Sodium Intake and Vascular Stiffness in Hypertension

Michel E. Safar, Mohamed Temmar, Augustine Kakou, Patrick Lacolley, Simon N. Thornton

The relationship between sodium and blood pressure (BP) continues to be the focus of intense research. In humans, the impact of sodium on systolic BP (SBP), diastolic BP (DBP), mean BP, and pulse pressure (PP) is currently thought to be quite similar for the 4 pressures and to occur practically with identical consequences (see reviews1–8). In this review, the effect of sodium on SBP is taken into consideration mainly for a very simple but important reason: in recent years, SBP and PP have become the parameters the most difficult to control in hypertensive subjects, which is the principal goal of most antihypertensive drugs.1

Central (aortic) SBP is a complex parameter that is influenced both by cardiac (stroke volume and ventricular ejection) and vascular (arterial and venous stiffness and wave reflections) factors.1 Stroke volume, the ratio between cardiac output and heart rate, depends not only on cardiac structure and function but also on venous return. Through the extracellular and intravascular spaces and their elastic properties, stroke volume and, hence, SBP are strongly associated with sodium balance, ie, with the relationship between sodium intake and its urinary elimination, and, finally, the traditional pressure-diuresis mechanism.3 This pathway, which mainly affects the venous circulation, requires a low and steady BP, together with a vast storage capacity for salt and water. Another important pathway affects the high-pressure pulsatile arterial system, in which the SBP level is achieved through increased arterial stiffness and wave reflections. These hemodynamic parameters are strongly influenced by sodium intake, and their anomalies are mostly seen in subjects >50 years old.1,2,5,7,9 Note that, in humans, the volume and elasticity of the arterial space are very low compared with the corresponding values for the venous system.1

We have 2 principal aims for this review. First, how does dietary sodium influence vascular stiffness and, through mechanisms affecting the venous circulation, modulate stroke volume and SBP, potentially leading to hypertension? Second, how does sodium intake adversely affect the arterial circulation and, through increased arterial stiffness and wave reflections, potentially worsen hypertension and exacerbate cardiovascular risk? These 2 questions are detailed successively after a brief historical review of the traditional relationships between sodium and BP and a summary of their interactions with the renin-angiotensin-aldosterone system (RAAS). Other hormonal factors, with the exception of antidiuretic hormone, are beyond the scope of this review.

Sodium, SBP, and Cardiovascular Risk: A Brief Historical Overview

Over the last few decades, a considerable body of evidence has shown major links along with cause-and-effect relationships between salt intake and BP. They have given rise to numerous publications and reviews, summarized here.1–8 In most studies, SBP and DBP were considered to be equivalent mechanical factors acting on the arterial wall, whether in the presence or absence of a high-sodium diet. Notably, several observations indicate a particular role of SBP, which, until recently, was seldom taken into account. First, in studies on chimpanzees on a high-salt and then a low-salt diet,8 high BP levels were explained almost exclusively by SBP, which was modified significantly by dietary sodium. Second, several clinical studies on the relationship between salt intake and BP were frequently of short duration, whereas salt sensitivity develops progressively with age, with the main consequences affecting SBP in older people, as a consequence of today’s longer life expectancy.2–8 At this point, it is important to define what we call “sodium sensitivity” in this review.

In humans, the BP response to an acute change of salt intake (or a diuretic) has been used to determine what is referred to as “salt sensitivity.” Those individuals in whom a severe sudden modification of salt intake or excretion causes the least change in arterial BP are termed “salt resistant,” whereas those in whom these manipulations induce large BP changes are referred as “salt sensitive.” In this context, various protocols have been proposed. In this text we consistently use the term to refer to observational relationships between dietary sodium and BP. This approach needs to be distinguished from controlled prospective studies in which the steady-state relationships between sodium intake and DBP, SBP, or mean BP are experimentally determined or differentiated from standardized Weinberger-type studies7 using salt depletion or from the acute pressure-natriuresis relationships, as performed in experimental animals by ma-
In summary, in humans, consistent interactions are observed between sodium intake and BP, but they predominantly affect SBP, particularly in populations >65 years old. The sodium excess may influence cardiovascular morbidity and mortality, particularly through its contribution to vascular stiffness and hormonal changes that act via the RAAS, whether it be considered a systemic or local system. It is evident that many other factors might interfere, eg, those inherent to antidiuretic hormone and osmolality changes.

**Sodium, SBP, and Effective Total Vascular Compliance**

In animal experiments, the most classic models of a high-sodium diet involve, at their initial phase, blood volume expansion and elevated cardiac output. On the basis of experiments in 70% nephrectomized dogs given large amounts of saline IV daily for 2 weeks, Guyton\(^4\) suggested that this protocol raised BP primarily through volume expansion and cardiac output increase and, secondarily, through an autoregulatory mechanism affecting resistance vessels. For that explanation, most hypotheses on how dietary salt increases BP incorporate Guyton’s\(^4\) principal supposition that the initial rise of arterial pressure is associated with increased blood and extracellular fluid volumes. In light of the impaired ability to excrete sodium of normotensive children with hypertensive parents and of young prehypertensive, genetically hypertensive rats,\(^4,6,16\) that postulate seemed theoretically reasonable. However, measurements of extracellular fluid volume in hypertensive subjects have never been shown to be modified consistently.\(^17,18\)

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Fluid volume of the vessels. Compliance is then defined as the blood volume throughout the vascular system according to the capacity of the vessels. Compliance is then defined as the blood volume; \( \Delta \text{V} \), divided by the change in central venous pressure; \( \Delta \text{CVP} \), ratio between the change of cardiac output and the change of central venous pressure (effective vascular compliance).

However, MCFP requires, by definition, the presence of a nonbeating heart and cannot be measured in humans. Therefore, an alternative index of capacitance function has to be defined. Results of studies conducted on animals and humans indicate that similar indices are observed when the circulation is not interrupted between blood-volume changes and pressures measured in different parts of the venous system. For example, the slope of the relationship between central venous pressure (\( \Delta \text{CVP} \)) and rapid (\(<3\text{-minute}) blood volume expansion (\( \Delta \text{V} \)) with iso-oncotic Dextran has the dimensions of compliance (milliliters per millimeter of mercury). To differentiate between the \( \Delta \text{V}/\Delta \text{CVP} \) ratio and the “true” compliance measured from \( \Delta \text{V}/\Delta \text{MCFP} \), the ratio was called “effective” total vascular compliance. This ratio was validated in men, using the Guyton model for this clinical application.

In hypertensive subjects, the slope of the curve plotting blood-volume expansion versus central venous pressure \( \Delta \text{V}/\Delta \text{CVP} \) is significantly lower than in normotensive controls (Table). In contrast, the curves of cardiac output versus blood-volume expansion are preserved, indicating maintained cardiac function despite cardiac hypertrophy in hypertensive individuals (Table). Under these conditions, at any given value of blood-volume expansion, central venous pressure increases more in hypertensive subjects than in normotensive controls, thereby incriminating the decreased effective compliance of the total vascular bed. “Effective” means that, during this very rapid (<3-minute) volume expansion using an iso-oncotic fluid, no consistent capillary filtration and/or neurohumoral adaptation existed. Because venous vascular hypertrophy is not observed in hypertensive subjects, the true challenge is to determine which factors might explain this reduced elasticity, i.e., that total and/or cardiopulmonary blood volume in hypertensive subjects remains constantly too large for the capacity of the intravascular space. This explanation is illustrated in a simple flowchart (Figure 1).

A large body of evidence supports the existence and physiological role of cardiopulmonary mechanoreceptors in animals and human subjects. When involvement of arterial baroreceptors is avoided, stimulation of cardiopulmonary receptors causes a general withdrawal of the sympathetic outflow, but the effect on renal sympathetic tone is most pronounced. Furthermore, it has been shown that cardiopulmonary receptors mediate systemic renin release through

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**Table. Indices of Volume Expansion, Cardiac Performance, and Effective Vascular Compliance in Hypertensive Patients and Normotensive Controls**

<table>
<thead>
<tr>
<th>Hemodynamic Indices</th>
<th>Normotensive Controls</th>
<th>Hypertensive Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{CO}/\Delta \text{V} ), min</td>
<td>2.28±0.20*</td>
<td>3.26±0.32*</td>
</tr>
<tr>
<td>( \Delta \text{CO}/\Delta \text{CVP} ), mL/min</td>
<td>353±35</td>
<td>371±41</td>
</tr>
<tr>
<td>( \Delta \text{V}/\Delta \text{CVP} ), mM/min</td>
<td>148±6</td>
<td>118±6†</td>
</tr>
<tr>
<td>( \Delta \text{V}/\Delta \text{CVP} ), mHg</td>
<td>2.16±0.09</td>
<td>1.56±0.07†</td>
</tr>
</tbody>
</table>

Data are ±1 SEM. This table is adapted from References 17 and 19. \( \Delta \text{CO}/\Delta \text{V} \) indicates the ratio between the change (\( \Delta \)) of cardiac output and the change of blood volume; \( \Delta \text{CO}/\Delta \text{CVP} \) ratio between the change of cardiac output and the change in central venous pressure; \( \Delta \text{V}/\Delta \text{CVP} \), ratio between the change of blood volume and the change of central venous pressure (effective vascular compliance).

*\( P<0.025 \)
†\( P<0.001 \)

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**Figure 1. Venous side of the circulation: an oversimplified flowchart under ideal physiological conditions.**
their effect on the renal juxtaglomerular apparatus. In subjects with mild-to-moderate essential hypertension, this renin-
reflex modulation remains operative but exerts reduced ef-
ectiveness compared with normal subjects.22 Finally, in hypotensive subjects, total blood volume and effective com-
piance of the vascular bed are significantly reduced. In the presence of preserved cardiac performance, central venous pressure is increased slightly but significantly.

That hemodynamic profile is consistent exclusively with compliance reduction greater than the corresponding intra-
vascular volume reduction, ie, with a relative increase of blood volume, which should then be associated with less renin release.17 This process might be a possible explanation for the inability to block renin release through age-dependent, diminished sensitivity of cardiopulmonary receptors if we were to assume the lack of adaptation or resetting of low-pressure stretch receptors.23 A similar mechanism could also result from age-dependent increased stiffness in the areas of high-pressure baroreceptors. Obviously, both types of recep-
tors should involve the role of systemic RAAS. This general interpretation agrees with the traditional concept that high-
salt intake lowers systemic RAAS activity, a situation that requires systemic AngII suppression but ignores local AngII contribution.1,3,22,23

Sodium, SBP, and Arterial Stiffness
One of our major goals in this review was to show that salt has an effect on the large artery wall and, thus, modulates vascular stiffness. Many potential mechanisms for this role have been published previously.1,24 However, it is important, initially, to distinguish between active and passive long-term effects on modifications of arterial wall stiffness. Thereafter, some cellular and molecular aspects will be addressed.

Sodium-Induced Change in Arterial Stiffness and BP
In genetic models of animal hypertension, as summarized previously,24 chronically high sodium intake is associated with aortic hypertrophy and development of the extracellular matrix (ECM) independent of BP. These alterations, often associated with increased stiffness and changed secretory properties of vascular smooth muscle (VSM) cells, are reversed by lowering sodium consumption and/or giving diuretics, independent of BP.1,24 The arterial changes are chronically modulated by hormonal counterregulatory mech-
isms because, when dietary sodium is high, bradykinin B2-receptor blockade by Hoe 140 engenders more carotid hypertrophy, and when sodium intake is normal, less aortic collagen accumulates because of AngII-specific type 1 recep-
tor activity.25,26

Several clinical investigations have now firmly established the BP-independent correlations between dietary sodium and arterial stiffness, regardless of whether systemic, regional, or local determinations were obtained.1,11,14 The first studies on the relationships between sodium intake and arterial stiffness were based on Chinese populations studied by Avolio et al.27 Pulse wave velocity (PWV), a classic marker of aortic stiffness, was measured in 2 groups of normal subjects living in either a rural or an urban community. Serum cholesterol was similar and low in both groups, whereas hypertension frequency and salt intake were significantly higher for the urban rather than the rural community. After adjustment for BP, the PWV of the rural group was consistently lower in the aorta arms and legs and increased less with age compared with the urban group. Thus, salt intake had an independent effect on arterial tone and arterial wall properties, with the former indirectly and the latter directly contributing to in-
creased PWV with age.

Another study was conducted in Australia.28 PWV was measured in normotensive subjects who voluntarily con-
sumed a low-salt diet and were compared with age- and BP-matched subjects on a normal-sodium diet. For subjects 20 to 66 years old, PWVs measured in the aorta, arms, and legs were consistently lower in the low-salt than the control group. Thus, adult subjects on a low-salt diet have less arterial stiffness independent of BP.

A longitudinal investigation was performed in Europe to evaluate sodium-induced changes of arterial diameter and stiffness in subjects with mild-to-moderate hypertension of middle age. A 2 month, randomized, double-blind study included 20 ambulatory hypertensive patients and used a crossover design.29 At the end of the study, BP was significa-
lantly lower during the low-salt than the normal-salt phase, but the BP changes were small. The brachial artery diameter was significantly larger during the low-salt period, whereas the carotid artery diameter was unchanged. Obviously, the changes of brachial artery diameter could not be attributed to the changes of distending pressure, because they indicated that moderate-salt restriction decreased BP while causing a parallel dilation of the brachial but not the carotid artery. Similar results were obtained in elderly patients with systolic hypertension and were significantly associated with changes in baroreflex sensitivity.30 To better understand these data, it is worth noting that high consumption of vegetables and fruits (higher levels of potassium than sodium) consistently lowered BP in hypertensive patients and considerably slow its development. Their role in association with less dietary sodium cannot be excluded.13,31

Cellular and Molecular Mechanisms
For many years, it has been accepted that SBP and DBP increase in parallel with excess sodium, causing vascular resistance to rise exclusively in association with modifications of small arteries, as shown by Blaustein’s32 theory on sodium-calcium exchange.1,14 From more recent studies, it is logical to link sodium with the structure and function not only of small but also of large arteries and, therefore, to arterial stiffness, independent of BP.

Two important prerequisites are necessary to understand the structural particularities of hypertensive large arteries under a high-sodium diet. First, the biological properties of arteries and veins are known to differ markedly. In vivo, these differences are amplified because the arterial and venous systems are not subjected to the same hemodynamic stresses.33 Thus, arterialization of veins has been studied, mainly using veins as arterial grafts.1,33 Arterialization is influenced by shear and/or tensile stresses but not by blood velocity and/or BP alone.33 It seems logical to admit that a given threshold
hemodynamic stress is required to obtain the desired modifications of veins.1,3,35 On the other hand, results obtained in recent studies showed that the endothelium and medium of large arteries respond to changing to a high-salt diet through mechanisms largely independent of BP.1,24 Genetic models of hypertensive rats, along with the approaches of molecular and cellular biology, are needed to further elucidate these alterations.24,34–36 Nevertheless, concomitant changes of local arterial diameter and distensibility have been poorly investigated in those genetic models.

Endothelial cells lining the artery lumen appear to serve as sensors of modified dietary salt intake, which generate signal-transduction events that lead to the production of transforming growth factor-β1, and NOS3 through modification of shear stress and possibly and potentially arterial stiffness.35,36 Altered expression of these effector molecules contributes greatly to the vascular responses to salt intake. As illustrated in Figure 2, increasing the extracellular sodium concentration may enhance endothelial cell stiffness under aldosterone, whereas cell stiffness remains significantly lower under specific blockade by eplerenone.34 Thickening of the arterial medium, mediated by growth factors, eg, transforming growth factor-β1, is quite important to consider and affects both muscle mass and ECM (primarily collagen fibers). It is worth noting that arterial hypertrophy is significantly more pronounced in the presence of cyclic rather than steady stress, finally leading to vascular remodeling and, potentially, to oxidative stress, inflammation, and fibrosis.1,32

Finally, independent of elastin and collagen, numerous ECM attachment molecules become active in response to excess sodium, particularly in older people with systolic hypertension and/or type 2 diabetes mellitus.1 ECM attachment molecules interact with VSM cells, VSM cells and glycosaminoglycans, or various collagen fibers (collagen cross-links).1,37 Because integrins transmit inside-out and outside-in signals capable of modulating changes of vascular responses, Lacolley and colleagues37–39 showed that adhesion molecules such as fibronectin (Fn) and its α5β1 integrin receptor may contribute greatly to this modulation of wall stiffness. Results of studies conducted on young and old spontaneously hypertensive rats, and using aortic Fn and integrin immunolabel, suggested that more attachment sites between VSM cells and the ECM might be responsible for enhanced arterial rigidity.37 In α5 integrin knockout mice, such mechanisms were shown to be operative under AngII infusion and implicated in the p38 mitogen-activated protein kinase and focal adhesion kinase pathways.39 This is supported by the AngII receptor antagonist eplerenone.40

In conclusion, enhanced stiffness of arteries is associated with aortic collagen accumulation and more attachment molecules between VSM cells and collagen fibers. Both are influenced by AngII and its selective blockade. It is worth noting that, in humans, arterial wall AngII is 1000-fold more abundant than systemic AngII. Under a high-salt diet, AngII-specific type 1 receptors are upregulated in the arterial system and are highly sensitive to selective angiotensin blockade.3,41,42 Thus, local RAAS appears to be one of the major mediators of vessel wall elasticity.

Finally, in hypertensive humans, gene polymorphisms of AngII-specific type 1 receptors, angiotensin-converting enzyme, and aldosterone synthase have been found to be associated with enhanced arterial stiffness and PP.1,24–43,44 Such gene polymorphisms are often linked with that of α-adducin and/or with a high-sodium diet in older subjects with systolic hypertension.43

**Perspectives**  
One of the major problems concerning the role of sodium in humans is that the history of this cation is much older than that of hypertension itself or even of Bright’s disease. For example, one of the basic concepts about salt and hypertension is that, in primitive populations, BP invariably does not increase with age and stable low BP is constantly associated with a chronic low-salt diet and, inversely, with a high-salt diet with high BP. When those populations were investigated, their life expectancies were much shorter than those observed in more recent population studies.45 On the other hand, in the
past, the role of potassium and the concept of multiple factors responsible for cardiovascular risk were totally absent from the literature. Today, all of these risk factors are found to be highly associated with excess sodium intake, as has been shown in some desert dwellers, like in the Algerian Sahara. It could be classically suggested that, in such populations, sodium excess might be responsible for the high BP. Alternatively, it could be advanced that metabolic disorders, eg, type 2 diabetes mellitus, are the predominant factors to consider and that their role is exacerbated by the presence of high-salt intake and/or a low-potassium diet.

Herein, we showed that high-salt intake may lead to severe modifications of the vascular endothelium and ECM with further enhancement of aortic stiffness, SBP, and PP, and, consequently, of cardiovascular risk. Additional clinical studies and basic research are needed in these fields, particularly regarding the role of arterial stiffness and wave reflections in the young and/or in prehypertensive states. Kidney alterations should also be taken into account, because reduced arterial and venous compliance in hypertension have been significantly associated with lower glomerular filtration rate, decreased renal blood flow, and/or increased renal filtration fraction.

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None.

References


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