dium and diuretics on the visco-elastic properties of the hypertensive arterial wall. Cross-sectional epidemiologic studies suggest that, at any given value of age and blood pressure, pulse wave velocity is lower in the presence of decreased sodium intake. Longitudinal studies indicate that, in hypertensive subjects, low sodium intake is associated with a larger brachial artery diameter than is high sodium intake. In hypertension in the elderly and in severe hypertension with end-stage renal disease, sodium overload causes a reduction in arterial compliance and distensibility unrelated to blood pressure changes. In animal studies, the diuretic compounds cycletanine and indapamide were shown to increase systemic and carotid compliance independently of blood pressure changes. In contrast, a crossover study of hypertensive subjects showed that the diuretic agent hydrochlorothiazide did not change arterial compliance and pulse wave velocity, whereas the calcium entry blocker, felodipine, improved these parameters. Nevertheless, indapamide decreased the pulse pressure on stroke volume ratio, a parameter used as a marker of aortic distensibility. Taken together, such studies indicate that sodium may act on the arterial wall independently of blood pressure changes. The contribution of counter regulatory mechanisms, possibly related to the renin-angiotensin and sympathetic nervous systems, might explain the differences between the clinical and experimental changes observed with diuretic compounds.

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For many years, the complex relationships between sodium levels and blood pressure have been analyzed using the same monotonous hemodynamic pathways.[1–3] Indeed, sodium intake acts on blood pressure and causes 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 indicated in the latter case. That sodium intake may influence the totality of the cardiovascular system in hypertension independently of the blood pressure changes themselves has not been widely considered. However, recent animal studies suggest that decreased sodium intake may improve cardiac hypertrophy independently of blood pressure changes[4] and that elevated sodium intake is associated with structural alterations in the large arteries, particularly those in the brain.[5]

Arterial compliance and distensibility are reduced in patients with essential hypertension, indicating an alteration in the damping function of large arteries, principally at the site of the aorta. Based on experimental studies indicating a negative relationship between pressure and compliance, it was long believed that the reduced visco-elastic properties of the arterial system in hypertensive patients was the simple mechanical consequence of the elevated distending blood pressure. However, recent studies in such subjects indicated that the magnitude of the reduction in compliance is not constantly correlated with the level of blood pressure, thus suggesting intrinsic alterations in the hypertensive arterial wall.[6] From this observation arises the possibility that sodium acts on arterial stiffness independently of the blood pressure level. Several arguments favor this possibility. First, sodium modifies arterial smooth muscle tone through different mechanisms involving sodium-potassium pumps,[7] calcium exchange,[8] activation of the sympathetic nervous sys-

tem,[9] and the action of natriuretic factors.[10,11] Second, changes in vasomotor tone affect the visco-elastic properties of the arterial wall both experimentally and in clinical studies.[6,12]

This report analyzed clinical, epidemiologic, and pharmacologic evidences of the effect of sodium on the mechanical properties of large arteries, with particular emphasis on the action of diuretic agents.

Cross-Sectional Studies

Aging is associated with increased arterial stiffness, increased arterial pressure, and a higher prevalence of hypertension. All are usually regarded as normal aging phenomena, and it is normally considered appropriate to adjust the normal range of arterial pressure and arterial stiffness for age.[13] However, it is well known that, in undeveloped societies with low dietary salt intake, arterial pressure rises to a lesser degree with increasing age, and the prevalence of hypertension is markedly less than in Western societies with regular salt intake.[14] Therefore, to establish an adequate relationship between arterial stiffness and salt intake, it is important to demonstrate that the relationship between arterial stiffness (measured noninvasively from pulse wave velocity) and salt intake is independent of the relationship between stiffness and mean arterial pressure for a given age range. Such relationships have been investigated in epidemiologic studies performed both in China and Australia by Avolio et al.[15,16]

Arterial pulse wave velocity was measured together with arterial pressure in two groups of healthy subjects living either in a rural or an urban community in China.[15] Serum cholesterol levels were similar and low in each group, whereas the prevalence of both hypertension and salt intake was significantly higher in the urban community. In the rural group, pulse wave velocity was consistently lower in the aorta, arm, and leg and increased to a lesser degree with age compared with the urban group. This finding was observed even when subjects with the same arterial pressure and of the same age were compared. Results in two ethnically similar populations with low serum cholesterol levels and low prevalence of hypertension and salt intake, therefore, suggested that salt intake had an independent effect on arteriolar tone and arterial wall properties, with the former indirectly and the latter directly contributing to increased arterial stiffness with age.

In Australia,[16] pulse wave velocity was measured in 57 normotensive subjects who voluntarily followed a low-salt diet (mean intake, 44 mmol/d sodium for a period ranging from 8 months to 5 years). Subjects who followed a regular diet were matched for age and mean arterial pressure with the low-salt group, and were used as a control group. For both samples, subjects were divided into three age subgroups. In subgroup 1 (aged 2 to 19 years), pulse wave velocity was similar in the control and low-salt groups. In subgroups 2 (20 to 44 years) and 3 (45 to 66 years), pulse wave velocity measured in the aorta, arms, and legs was consistently lower in the low-salt than in the control group. The findings suggested that normotensive adult subjects who followed a low-salt diet have reduced arterial stiffness, and that this effect was independent of blood pressure.

In conclusion, results in a small number of cross-sectional epidemiologic studies suggested that salt intake may influence arterial stiffness in a manner that is independent of blood pressure, and that this influence is possibly more pronounced in older than in younger subjects.

Sodium-Induced Changes in Arterial Diameter and Stiffness

In recent years, some longitudinal studies focused on the sodium-induced changes in arterial diameter and stiffness and were performed in three different populations: subjects with mild to moderate essential hypertension in middle age; elderly subjects with systolic hypertension; and dialyzed patients with end-stage renal disease.

The hemodynamic effect of a moderately low salt diet was investigated in a 2-month, randomized, double-blind, crossover study in 20 hypertensive ambulatory patients.[17] Mean age was 42 ± 2 years (± standard deviation). All subjects followed a 9-week low salt diet. During this period they received capsules containing either lactose or NaCl (70 mEq/d) in 4-week treatment periods, separated by a 1-week wash-out period. Hemodynamic and biological parameters were evaluated at the day of randomization and at the end of the 4th and 9th weeks. Therefore, low sodium diet (LSD) was defined as a NaCl restriction period with lactose capsules, and normal sodium diet (NSD) as a NaCl restriction period with capsular salt supplementation. Blood pressure was significantly lower during the LSD compared with the NSD group, but the blood pressure changes were small: 6.5 ± 1.5 mm Hg for systolic blood pressure ($p < 0.001$) and 3.7 ± 1.1 for diastolic blood pressure ($p < 0.001$). This decrease in blood pressure was associated with a decrease in peripheral resistance in the carotid and forearm circulations (Figure 1). Of interest, the brachial artery diameter was larger during the LSD ($p < 0.01$), whereas the carotid artery diameter was unchanged (Figure 1). The brachial artery diameter changes were not related to the blood pressure changes but were positively related to the age of the patients (Figure 2) and negatively correlated with the basal intracellular (red cells) sodium content. These findings suggested that moderate, low salt restriction was indeed capable of decreasing blood pressure and lowering peripheral resistance in the carotid and forearm circulations but caused in parallel a brachial, but not carotid, dilatation. Therefore, the study showed that there are differences in salt dependence among different peripheral arteries, independent of blood pressure changes.

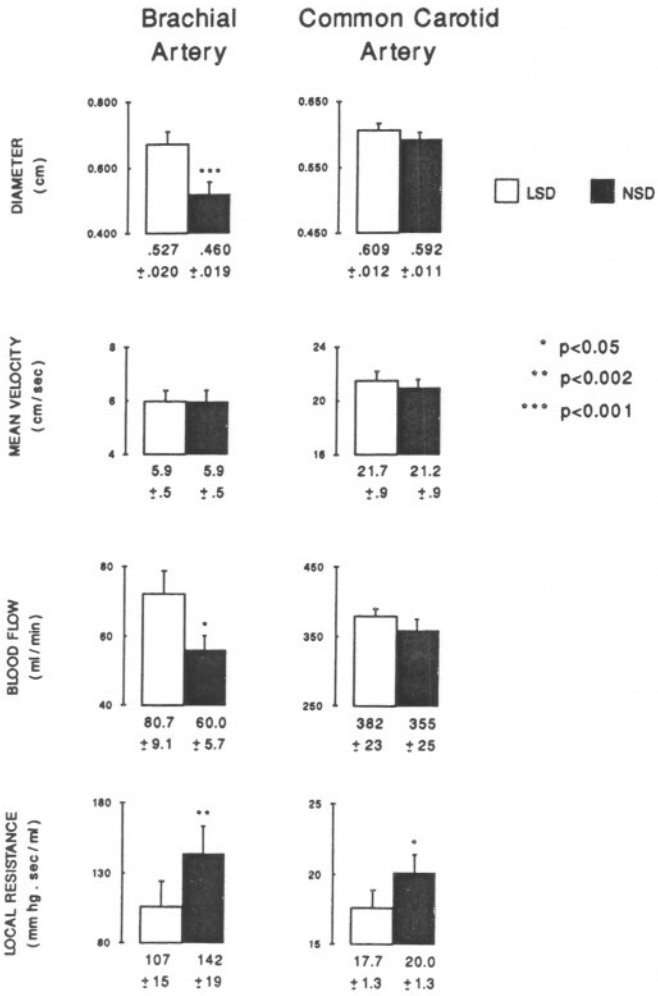

Figure 1. Sodium intake in hypertensive subjects: Long term cross over study on the brachial and the carotid circulation.[17] LSD = low sodium diet; NSD = normal sodium diet.

Because Myers and Morgan[18] showed that salt intake was associated with larger increases in blood pressure in older than in younger subjects, and that these changes were more pronounced with regard to systolic than diastolic blood pressure, it seems likely that the higher sensitivity of systolic pressure to sodium in older people might be mediated by a sodium-induced increase in the rigidity of the arterial wall. Further support for this hypothesis was obtained from the study of intravenous administration of isotonic saline (2 L in 120 min) to elderly subjects with systolic hypertension and arteriosclerosis obliterans of the lower limbs.[19] In such patients, isotonic saline caused a significant increase in systolic pressure, whereas diastolic and mean arterial pressure did not change significantly. No comparable results on blood pressure were observed in age- and sex-matched normotensive controls. Before saline infusion, forearm arterial compliance was found to be

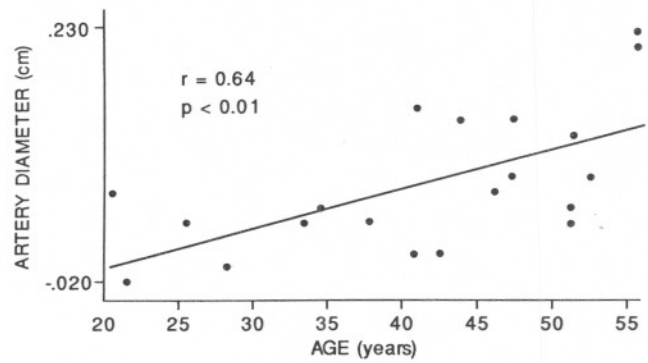

Figure 2. Effect of sodium intake on the change in brachial artery diameter of hypertensive subjects: Role of age.[17]

reduced, indicating that increased stiffness of the arterial wall contributed to the mechanism of untreated systolic hypertension in these patients. After saline infusion, a further decrease in forearm arterial compliance was observed along with the increase in systolic blood pressure. Such findings strongly suggested that the reduction in arterial compliance after isotonic saline was due to sodium-induced mechanisms acting on the arterial wall independently of the changes in blood pressure.

Similar observations were made in patients with severe hypertension and end-stage renal disease undergoing hemodialysis.[20] Such patients are characterized by striking arterial damage involving calcifications, enlarged aortic diameter, and increased indices of arterial stiffness. In subjects who did not receive antihypertensive treatment, pulse wave velocity increased and was shown to be strongly associated with positive sodium balance, as assessed from interdialytic weight

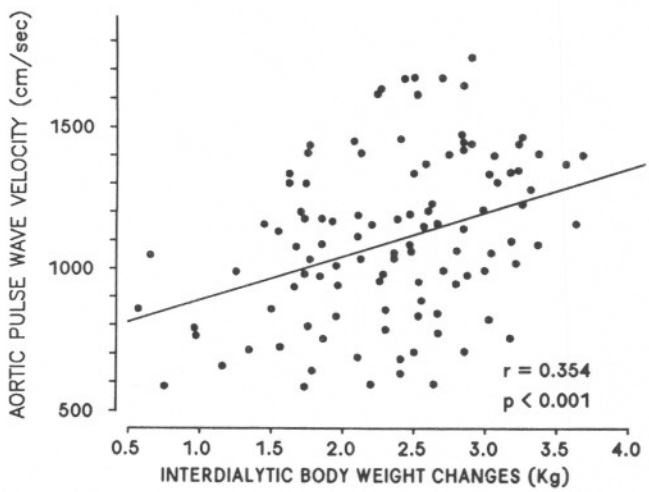

Figure 3. Untreated patients with severe hypertension and end stage renal disease: Relationship between interdialytic weight gain and aortic pulse wave velocity as a marker of aortic stiffness.[20]

gain (Figure 3). This finding was shown to be independent of age and blood pressure level. After long-term treatment by the calcium blocker nitrendipine, blood pressure decreased rapidly. Pulse wave velocity also significantly decreased, 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.

Finally, clinical studies have strongly suggested that sodium intake influences the geometry and stiffness of the arterial wall independently of blood pressure changes. This finding was observed particularly in older subjects and in patients with advanced hypertension and end-stage renal disease. Because changes in smooth muscle tone are known to affect visco-elastic properties of the arterial wall in hypertensive subjects[6,12] and because sodium is known to act on arterial smooth muscle tone,[7-11] the complex relationships between sodium and the arterial wall may be considered to be largely independent of blood pressure changes.

Diuretic-Induced Changes in Arterial Stiffness

Studies of the effects of diuretics on arterial stiffness in hypertension have been based on both experimental and clinical recent data.

Experimental Data. Two different diuretic compounds were investigated: indapamide and cycletanine. For indapamide,[21] an experimental model of in situ isolated carotid artery was used to evaluate the static mechanical properties of the arterial wall in 12-week-old Wistar and deoxycorticosterone acetate- (DOCA-) salt hypertensive rats. The rats were made hypertensive by left kidney removal, DOCA (50 mg) tablet implantation for 2 weeks, and saline diet (NaCl 9% solution as beverage). Normotensive control rats and DOCA-salt hypertensive rats received indapamide (10 mg/kg) or placebo by gavage 12 hours and 1 hour before measurements were obtained. In anesthetized, intubated and ventilated rats, a first catheter was introduced into the ascending aorta through the right carotid artery. A perivascular ultrasonic flow probe was placed around the ascending aorta, allowing simultaneous recording of the phasic ascending aortic pressure and flow. Systolic and diastolic pressure, cardiac output, and heart rate were directly measured. After hemodynamic measurements, a segment of the left carotid artery was then isolated in vivo and its volume-pressure relationship was recorded before and 30 minutes after total abolition of the vascular muscle tone by a potassium cyanide (KCN) solution. The carotid compliance (μL/mm Hg) was calculated for every pressure step as the slope of the volume-pressure curves. Indapamide significantly reduced the arterial pressure in hypertensive rats, and this result was related to a marked decrease in total peripheral resistance. Systemic arterial compliance was significantly increased by treatment with indapamide in the hypertensive group. Furthermore, there were significant differences in carotid compliance in Wistar and DOCA-salt animals. Maximal values of carotid compliance measured for pressure values close to the operating pressure in both groups were significantly higher in the untreated DOCA-salt group than in the normotensive Wistar group. Maximal values of carotid compliance were increased by 32% and 30% ($p < 0.01$) after KCN poisoning in Wistar and DOCA-salt rats, respectively. Treatment by indapamide induced a significant increase in carotid compliance in both the normotensive and hypertensive groups (+18% and +30%, respectively; $p < 0.01$). Although there was a reserve of carotid compliance in Wistar rats pretreated with indapamide (significant decrease in stiffness after KCN poisoning), there was no further increase in carotid compliance in hypertensive rats when KCN poisoning was performed after treatment with indapamide. The results suggested (1) that in the first weeks of hypertension induced by DOCA and salt diet, a significant decrease in arterial stiffness occurred, possibly related to modifications in vascular connective tissues and arterial vascular smooth muscle tone as previously reported;[22] and (2) acute treatment with indapamide induced an increase in arterial compliance in both normotensive and hypertensive rats.

In another study,[23] the effects of cycletanine (3 mg/kg) on the systemic hemodynamics and mechanical properties of the arterial wall were tested in 12-week-old normotensive Wistar Kyoto (WKYs) rats and spontaneously hypertensive rats (SHRs). The mechanical properties of the arterial wall were assessed using three independent methods: the characteristic impedance of the ascending aorta, systemic arterial compliance, and compliance of the carotid artery. Characteristic impedance and systemic compliance were calculated from phasic records of pressure and flow in the ascending aorta; carotid compliance was measured in situ with or without smooth muscle cell activity (obtained using potassium cyanure [KCN]). After chronic therapy by daily gavage for 15 days, there were no significant changes in either WKYs or SRHs in terms of arterial blood pressure, cardiac output, and heart rate. In contrast, characteristic impedance, systemic compliance, and passive distensibility of the isolated carotid arteries were significantly improved in treated groups. From the effect of potassium cyanure, it appeared that the increase in carotid compliance reflected modifications in the smooth muscle tone of the arterial wall after cycletanine chronic therapy. Although the exact mechanisms of the observed changes in arterial mechanics remained unclear, the study showed that, in experimental hypertension, cycletanine affected distensibility and compliance of large arteries independently of significant changes in blood pressure.

Clinical Data. This issue was recently reviewed based on personal data on hydrochlorothiazide[24] and recent

Table 1. Arterial Changes After Hydrochlorothiazide vs. Félodipine in Subjects with Essential Hypertension[24]

	Baseline	Félodipine	HCZ	p Value
Systolic blood pressure (mm Hg)	162 ± 12	140 ± 17	150 ± 13	<0.02
Diastolic blood pressure (mm Hg)	96 ± 9	85 ± 9	89 ± 9	<0.05
CF–PWV (m/s)	10.9 ± 2.0	9.2 ± 1.8	10.1 ± 2	<0.005
FT–PWV (m/s)	12.8 ± 1.7	11.1 ± 1.9	12.2 ± 1.7	<0.005
CR–PWV (m/s)	11.7 ± 1.9	10.0 ± 2	11.8 ± 1.8	<0.005
Brachial artery diameter (cm)	0.437 ± 0.06	0.449 ± 0.06	0.431 ± 0.05	<0.05
Brachial vascular resistance (dyne · s · cm^{-4})	140 ± 40	72 ± 30	92 ± 46	<0.05
Brachial artery compliance (dyne · $cm^{-4} \cdot 10^{-7}$)	1.13 ± 0.48	1.71 ± 0.83	1.19 ± 0.57	<0.005

Values are mean ± 1 standard deviation.

CF = carotid-femoral; CR = carotid-radial; FT = femero-tibial; PWV = pulse wave velocities.

studies on indapamide.[25] The antihypertensive and arterial effects of the diuretic compound, hydrochlorothiazide (HCZ), were compared with those of the calcium-entry blocker, felodipine, in patients with essential hypertension.[24] After a 1-month placebo-period, the patients were included in a double blind, crossover and randomized study. All received either hydrochlorothiazide (25–50 mg) or felodipine (5–10 mg) once a day for 6 weeks. Hemodynamic investigations at the end of the placebo and each treatment period included blood pressure and regional pulse wave velocities using a doppler technique for the carotid-femoral, femorotibial, and carotid-radial (CR) areas. Arterial diameter, blood flow, and vascular resistance and compliance were measured at the site of the brachial artery using a bidimensional Doppler system.[6] The study showed that, whereas felodipine decreased blood pressure more substantially than hydrochlorothiazide and increased arterial distensibility in the aortic and limbs circulations, the diuretic compound had absolutely no arterial effect despite significant but modest blood pressure reduction (Table 1).

In another study using indapamide,[25] systemic arterial compliance, assessed by the ratio of stroke volume to pulse pressure, was determined in ten patients with essential hypertension who were treated with placebo or indapamide (2.5 mg/d) in a crossover, single-blind study. After 3 months of therapy, mean arterial pressure was significantly reduced as was total peripheral vascular resistance. Significant increases occurred in cardiac index and arterial compliance. A significant direct correlation was found between compliance and baroreceptor sensitivity assessed during induced increase and reduction of blood pressure obtained with phenylephrine. The results supported the conclusion that chronic treatment with indapamide enhanced arterial compliance. Whether this was due to blood pressure reduction or to a drug-induced arterial effect remains to be investigated.

The indapamide arterial effect on systemic compliance was not observed on other arteries, such as the brachial artery. In this particular case, indapamide did not change brachial artery diameter despite a significant blood pressure reduction.[26] Compliance and distensibility were unchanged[26] or poorly modified.[27] Nevertheless, the lack of change in arterial diameter in the presence of the fall in blood pressure proved a shift of the pressure-diameter curve toward lower values of blood pressure and, therefore, indicated diuretic-induced changes in the arterial wall.[25] A similar finding was observed with the antialdosterone compound, canrenone.[28] Moreover, whereas acute administration of ouabain did not change brachial artery diameter in untreated hypertensives, after canrenone, acute ouabain produced a brachial artery constriction, again indicating a diuretic-induced change in the arterial wall.

Finally, sodium acts on the arterial wall independently of blood pressure changes. However, the arterial modifications produced by diuretic agents are relatively small in hypertensive humans, and this point remains difficult to explain. Potassium changes are an unlikely explanation because indapamide and canrenone, which have opposite effects on serum potassium, produce the same arterial changes.[26] Because indapamide had more substantial arterial effects than hydrochlorothiazide, differences in drug biochemical structure and dosage may be involved.[29,30] However, the most satisfying explanations result from two observations. First, the antihypertensive effect of diuretics is modest, with a small resulting passive increase in arterial compliance. Second, diuretics cause counterregulatory mechanisms involving an activation of the renin-angiotensin and autonomic nervous systems, which both favor arterial constriction.[31] It is suggested, therefore, that all these factors contribute to modulation of the relaxing process induced by salt and water depletion.

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