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Vascular Effects of Dietary Salt

David G. Edwards and **William B. Farquhar**

Department of Kinesiology and Applied Physiology, University of Delaware, Newark, DE

Abstract

Purpose of review—High dietary salt intake is detrimental in hypertensive and/or salt sensitive individuals, however there are a large number of normotensive salt resistant individuals for whom dietary salt may also be harmful as a result of salt's blood pressure independent effects. This review will focus on the growing evidence that salt has adverse effects on the vasculature independent of blood pressure.

Recent findings—Data from both animal and human studies provide evidence that salt impairs endothelial function and increases arterial stiffness independent of blood pressure. High dietary salt results in oxidative stress and increased endothelial cell stiffness which impair endothelial function whereas transforming growth factor beta promotes increased arterial stiffness in the presence of endothelial dysfunction.

Summary—Health Policies and most clinical research are focused on the adverse effects of dietary salt on blood pressure however there is an increasing body of evidence to support a deleterious effect of dietary salt on endothelial function and arterial stiffness independent of blood pressure. Endothelial dysfunction and increased arterial stiffness are predictors of cardiovascular disease, therefore reducing excess dietary salt should be considered important for overall vascular health in addition to blood pressure.

Keywords

salt; sodium; endothelial function; arterial stiffness

Introduction

The average intake of sodium for most Americans exceeds 3200 mg per day (1) and is considered an important factor in the development of hypertension (2, 3). Approximately 1 out of 3 US adults are hypertensive and the prevalence of hypertension increases with age (4). Dietary sodium restriction is considered an important lifestyle modification for individuals with hypertension (5). Many organizations provide information on the benefits of reducing sodium in the diet including the National Institutes of Health, Centers for Disease Control, American Heart Association, and the World Health Organization.

Address for correspondence: David G. Edwards, PhD (dge@udel.edu), Department of Kinesiology and Applied Physiology, 201Q HSC, 540 South College Avenue, Newark, DE 19713, Phone: (302) 831-3363, Fax: (302) 831-3693.

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Salt sensitivity of blood pressure (BP) can be described as an increase in BP going from a low salt to a high salt diet. Although there are many ways in which salt sensitivity has been determined and defined, research has demonstrated that older adults are more salt sensitive than younger adults and African Americans are more salt sensitive than Caucasians (6, 7). Further, both normotensive and hypertensive individuals can be salt sensitive (8). Indeed, salt sensitivity in normotensive individuals predicts future hypertension (9) and salt sensitive BP is associated with increased mortality in both normotensive and hypertensive adults (8, 9).

Clearly there is a large proportion of the population for which high levels of dietary consumption of sodium is detrimental (i.e. hypertension and/or salt sensitive individuals). However, the majority of younger individuals are normotensive and salt resistant which raises the question as to whether dietary sodium consumption matters in these individuals. The Trials of Hypertension suggests that sodium may have detrimental effects beyond its effect on BP. In these studies sodium reduction reduced long-term risk of cardiovascular events with very little change in BP (SBP -1.7 mmHg, DBP -0.8 mmHg) (10). The appreciation that sodium may have detrimental effects in addition to raising BP is not new (11, 12) but there has been a recent increased interest on the vascular effects of sodium apart from BP (12). This review will focus on the BP independent effects of sodium on the vasculature that is particularly relevant given the current debate over recommended levels of dietary sodium consumption. The purpose of this review however is not to discuss the appropriate level of sodium consumption but the deleterious vascular effects of high salt.

Dietary Salt and Endothelial Function

The endothelium has been the focus of much research since it was shown that it was more than a simple barrier and plays a critical role in mediating vascular relaxation (13). The most important and studied endothelial derived vasodilator is nitric oxide (NO). In addition to vasodilation, NO has anti-atherogenic properties that include inhibition of: platelet adhesion and aggregation, leukocyte adhesion and migration, smooth muscle cell proliferation, and inflammation. It is now recognized that impaired endothelial function is a primary event in the development of atherosclerosis. Endothelial dysfunction has been linked to the pathogenesis of atherosclerosis and acute cardiovascular events, occurs early before angiographic evidence of disease (14), and has been shown to be a predictor of future cardiovascular events in patients with coronary artery disease (15, 16) and in a population-based study of adults (17). Endothelial function is impaired in cardiovascular disease (15, 16) as well as by the presence of cardiovascular risk factors such as diabetes (18) and aging (19). Since endothelial dysfunction is predictive of cardiovascular events, an understanding of factors that may contribute to reduced endothelial function – such as dietary salt – is important. Hypertension is associated with reduced endothelial function (20) so elucidating any effect of salt on the endothelium independent of BP is essential as it may shift our understanding to where dietary salt is no longer linked solely to BP, but rather, to vascular health, which has potentially significant Public Health implications.

Basal synthesis of NO is increased by short term high salt intake that is important in facilitating sodium excretion (21, 22) but there is evidence that stimulated NO synthesis is

reduced by high salt intake that likely has implications for local blood flow regulation (12). Rodent studies have provided evidence that sodium impairs endothelial function without alterations in BP. Deleterious changes in the vasculature from excess salt have been documented in spontaneously hypertensive rats, normotensive Wistar-Kyoto rats, and Sprague-Dawley rats, in which BP is unaltered during the early stages of exposure to a high salt diet (23-25). A high salt diet impairs aortic and mesenteric endothelial function in Sprague-Dawley rats without altering resting BP (26-28). Similar findings have been observed in mice (29).

Data from human studies support the aforementioned work done in rodents. A reduced vasoconstrictor response to L-NMMA (a competitive inhibitor of endothelial NO synthase) after 5 days of high dietary salt was reported in healthy, normotensive men indicating reduced basal levels of endothelial-derived NO (30). Additionally, impairments in endothelial function, assessed via acetylcholine (Ach)-induced increases in forearm blood flow, were also observed indicating reduced stimulated NO production (30). However, increases in systolic BP during acute salt loading were also observed (30) making it difficult to separate any direct detrimental effects of salt intake on endothelial function from the effects on BP. In order to investigate the effects of high dietary salt intake on endothelial function independent of BP we studied normotensive salt resistant individuals in a randomized controlled feeding studies in which subjects consumed 7 days each of a high and low salt diet which was provided to them. For the purposes of these studies salt resistance was defined as a change in 24-hour MAP ≤ 5 mmHg between low and high salt diets. Seven days of the high salt diet resulted in reduced brachial artery flow mediated dilation (FMD) (31), the most common and widely accepted non-invasive measure of conduit artery endothelial dependent dilation in humans (32). Additionally, high salt reduced cutaneous vasodilation in response to local heating, a measure of microvascular function (33) which is largely an endothelial derived NO mediated response (34, 35). Taken together these studies demonstrate that dietary salt loading impairs endothelial function independent of BP in healthy, normotensive adults.

Data from populations at higher risk for cardiovascular disease also provide evidence for a deleterious effect of salt on endothelial function. Brachial artery FMD has been shown to be greater in overweight and obese normotensive adults following 2 weeks on a low salt diet compared to 2 weeks of a usual salt diet in a randomized crossover study (36). BP also decreased in this study therefore the beneficial effects of salt reduction on FMD cannot be separated from the effects of lower BP, however more recently Dickinson and colleagues reported a modest reduction of dietary salt (3g/day) from a usual salt diet for 6 weeks resulted in improved FMD in normotensive overweight and obese individuals independent of BP (37). Cross-sectional data from middle-aged and older adults with elevated systolic BP suggests that habitual low salt intake is associated with higher FMD (38). Jablonski et al (39) followed up on these findings and reported that dietary sodium restriction in middle age and older adults with moderately elevated systolic BP (130-159 mmHg) improved both brachial artery FMD and the forearm blood flow response to Ach. Systolic BP was reduced by ~12 mmHg in this study however the improvement in endothelial function remained after correction for systolic BP suggesting the improvement in endothelial function occurred beyond the effect of lower BP.

The studies described above were composed of both men and women however there is evidence that sex differences may exist in the vascular response to dietary salt. In a study of two groups of men and women who followed either a low salt or high salt diet for 5 days, the NO component of the forearm blood flow response to Ach was reduced in the group of men who consumed the high salt diet compared to the group that consumed the low salt diet whereas there was no difference between the 2 groups of women (40). More recently, 7 days of high salt reduced FMD in both normotensive salt resistant men and women however FMD was lower in the men compared to women on the high salt diet (41). These two studies suggest a potentially greater sensitivity of the vasculature to high salt in men.

Potential Mechanisms of Reduced Endothelial Function by High Salt

Oxidative stress, an imbalance between reactive oxygen species (ROS) production and scavenging is widely thought to contribute to the development of cardiovascular disease and an increase in ROS generation is one mechanism by which a high salt diet appears to impair endothelial function. A well accepted mechanism for reduced NO bioavailability is the rapid reaction of NO with elevated levels of superoxide (Figure 1). A number of rodent studies have demonstrated that superoxide levels are higher in resistance arteries (26-28) and venules (26, 27) on a high salt diet. Indeed, rodent studies have reported that the decline in stimulated NO during dietary salt loading result from an increase in ROS (27, 28). Ach-induced endothelium-dependent dilation was reduced in normotensive rats fed a high-salt diet compared with rats fed a low-salt diet and exposure to ROS scavengers improved arteriolar responsiveness to Ach (27). In humans, local infusion of ascorbic acid reversed the impaired cutaneous vasodilation to local heat observed following 7 days of high salt by increasing the NO component of vasodilation (33). In middle age and older adults with elevated SBP on a normal sodium diet, ascorbic acid improved both conduit and resistance vessel endothelial function but this effect was abolished by dietary sodium restriction (39). In addition to scavenging NO, ROS may lead to oxidation of tetrahydrobiopterin (BH_4), a critical cofactor for eNOS (Figure 1). This leads to reduced NO synthesis and increased generation of superoxide. In a rodent study, a high salt diet reduced BH_4 levels compared to a normal diet as a result of increased BH_4 oxidation as indicated by an increased ratio of BH_2/BH_4 (42). In the aforementioned study in middle age and older adults, oral BH_4 improved both conduit and resistance vessel endothelial function on a normal sodium diet but this effect was abolished by dietary sodium restriction (39) providing additional support for salt-induced declines in BH_4.

The primary source of ROS during dietary salt loading appears to be superoxide (28, 29), and there is evidence for its production via NADPH oxidase (27, 28), xanthine oxidase (27, 28), and eNOS (29). In addition to increased ROS production, a reduction in endogenous antioxidant capacity for scavenging ROS may also play a role in the deleterious effects of high salt. Superoxide dismutase (SOD) is important for scavenging superoxide and a high salt diet has been shown to reduce SOD expression and activity (43, 44). The mechanism by which salt reduces SOD has been demonstrated to be through the suppression of angiotensin II (Ang II) that accompanies a high salt diet (Figure 1). When subpressor doses of Ang II are given to rodents on a high salt diet, oxidative stress and endothelial dysfunction are prevented (45, 46). Recently Durand and Lombard examined the effect of subpressor Ang II

in high salt fed congenic Ren1-BN rats which have rescued Ach induced dilation and increased Cu/Zn SOD compared to their parental Dahl salt sensitive strain (43). They found that high salt prevented Ach induced dilation of the middle cerebral artery and reduced both Cu/Zn and Mn SOD expression whereas Ang II restored MCA dilation and increased Cu/Zn SOD (43). These results lend additional support the idea that prevention of Ang II suppression during high salt prevents endothelial dysfunction via maintenance of SOD. There are no data in humans that have examined the role of high salt-induced suppression of Ang II on oxidative stress and endothelial function. This may be an important mechanism in studies where Ang II levels are suppressed (31, 33) however endothelial function also has been shown to improve during more moderate reductions in sodium when Ang II levels do not change (37, 39).

In addition to oxidative stress a high salt diet may have a direct effect on endothelial function by altering endothelial cell stiffness. Increased extracellular sodium concentrations in the presence of physiologic levels of aldosterone have been shown to stiffen endothelial cells and reduce NO synthesis, an effect that can be inhibited by the epithelial sodium channel (ENaC) inhibitor amiloride (47). Elevated extracellular sodium levels lead to an increase the abundance of ENaC on endothelial cells (48) (abbreviated EnNaC (49)) in addition to damaging the endothelial glycocalyx (eGC)(50). The eGC is thought to play a role in buffering sodium ions such that when it becomes damaged sodium is permitted to enter endothelial cells via EnNaC resulting in cell stiffening (49). Jeggle and coworkers examined the role of EnNaC in stiffening the endothelium in Liddle mice that have an increase in EnNaC abundance (51). They found that endothelial cells from Liddle mice had increased cortical stiffness in the presence of aldosterone *in situ* however they did not assess endothelial function in this study. Accompanying cell studies provided further evidence that EnNaC abundance determines cell stiffness (51). Old mice have greater numbers of EnNaC and higher cortical stiffness at baseline and following the addition of high sodium ex vivo that likely contributes to endothelial dysfunction with age (52). It appears that high sodium leads to disturbed eGC, increased EnNaC abundance and reduced NO synthesis (49) however the role these channels on vessel function during high salt has yet to be investigated in animal models or humans.

Dietary Salt and Arterial Stiffness

An increase in arterial stiffness increases systolic BP and left ventricular workload and hypertrophy as well as decreases diastolic pressure that can result in reduced coronary blood flow (53). Measures of arterial stiffness have been shown to be predictors of cardiovascular events in hypertension (54, 55) and kidney disease (56, 57). In apparently healthy subjects, aortic pulse wave velocity (PWV) was shown to be an independent predictor of heart disease and stroke (58). Therefore, similar to endothelial function, understanding mediators of arterial stiffness is of clinical importance.

Animal studies of hypertension demonstrate that elevated dietary salt can increase arterial stiffness and that this effect is independent of BP (reviewed by Safar et al (59)). Reduced dietary sodium has also been shown to lower arterial stiffness in hypertensive humans (60, 61). Cross-sectional studies in humans provide evidence of an independent effect of salt on

arterial stiffness. In a study of two groups of Chinese populations, a rural population that consumed lower salt compared to an urban population that consumed higher salt, pulse wave velocity was lower (i.e., better) in the rural group when the groups were compared at similar BPs (62). Similarly, arterial stiffness was lower in a group consuming a low salt diet compared to an age and BP matched group who consumed normal salt (63). The mechanism by which dietary salt increases arterial stiffness appears to be due to the pro-fibrotic effects of transforming growth factor-β (TGF-β)(64). When rats were fed a high salt diet for 7 days endothelial production of TGF-β increased without an increase in BP (22). Basal levels of NO production are increased short term by high salt, via TGF-β signaling, which may help reduce the deleterious effect of TGF-β initially (21, 22) but as has been described above, endothelial function and stimulated NO synthesis are reduced by high salt intake. Thus, high dietary salt likely stiffens arteries via TGF-β that is unrestrained due to high-salt induced reductions in NO bioavailability. The effects of TGF-β may be further amplified in clinical populations with already reduced endothelial function (65).

Potential of Potassium to Combat Deleterious Effects of Salt

It is important to briefly mention the potential importance of potassium in mitigating the deleterious effects of high salt. Large trials have provided evidence that the interaction of sodium and potassium consumption may be important as higher urinary sodium to potassium excretion ratio is associated with increased risk of cardiovascular disease (66, 67). There is evidence that potassium supplementation can reduce BP (68) however there are limited studies of vascular function and potassium consumption. Endothelial cell studies indicate that potassium can soften cells and increase NO synthesis (69) while increased dietary potassium has been shown to inhibit vascular production of TGF-β in rats fed a high salt diet (70). Future studies are warranted to examine the interaction of potassium and sodium on vascular function.

Conclusion

Health Policies and most clinical research are focused on the adverse effects of dietary salt on BP however there is an increasing body of evidence to support a deleterious effect of dietary salt on endothelial function and arterial stiffness independent of BP. The mechanisms responsible continue to be elucidated. Endothelial dysfunction and increased arterial stiffness are predictors of cardiovascular disease and data from Framingham indicate that both are associated with incident hypertension (71). Therefore, reducing excess dietary salt should be considered important for overall vascular health in addition to BP.

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Key Points

- Dietary salt has health implications for hypertensive and/or salt sensitive individuals as well as normotensive salt resistant individuals due to salt's blood pressure independent effects.
- High dietary salt results in impaired endothelial function and increased arterial stiffness, both predictors of cardiovascular disease, independent of changes in blood pressure
- Reducing excess dietary salt should be considered important for overall vascular health in addition to blood pressure.

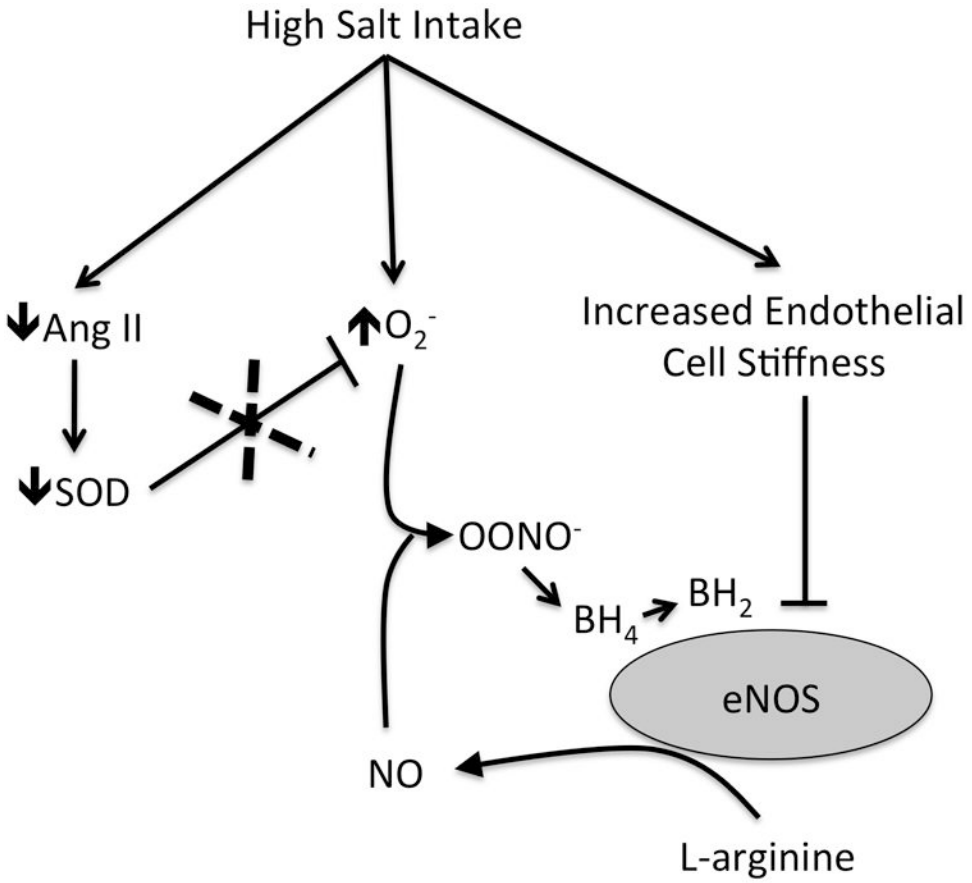

Figure 1.

Proposed mechanisms by which high salt intake leads to reduced nitric oxide (NO) bioavailablilty. High salt leads to increased superoxide (O_2^-) production and suppression of angiotensin II (Ang II) which leads to decreased superoxide dismutase (SOD) expression and activity reducing scavenging of O_2^-. NO bioavailability is decreased by the following: 1) via reaction of NO with O_2^- to form peroxynitrite ($OONO^-$); 2) oxidation of endothelial nitric oxide synthase (eNOS) cofactor tetrahydrobiopterin (BH_4) reducing NO synthesis; and 3) an increase in endothelial cell stiffness which leads to decreased synthesis of NO.