Chapter

The Effect of Dietary Sodium Restriction on Vascular Stiffness in Hypertension

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Abstract

Increased salt consumption is believed to induce high blood pressure (BP)-mediated organ damage, although it is not yet clear whether it reflects a generalized micro- and macrovascular malfunction independent of BP. Exceeding dietary sodium intake is acknowledged to be the main modifiable environmental risk factor for cardiovascular events that accounts for an increase in blood pressure and induces hypertension (HTN)-related target organ damage. Arterial stiffness is well known as an independent cardiovascular risk factor, and sodium intake may be a determinant of arterial stiffness. Even so, the studies that investigated the effect of dietary sodium reduction intake on arterial stiffness in humans provided inconclusive results. Therefore, we aim to perform a review of the available evidence of salt restriction and arterial stiffness and its impact on hypertensive patients.

Keywords: salt intake, dietary sodium, arterial stiffness, blood pressure, hypertension

1. Introduction

Hypertension (HTN) is a significant risk factor for cardiovascular disease (CVD), a *major cause of premature death worldwide*, and has been identified as one of the strongest risk factors in the global burden of disease [1, 2]. Hypertension guidelines frequently recommend salt reduction as an important simple strategy to reduce high blood pressure (BP) [2–4]. This recommendation is usually extended to individuals with normal BP as well as those at risk of becoming hypertensive [5].

The pressure-natriuresis mechanism that was first described by Guyton et al. [6] proposes a linkage between dietary sodium intake and renal sodium handling. This hypothesis says that, in normal individual, the consumption of high amounts of sodium in the diet will cause a transient increase in BP that promotes a higher excretion of sodium by the kidney. The kidney excretes the excess of sodium, leading to normal blood pressure restoration. This hypothesis elucidates how blood pressure is sustained over the time, although the daily variation in sodium intake is reported among most individuals [6–8].

Excess dietary sodium consumption has several known detrimental effects on blood pressure [8–10] and has been associated with a higher risk of stroke and renal impairment [11, 12]. Accordingly, there is a strong evidence from randomized controlled trials that a moderate reduction in dietary salt intake safely and effectively reduces BP and urinary albumin excretion rate both in hypertensive and diabetic patients [13, 14]. Likewise, evidence from epidemiological and clinical studies also suggested an association between regular dietary salt intake and pulse wave velocity (PWV) [15–17].

This association between dietary salt consumption and pulse wave velocity is also supported by experimental evidence in animal models of structural and functional changes caused by high salt regimens on the arterial wall above and beyond the effect of high BP [18–20]. These changes on arterial wall are believed to be induced by both reduced bioavailability of nitric oxide and a deficient response of the local renin-angiotensin system to high sodium consumption [21]. Some interventional studies in man have investigated the effect of reduction in salt intake on arterial stiffness, but their results were not conclusive mainly because of the low statistical power of most of them [22–25].

Results from a systematic review and meta-analysis of the available clinical trials testing the effect of sodium intake restriction on PWV as a proxy for arterial stiffness, with null hypothesis being that restriction of sodium intake does not affect arterial stiffness, indicated that restriction of dietary sodium intake reduces arterial stiffness. The authors have suggested that this effect seems to be at least in part independent of the changes in blood pressure [26].

To date, the evidence on the effects of dietary sodium restriction on pulse wave velocity is still conflicting. Accordingly, this review aims to contribute to increase the knowledge about the effects of sodium restriction on arterial stiffness in the context of hypertension.

2. Effects of sodium reduction on blood pressure

High sodium intake is linked to a higher risk of stroke, left ventricular hypertrophy, and renal impairment and can impair the arterial vasculature and endothelial function [10, 22, 27–29]. A moderate reduction in dietary sodium to achieve a sodium intake between 1.5 and 2.3 g/day may be cardioprotective independent of the BP pathway, but the evidence is not conclusive in this regard. It also may not be safe to recommend sodium restriction in older adults with diabetes or those with established CVD [3].

Evidence indicates that reducing sodium intake significantly lowers blood pressure in both men and women. Sodium is found not only in table of salt but also in a variety of foods, including cream, eggs, milk, shellfish, meat, and many other processed foods. The World Health Organization (WHO) recommendations indicate a reduction in sodium intake to lower blood pressure and risk of stroke, cardiovascular disease, and coronary heart disease in adults [30].

The current recommendations in most countries around the world are to reduce salt intake from about 9–12 g/day to 5–6 g/day [31]. Much evidence supports that such a reduction in salt intake lowers blood pressure. The WHO recommends a reduction to <2 g/day sodium (5 g/day salt) in adult individuals [30, 31].

The effects of sodium reduction on blood pressure have been evaluated in many studies. In their study that evaluated the effect of sodium reduction on blood pressure, D'Elia et al.'s [26] pooled analyses showed a significant reduction of both systolic blood pressure (SBP) (mean difference, −5.82 mmHg;

95% IC, −8.42 to −3.43 mmHg) and diastolic blood pressure (DBP) (mean difference, −2.75 mmHg; 95% IC, −3.67 to −1.87 mmHg) upon the reduction of sodium intake.

Evidence also shows that a modest reduction in salt intake for a couple of weeks (4 or more weeks) causes important and significant lowering in blood pressure levels in both normal and hypertensive individuals, independent of sex and ethnicity [13]. Salt reduction is linked to a mild increase in noradrenaline, aldosterone, and plasma renin activity, and no significant change in lipid concentrations. These results may support a reduction in population salt consumption, which would lower population mean blood pressure and thereby reduce cardiovascular risk outcomes. In their meta-analysis, He et al. [13] have shown that a modest reduction in salt intake, as currently recommended, has a significant effect on blood pressure both in individuals with hypertension and in those with normal blood pressure. The fall in blood pressure is seen in white and black individuals irrespective of their gender. These findings provide additional support for reducing salt intake in the population.

3. Effect of sodium intake reduction on pulse wave velocity

Evidences suggest that salt intake plays an important role on blood pressure regulation, and it is also suggested a direct effect of salt on large artery wall that modulates vascular stiffness [14].

Pulse wave velocity is known to be associated with BP and age [26, 32, 33]. In a recent study where the authors have evaluated the effect of salt restriction on pulse wave velocity, no significant statistical differences were detected. Although sodium restriction reduced SBP and DBP in the combined analysis of all studies, results of the meta-regression analysis, however, indicated that the effect of salt restriction on arterial stiffness did not depend on changes in blood pressure. In fact, in one of the studies included in the meta-analysis, there was a significantly greater reduction in pulse wave velocity in black than white and Asian hypertensive patients, despite the fact that the three ethnic groups had similar reductions in blood pressure [34].

Another study evaluating the long-term sodium restriction showed an improvement in arterial stiffness independently of the changes in BP [35]. The authors did not detect a dose dependence in the pooled association between salt restriction and reduction of PWV. Accordingly, the lack of a dose-related effect in the range of salt reduction applied in the available studies might be the possible cause of these results.

In subgroup analyses of nine cohorts that evaluated the effect of sodium restriction on PWV including prehypertensive and/or hypertensive participants, whereas in the five cohorts that enrolled non-hypertensive individuals, an inverse trend was detected, but this difference was not statistically significant. A larger effect of sodium reduction on PWV was also seen in the three cohorts that included hypertensive patients under antihypertensive treatment (5.07%) than in the cohorts enrolling untreated normotensive or prehypertensive individuals (1.70%): again, however, this difference was not statistically significant [14].

More recently, a study using a hypothetical model to analyze the association between salt intake and PWV (carotid-femoral) through direct and mediating pathways that aimed to investigate whether the association between salt intake and arterial stiffness also has a sex-specific pattern has demonstrated that high salt intake has a direct and independent effect increasing on arterial stiffness regardless of sex. The authors also concluded that the association between salt intake and arterial stiffness is more dependent on BP in normotensive women than it is

in normotensive men. As stated by the authors, these results highlight the need for a sex-specific approach in the evaluation of cardiovascular risk associated with dietary habits [36].

Furthermore, Grigorova et al. [37] have demonstrated that high salt intake was associated with an increase in Na/K-ATPase inhibitor marinobufagenin (MBG) levels, and an activation of the transforming growth factor-beta (TGF-β) mediated pro-fibrotic pathway in the vasculature, leading to an increase of aortic stiffness without elevation of BP. MBG activated TGFβ1 pro-fibrotic pathway in cultural vascular smooth muscle cell (VSMC), indicating a fundamental role of MBG in the development of fibrosis via the Na/K-ATPase signaling function. The decrease in salt consumption restored the aortic elasticity through inactivation of the TGF-β pathway. Therefore, decreasing salt consumption can improve vascular elasticity and lower the risk of cardiovascular disease by MBG level reduction [37].

4. Renal sodium handling, blood pressure, and vascular compliance

The relationship between sodium intake and blood pressure regulation has been suggested through animal experiments indicating that a high-sodium diet, at their initial phase, leads to volume expansion and cardiac output increases. Based on experiments including mainly nephrectomized dogs that received a large amount of saline solution daily for 2 weeks, Guyton [7] suggested that the BP increases mainly through two mechanisms: (1) volume expansion and cardiac output increases and (2) an autoregulatory mechanism that affects the vessel resistance. Accordingly, the hypothetic mechanism on how dietary salt increases blood pressure includes Guyton's main theory that the increase in blood pressure is initially associated with an increase in extracellular fluid and blood volumes [7, 15, 26]. According to Guyton's hypothesis, in the hypertension pathophysiology, irrespective of the causal factor, the pressure-natriuresis relationship in the kidney is always involved, with higher blood pressures being required to eliminate a higher given sodium load [38]. However, it has never been demonstrated that measurements of extracellular fluid volume in hypertensive individuals are modified consistently. All of the authors found that the volumes of extracellular fluid and exchangeable sodium were normal in hypertensive individuals [39, 40].

The only similitudes were the lower ratio between intravascular and interstitial fluid volumes and smaller plasma volume, indicating unbalanced division in hypertensive patients [39]. Additionally, high levels of atrial natriuretic peptide hormone, lower levels of plasma renin, and an increased capacity of plasma to inhibit Na^{+}/K^{+}-ATPase were observed in these patients [15, 41, 42]. In fact, all these apparent paradoxes can be easily understood when we observe that, in hypertensive patients, if total vascular compliance is reduced, a slight decrease in intravascular volume can be too large for the capacity of the corresponding vascular space [39].

Vascular compliance establishes the volume-pressure relationship or the volume within a vascular segment and the blood pressure that is generated by the presence of that blood volume. It is simply the basic concept of compliance applied to a vascular segment and represents a classic index of the elasticity of the intravascular compartment, from the slope of the curve plotting changes of blood volume (ΔV) versus changes of intravascular pressure (ΔP) [6].

Within a narrow range of volume and pressure changes, the linear relationship curve between both variables is used to define the compliance as the slope ΔV/ΔP [6]. In a clustered circulation model, the vascular compliance expresses the sum of complacencies of all vascular segments, including arteries and veins [43]. Accordingly, Guyton [6] has defined "total" vascular compliance based on

experimental animal models as the relationship between the mean circulatory filling pressure (MCFP) and blood volume. The MCFP is the pressure that is registered throughout the entire circulatory system if the heart is suddenly stopped and the blood volume is redistributed entirely in the vascular system taking into account the capacity of the vessels. Vascular compliance is then defined as the product of volume change and mean circulatory filling pressure. However, as the MCFP measurement implies the presence of a non-beating heart, in humans, it cannot be measured. Therefore, an alternative index of the capacitance function had to be defined.

Evidence from studies in both animals and humans has shown that similar indices are observed in cases where the circulation is not interrupted between blood volume changes and pressures measured throughout the different parts of the venous system [6, 37]. For example, the relationship between rapid blood volume expansion (ΔV) and central venous pressure (ΔCVP) with a plasmatic expander such as dextran has the dimensions of compliance [39, 44]. The "true" vascular compliance measured from ΔV/ΔMCFP ratio is also called "effective" total vascular compliance to differentiate it from the ΔV/ΔMCFP ratio [39, 45].

Compared to the normotensive patients, the slope of the curve plotting blood-volume versus central venous pressure (ΔV/ΔCVP) is markedly lower in hypertensive subjects [39, 45]. On the other hand, there are no changes in curves of cardiac output versus blood volume expansion, indicating that the cardiac function is maintained despite cardiac structural modifications in hypertensive individuals. At these conditions, compared to non-hypertensive individuals, in hypertensive patients, the central venous pressure increases more, and the decrease in the effective compliance of the vascular bed is pointed out as the responsible factor for this phenomenon [46, 47].

Evidence suggests that renal sodium handling is the main factor influencing the level of intra- and extrarenal blood pressure and is regulated by complex physiological and inflammatory mediators, hormones, and the sympathetic nervous system [48]. Therefore, a compromised kidney capacity to eliminate sodium in response to increased blood pressure is a major factor for a sustained increase in blood pressure, irrespective of the primary cause.

The changes registered in plasma sodium levels exert their effects on the vascular system, affecting not only the small resistance arteries but also the large artery properties leading to an increase in arterial stiffness and consequent decrease in vascular compliance [49].

Both observational and longitudinal studies have suggested that lower sodium intake is associated with lower wave pulse velocity. Evidence suggests that in hypertensive patients, a low sodium intake is associated with a larger brachial artery diameter than that seen with a high sodium intake [50]. A sodium overload reduces arterial distensibility and compliance irrespective of blood pressure changes in hypertension in the elderly and in severe hypertension patients with end-stage renal disease [51].

5. Sodium-induced change in arterial stiffness and BP

A considerable body of evidence has shown major links along with cause-and-effect relationships between salt intake and BP [15, 16, 52]. In many studies, both SBP and DBP had a similar effect regarding their action on the arterial wall, regardless of the presence of a high-sodium diet or not. Remarkably, many observational studies suggest a special role of systolic blood pressure, which, until recently, was rarely considered.

Evidence from studies of genetic models of animal hypertension suggested that long-term high sodium intake is associated with increased intima-media thickness due to the extracellular matrix (ECM) development and aortic hypertrophy regardless of blood pressure. These changes caused by high sodium consumption and often associated with increased arterial stiffness and changes in smooth vascular cells properties are reversed by reducing sodium and/or giving diuretics [16, 53].

Hormonal counterregulatory mechanisms that modulate arterial changes act chronically in the presence of a high-sodium diet because bradykinin β2-receptor blockage by Hoe-140 (selective B_2 bradykinin receptor antagonist that suppresses the effects of bradykinin) produces more carotid hypertrophy, while in case of normal sodium intake, less aortic collagen accumulates due to AngII-specific type 1 receptor activity [54, 55].

Several studies have consistently established an independent correlation between sodium dietary intake, arterial stiffness, and blood pressure, regardless of whether systemic, regional, or local determinations were present [16, 56]. In a study addressing the relationship between sodium intake and arterial stiffness based on the Chinese populations, Avolio et al. [57] have found that sodium intake has an independent effect on arteriolar tone and arterial wall properties, with the former indirectly and the later directly contributing to increased arterial stiffness with age. In the same study, the comparison of salt intake between urban and rural subjects, as determined by urinary sodium excretion, was greater in the urban subjects (13.3 g NaCl/day) than in rural ones (7.3 g NaCl/day). This difference was related to higher arterial stiffness and hypertension prevalence and lesser vascular compliance in urban subjects. Salt intake had, therefore, an independent effect on arterial structural and functional properties, with the arterial wall directly and arterial tone indirectly contributing to increased PWV with age [16]. Another study from Australia involving young and middle-aged (20–66 years old) normotensive subjects on a low-salt diet who were compared with age- and BP-matched subjects on a normal-sodium diet showed adult subjects on a low-sodium diet have lower arterial stiffness independent of blood pressure [35].

On the other hand, the benefits of a low-salt diet on blood pressure seem to be greater in hypertensive patients than in normotensive ones. A systematic review carried out by Graudal et al. [58] that included 185 randomized controlled trials found that sodium reduction from an average high usual sodium intake level (201 mmol/day) to an average level of 66 mmol/day, which is below the recommended upper level of 100 mmol/day (5.8 g salt), resulted in a small decrease (1/0 mmHg) in systolic and diastolic BP in white normotensive patients and a decrease in systolic and diastolic BP of 5.5/2.9 mmHg in white hypertensive patients. The decrease of blood pressure was even greater in black and Asian populations.

Moore et al. [59] in their study addressing the effect of low sodium intake on the blood pressure levels among Framingham Offspring Study adults even found paradoxical results. These authors analyzed dietary data from 2632 subjects (normotensive men and women) aged 30–64 years old who were part of the Framingham Offspring Study. Over 16 years of follow-up, systolic and diastolic blood pressures decreased with increasing sodium intake (≥2.5 g). Mean systolic and diastolic blood pressures of 129.5 mmHg and 75.6 mmHg, respectively, were seen among subjects in the high-sodium and high-potassium (≥2.3 g) groups compared with 135.4 mmHg and 79.0 mmHg, respectively, among people in the low-sodium (<2.5 g) and low-potassium (<2.3 g) groups.

6. Possible mechanisms of the effect of sodium intake reduction on arterial stiffness

Animal studies of hypertension demonstrate that elevated salt consumption can increase arterial stiffness and this effect is independent of BP as reviewed by Safar et al. [52]. On the other hand, reduced dietary sodium has been shown to lower arterial stiffness in humans with hypertension [27, 60]. Cross-sectional studies in humans have provided evidence of an independent effect of salt on arterial stiffness.

Experimental studies on animal models did show that changes in sodium intake have effects on arterial structure and function independent of blood pressure [18, 61]. Studies carried out in normotensive rats have shown that these changes might be associated with increased production of transforming growth factor-beta 1 (TGF-β1), decreased endothelial nitric oxide synthase expression, and reduced bioavailability of endothelial nitric oxide induced by a high-salt diet [18, 37, 61–63]. TGF-β is a family of three pleiotropic growth factors that have complex effects on cell growth and differentiation and organ development, but they are particularly important in the expression of extracellular matrix proteins and vascular and renal fibrosis promotion in a variety of disease states [64]. The TGF-β1 is considered the most important mammalian TGF-β family member synthesized by many cell types including endothelium. It is secreted by endothelium acting, basically, on adjacent vascular smooth muscle and seems to be involved in blood pressure regulation [37].

The reduction of salt intake in the diet can affect the vascular properties by reducing the production of TGF-β. The study by Grigorova et al. [37] has investigated whether high salt intake stimulates the production of MBG, an endogenous steroidal Na^+/K^+-ATPase ligand which activates transforming growth factor-beta pro-fibrotic signaling in young normotensive rats and whether these changes can be reversed by reducing salt to a normal salt level. Their data have suggested that a decrease in salt consumption could help to restore vascular properties such as the aortic elasticity and lower the risk of cardiovascular disease by reducing the production of the pro-fibrotic factor MBG.

The local renin-angiotensin-aldosterone system (RAAS) is believed to be one of the most important mediators of vascular wall elasticity at the heart, vessels, and kidneys [19, 65]. At the cardiovascular system, high sodium intake increases the AT1 receptor expression and promotes vascular damage [19]. Evidence from experimental studies has shown that there was a decrease in aortic collagen accumulation and improvement of vascular, cardiac, and renal function and an AT1 receptor blocker during the high salt intake diet [12, 19, 66]. Additionally, high sodium intake has been reported to increase the vascular angiotensin-converting enzyme levels, which opposes to the effects of concomitant renin suppression [67]. Studies carried out in hypertensive subjects found gene polymorphisms of aldosterone synthase enzyme and AT1 receptor that was significantly associated with higher PWV [68, 69].

Stocker et al. [70] in their study discussing the recent evidence to support the role of plasma or cerebrospinal fluid hypernatremia as a key mediator of sympathoexcitation and elevated blood pressure have found that both experimental and clinical studies suggested that a high dietary salt increases plasma and cerebrospinal fluid sodium concentration. Sodium concentration variation modulates the sympathetic neurons in rostral medulla by activating the osmoreceptors in the rostral nervous system that is responsible for the tone of basal sympathetic vasomotor [70–73].

The evidence also point outs the high dietary salt intake is one of the most important factors to the activation of the sympathetic nervous system, which is one of the main contributing factors for the pathogenesis of salt-sensitive hypertension [69, 74]. Although not well understood, it is proposed that increased salt intake causes salt retention and raises plasma sodium chloride concentrations, which activates sodium/osmoreceptors to trigger sympathoexcitation [75]. Some studies have suggested that vascular properties such as arterial compliance may be affected by sympathetic nervous activity, independently of its effects on BP [76]. Therefore, the reduction of salt intake decreases the excitability of the sympathetic nervous system and interferes with its effects on vascular properties reducing the arterial stiffness.

7. Conclusions

Health recommendations and most clinical studies have been focused on the adverse effects of salt dietary on blood pressure. However, evidence to support a deleterious effect of dietary salt on endothelial function and arterial stiffness independent of BP is increasing. The mechanisms responsible continue to be elucidated. Endothelial dysfunction and increased arterial stiffness are predictors of cardiovascular disease, and data from clinical trials have indicated that both are associated with incident hypertension. Therefore, reducing excessive salt intake in the diet should be considered important for overall vascular health in addition to blood pressure control.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Bromfield S, Muntner P. High blood pressure: The leading global burden of disease risk factor and the need for worldwide prevention programs. Current Hypertension Reports. 2013;**15**(3):134-136. DOI: 10.1007/s11906-013-0340-9

[2] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. Lancet. 2005;**365**:217-223. DOI: 10.1016/S0140-6736(05)17741-1

[3] Kelly J, Khalesi S, Dickinson K, Hines S, Coombes JS, Todd AS. The effect of dietary sodium modification on blood pressure in adults with systolic blood pressure less than 140 mmHg: A systematic review. JBI Database of Systematic Reviews and Implementation Reports. 2016;**14**(6):196-237. DOI: 10.11124/jbisrir-2016-002410

[4] National Heart Foundation of Australia. Heart Foundation Guideline for the Diagnosis and Management of Hypertension in Adults. 2016. Available from: http://heartfoundation.org.au/for-professionals/clinical-information/hypertension

[5] National Health and Medical Research Council. Australian Guidelines Dietary Eat for Health. Australian Dietary Guidelines. 2013. Available from: https://www.nutritionaustralia.org/national/resource/australian-dietary-guidelines-2013

[6] Guyton AC. The surprising kidney-fluid mechanism for pressure control—Its infinite gain! Hypertension. 1990;**16**(6):725-730. DOI: 10.1161/01.hyp.16.6.725

[7] Guyton AC. Blood pressure control—Special role of the kidneys and body fluids. Science. 1991;**252**(5014):1813-1816. DOI: 10.1126/science.2063193

[8] Cappuccio FP, Markandu ND, Carney C, Sagnella GA, MacGregor GA. Double-blind randomised trial of modest salt restriction in older people. Lancet. 1997;**350**(9081):850-854. DOI: 10.1016/S0140-6736(97)02264-2

[9] Strazzullo P. Reducing sodium and increasing potassium intake. British Medical Journal. 2013;**346**:f2195. DOI: 10.1136/bmj.f2195

[10] Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: Systematic review and meta-analyses. British Medical Journal. 2013;**346**:f1326. DOI: 10.1136/bmj.f1326

[11] Yu HCM, Burrell LM, Black MJ, Wu LL, Dilley RJ, Cooper ME, et al. Salt induces myocardial and renal fibrosis in normotensive and hypertensive rats. Circulation. 1998;**98**(23):2621-2628. DOI: 10.1161/01.cir.98.23.2621

[12] Matavelli LC, Zhou X, Varagic J, Susic D, Frohlich ED. Salt loading produces severe renal hemodynamic dysfunction independent of arterial pressure in spontaneously hypertensive rats. American Journal of Physiology-Heart and Circulatory Physiology. 2007;**292**(2):H814-H819. DOI: 10.1152/ajpheart.00671.2006

[13] He FJ, Li J, MacGregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. British Medical Journal. 2013;**346**:f1325. DOI: 10.1136/bmj.f1325

[14] D'Elia L, Rossi G, Di Cola MS, Savino I, Galletti F, Strazzullo P. Meta-analysis of the effect of dietary sodium restriction with or without concomitant renin-angiotensin-aldosterone system–inhibiting treatment on albuminuria. Clinical Journal of the American Society

of Nephrology. 2015;**10**(9):1542-1552. DOI: 10.2215/CJN.09110914

[15] Meneton P, Jeunemaitre X, De Wardener HE, Macgregor GA. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiological Reviews. 2005;**85**(2):679-715. DOI: 10.1152/physrev.00056.2003

[16] Safar ME, Temmar M, Kakou A, Lacolley P, Thornton SN. Sodium intake and vascular stiffness in hypertension. Hypertension. 2009;**54**:203-209. DOI: 10.1161/HYPERTENSIONAHA.109.129585

[17] Park S, Park JB, Lakatta EG. Association of central hemodynamics with estimated 24-h urinary sodium in patients with hypertension. Journal of Hypertension. 2011;**29**(8):1502-1507. DOI: 10.1097/HJH.0b013e3283486311

[18] Ying WZ, Sanders PW. Dietary salt increases endothelial nitric oxide synthase and TGF-β1 in rat aortic endothelium. American Journal of Physiology-Heart and Circulatory Physiology. 1999;**277**(4):H1293-H1298. DOI: 10.1152/ajpheart.1999.277.4.H1293

[19] Nickenig G, Strehlow K, Roeling J, Zolk O, Knorr A, Böhm M. Salt induces vascular AT1 a receptor overexpression in vitro and in vivo. Hypertension. 1998;**31**(6):1272-1277. DOI: 10.1161/01.hyp.31.6.1272

[20] Et-Taouil K, Schiavi P, Lévy BI, Plante GE. Sodium intake, large artery stiffness, and proteoglycans in the spontaneously hypertensive rat. Hypertension. 2001;**38**:1172-1176. DOI: 10.1161/hy1101.96740

[21] Ni Z, Vaziri ND. Effect of salt loading on nitric oxide synthase expression in normotensive rats. American Journal of Hypertension. 2001;**14**(2):155-163. DOI: 10.1016/s0895-7061(00)01234-6

[22] Dickinson KM, Keogh JB, Clifton PM. Effects of a low-salt diet on flow-mediated dilatation in humans. The American Journal of Clinical Nutrition. 2009;**89**(2):485-490. DOI: 10.3945/ajcn.2008.26856

[23] Todd AS, MacGinley RJ, Schollum JBW, Williams SM, Sutherland WHF, Mann JI, et al. Dietary sodium loading in normotensive healthy volunteers does not increase arterial vascular reactivity or blood pressure. Nephrology. 2012;**17**(3):249-256. DOI: 10.1111/j.1440-1797.2011.01550.x

[24] McMahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Johnson DW, et al. A randomized trial of dietary sodium restriction in CKD. Journal of the American Society of Nephrology. 2013;**24**(12):2096-2103. DOI: 10.1681/ASN.2013030285

[25] Gijsbers L, Dower JI, Mensink M, Siebelink E, Bakker SJL, Geleijnse JM. Effects of sodium and potassium supplementation on blood pressure and arterial stiffness: A fully controlled dietary intervention study. Journal of Human Hypertension. 2015;**29**(10):592-598. DOI: 10.1038/jhh.2015.3

[26] D'Elia L, Galletti F, Fata EL, Sabino P, Strazzullo P. Effect of dietary sodium restriction on arterial stiffness: Systematic review and meta-analysis of the randomized controlled trials. Journal of Hypertension. 2018;**36**(4):734-743. DOI: 10.1097/HJH.0000000000001604

[27] Todd AS, MacGinley RJ, Schollum JBW, Johnson RJ, Williams SM, Sutherland WHF, et al. Dietary salt loading impairs arterial vascular reactivity. The American Journal of Clinical Nutrition. 2010;**91**(3):557-564. DOI: 10.3945/ajcn.2009.28645

[28] Larson C, Vaidya A, Williams JS. Influence of dietary sodium modulation

on electrocardiographic voltage criteria for left ventricular hypertrophy in normotensive individuals. Journal of Investigative Medicine. 2012;**60**(1):39-43. DOI: 10.2310/JIM.0b013e31823d05ab

[29] Krekels M, Kroon A, de Leeuw P. Sodium intake as a modulator of kidney function. Current Hypertension Reviews. 2015;**11**(1):57-60. DOI: 10.2174/1573402111666150530204512

[30] WHO. Guideline: Sodium Intake for Adults and Children. World Health Organization; 2012. Available from: https://apps.who.int/iris/handle/10665/77985

[31] World Health Organization. Mapping Salt Reduction Initiatives in the WHO European Region. Europe: WHO Regional Office; 2013. Available from: https://www.knowledge-action-portal.com/en/content/mapping-salt-reduction-initiatives-who-european-region

[32] McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: Differential effects on wave reflection and aortic pulse wave velocity—The Anglo-Cardiff Collaborative Trial (ACCT). Journal of the American College of Cardiology. 2005;**46**(9):1753-1760. DOI: 10.1016/j.jacc.2005.07.037

[33] Cecelja M, Jiang B, McNeill K, Kato B, Ritter J, Spector T, et al. Increased wave reflection rather than central arterial stiffness is the main determinant of raised pulse pressure in women and relates to mismatch in arterial dimensions. A twin study. Journal of the American College of Cardiology. 2009;**54**(8):695-703. DOI: 10.1016/j.jacc.2009.04.068

[34] He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, et al. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in White, Black, and Asian mild hypertensives. Hypertension. 2009;**54**(3):482-488. DOI: 10.1161/HYPERTENSIONAHA.109.133223

[35] Avolio AP, Clyde KM, Beard TC, Cooke HM, Ho KK, O'Rourke MF. Improved arterial distensibility in normotensive subjects on a low salt diet. Arteriosclerosis. 1986;**6**(2):166-169. DOI: 10.1161/01.atv.6.2.166

[36] Baldo MP, Brant LCC, Cunha RS, Molina MDCB, Griep RH, Barreto SM, et al. The association between salt intake and arterial stiffness is influenced by a sex-specific mediating effect through blood pressure in normotensive adults: The ELSA-Brasil study. Journal of Clinical Hypertension (Greenwich, Conn.). 2019;**21**(12):1771-1779. DOI: 10.1111/jch.13728

[37] Grigorova YN, Wei W, Petrashevskaya N, Zernetkina V, Juhasz O, Fenner R, et al. Dietary sodium restriction reduces arterial stiffness, vascular TGF-β-dependent fibrosis and marinobufagenin in young normotensive rats. International Journal of Molecular Sciences. 2018;**19**(10):3168. DOI: 10.3390/ijms19103168

[38] Granger JP. Pressure natriuresis. Role of renal interstitial hydrostatic pressure. Hypertension. 1992;**19**(suppl I):I9-I17. DOI: 10.1161/01.HYP.19.1_Suppl.I9

[39] Laurent S, London G, Marchais S, Pannier B, Safar M. Vascular compliance in hypertension: Therapeutic implications. Journal of Cardiovascular Pharmacology. 1987;**8**(3):208-213. DOI: 10.1007/s11892-008-0036-8

[40] Tarazi RC. Hemodynamic role of extracellular fluid in hypertension. Circulation Research. 1976;**38**(6 Suppl 2):73-83. DOI: 10.1161/01.res.38.6.73

[41] De Wardener HE, MacGregor GA. Sodium and blood pressure. Current Opinion in Cardiology. 2002;**17**(4):360-367

[42] Guyton AC. Kidneys and fluids in pressure regulation: Small volume but large pressure changes. Hypertension. 1992;**19**(1 Suppl):I2-I8. DOI: 10.1161/01.hyp.19.1_suppl.i2

[43] Safar ME, London GM. Arterial and venous compliance in sustained essential hypertension. Hypertension. 1987;**10**(2):133-139. DOI: 10.1161/01.hyp.10.2.133

[44] Safar ME, London GM, Levenson JA, Simon AC, Chau NP. Rapid dextran infusion in essential hypertension. Hypertension. 1979;**1**:615-623. DOI: 10.1161/01.HYP.1.6.615

[45] Chau NP, Coleman TG, London GM, Safar ME. Meaning of the cardiac output-blood volume relationship in essential hypertension. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 1982;**243**(3):R318-R328. DOI: 10.1152/ajpregu.1982.243.3.R318

[46] Simon G, Illyes G, Csiky B. Structural vascular changes in hypertension: Role of angiotensin II, dietary sodium supplementation, blood pressure, and time. Hypertension. 1998;**32**(4):654-660. DOI: 10.1161/01.hyp.32.4.654

[47] Thakali KM, Galligan JJ, Fink GD, Watts SW. Arterial and venous function in hypertension. In: Lip GYH, Hall JE, editors. Comprehensive Hypertension. Edinburgh, United Kingdom: Elsevier; 2007:205-212. DOI: 10.1016/B978-0-323-03961-1.50022-2

[48] Samuel SA, Francis AO, Anthony OO. Role of the kidneys in the regulation of intra- and extra-renal blood pressure. Annals of Clinical Hypertension. 2018;**2**:048-058. DOI: 10.29328/journal.ach.1001011

[49] Grillo A, Salvi L, Coruzzi P, Salvi P, Parati G. Sodium intake and hypertension. Nutrients. 2019;**11**(9):1970. DOI: 10.3390/nu11091970

[50] Safar ME, Asmar RG, Benetos A, London GM, Lévy BI. Sodium, large arteries and diuretic compounds in hypertension. Journal of Hypertension. 1992;**10**(6):S133-S136

[51] Safar M, Laurent S, Safavian A, Pannier B, Asmar R. Sodium and large arteries in hypertension. Effects of indapamide. American Journal of Medicine. 1988;**84**(1B):15-19

[52] Denton D, Weisinger R, Mundy NI, Wickings EJ, Dixson A, Moisson P, et al. The effect of increased salt intake on blood pressure of chimpanzees. Nature Medicine. 1995;**1**(10):1009-1016. DOI: 10.1038/nm1095-1009

[53] Safar ME, Thuilliez C, Richard V, Benetos A. Pressure-independent contribution of sodium to large artery structure and function in hypertension. Cardiovascular Research. 2000;**46**(2):269-276. DOI: 10.1016/s0008-6363(99)00426-5

[54] Benetos A, Levy BI, Lacolley P, Taillard F, Duriez M, Safar ME. Role of angiotensin II and bradykinin on aortic collagen following converting enzyme inhibition in spontaneously hypertensive rats. Arteriosclerosis, Thrombosis, and Vascular Biology. 1997;**17**(11):3196-3201. DOI: 10.1161/01.atv.17.11.3196

[55] Partovian C, Benetos A, Pommiès JP, Mischler W, Safar ME. Effects of a chronic high-salt diet on large artery structure: Role of endogenous bradykinin. The American Journal of Physiology. 1998;**274**(5):H1423-H1428. DOI: 10.1152/ajpheart.1998.274.5.H1423

[56] Mercier N, Labat C, Louis H, Cattan V, Benetos A, Safar ME, et al. Sodium, arterial stiffness, and cardiovascular mortality in hypertensive rats. American Journal of Hypertension. 2007;**20**(3):319-325. DOI: 10.1016/j.amjhyper.2006.09.002

[57] Avolio AP, Fa-Quan D, Wei-Qiang L. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: Comparison between urban and rural communities in China. Circulation. 1985;**71**(2):202-210. DOI: 10.1161/01.cir.71.2.202

[58] Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database of Systematic Reviews. 2017;(4) Art. No.: CD004022. DOI: 10.1002/14651858.CD004022.pub4

[59] Moore LL, Singer MR, Bradlee MR. Low sodium intakes are not associated with lower blood pressure levels among Framingham Offspring study adults. The FASEB Journal. 2017;**31**(1_supplement):446.6

[60] Gates PE, Tanaka H, Hiatt WR, Seals DR. Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. Hypertension. 2004;**44**(1):35-41. DOI: 10.1161/01.HYP.0000132767.74476.64

[61] Ying WZ, Sanders PW. Dietary salt modulates renal production of transforming growth factor-β in rats. American Journal of Physiology-Heart and Circulatory Physiology. 1998;**274**(4):F635-F641. DOI: 10.1152/ajprenal.1998.274.4.F635

[62] Matsuoka H, Itoh S, Kimoto M, Kohno K, Tamai O, Wada Y, et al. Asymmetrical dimethylarginine, an endogenous nitric oxide synthase inhibitor, in experimental hypertension. Hypertension. 1997;**29**(1 Pt 2):242-247. DOI: 10.1161/01.hyp.29.1.242

[63] Edwards DG, Farquhar WB. Vascular effects of dietary salt. Current Opinion in Nephrology and Hypertension. 2015;**24**(1):8-13. DOI: 10.1097/MNH.0000000000000089

[64] Border WA, Okuda S, Languino LR, Sporn MB, Ruoslahti E. Suppression of experimental glomerulonephritis by antiserum against transforming growth factor beta 1. Nature. 1990;**346**(6282):371-374. DOI: 10.1038/346371a0

[65] Derynck R, Jarrett JA, Chen EY, et al. Human transforming growth factor-beta complementary DNA sequence and expression in normal and transformed cells. Nature. 1985;**316**(6030):701-705. DOI: 10.1038/316701a0

[66] Frohlich ED. The salt conundrum: A hypothesis. Hypertension. 2007;**50**(1):161-166. DOI: 10.1161/HYPERTENSIONAHA.107.088328

[67] Kocks MJA, Buikema H, Gschwend S, Boomsma F, De Zeeuw D, Navis G. High dietary sodium blunts effects of angiotensin-converting enzyme inhibition on vascular angiotensin I-to-angiotensin II conversion in rats. Journal of Cardiovascular Pharmacology. 2003;**42**(5):601-606. DOI: 10.1097/00005344-200311000-00004

[68] Pojoga L, Gautier S, Blanc H, Guyene TT, Poirier O, Cambien F, et al. Genetic determination of plasma aldosterone levels in essential hypertension. American Journal of Hypertension. 1998;**11**(7):856-860. DOI: 10.1016/s0895-7061(98)00048-x

[69] Benetos A, Gautier S, Ricard S, Topouchian J, Asmar R, Poirier O, et al.

Influence of angiotensin-converting enzyme and angiotensin II type 1 receptor gene polymorphisms on aortic stiffness in normotensive and hypertensive patients. Circulation. 1996;**94**(4):698-703. DOI: 10.1161/01.cir.94.4.698

[70] Stocker SD, Monahan KD, Browning KN. Neurogenic and sympathoexcitatory actions of NaCl in hypertension. Current Hypertension Reports. 2013;**15**(6):538-546. DOI: 10.1007/s11906-013-0385-9

[71] Bourque CW. Central mechanisms of osmosensation and systemic osmoregulation. Nature Reviews. Neuroscience. 2008;**9**(7):519-531. DOI: 10.1038/nrn2400

[72] Brooks VL, Freeman KL, O'Donaughy TL. Acute and chronic increases in osmolality increase excitatory amino acid drive of the rostral ventrolateral medulla in rats. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2004;**287**(6):R1359-R1368. DOI: 10.1152/ajpregu.00104.2004

[73] Weiss ML, Claassen DE, Hirai T, Kenney MJ. Nonuniform sympathetic nerve responses to intravenous hypertonic saline infusion. Journal of the Autonomic Nervous System. 1996;**57**(1-2):109-115. DOI: 10.1016/0165-1838(95)00108-5

[74] Simmonds SS, Lay J, Stocker SD. Dietary salt intake exaggerates sympathetic reflexes and increases blood pressure variability in normotensive rats. Hypertension. 2014;**64**(3):583-589. DOI: 10.1161/HYPERTENSIONAHA.114.03250

[75] Brooks VL, Haywood JR, Johnson AK. Translation of salt retention to central activation of the sympathetic nervous system in hypertension. Clinical and Experimental Pharmacology & Physiology. 2005;**32**(5-6):426-432. DOI: 10.1111/j.1440-1681.2005.04206.x

[76] Mangoni AA, Mircoli L, Giannattasio C, Mancia G, Ferrari AU. Effect of sympathectomy on mechanical properties of common carotid and femoral arteries. Hypertension. 1997;**30**(5):1085-1088. DOI: 10.1161/01.hyp.30.5.1085