

# Sodium, large arteries and diuretic compounds in hypertension

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**Background:** Clinical and experimental data have shown that different antihypertensive drugs do not cause similar changes in arterial compliance for an equipotent blood pressure reduction. There are no clear data on the effects of sodium and diuretics on the visco-elastic properties of the hypertensive arterial wall.

**Data analysis:** Cross-sectional epidemiological studies suggest that for given values of age and blood pressure, pulse wave velocity is lower in the presence than in the absence of a low sodium intake. Longitudinal studies indicate that in hypertensive subjects, a low sodium intake is associated with a larger brachial artery diameter than that seen with a high sodium intake. In hypertension in the elderly and in severe hypertension with end-stage renal disease, a sodium overload reduces arterial compliance and distensibility independently of blood pressure changes. In animal studies, the diuretic compounds cycletanine and indapamide increase systemic and carotid compliance independently of blood pressure changes. In contrast, in a crossover study in hypertensive subjects, the diuretic agent hydrochlorothiazide did not change arterial compliance and pulse wave velocity while the calcium entry-blocker felodipine did improve these hemodynamic parameters.

**Conclusion:** The studies reviewed indicate that sodium may act on the arterial wall independently of blood pressure changes. The contribution made by counter-regulatory mechanisms, which may be related to the renin-angiotensin and the sympathetic nervous systems, might explain the differences between the clinical and the experimental changes observed with diuretic compounds.

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## Introduction

For many years, the complex relationships between sodium levels and blood pressure have been analyzed using the same routine approach to hemodynamic pathways. This work has shown that a high sodium intake may affect blood pressure, causing hypertension either by an increase in blood flow (short-term effect) or an increase in vascular resistance (long-term effect), with a change in arteriolar tone in the latter case. The possibility that a high sodium intake may influence the entire cardiovascular system in hypertension independently of blood pressure changes has not been widely considered. However, recent animal studies suggest that a decreased sodium intake may

improve cardiac hypertrophy independently of blood pressure changes [1] and that an elevated sodium intake is associated with structural alterations in the large arteries, particularly in the brain [2].

Systemic arterial compliance and distensibility are reduced in patients with essential hypertension. On the basis of experimental studies indicating a negative relationship between pressure and compliance, it was believed for a long time that the reduced visco-elastic properties of the arterial system in hypertensive patients were the simple mechanical consequence of the elevated distending blood pressure. However, recent studies indicate that the magnitude of the reduction in compliance is not constantly correlated with the level

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of blood pressure, thus suggesting intrinsic alterations to the hypertensive arterial wall [2]. It therefore seems possible that sodium might affect arterial stiffness independently of the blood pressure level. There are several arguments in favor of this possibility. First, sodium modifies arterial smooth muscle tone through different mechanisms, involving sodium-potassium pumps, calcium exchange, activation of the sympathetic nervous system and the action of natriuretic factors. Second, changes in vasomotor tone affect the visco-elastic properties of the arterial wall both experimentally and in clinical studies [3,4]. Cross-sectional epidemiologic studies have indicated that the level of sodium intake might influence pulse wave velocity independently of age, blood pressure and plasma cholesterol [5,6].

In the present report, clinical, epidemiological and pharmacological evidence for the effect of sodium on the mechanical properties of large arteries is analyzed, with particular emphasis on the action of diuretic agents.

### **Sodium-induced changes in arterial diameter and stiffness**

In recent years, three longitudinal studies have focused on sodium-induced changes in arterial diameter and stiffness in three different types of hypertensive conditions, mild to moderate essential hypertension in young to middle age, systolic hypertension in the elderly and dialyzed patients with end-stage renal disease.

#### **Effects of salt intake in mild to moderate essential hypertension in young to middle-aged subjects**

The hemodynamic effect of a moderately low salt diet was investigated in a 2-month, randomly allocated, double-blind crossover study in 20 hypertensive ambulatory patients [7]. All subjects spent 9 weeks on a low-salt diet. During this period they took capsules containing either lactose or sodium chloride (70 mmol/day) in 4-week treatment periods, separated by a 1-week washout period. Thus, a low-sodium diet was defined as a period of sodium chloride restriction with ingestion of lactose capsules, and a normal-sodium diet as a period of sodium chloride restriction supplemented by sodium chloride capsules. The results showed that blood pressure was significantly lower during the low- compared to the normal-sodium period but the blood pressure changes were small. The decrease in blood pressure seen during the low-sodium period was associated with a decrease in peripheral resistance in the carotid and forearm circulations. However, the brachial artery diameter was significantly larger during the low-sodium period, whereas the carotid artery diameter was unchanged. The changes in brachial artery diameter were not related to blood pressure changes but were positively

related to the age of the patients, and negatively correlated with the basal intracellular (erythrocyte) sodium content. Thus, a moderate salt restriction decreased blood pressure and reduced peripheral resistance in the carotid and forearm circulations while causing a parallel dilation of the brachial but not the carotid artery.

#### **Effects of salt intake on hypertension in the elderly and in end-stage renal disease**

Since Myers and Morgan [8] found that a high salt intake was associated with larger increases in blood pressure in older than in younger subjects, it seems likely that the higher sensitivity of systolic pressure to sodium in the elderly might be mediated by a sodium-induced increase in the rigidity of the arterial wall. Further support for this hypothesis has been obtained from a study on the effects of an intravenous administration of isotonic saline (2 liters in 120 min) to elderly subjects with systolic hypertension and arteriosclerosis obliterans of the lower limbs [9]. In these patients, the isotonic saline caused a significant decrease in forearm arterial compliance in parallel with an increase in systolic blood pressure with no change in diastolic blood pressure, suggesting that the reduction in arterial compliance following the isotonic saline was due to sodium-induced mechanisms acting on the arterial wall independently of the changes in blood pressure. Similar observations have been made in patients with severe hypertension and end-stage renal disease undergoing hemodialysis. These patients were characterized by striking arterial damage, involving calcification, enlarged aortic diameter and increased indices of arterial stiffness [10]. In subjects who were not undergoing antihypertensive treatment, pulse wave velocity was increased and was strongly associated with a positive sodium balance, as assessed from the interdialytic weight gain (Fig. 1). This finding was independent of age and blood pressure levels. During long-term treatment with the calcium blocker nitrendipine, blood pressure decreased rapidly. Pulse wave velocity also decreased significantly but the decrease occurred later, and therefore was poorly correlated with the blood pressure reduction. Again, the changes in pulse wave velocity were strongly associated with the interdialytic weight changes, indicating strong interactions between sodium balance and arterial stiffness in this particular population.

#### **Diuretic-induced changes in arterial stiffness**

Recent findings on the effects of diuretics on arterial stiffness in hypertension are based on both experimental and clinical data.

In animals, two different diuretic compounds were investigated, indapamide and cycletanone. For indapamide [11], an experimental model of the *in situ* isolated carotid artery was used to evaluate the

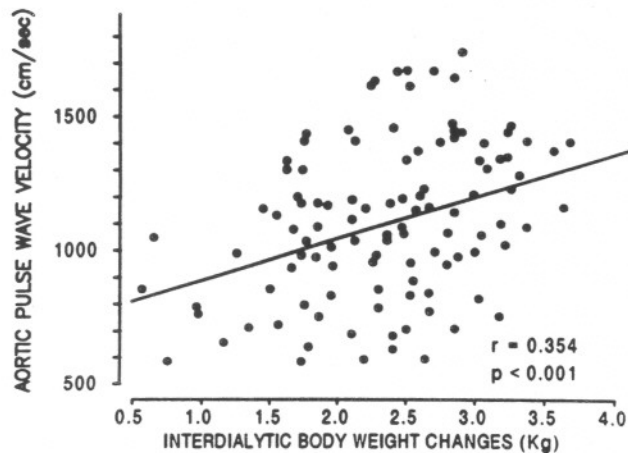


Fig. 1. Relationship between interdialytic weight gain and aortic wave velocity as a marker of aortic stiffness in untreated patients with severe hypertension and end-stage renal disease [10].  $r = 0.354$ ;  $P < 0.001$ .

static mechanical properties of the arterial wall in 12-week-old Wistar and deoxycorticosterone acetate (DOCA)-salt hypertensive rats. The indapamide treatment induced a significant increase in carotid compliance, both in the normotensive and hypertensive groups, independently of changes in transmural pressure. In another study [12], the effects of cicletanine on the systemic hemodynamics and the mechanical properties of the arterial wall were tested in normotensive Wistar-Kyoto (WKY) and spontaneously hypertensive rats (SHR). After chronic therapy by daily gavage for 15 days, there were no significant changes in either WKY and SHR in terms of arterial blood pressure; in contrast, systemic compliance and passive distensibility of the isolated *in situ* carotid arteries were significantly improved in the treated animals. Thus, cicletanine affected the distensibility and compliance of large arteries independently of significant changes in blood pressure.

The clinical findings discussed here are based on our own studies with hydrochlorothiazide [13] and recent work on indapamide [14]. The antihypertensive and the arterial effects of the diuretic compound hydrochlorothiazide were compared to those of the calcium-entry blocker felodipine in patients with es-

sential hypertension in a double-blind crossover study [13]. Whereas felodipine decreased blood pressure more substantially than hydrochlorothiazide and improved arterial distensibility (evaluated from pulse wave velocity) in the aorta and the upper and lower limbs, the diuretic compound had absolutely no arterial effect despite a significant but modest blood pressure reduction (Table 1). In another study using indapamide [14], systemic arterial compliance, as assessed by the ratio between stroke volume and pulse pressure, increased in patients with essential hypertension. However, the indapamide effect on systemic compliance was not observed in other arteries, such as the brachial artery. In this particular case, indapamide did not substantially change the brachial artery diameter and distensibility despite a significant blood pressure reduction [15,16]. A similar finding was observed with the anti-aldosterone compound canrenone [17]. Whereas an acute administration of ouabain did not change the brachial artery diameter in untreated hypertensives, following pretreatment with canrenone the acute administration of ouabain produced brachial artery constriction [17], again suggesting a diuretic-induced change in the arterial wall that was independent of blood pressure changes.

## Conclusion

Sodium undoubtedly affects the arterial wall, independently of blood pressure changes. However, the arterial modifications produced by diuretic agents are relatively small in hypertensive humans, and this remains difficult to explain. Potassium changes are an unlikely explanation, since indapamide and canrenone, which have opposing effects on serum potassium, produce the same arterial changes [15]. Since indapamide had more substantial arterial effects than hydrochlorothiazide, differences in the biochemical structure and/or the drug dose may be involved. However, the most satisfying explanations arise from two observations. First, the antihypertensive effect of diuresis is modest, with a very small possibility of producing a passive increase in arterial compliance. Second, diuretics activate counter-regulatory mechanisms, in-

Table 1. Arterial changes following treatment with hydrochlorothiazide versus felodipine in a crossover study in subjects with essential hypertension.

	Baseline	Felodipine	Hydrochlorothiazide
Systolic blood pressure (mmHg)	162 ± 12	140 ± 17	150 ± 13**
Diastolic blood pressure (mmHg)	96 ± 9	85 ± 9	89 ± 9*
Carotid-femoral pulse wave velocity (m/s)	10.9 ± 2.0	9.2 ± 1.8	10.1 ± 2***
Femoro-tibial pulse wave velocity (m/s)	12.8 ± 1.7	11.1 ± 1.9	12.2 ± 1.7***
Carotid-radial pulse wave velocity (m/s)	11.7 ± 1.9	10.0 ± 2	11.8 ± 1.8***
Brachial artery diameter (cm)	0.437 ± 0.06	0.449 ± 0.06	0.431 ± 0.05*
Brachial vascular resistance (dyn/s cm <sup>-4</sup> )	104 ± 40	72 ± 30	92 ± 46*
Brachial artery compliance (dyn/cm <sup>4</sup> 10 <sup>-7</sup> )	1.13 ± 0.48	1.71 ± 0.83	1.19 ± 0.57***

Means ± SD. \* $P < 0.05$ , \*\* $P < 0.02$ , \*\*\* $P < 0.05$ , versus felodipine.

cluding activation of the renin-angiotensin system and the autonomic nervous system, both of which favour arterial constriction [3]. It is therefore suggested that all these factors contribute to modulate the relaxing process induced by salt and water depletion.

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