiratory alkalization together may be a solution. When this hypothesis is proven, regulated, controlled breathing might be a key to a long, healthy life.

Conflict of Interest

The author declares to have no conflict of interest.

Acknowledgements

The author would like to thank Ms Krisztina Toth for proofreading the manuscript.

Bibliography

1. Bruton A and Holgate ST. "Hypocapnia and asthma: a mechanism for breathing retraining?". *Chest* 127.5 (2005): 1808-1811.
2. Sikter A., *et al*. "New aspects in the pathomechanism of diseases of civilization, particularly psychosomatic disorders. Part 1. Theoretical background of a hypothesis". *Neuropsychopharmacologia Hungarica* 19.2 (2017): 95-105.
3. Hayflick L. "Entropy explains aging, genetic determinism explains longevity, and undefined terminology explains misunderstanding both". (Editorial) *PLoS Genetics* 3.12 (2007): e220.
4. Goldstein DS and Kopin IJ. "Evolution of concept of stress". *Stress* 10 (2007): 109-120.
5. Bitman-Lotan E and Orian A. "Nuclear organization and regulation of the differentiated state". *Cellular and Molecular Life Sciences* 78.7 (2021): 3141-3158.
6. Fisher AG. "Cellular identity and lineage choice". *Nature Reviews Immunology* 2.12 (2002): 977-982.
7. Orlov SN and Hamet P. "Intracellular monovalent ions as second messengers". *The Journal of Membrane Biology* 210.3 (2006): 161-172.
8. Newton AC., *et al*. "Second messengers". *Cold Spring Harbor Perspectives in Biology* 8.8 (2016): a005926.
9. Sikter A. "Psychosomatic molecular mechanisms of metabolic syndrome and type 2 diabetes. Part 1. A theory for modelizing the cytoplasm and diseases". *Acta Scientific Medical Sciences* 4.1 (2020): 124-140.
10. McEwen BS and Stellar E. "Stress, adaptation and the individual. Mechanisms leading to disease". *Archives of Internal Medicine* 153 (1993): 2093-2101.
11. Brouillard C., *et al*. "Long-lasting bradypnea by repeated social defeat". *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 311 (2016): R352-364.
12. Sikter A., *et al*. "New aspects in the pathomechanism of diseases of civilization, particularly psychosomatic disorders. Part 2. Chronic hypocapnia and hypercapnia in the medical practice". *Neuropsychopharmacologia Hungarica* 19.3 (2017): 159-169.
13. Relman AS. "Metabolic consequences of acid-base disorders". *Kidney International* 1 (1972): 347-359.
14. Sikter A. "Hypocapnia and mental stress can trigger vicious circles in critically ill patients due to energy imbalance: a hypothesis presented through cardiogenic pulmonary oedema". *Neuropsychopharmacologia Hungarica* 20.2 (2018): 65-74.

15. Panel M., *et al*. "Mitochondria and aging: A role for the mitochondrial transition pore?". *Aging Cell* 17.4 (2018): e12793.

16. Peuhkurinen KJ. "Ischemic heart disease at the cellular level". *IJBEM* 2.1 (2000): 1-9.

17. Deprez MA., *et al*. "pH homeostasis links the nutrient sensing PKA/TORC1/Sch9 ménage-à-trois to stress tolerance and longevity". *Microbial Cell* 5.3 (2018): 119-136.

18. Laffey JG., *et al*. "Therapeutic hypercapnia reduces pulmonary and systemic injury following In Vivo lung reperfusion". *American Journal of Respiratory and Critical Care Medicine* 162 (2000): 2287-2294.

19. Jaul E and Barron J. "Age-related diseases and clinical and public health implications for the 85 years old and over population". *Frontiers in Public Health* 5 (2017): 335.

20. Osanai T., *et al*. "Intracellular protons accelerate aging and switch on aging hallmarks in mice". *Journal of Cellular Biochemistry* 119.12 (2018): 9825-9837.

21. Sikter A and Sonne C. "Is the Primary Aetiology of Hypertension Unknown? Novel Views on Previous Assumptions". *Acta Scientific Medical Sciences* 5.8 (2021): 47-53.

22. Anderson DE and Brady JV. "Preavoidance blood pressure elevations accompanied by heart rate decreases in the dog". *Science* 172.3983 (1971): 595-597.

23. Anderson DE., *et al*. "Racial differences in resting end-tidal CO2 and circulating sodium pump inhibitor". *American Journal of Hypertension* 14 (2001): 761-767.

24. Anderson DE., *et al*. "Capnometric feedback training decreases 24-h blood pressure in hypertensive postmenopausal women". *BMC Cardiovascular Disorder* 21.1 (2021): 447.

25. Rosskopf D., *et al*. "Membrane sodium-proton exchange and primary hypertension". *Hypertension* 21 (1993): 607-617.

26. Chipperfield AR and Harper AA. "Chloride in smooth muscle". *Progress in Biophysics and Molecular Biology* 74.3-5 (2006): 175-221.

27. Schwartz WB., *et al*. "Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. II. Recovery, with special reference to the influence of chloride intake". *Journal of Clinical Investigation* 40.7 (1961): 1238-1249.

28. Grollman A., *et al*. "Sodium restriction in the diet for hypertension". *JAMA* 129.8 (1945): 533-537.

29. McCallum L., *et al*. "The hidden hand of chloride in hypertension". *Pflugers Arch* 467.3 (2015): 595-603.

30. Rosendorff C. "The renin-angiotensin system and vascular hypertrophy". *JACC* 28.4 (1996): 803-812.

31. Ghike SM. "Metabolic syndrome - A truly psychosomatic disorder? A global hypothesis". *Medical Hypotheses* 97 (2016): 46-53.

32. Santos MA., *et al*. "Emotional stress evaluation of patients with moderate and severe sleep apnea syndrome". *International Archives of Otorhinolaryngology* 21.1 (2017): 28-32.

33. Resnick LM., *et al*. "Intracellular pH in human and experimental hypertension". *Proceedings of the National Academy of Sciences of the United States of America* 84.21 (1987): 7663-7667.

34. Aryal D., *et al*. "Chronic metabolic acidosis elicits hypertension via upregulation of intrarenal angiotensin II and induction of oxidative stress". *Antioxidants (Basel)* 10.1 (2021): 2.

35. Frassetto L and Sebastian A. "Age and systemic acid-base equilibrium: analysis of published data". *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* 51.1 (1996): B91-99.

36. Adeva MM and Souto G. "Diet-induced metabolic acidosis". *Clinical Nutrition* 30.4 (2011): 416-421.

37. Sikter A and Sonne C. "A new hypothesis on vascular calcification: the exhausting buffer syndrome (EBS)". *Neuropsychopharmacologia Hungarica* 23.1 (2021): 215-220.

38. Wagner CA. "Effect of Mineralocorticoids on Acid-Base Balance". *Nephron Physiology* 128 (2014): 26-34.

39. Zhou Y., *et al*. "Effects of angiotensin II on the CO2 dependence of HCO3- reabsorption by the rabbit S2 renal proximal tubule". *American Journal of Physiology - Renal Physiology* 290.3 (2006): F666-673.

40. Wakabayashi I., *et al*. "Intracellular pH as a determinant of vascular smooth muscle function". *Journal of Vascular Research* 43.3 (2006): 238-250.

41. Melamed ML and Raphael KL. "Metabolic Acidosis in CKD: A Review of Recent Findings". *Kidney Medicine* 3.2 (2021): 267-277.

42. Wesson DE. "Is NaHCO3 an antiaging elixir?" *American Journal of Physiology - Renal Physiology* 311 (2016): F182-F183.

43. Di Iorio BR., *et al*. "Treatment of metabolic acidosis with sodium bicarbonate delays progression of chronic kidney disease: the UBI Study". *Journal of Nephrology* 32.6 (2019): 989-1001.

44. Leibrock CB., *et al*. "Bicarbonate-sensitive calcification and lifespan of klotho-deficient mice". *American Journal of Physiology - Renal Physiology* 310 (2016): F102-F108.

45. Forni LG., *et al*. "The Janus faces of bicarbonate therapy in the ICU: not sure!" *Intensive Care Medicine* 46.3 (2020): 522-524.

46. Navaneethan SD., *et al*. "Effects of treatment of metabolic acidosis in CKD: A systematic review and meta-analysis". *Clinical Journal of the American Society of Nephrology* 14.7 (2019): 1011-1020.

47. Neubauer B., *et al*. "Angiotensin II short-loop feedback: Is there a role of Ang II for the regulation of the renin system in vivo?" *Hypertension* 71 (2018): 1075-1082.

48. Meyer DJ., *et al*. "Na/K pump mutations associated with primary hyperaldosteronism cause loss of function". *Biochemistry* 58.13 (2019): 1774-1785.

49. Jean-Louis G., *et al*. "Cardiovascular disease risk reduction with sleep apnea treatment". *Expert Review of Cardiovascular Therapy* 8.7 (2010): 995-1005.

50. Iftikhar IH., *et al*. "Effects of continuous positive airway pressure on blood pressure in patients with resistant hypertension and obstructive sleep apnea: a meta-analysis". *Journal of Hypertens* 32.12 (2014): 2341-2350.