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Review Article

Is the Primary Aetiology of Hypertension Unknown? Novel Views on Previous Assumptions

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Abstract

Most details of primary hypertension are known, however, it is still unclear how and why the increased activity of angiotensin II and aldosterone cause developing primary hypertension seen worldwide. Here we hypothesize that primary hypertension is an age-related disease initiated by the acidification of the intracellular milieu. The renin-angiotensin-aldosterone system (RAAS), like many other hormones, work through feedback mechanisms, with aldosterone restoring pH and electrolyte changes produced by respiratory acidosis in targeted cardiovascular and kidney cells. High NaCl intake enhances the effect of aldosterone (salt-sensitive hypertension). By contrast, angiotensin II restores H^+ and electrolyte abnormalities caused by metabolic acidosis in the targeted cells (salt-resistant hypertension). Aldosterone and angiotensin II decrease H^+ concentration synergistically, but act antagonistically on Cl^- to HCO_3^- concentrations. However, both hormones overcompensate acidosis and increase Na^+ retention leading to increased circulatory resistance, hypertension, and left-heart hypertrophy by a cascade of events. If this hypothesis is true, the cause of essential hypertension is chronic respiratory and metabolic acidosis and RAAS activation. Preventing age-related intracellular acidosis through a non-hormonal way could prevent pathophysiological blood pressure elevation. It is a challenge to mitigate pCO_2 level permanently and we, therefore, recommend a salt mixture of KH_2PO_4 and other Mg^{2+}, K^+, Ca^{2+} and phosphate salts to relieve the withdrawal symptoms in hypercapnia.

Keywords: Intracellular Acidosis; RAAS as a Feedback Mechanism; Salt-resistant Hypertension; Salt-Sensitive Hypertension; Weaning from Hypercapnia

Abbreviations

COPD: Chronic Obstructive Pulmonary Diseases; CPAP: Continuous Positive Airway Pressure; EBS: Exhausting Buffer Syndrome; EC: Extracellular; IC: Intracellular; NBCn1: Natrium-Bicarbonate Cotranspoter n1; NHE-1: Natrium-Hydrogen Exchanger-1; RAAS: Renin-Angiotensin-Aldosterone System; VSMCs: Vascular Smooth Muscle Cells

Introduction

It is generally accepted that overproduction and increased activity of the renin-angiotensin system and aldosterone are the direct cause of primary hypertension. Aldosterone is part of the renin-angiotensin-aldosterone system (RAAS), but partly independently enhances sodium chloride sensitivity of hypertension [1]. It is also clear that the effect of excessive table salt consumption on hypertension is primarily related to its chloride content, which is connected to Na^+ [2]. Both angiotensin and aldosterone concentrations increase during metabolic acidosis giving feedback and trying to neutralize intracellular acidosis on their targeted cells, e.g. in vascular smooth muscle cells (VSMCs) [3,4]. In addition, the effects of angiotensin increases due to low intracellular HCO_3^- concentration, while elevated cytosolic HCO_3^- concentration

increases the aldosterone and sodium chloride effects on the targeted cells [1].

Most of the details of how RAAS causes ionic changes to alkalinize the intracellular milieu are known, showing increased Na^+ and Ca^{2+} concentrations in vascular smooth muscle and myocardial cells, leading to hypertrophy and increased systemic vascular resistance [1]. The causes and pathogenesis of secondary hypertension are well known or elucidated by thorough clinical investigation [5]. By contrast, despite intensive research, the pathophysiologic mechanism of primary hypertension remains unclear, which is why it is also called essential [6]. Recently, it was shown that metabolic acidosis might elicit blood pressure elevation via upregulation of intra-renal angiotensin, being a co-factor in the development of primary hypertension [7]. Primary hypertension is associated with impaired acid-base metabolism, and there may be an association between hypoventilation elicited by chronic psychic stress, persistent pCO_2 elevations, and salt-sensitive hypertension [8,9]. However, in the case of hypertension, acidosis is overcompensated in the VSMCs. It seems the regulation tries to compensate for all ionic deviations (e.g. also of Cl^- and HCO_3^- alterations) - meanwhile, increasingly severe ion- and consequently causes metabolic disturbance being the ripple effect. The goal can only be the restoration of the original intracellular ionic surroundings and pH, i.e. the elimination of intracellular acidosis.

Here we suggest a speculation about the aetiology of the cardiometabolic syndrome and our newly proposed exhausting buffer syndrome (EBS), defined as the chronic systemic intracellular acidification due to fixed acids' retention. We also assume that intracellular acidosis, caused by a number of different factors such as chronic kidney disease, obstructive sleep apnoea, or acidic diets might be the basis of vascular calcification and primary hypertension [10].

Salt-sensitive hypertension

Salt-sensitive hypertension is defined as an increase in blood pressure of 10% or greater due to a diet rich in salt, which, in the presence of aldosterone, increases the NaCl content in the target cells and increases blood pressure [11]. In salt-resistant hypertension, the aldosterone concentration is reduced during the high salt diet, and blood pressure does not rise. By contrast, in low-renin hypertension, aldosterone level decreases, but the aldosterone-to-renin ratio and blood pressure increase (relative aldosterone excess) [12]. A number of inherited salt-sensitive hypertension pathways are linked to sympathetic activations [13-15] while we here discuss acquired salt-sensitive hypertension due to parasympathetic activation [16]. Physiologically, renal blood flow increases when dietary sodium chloride intake increases. In the patients who are having salt-sensitive hypertension, no changes are observed in renal circulation, and a part of the excessive NaCl was retained [17]. For comparison, relatively mild hypercapnia decreases renal arterial flow; and in COPD, hypercapnia is characterized by hormonal disturbance and salt retention, where the aldosterone level does not diminish either during salt retention [18,19]. Hypercapnia induces catabolic effects by causing changes in the tertiary structure of cellular proteins [20]. The assessment of systematic pathophysiological effects of chronic mild hypercapnia may prove that this chronic mild hypercapnia is precisely the biochemical force that triggers cardiometabolic syndrome, including - among other things - type 2 diabetes, salt-sensitive hypertension, vascular calcification and depression [21]. Obstructive sleep apnoea, cardiometabolic syndrome, salt-sensitive hypertension correlate and overlap, and this inhibited breathing and chronic low-grade hypercapnia lead to intracellular acidosis, which is the hypothesized leading cause of cardiometabolic syndrome [9,10,22,23].

We believe that the physiological range of arterial pCO_2 is poorly defined (35 - 45 mmHg) and recommend 38 - 42 mmHg for the normal range of pCO_2 levels under 50 years, currently accepted by the minority [24]. Others argue that the upper limit of normal arterial pCO_2 should gradually decrease with age due to intracellular acidification caused by the inevitable deterioration of renal function resulting in the exhausting buffer syndrome [25,26]. That is, we think that both obstructive sleep apnoea and obesity hypoventilation increase pCO_2 to pathophysiological level. Salt-sensitive hypertension is much more frequent in African - Americans than white Americans, likely due to genetic differences [27]. The elevation of pCO_2 correlated with the blood pressure sensitivity to high sodium intake and the prevalence of primary hypertension in African Americans above 50 years of age [27]. Nevertheless, Anderson's behavioural chronic stress mechanism may also explain the high prevalence of salt-sensitive hypertension in the African - American population that may be partially acquired [28]. We agree with Anderson that persistent, mild hypercapnia may cause acquired salt-sensitive hypertension [9,10]. The intracellular pH chan-

ges due to hypercapnia have a primary role, so the pH regulation takes precedence over other ions. A high intake of NaCl promotes alkalization through the sodium-hydrogen exchanger (NHE-1) and NaCl entry to these VSMCs by aldosterone [17,29,30]. Aldosterone acts on the NHE-1, alkalizes the VSMCs cytosol and increases their Na^+ content, triggering events of cascades leading to hypertrophy, increased vascular resistance and blood pressure elevation. Effects of aldosterone and a high intake of NaCl synergistically support each other. NaCl, more specifically the extracellular-to-intracellular (EC/IC) Cl^- ratio, plays a significant role in regulating salt-sensitive hypertension. The salt sensitivity depends on the EC/IC chloride gradient, which is increased in hypercapnic acidosis and decreased in metabolic acidosis [31]. It would explain the correlation why chronic hypercapnia would cause sodium-chloride sensitive hypertension while salt-resistant hypertension remains in metabolic acidosis. As the bicarbonate level changes, the chloride level changes inversely; i.e. in chronic hypercapnic acidosis, the cytosolic Cl^- concentration decreases; in metabolic acidosis, it increases [32].

Salt-resistant hypertension

It was suggested decades ago that intracellular acidosis plays an essential role in the pathophysiology of hypertension (and also diabetes) [33]. Since then, the research in acid-base equilibrium has increased [8], and it is now known that acidosis increases both aldosterone and angiotensin II levels [3,4]. Recently, it was shown that metabolic acidosis could trigger blood pressure elevation in an animal model; thus, it is likely a pathophysiological factor in the development of primary hypertension [7]. In the previous section, we discussed how chronic mild hypercapnic acidosis could trigger acquired salt-sensitive hypertension, while we here demonstrate a link between metabolic acidosis, angiotensin II production, and salt-resistant hypertension. The transition between salt-sensitive and -resistant hypertension is not sharp, because both aldosterone and angiotensin II effects are strongly related (RAAS) and cardiometabolic syndrome and exhausting buffer syndrome are also overlapping [10]. Intracellular ions, such as Cl^- and HCO_3^- levels, as well as pH play a decisive role in regulation [31-34]. Here we discuss changes in RAAS protagonists due to alterations in intracellular ionic milieu, which are feedback mechanisms that try to restore the original intracellular electrolytes.

The most important membrane receptor of angiotensin II is the Na^+/HCO_3^- cotransporter NBCn1, and its most essential target cells - similarly to NHE-1 - are VSMCs and myocardial cells [1]. There are many similarities between the effects of NHE-1 and NBCn1 isoforms. Both occur in the membrane of VSMCs important for the regulation of hypertension, decrease H^+ and increase Na^+ concentrations in targeted cells and increase Na^+/Ca^{2+} exchange and contractility [1]. However, NHE-1 increases intracellular Cl^- concentration in the targeted cells; by contrast, NBCn1 decreases it, as Cl^- and HCO_3^- concentrations are inversely related. Both aldosterone and angiotensin II also regulate the acid-base balance through renal functioning. Both increases renal acid secretion, but aldosterone also increases the Cl^- reabsorption [34]. In contrast, angiotensin II is one of the most potent hormonal stimulators of renal HCO_3^- reabsorption, and acid-base regulation by aldosterone or angiotensin differs [34]. Aldosterone seeks to eliminate respiratory acidosis, while angiotensin II seeks to eliminate metabolic acidosis and its consequences [35]. We hypothesize salt-resistant hypertension would be related to intracellular metabolic acidosis, angiotensin II and NCBn1.

Most chronic kidney diseases are usually characterized by progressive deterioration and secondary hypertension [36] and severe, untreated hypertension leads to chronic kidney damage [37]. We believe that age-related decrease in renal functioning is also inducing intracellular metabolic acidosis, which triggers a compensatory release of renal paracrine hormones such as angiotensin II, aldosterone and endothelin-1 [38]. Intracellular metabolic acidosis can be both the cause and consequence of the deterioration. The age-related intracellular metabolic acidosis due to decreased kidney functioning can further enhance the acidosis, but this vicious circle may stop during the elimination of acidosis.

Altogether, this suggests that both metabolic and hypercapnic acidosis increase intracellular H^+ concentrations increasing, 50+ years of age. These two mechanisms create different syndromes and clinical images. The former is the ensemble defined by the authors as exhausting buffer syndrome, the latter is the cardiometabolic syndrome. The former is salt-resistant, and the latter exerts salt-sensitive hypertension. Due to the overlap, mechanisms are difficult to separate. Concerning intracellular ionic conditions, both lower the intracellular pH, while they behave oppositely regarding intracellular Cl^- to HCO_3^- ratio and pCO_2 levels. The two types of acidosis can be brought to a common denominator by compensating for the decrease in intracellular pH above 50 years by reducing

pCO_2 levels by about 1 - 3 mmHg [25,26]. The reduction of metabolic acidosis with HCO_3^- therapy can only be used to a limited extent (see testing section).

Testing the hypothesis

The number of researchers who consider intracellular metabolic acidosis to be the leading cause of many age-related diseases is growing. The chronic kidney disease is regarded as a human model of accelerated ageing. The number of studies using sodium bicarbonate therapy as a general solution of metabolic acidosis also increases [39,40]. It appears that bicarbonate therapy may be effective even in the prevention of vascular calcification [41], but the HCO_3^- administration should be limited, because it generates an adverse effect increasing in pCO_2 levels, thus triggering intracellular respiratory acidosis [42]. A strategy for restoring mixed intracellular acidosis due to respiratory and metabolic acidosis can be that we should reduce pCO_2 levels to slightly below 40 mmHg [25,26].

It is usually hard to change the breathing habit or decrease pCO_2 levels, because the breathing regulation fixes it, and the individual's breathing becomes a habit. It is a well-known phenomenon that when the pCO_2 level is reduced (e.g. in the case of COPD) by a breathing machine, in the end, it is difficult to wean from the respirator. We are faced with a similar phenomenon if we want to intentionaly change the respiration frequency or depth, thus reduce the pCO_2 level. (This breathing training is recently referred to as „breathing biofeedback"). The success of testing depends on whether we can effectively and permanently increase the respiration minute volume. Therefore, all sorts of tricks need to be figured out.

Theoretically, several methods are possible as outlined below:

First, 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 as well as blood pressure. However, this may be a consequence of the reduction of hypoxia or hypercapnia [43,44]. Therefore, we suggest lowering the average pCO_2 below 40 mmHg by CPAP.

Secondly, the biofeedback of breathing, a computer-controlled breathing training, is based on voluntary alteration of respiration, affecting the pCO_2 level. A new breathing training method using capnography appears to be suitable for a permanent mild reduction of the pCO_2 level [45].

Thirdly, intentional therapeutic alteration of the pCO_2 level moves the patient from a stable position to a labile one. Decreased pCO_2 levels result in a reduction in intracellular acidosis, a sudden onset of cellular anabolic metabolism, and essentially the development of the refeeding syndrome [46]. Severe hypophosphatemia occurs when the pCO_2 level is decreasing, and it is a significant cause of the "difficult-to-wean" phenomenon [47], usually accompanied by hypomagnesaemia and hypokalemia [48]. There is a inevitable loss in bone mass during acidosis [25], however, after pH restoring, the tissue rebuild phosphate and Ca^{2+}, resulting in hypocalcemia and hypophosphatemia (hungry bone syndrome) [49].

We believe and know that there should be a salt mixture that not only restores the electrolyte deficiency caused by decrease in pCO_2 but, at the same time, also decreases pCO_2 levels [50]. Its composition may vary slightly from individual to individual, but its essential constituent is KH_2PO_4, which increases breathing and decreases pCO_2 level. This call for a K_2HPO_4 supplement; the ratio of KH_2PO_4/K_2HPO_4 - according to this testing hypothesis - is able to regulate the breathing and pCO_2 levels. If the ratio of two phosphate salts administered increases, the pCO_2 will decrease and vice versa. The amount to be administered should be titrated individually based on laboratory findings monitoring. It is advisable to satisfy with Mg^{2+}, Ca^{2+}, Zn^{2+}, other ions, trace elements and vitamins, as described for refeeding and hungry bone syndromes. Therefore, we call for treatment, including that physiological salt mixture that reduces mild hypercapnia and improves metabolism and lowers high blood pressure.

Conclusion

Sufficient literature data is available to puzzle out the main features of the pathophysiology of age-related or civilization diseases, such as primary hypertension. The signs of intracellular acidosis already manifest in more than 90% of people over 50 years. In most cases, metabolic acidosis and respiratory acidosis co-occur; where one predominates, the other does not, thus they overlap. Chronic kidney disease (as an example of metabolic acidosis) and obstructive sleep apnea (as a respiratory acidosis) are considered human models for accelerated ageing. The former manifests itself primarily in the form of exhausting buffer syndrome, the latter that of cardiometabolic syndrome. In both, there is intracellular acidosis, but the cytosolic Cl^-/HCO_3^- ratio is higher in EBS than in cardiometabolic syndrome. Regarding primary hypertension: in metabolic acidosis, angiotensin II triggers salt-resistant hypertension in

VSMCs via NBCn1 receptors, while in chronic respiratory acidosis, aldosterone and high NaCl levels together trigger salt-sensitive hypertension through NHE-1.

Increases in both aldosterone and angiotensin II levels can be initiated by intracellular H^+ [3,4]. If this statement is confirmed and the process can be stopped by intracellular alkalinization, on the other hand, the "essential" name can no longer be used. This hypothesis points not only to the paramount importance of intracellular pH and the extreme pH sensitivity of proteins, but also to the fact that ions considered to be insignificant such as Cl^- do have metabolism regulatory roles, and the intracellular ion milieu as a whole is an integral part of the second messenger system [46].

Like many other hormonal systems, RAAS functions as a feedback system that seeks to restore intracellular pH. Still, its activity is mainly limited to VSMCs, myocardial and certain kidney cells, serving only a relatively small slice of the body's tissue regulation. It has pathophysiological effects, because the impact in the target cells exceeds the target.

What to do? The testing menu suggested by the authors is easy to check; the result determines everything.

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