Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Invited Review

J Hypertens Res (2019) 5(2):65–74

Salt and Hypertension

Adrian Covic[1], Stefana Catalina Bilha[2*], Dragos Scripcariu[3], Mehmet Kanbay[4]

[1]Nephrology Department, Dialysis and Renal Transplant Center, "C.I. Parhon" University Hospital, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[2]Endocrinology Department, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[3]Surgery Department, Regional Institute of Oncology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[4]Department of Medicine, Division of Nephrology, Koc University School of Medicine, Istanbul, Turkey

Received: March 16, 2019, Accepted: June 3, 2019

Abstract

Excessive salt intake is a modifiable risk factor for arterial hypertension and cardiovascular diseases – the main cause of death worldwide. However, the underlying mechanisms still lack full comprehension, as novel hypotheses challenge the fundamental Guytonian view of hypertension, according to which salt-sensitive sustained hypertension occurs only if there is a certain degree of sodium excretion impairment. According to the vasodysfunction theory, it is rather the aberrant vascular resistance that initiates arterial hypertension in response to salt loading. The 3-compartment model of sodium distribution was also proposed to mediate salt-induced hypertension: the skin seems to mimic the renal countercurrent system, with sodium deposition and hypertonicity mediated by the macrophages, thus supporting the homeostatic and blood pressure (BP) regulatory functions of the immune cells. New perspectives brought into light the glucocorticoid-driven catabolic state in salt-sensitive hypertension, which ensures the osmotic gradient necessary for solitary sodium excretion without significant change in urine volume. Further on, salt consumption increases plasma sodium concentration and osmolarity, which in turn raises the blood pressure via copeptin and vasopressin. Extracellular overhydration in most hypertensive patients is subtle and clinically silent, while a negative hydration status improves vascular and cardiac parameters, even in non-CKD patients. We showed that salt negatively impacts blood pressure via arterial stiffness. Finally, the relationship between salt and cardiovascular disease appears U-shaped, demonstrating once again that lowering sodium diet does not follow the "one size fits it all". Ultimately this endorses using a patient –personalized approach to treat hypertension.

Keywords: hypertension, sodium, salt intake

Introduction

The daily usual sodium consumption is almost 2-fold higher than the World Health Organization (WHO) – recommended 2.0 g per day for the general population (corresponding to 5 g of salt daily) [1,2]. At the same time, excessive salt intake is a modifiable risk factor for arterial hypertension and cardiovascular diseases. In turn, these are the highest causes of mortality worldwide [2].

Strong evidence supports the beneficial effect of low dietary sodium intake for lowering blood

*Correspondence to: Dr. Stefana Catalina BILHA, MD,PhD
Endocrinology Department, "Grigore T. Popa"
University of Medicine and Pharmacy,
No. 16 University Street, 700115, Iasi, Romania.
Tel.: 0040752092550, e-mail:stefanabilha@gmail.com

pressure (BP) values (3.4 to 3.8 mm Hg for systolic and 1.5 mm Hg for diastolic BP, respectively) [1,3]. Conversely, sodium/salt intake above recommended thresholds independently increases the risk of death due to cardiovascular events (coronary heart disease and stroke) [1,3,4], and it is also linked to new-onset atrial fibrillation [5] and chronic kidney disease (CKD) [6]. As such, a 30% reduction in mean sodium intake is one of the nine global targets established by WHO [2] and a trial evaluating the efficacy of a mobile app promoting low-sodium food-items in hypertensive patients is currently ongoing [7].

Surprisingly, the bona fide association between salt, – hypertension and cardiovascular – (CV) disease, is still not completely understood. How does salt increase BP? While impaired natriuresis may lead to hypertension [8], recent re-analyses call this into question. Numerous critiques have been raised regarding the classic Guytonian [9] view of hypertension, according to which sodium excretion by the kidney eventually sets the rules for long-term changes in BP. This review aims to address recent novel theories in salt-sensitive hypertension.

The classic Guytonian model

Sodium is the main extracellular cation with a critical role in body fluid regulation. The sodium and water balance homeostasis is maintained by: [1] thirst/antidiuretic hormone, [2] the renin-angiotensin-aldosterone system with vasoactive properties and [3] the kidney – via natriuresis [10]. Fluid balance determines the cardiac output, one of the two definers of arterial BP (the other being represented by peripheral resistance) [11].

In 1972, Guyton [9] proposed a rigorous, calculus-based mathematical model for circulatory and kidney dynamics, according to which renal pressure natriuresis is the crucial event in the genesis of salt-induced hypertension (Figure 1). It is still considered a cornerstone of hypertension pathogenesis [12]: excessive salt intake stimulates thirst-induced high fluid intake, thus leading to an increased blood volume and high cardiac output [9]. These transient changes are not accompanied, however, by a proportional increase in arterial pressure, due to compensatory mechanisms that come into play: baroreceptor activation followed by sympathetic nervous system depression and a decrease in peripheral arterial resistance due to the vasodilator stretching effect of the initially elevated BP [9]. Further on, baroreceptors start to adapt, leading to the recovery of sympathetic activity, while the long-term excessive blood flow leads to constriction and increased peripheral artery resistance, all favoring BP increase [9]. This is when the fundamental role of the kidney is revealed: pressure natriuresis promotes sodium excretion, leading to extracellular fluid contraction and return of the BP to the homeostatic point.

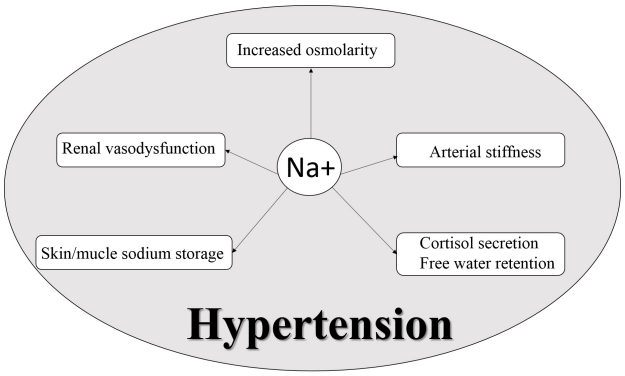

Figure 1. Guytonian model of salt-sensitive hypertension

Thus, Guyton salt-sensitive sustained hypertension occurs only if there is a certain degree of sodium excretion impairment (the "natriuretic handicap"[13]): genetic or acquired kidney dysfunction requests higher BP values in order to maintain efficient pressure natriuresis and sodium homeostasis [14,15]. The sodium balance is maintained at the expense of increased renal perfusion pressure, leading to end-organ damage [16].

This fundamental model has recently been challenged by data demonstrating a pivotal role for the vascular response to salt, the existence of a third salt-storage compartment, by novel mechanisms of salt excretion or by the sodium-osmolality-hypertension theory (Figure 2), as discussed below [14].

Changing landscape

1. The renal vaso-dysfunction theory

The natriuretic dysfunction theory has recently been challenged by Kurtis et al. [17], starting from the simple observation that salt-sensitive

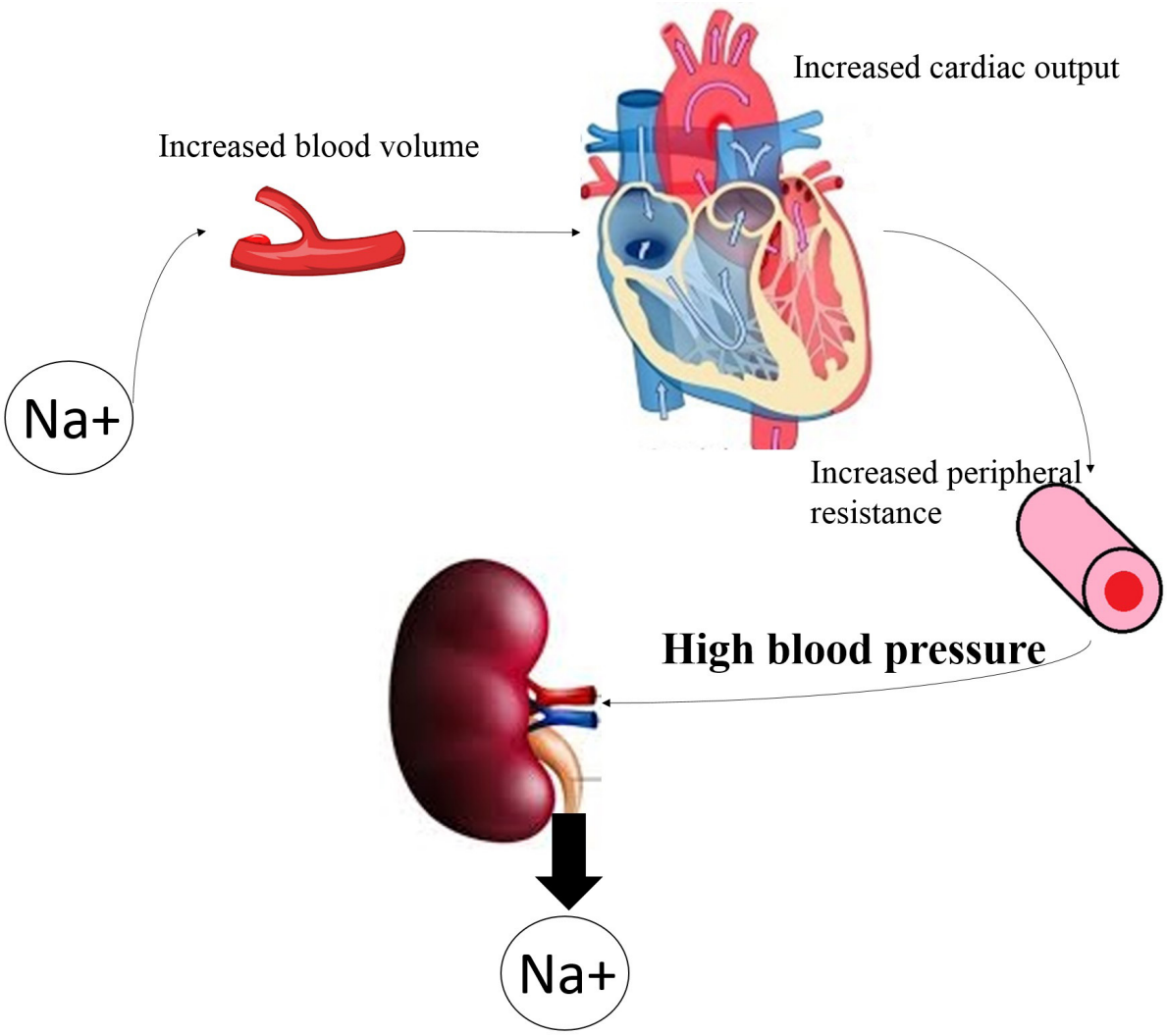

Figure 2. Changing landscape – novel theories regarding salt-sensitive hypertension

hypertensive subjects usually do not have impaired sodium excretion. Therefore, these patients have greater cumulative sodium retention compared to normotensive salt-resistant controls [18,19]. Moreover, there seem to be no significant differences in terms of cardiac output between salt-sensitive hypertensives and normal salt-resistant controls [17]. Salt has proven to be independently linked to cardiovascular events, suggesting a detrimental vascular effect beyond those mediated by salt-sensitive high BP [4,13]. These observations are the foundation of the vaso-dysfunction theory proposed by Kurtz et al. [13,17], focusing on the aberrant vascular resistance that initiates arterial hypertension in response to salt loading, rather than the subnormal sodium excretion [20].

It is still the kidney that initiates the vicious cycle, this time through an impairment of renal vasodilation. Indeed, renal vascular resistance is abnormally increased in salt-sensitive hypertensive subjects compared to normal BP salt-resistant individuals [17] and also directly related to the rise in BP values. Moreover, renal vascular dysfunction increases the systemic vascular resistance, initiating salt-induced hypertension according to Kurtz et al. [13].

Animal models have demonstrated a salt-mediated impairment of nitric oxide (NO) synthesis, with activation of the endothelin system and renal vasoconstriction [21]. The role of salt-induced NO impairment was confirmed by Hoffmann et al. [22], who demonstrated that NO polymorphism synthase increases BP sensitivity to salt in susceptible individuals [22]. Salt may also interfere with the metabolism of asymmetric dimethylarginine (ADMA), which in turn inhibits NO production

and thus promotes vascular dysfunction and BP rise [19,23–25]. Last but not least, the plasma sodium increase augments the activity of sodium channels in the endothelial cells, leading to endothelial cell stiffness and impaired NO bioavailability [13,26,27].

In support of the central role of the kidney in the genesis of hypertension lies the older theory according to which "kidney transplantation transfers hypertension". According to the kidney cross-transplantation studies performed by Dahl on salt-sensitive and salt-resistant rats, the pro-hypertensive genotype of the donor kidney will determine a significant BP increment in a genetically normotensive recipient and vice versa: the transplantation of a "normotensive" kidney will successfully cure hypertension in the recipient [28]. The post-transplantation pressor effect of the kidney is caused by an increase in sodium reabsorption in the proximal tubule together with an increased vascular resistance in the preglomerular vessels [29]. Although much harder to prove in humans, old clinical studies support this observation in human kidney transplant recipients, also [30]. As BP in recipients themselves may rise due to numerous factors after transplantation, Guidi et al.[31] compared kidney graft recipients according to their family history of hypertension. In patients with a familial "normotensive" kidney, the transplantation of a "hypertensive" kidney increased by 10-fold the requirement of anti-hypertensive medication.

Although the kidney hypertension transplantation hypothesis was afterwards revisited by Churchill et al. who demonstrated that extrarenal genotype variants also contribute to the inherited BP regulation [32], recent data still support the correction of hypertension after transplantation if the renal graft is received from an unrelated donor [33].

Finally, the renal vasodysfunction theory does not preclude increased sodium load and cardiac output – which appear to be physiological consequences of an excessive sodium diet in both salt-sensitive hypertensive patients and in normotensive salt-resistant subjects [13].

2. A third salt-storage compartment: the skin

Classical sodium homeostasis was challenged by Titze et al.[34], who demonstrated that sodium storage takes place in the skin – the 3-compartment model. Thus, electrolyte balance also relies on extrarenal regulatory pathways that do not respect the traditional general belief that electrolyte concentrations are equilibrated between blood and the interstitium [14]. The skin seems to mimic the renal countercurrent system, with sodium deposition and hypertonicity [35–37]. In response to sodium overload, macrophages act as local osmosensors and activate tonicity-responsive enhancer-binding protein (TONEBP/NFAT5) – a transcription factor for vascular endothelial growth factor C (VEGFC), which in turn reconstitutes the local lymphatic capillary network in order to increase electrolyte clearance and also promotes NO synthesis [37]. In TONEBP or VEGFC – deficient models, the exposure to a high-salt diet increases BP values [37,38]. This theory supports the homeostatic and BP regulatory functions of the immune cells. Interestingly, age is associated with decreased VEGFC circulating levels in hemodialysis patients. Moreover, older hemodialysis patients proved to have higher skin and muscle sodium storage and lower VEGFC concentrations compared to age-matched healthy controls. Hemodialysis was more efficient in removing sodium from the skin in patients that had higher VEGFC levels [39].

Laffer et al.[40] observed that salt-sensitive normotensives not only have an impaired vasodilator response to sodium loading, but also gain weight and fail to fully correct water retention after salt deprivation. On the contrary, salt-resistant normotensives do not exhibit weight gain [40]. Hence, salt and water retention in the interstitial compartment may relate to vascular dysfunction in salt-sensitive hypertension; this mechanism may be more meaningful in men, as they tend to store more sodium in the skin compared to women [14,40,41].

Moreover, sodium and water kinetics are highly variable between patients, depending on osmotic set point and diet [41]. Following hypertonic saline infusion in healthy individuals, approximately one half of the sodium is excreted in the urine, the remainder being stored in skin and muscle [42]. In the dialysis population, a perfect model for sodium and water assessment (see below), prescribing individualized dialysis sodium improves not only dry weight and blood pressure, but also the clinical perception, with diminished thirst and salt and water intake in these patients [41,43,44].

In this regard, ^{23}NaMRI is currently developing as an experimental tool to quantify tissue sodium in dialysis patients [41].

3. How do the kidneys excrete salt when the intake is high? New perspectives

A 6g/day dietary salt increase leads to a reduction of free water excretion with subsequent water retention [45]. This may be explained by the increased circulating cortisol in salt-sensitive subjects, compared to normotensive salt-resistant individuals who have decreased plasma cortisol [46]. An increase in sodium concentration of the cerebrospinal fluid triggers the secretion of oubain-like substances in the hypothalamus, consequently activating the adrenals and also the sympathetic nervous system [41]. The glucocorticoid-driven catabolic state increases urea production and recycling in order to ensure the osmotic gradient necessary for the renal concentration mechanism, allowing solitary sodium excretion without significant changes in urine volume. Glucocorticoid action also promotes metabolic water production, leading to water retention [47].

At constant salt intake, urinary sodium excretion exhibits an about-weekly pattern and is associated with intermittent sodium storage [48]. However, total body sodium is associated with longer infradian rhythm periods that are not accompanied by significant differences in weight and extracellular fluid. Total body sodium variability is rather under rhythmic hormonal control, related to urinary aldosterone and cortisol excretion [48]. Aldosterone exhibits salt-independent about-half-weekly rhythmical secretion, promoting renal concentration-mediated free water reabsorption. This mechanism is counterbalanced by the salt-independent semiseptan rhythmical secretion of cortisol, which promotes urine dilution and water surplus excretion. This cyclic generation of a water excess under hormonal control that is exerted through the renal concentration and dilution processes demonstrates in a unique manner the autonomous component of body fluid homeostasis [45,48].

4. Sodium – osmolarity – hypertension

Salty meals significantly increase plasma sodium concentration and osmolarity, compared to low sodium diets. Salt may play a role in acutely elevating BP through its effects on plasma osmolarity, as a 1mmol/L increase in plasma sodium increases systolic BP (SBP) by at least 1.91 mm Hg in the linear regression performed by Suckling et al.[49]. To confirm this hypothesis, a recent study investigated whether the acute effect of salt on BP is blunted by maintaining a stable osmolarity through concomitant water ingestion: patients receiving 3 g of salt with and without water were compared [50]. Patients receiving soup with 3 g of salt showed a 6mOsm/L change in osmolarity, a 2.5 mmol/l increase in plasma sodium and a 10 mm Hg increase SBP after 2 hours. When on the next visit the same patients drank the same salty soup but with water loading this time, the foreseen changes in plasma osmolarity, plasma sodium and BP were prevented. Thus, the central event in salt-induced raise of BP seems to be the change in plasma osmolarity, rather than the amount of salt. Copeptin, a marker of vasopressin release, increases when osmolarity is high and is supposed to mediate the salt-osmolarity-hypertension triangle. An argument is the blunted effect of salty soup and water ingestion compared with only salty soup on copeptin secretion. Therefore, attention must be paid to the concomitant water ingestion when assessing the association between salt and hypertension [50].

Salt and water matter and the dialysis population is the perfect model to demonstrate this by combining anuria, the absence of functional kidneys and the removal of sodium/water during hemodialysis sessions. In a large cohort study of 39 566 incident end-stage renal disease (ESRD) patients from the EuCliD5 database, baseline overhydration was associated with an increased mortality risk, no matter the BP category [51]. Moreover, there was a linear relationship between the decrease in fluid overload and the decrease in SBP before dialysis ($r=0.55$, $p<0.001$) [52]. The EuroBCM study cohort also demonstrated a high frequency of hypervolemia among peritoneal dialysis patients and the misleading interpretation of BP values in evaluating volume status. In this context, dietary measures along with individualized dialysis prescription should be part of the routine medical care in order to avoid hypervolemia [53]. A pilot randomized controlled trial performed in

our center showed that bioimpedance-guidance is superior to clinical judgement-guided ultrafiltration for strict volume control in terms of improving arterial stiffness and systolic BP in hemodialysis patients [54].

High BP values are associated with bioimpedance-proven increased extracellular water in the general population, too [55]. Negative hydration status leads to significantly lower systolic and diastolic BP values, decreased carotid intima-media thickness, higher flow-mediated dilation arteries and lower left ventricular mass index and end-diastolic diameter in primary non-CKD hypertensive patients [56].

As extracellular overhydration in most hypertensive patients is subtle and clinically unapparent, our group proposed a new paradigm for the routine management of hypertension: office BP measurement with concurrent bioimpedance volume assessment. Our algorithm stratifies patients into four categories depending on volume and BP, thus allowing tailored antihypertensive treatment in order to minimize end-organ damage [57].

5. Sodium, arterial stiffness, renal function

Salt-sensitive individuals are unable to modulate peripheral vascular resistance in response to salt loading (vasodilation) and depletion (vasoconstriction), possibly due to the high ratio between alfa- and beta-adrenoreceptors that occurs secondary to high sodium intake or due to the increased interstitial compartment sodium storage in these subjects (see above) [41].

As already discussed above, rigorous salt and water restriction ameliorates arterial stiffness in both ESRD and primary hypertensive non-CKD patients [54,55]. We tested whether the effect of sodium upon SBP is mediated by arterial stiffness or by the estimated glomerular filtration rate (eGFR) on 1599 adults without CKD from the SEPHAR III study. In this study, urinary sodium excretion was found to influence SBP both directly and indirectly: the pulse wave velocity (PWV) – mediated effect of urinary sodium upon BP accounts for 23.9% of the total effect in hypertensive patients. Furthermore, PWV also impacts the eGFR and has its own effects on the SBP. When taking this into account, the overall indirect effect mediated by PWV and PWV-induced eGFR changes accounts for 27.7% of the total effect of urinary sodium upon SBP in hypertensive patients [58]. These relationships were somewhat similar in normotensive patients, but the effect was less pronounced in normotensive patients [58].

Treatment considerations

A 4.4 g of salt (1.75 g of sodium) reduction in daily intake is associated with a mean 4.2/2.1 mm Hg reduction in SBP/diastolic BP (DBP) in the general population, as demonstrated by a meta-analysis of 34 trials [59]. The effect of salt restriction is more pronounced in the elderly (>45 years), in hypertensives compared with normotensives (-5.4/-2.8 mm Hg change in SBP/DBP), in patients with medication-resistant hypertension (-22.7/-9.1 mm Hg change in SBP/DBP) and in diabetics (-5 mm Hg change in SBP) [59–62].

A very recent network meta-analysis performed on 25 studies comparing the efficacy of antihypertensive agents in salt-sensitive hypertension found that in the case of non-obese salt-sensitive hypertensive patients, calcium channel blockers combined with thiazides and moderate salt intake was the optimal choice for reducing BP. On the other side, in obese salt-sensitive hypertensives, calcium channel blockers together with metformin and moderate salt intake was the optimal therapy for decreasing BP [63].

Sodium restriction helps improve day and night SBP, proteinuria and hydration status in CKD patients as well [64,65]. When comparing the salt restriction only regimen (strict salt restriction and insistent ultrafiltration) to anti-hypertensive based strategies in hemodialysis patients, BP values were similar, but left ventricular systolic and diastolic functions were better preserved with the salt restriction regimen [66].

According to the SEPHAR III study, salt intake is significantly higher in newly diagnosed and in known but untreated/uncontrolled hypertension [67]. By lowering BP and preventing hypertension, sodium reduction should theoretically reduce cardiovascular disease, especially in the light of an independent relationship between excessive sodium consumption and adverse cardiovascular events [1,3,4]. However, the effect of reduced dietary sodium

on cardiovascular events remains unclear: a pooled analysis of 133118 individuals from 49 countries in four prospective studies demonstrated that a urinary excretion of both more than 7g/day and less than 3g/day were associated with an increased risk of mortality and cardiovascular events in hypertensive patients, suggesting a U-curve phenomenon. Interestingly, in the normotensive population, only the reduced sodium excretion was associated with an increased cardiovascular risk [68]. Thus, lowering sodium diet does not follow the "one size fits it all" and confirms our theory regarding prescribing a tailored regimen to lower BP.

Conclusions

Guyton's vision of the kidney as a central player in blood pressure regulation has stood the test of time, however as mechanisms of sodium homeostasis are better understood, portions of Guyton's work may not fully explain pathophysiology sufficient for modern hypertensive patients. This review covered three main concepts that aim to enhance upon Guyton's work; the sodium-endothelial dysfunction mechanism, the three compartment theory, and the sodium-osmolarity-hypertension or sodium-arterial stiffness-renal function theory. Further studies will ultimately determine which of these mechanisms are accepted in the treatment of this challenging disease process.

Conflict of interest

The authors confirm that there are no conflicts of interest

References

1. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, et al. Global Sodium Consumption and Death from Cardiovascular Causes. N Engl J Med. 2014; 371:624-634. doi: 10.1056/NEJMoa1304127
2. World Health Organization. Global status report on noncommunicable diseases 2014. WHO: WHO Press; 2014. ISBN 9789241564854p.
3. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ. 2013; 346:f1326. doi: https://doi.org/10.1136/bmj.f1326
4. Morimoto A, Uzu T, Fujii T, Nishimura M, Kuroda S, et al. Sodium sensitivity and cardiovascular events in patients with essential hypertension. Lancet. 1997; 350(9093):1734–7. doi: 10.1016/S0140-6736(97)05189-1
5. Pääkkö TJW, Perkiömäki JS, Silaste M-L, Bloigu R, Huikuri H V., et al. Dietary sodium intake is associated with long-term risk of new-onset atrial fibrillation. Ann Med. 2018;1–10. doi: 10.1080/07853890.2018.1546054
6. Smyth A, O'Donnell MJ, Yusuf S, Clase CM, Teo KK, et al. Sodium Intake and Renal Outcomes: A Systematic Review. Am J Hypertens. 2014;27(10):1277–84. doi: 10.1093/ajh/hpt294
7. Dorsch MP, An LC, Hummel SL. A novel just-in-time contextual mobile app intervention to reduce sodium intake in hypertension: protocol and rationale for a randomized controlled trial (LowSalt4Life Trial). JMIR Res Protoc. 2018; 7(12):e11282. doi: 10.2196/11282
8. Ivy JR, Bailey MA. Pressure natriuresis and the renal control of arterial blood pressure. J Physiol. 2014; 592(18):3955–67. doi: 10.1113/jphysiol.2014.271676
9. Guyton AC, Coleman TG, Granger HJ. Circulation: Overall Regulation. Annu Rev Physiol. 1972; 34(1):13–44. doi:10.1146/annurev.ph.34.030172.000305
10. Stolarz-Skrzypek K, Bednarski A, Czarnecka D, Kawecka-Jaszcz K, Staessen JA. Sodium and potassium and the pathogenesis of hypertension. Curr Hypertens Rep. 2013; 15(2):122–30. doi: 10.1007/s11906-013-0331-x.
11. Rust P, Ekmekcioglu C. Impact of salt intake on the pathogenesis and treatment of hypertension. 2016; 956: 61–84. doi: 10.1007/5584_2016_147
12. Oparil S, Zaman A, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med. 2003; 139:761-776.
13. Kurtz TW, DiCarlo SE, Pravenec M, Morris RC. Changing views on the common physiologic abnormality that mediates salt sensitivity and initiation of salt-induced hypertension: Japanese research underpinning the vasodysfunction theory of salt sensitivity. Hypertens Res. 2019; 42(1):6–18. doi:10.1038/s41440-018-0122-5
14. Titze J, Luft FC. Speculations on salt and the genesis of arterial hypertension. Kidney Int. 2017;91(6):1324–35. doi: 10.1016/j.kint.2017.02.034
15. Pao AC. Update on the Guytonian view of hypertension. Curr Opin Nephrol Hypertens. 2014; 23(4):391–8. doi: 10.1097/01.mnh.0000450777.17698.8e
16. Hall JE. Renal dysfunction, rather than nonrenal vascular dysfunction, mediates salt-induced hypertension.

Circulation. 2016; 133(9):894–906. doi: 10.1161/CIRCULATIONAHA.115.018526

17. Kurtz TW, DiCarlo SE, Pravenec M, Morris RC. The pivotal role of renal vasodysfunction in salt sensitivity and the initiation of salt-induced hypertension. Curr Opin Nephrol Hypertens. 2018; 27(2):83–92. doi: 10.1097/MNH.0000000000000394
18. Wedler B, Brier ME, Wiersbitzky M, Gruska S, Wolf E, et al. Sodium kinetics in salt-sensitive and salt-resistant normotensive and hypertensive subjects. J Hypertens. 1992; 10(7):663–9.
19. Schmidlin O, Forman A, Leone A, Sebastian A, Morris RC. Salt sensitivity in blacks: evidence that the initial pressor effect of NaCl involves inhibition of vasodilatation by asymmetrical dimethylarginine. Hypertension. 2011; 58(3):380–5. doi: 10.1161/HYPERTENSIONAHA.111.170175
20. Morris RC, Schmidlin O, Sebastian A, Tanaka M, Kurtz TW. Vasodysfunction that involves renal vasodysfunction, not abnormally increased renal retention of sodium, accounts for the initiation of salt-induced hypertension. Circulation. 2016; 133(9):881–93. doi: 10.1161/CIRCULATIONAHA.115.017923
21. Barton M, Vos I, Shaw S, Boer P, D'Uscio L V, et al. Dysfunctional renal nitric oxide synthase as a determinant of salt-sensitive hypertension: mechanisms of renal artery endothelial dysfunction and role of endothelin for vascular hypertrophy and glomerulosclerosis. J Am Soc Nephrol. 2000; 11(5):835–45.
22. Hoffmann IS, Tavares-Mordwinkin R, Castejon AM, Alfieri AB, Cubeddu LX. Endothelial nitric oxide synthase polymorphism, nitric oxide production, salt sensitivity and cardiovascular risk factors in Hispanics. J Hum Hypertens. 2005; 19(3):233–40. doi: 10.1038/sj.jhh.1001801
23. Vallance P, Leone A, Calver A, Collier J, Moncada S. Endogenous dimethylarginine as an inhibitor of nitric oxide synthesis. J Cardiovasc Pharmacol. 1992; 20 Suppl 12:S60-2.
24. Achan V, Broadhead M, Malaki M, Whitley G, Leiper J, et al. Asymmetric dimethylarginine causes hypertension and cardiac dysfunction in humans and is actively metabolized by dimethylarginine dimethylaminohydrolase. Arterioscler Thromb Vasc Biol. 2003; 23(8):1455–9. doi: 10.1161/01.ATV.0000081742.92006.59
25. Feng W, Dell'Italia LJ, Sanders PW. Novel paradigms of salt and hypertension. J Am Soc Nephrol. 2017; 28(5):1362–9. doi: 10.1681/ASN.2016080927
26. Warnock DG, Kusche-Vihrog K, Tarjus A, Sheng S, Oberleithner H, et al. Blood pressure and amiloride-sensitive sodium channels in vascular and renal cells. Nat Rev Nephrol. 2014; 10(3):146–57. doi: 10.1038/nrneph.2013.275
27. Kusche-Vihrog K, Tarjus A, Fels J, Jaisser F. The epithelial Na+ channel. Curr Opin Nephrol Hypertens. 2014; 23(2):143–8. doi: 10.1097/01.mnh.0000441054.88962.2c
28. Dahl KL, Heine M, Thompson K. Genetic influence of the kidneys on blood pressure: Evidence from chronic renal homografts in rats with opposite predispositions to hypertension. Circ Res. 1974; 34(1974): 94-101.
29. Cusi D, Bianchi G. Renal mechanisms of genetic hypertension: From the molecular level to the intact organism. Kidney Int. 1996; 49(1996): 1754-9.
30. Curtis JJ, Luke RG, Dustan HP, Kashgarian M, Whelchel JD, et al. Remission of essential hypertension after renal transplantation. N Engl J Med. 1983; 309(17):1009-15. doi: 10.1056/NEJM198310273091702
31. Guidi E, Menghetti D, Milani S, Montagnino G, Palazzi P et al. Hypertension may be transplanted with the kidney in humans: a long-term historical prospective follow-up of recipients grafted with kidneys coming from donors with or without hypertension in their families. J Am Soc Nephrol. 1996; 7(8):1131-8.
32. Churchill PC, Churchill MC, Bidani AK, Kurtz TW. Kidney-specific chromosome transfer in genetic hypertension: The Dahl hypothesis revisited. Kidney Int. 2001; 60(2): 705-14. doi: 10.1046/j.1523-1755.2001.060002705.x
33. Tantisattamo E, Vutthikraivit W, Sukhumthammarat W, Putthapiban P. Kidney transplantation from non-hypertensive unrelated donor: correction of post-transplant hypertension (Abstract). Circulation. 2016; 134(Suppl 1):A14093.
34. Titze J, Dahlmann A, Lerchl K, Kopp C, Rakova N, et al. Spooky sodium balance. Kidney Int. 2014; 85:759–67. doi:10.1038/ki.2013.367
35. Linz P, Santoro D, Renz W, Rieger J, Ruehle A, et al. Skin sodium measured with ^{23} Na MRI at 7.0 T. NMR Biomed. 2014; 28(1):54-62. doi: 10.1002/nbm.3224
36. Hofmeister LH, Perisic S, Titze J. Tissue sodium storage: evidence for kidney-like extrarenal countercurrent systems? Pflügers Arch – Eur J Physiol. 2015; 467(3):551–8. doi: 10.1007/s00424-014-1685-x.
37. Wiig H, Schröder A, Neuhofer W, Jantsch J, Kopp C, et al. Immune cells control skin lymphatic electrolyte homeostasis and blood pressure. J Clin Invest. 2013; 123(7):2803–15. doi: 10.1172/JCI60113

38. Machnik A, Neuhofer W, Jantsch J, Dahlmann A, Tammela T, et al. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C–dependent buffering mechanism. Nat Med. 2009; 15(5):545–52. doi: 10.1038/nm.1960
39. Dahlmann A, Dörfelt K, Eicher F, Linz P, Kopp C, et al. Magnetic resonance-determined sodium removal from tissue stores in hemodialysis patients. Kidney Int. 2015; 87(2):434–41. doi: 10.1038/ki.2014.269
40. Laffer CL, Scott RC, Titze JM, Luft FC, Elijovich F. Hemodynamics and salt-and-water balance link sodium storage and vascular dysfunction in salt-sensitive subjects. Hypertension. 2016; 68(1):195–203. doi: 10.1161/HYPERTENSIONAHA.116.07289
41. Canaud B, Kooman J, Selby NM, Taal M, Francis S, et al. Sodium and water handling during hemodialysis: new pathophysiologic insights and management approaches for improving outcomes in end-stage kidney disease. Kidney Int. 2019; 95(2): 296-309. doi: https://doi.org/10.1016/j.kint.2018.09.024
42. Olde Engberink RHG, Rorije NMG, van den Born B-JH, Vogt L. Quantification of nonosmotic sodium storage capacity following acute hypertonic saline infusion in healthy individuals. Kidney Int. 2017; 91(3):738–45. doi: 10.1016/j.kint.2016.12.004
43. Basile C, Lomonte C. A neglected issue in dialysis practice: haemodialysate. Clin Kidney J. 2015; 8(4):393–9. doi: 10.1093/ckj/sfv038
44. Raimann JG, Thijssen S, Usvyat LA, Levin NW, Kotanko P. Sodium alignment in clinical practice-implementation and implications. Semin Dial. 2011; 24(5):587–92. doi: 10.1111/j.1525-139X.2011.00973.x
45. Rakova N, Kitada K, Lerchl K, Dahlmann A, Birukov A, et al. Increased salt consumption induces body water conservation and decreases fluid intake. J Clin Invest. 2017; 127(5):1932–43. doi: 10.1172/JCI88530
46. Kerstens MN, van der Kleij FGH, Boonstra AH, Sluiter WJ, Koerts J, Navis G, et al. Salt loading affects cortisol metabolism in normotensive subjects: relationships with salt sensitivity. J Clin Endocrinol Metab. 2003; 88(9):4180–5. doi: 10.1210/jc.2002-021625
47. Kitada K, Daub S, Zhang Y, Klein JD, Nakano D, Pedchenko T, et al. High salt intake reprioritizes osmolyte and energy metabolism for body fluid conservation. J Clin Invest. 2017; 127(5):1944–59. doi: 10.1172/JCI88532
48. Rakova N, Jüttner K, Dahlmann A, Schröder A, Linz P, Kopp C, et al. Long-term space flight simulation reveals infradian rhythmicity in human Na+ balance. Cell Metab. 2013; 17(1):125–31. doi: 10.1016/j.cmet.2012.11.013
49. Suckling RJ, He FJ, Markandu ND, MacGregor GA. Dietary salt influences postprandial plasma sodium concentration and systolic blood pressure. Kidney Int. 2012; 81(4):407–11. doi: 10.1038/ki.2011.369
50. Kanbay M, Aslan G, Afsar B, Dagel T, Siriopol D, et al. Acute effects of salt on blood pressure are mediated by serum osmolality. J Clin Hypertens. 2018; 20(10):1447–54. doi: 10.1111/jch.13374
51. Zoccali C, Moissl U, Chazot C, Mallamaci F, Tripepi G, et al. Chronic fluid overload and mortality in ESRD. J Am Soc Nephrol. 2017; 28(8):2491–7. doi: https://doi.org/10.1681/ASN.2016121341
52. Moissl U, Arias-Guillén M, Wabel P, Fontseré N, Carrera M, et al. Bioimpedance-guided fluid management in hemodialysis patients. Clin J Am Soc Nephrol. 2013; 8(9):1575–82. doi: 10.2215/CJN.12411212
53. Van Biesen W, Williams JD, Covic AC, Fan S, Claes K, et al. Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBCM) Study Cohort. PLoS One. 2011; 6(2):e17148. doi: 10.1371/journal.pone.0017148
54. Onofriescu M, Hogas S, Voroneanu L, Apetrii M, Nistor I, et al. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. Am J Kidney Dis. 2014; 64(1):111–8. doi: 10.1053/j.ajkd.2014.01.420
55. Hür E, Özişik M, Ural C, Yildiz G, Mağden K, et al. Hypervolemia for hypertension pathophysiology: a population-based study. Biomed Res Int. 2014; 2014:1–9. doi 10.1155/2014/895401
56. Yeşiltepe A, Dizdar OS, Gorkem H, Dondurmacı E, Ozkan E, et al. Maintenance of negative fluid balance can improve endothelial and cardiac functions in primary hypertensive patients. Clin Exp Hypertens. 2017; 39(6):579–86. doi: 10.1080/10641963.2017.1291663
57. Covic A, Voroneanu L, Goldsmith D. E-mail routine bioimpedance-derived volume assessment for all hypertensives: a new paradigm. Am J Nephrol. 2014; 40:434–40. doi: https://doi.org/10.1159/000369218
58. Siriopol D, Covic A, Iliescu R, Kanbay M, Tautu O, et al. Arterial stiffness mediates the effect of salt intake on systolic blood pressure. J Clin Hypertens. 2018; 20(11):1587–94. doi: 10.1111/jch.13399
59. 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. BMJ. 2013; 346(apr03 3):f1325–f1325. doi: 10.1136/bmj.f1325

60. Bray GA, Vollmer WM, Sacks FM, Obarzanek E, Svetkey LP, et al. A further subgroup analysis of the effects of the DASH diet and three dietary sodium levels on blood pressure: results of the DASH-Sodium Trial. Am J Cardiol. 2004; 94(2):222–7. doi:10.1016/j.amjcard.2004.03.070
61. Pimenta E, Gaddam KK, Oparil S, Aban I, Husain S, et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension. Hypertension. 2009; 54(3):475–81. doi: 10.1161/HYPERTENSIONAHA.109.131235
62. Suckling RJ, He FJ, Markandu ND, MacGregor GA. Modest salt reduction lowers blood pressure and albumin excretion in impaired glucose tolerance and type 2 diabetes mellitus. Hypertension. 2016; 67(6):1189–95. doi: 10.1161/HYPERTENSIONAHA.115.06637
63. Qi H, Liu Z, Cao H, Sun WP, Peng WJ, et al. Comparative efficacy of antihypertensive agents in salt-sensitive hypertensive patients: a network meta-analysis. Am J Hypertens. 2018; 31(7):835–46. doi: 10.1093/ajh/hpy027
64. Mcmahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, et al. A randomized trial of dietary sodium restriction in CKD. J Am Soc Nephrol. 2013; 24:2096–103. doi: 10.1681/ASN.2013030285
65. Saran R, Padilla RL, Gillespie BW, Heung M, Hummel SL, et al. A randomized crossover trial of dietary sodium restriction in stage 3–4 CKD. Clin J Am Soc Nephrol. 2017; 12(3):399–407. doi: 10.2215/CJN.01120216
66. Kayikcioglu M, Tumuklu M, Ozkahya M, Ozdogan O, Asci G, et al. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. Nephrol Dial Transplant. 2008; 24(3):956–62. doi: 10.1093/ndt/gfn599
67. Dorobantu M, Tautu O, Dimulescu D, Sinescu C, Gusbeth-Tatomir P, et al. Perspectives on hypertension's prevalence, treatment and control in a high cardiovacular risk East European country: data from SEPHAR III survey. J Hypertens. 2018; 36(3):690-700. doi: 10.1097/HJH.0000000000001572
68. Mente A, O'Donnell M, Rangarajan S, Dagenais G, Lear S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. Lancet. 2016; 388(10043):465–75. doi: 10.1016/S0140-6736(16)30467-6