The relationship between blood pressure (BP) and sodium intake is well documented. Large observational studies have shown that sodium chloride (NaCl) intake is directly related to BP, whereas various interventional studies demonstrated a relationship between the reduction in NaCl intake and magnitude of BP reduction. Similarly, a low-potassium diet is associated with high BP and increased cardiovascular risk. In the Intersalt Study, urinary potassium excretion (a surrogate for intake) was associated with a lower BP after adjustment for various confounders, including urinary sodium excretion.

The effects of dietary sodium and potassium on BP are closely related. The first strain of rats bred by Dahl for the trait of “salt sensitivity” demonstrated less NaCl-induced hypertension when potassium intake was high. Well-controlled human studies subsequently showed that the BP-rising effect of extremely high NaCl intake can be blunted by potassium supplementation. Clinical trials showed that potassium supplementation modestly reduces BP, an effect that is, however, enhanced in blacks and in the presence of a high-sodium diet. Conversely, hypertension in potassium deficiency is associated with increased renal sodium reabsorption, whereas sodium restriction may prevent the development of hypertension induced by potassium restriction. Recent literature has identified regulatory pathways of tubular sodium and potassium handling (e.g., those mediated by with-no-lysine-kinase 1) that may, at least partially, mediate sodium and potassium handling (eg, those mediated by the endothelium, which is an important consideration in light of experimental data suggesting that NaCl and potassium have BP-independent effects on endothelial function. The effect of dietary NaCl on the

In this issue of Hypertension, Redelinghuys et al3 report on the independent relationship between sodium and potassium urinary excretion (measured as surrogates of dietary intake) to brachial PP, 24-hour PP, carotid-femoral pulse wave velocity (a marker of aortic stiffness), and various aortic pulsatile hemodynamic indices assessed with the use of a generalized transfer function applied to the radial pressure wave form, among 635 black adults from Johannesburg, South Africa. The main findings of the study are that, in this population in which average sodium intake was high and potassium intake was low, the urinary sodium/potassium (Na+ / K+) ratio independently correlated with higher central PP, 24-hour PP, central forward wave amplitude, central augmented pressure, and augmentation index but not with office brachial PP or carotid-femoral pulse wave velocity. This was true even in models that adjusted for mean pressure. Interestingly, sodium excretion correlated positively, whereas potassium excretion correlated negatively, with adverse pulsatile hemodynamics, but in contrast to relationships found for the Na+/K+ ratio, these relationships disappeared after adjustment for mean pressure. The authors suggest that abnormalities in central hemodynamics may underlie the adverse effect of a high-sodium/low-potassium diet on cardiovascular risk.

The observations by Redelinghuys et al3 are relevant because the association between dietary sodium/potassium intake and cardiovascular disease cannot be fully explained by brachial BP in animal or human studies. The suggestion that central hemodynamics may mediate such association is an intriguing possibility that requires further investigation. As Redelinghuys et al3 duly note, their study cannot assess causality; however, it does raise important questions regarding the potential mechanisms underlying their observations. Some clues may lie in the pattern of the observed hemodynamic relationships. The authors found a relationship between the urinary Na+/K+ ratio and a higher augmentation index, suggesting increased wave reflections. Wave reflections arise when the energy wave generated by the left ventricle is transmitted by conduit vessels, partially reflected at multiple sites of impedance mismatch along the arterial tree and conducted back to the heart, merging into a “net” reflected wave, which augments mid-to-late central systolic (and pulse) pressure. It is generally accepted that muscular arteries and smaller vessels are the main sites of wave reflections, and it has been demonstrated that the tone of these vessels can modulate the magnitude of reflections. In turn, such tone is regulated by the endothelium, which is an important consideration in light of experimental data suggesting that NaCl and potassium have BP-independent effects on endothelial function. The effect of dietary NaCl on the

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endothelium may be mediated through transforming growth factor-β1 and NO. Dietary potassium supplementation enhances endothelium-dependent responses to acetylcholine in the aorta of NaCl-loaded hypertensive Dahl salt-sensitive rats and hypertensive stroke-prone spontaneously hypertensive rats, effects that are at least partially BP independent. Intrabrachial infusion of potassium chloride potentiates NO-dependent, endothelial-dependent vasodilation induced by acetylcholine in the forearm of hypertensive humans. Furthermore, a recent randomized, double-blind crossover placebo-controlled trial among 42 hypertensive individuals (including 10 blacks) demonstrated that potassium supplementation with either potassium bicarbonate or potassium chloride (64 mmol/d of K⁺) for 4 weeks improves endothelial function without a significant change in office BP, although a modest effect was detected on brachial 24-hour and daytime systolic BP with potassium chloride. This effect could not be attributed to changes in natriuresis. Interestingly, in this study, potassium supplementation significantly reduced left ventricular hypertrophy and improved diastolic function, both of which are sensitive to the effect of late systolic load on the heart that occurs from wave reflections.

It is worth noting that target organs (kidneys, heart, and brain) are exposed to aortic rather than brachial pressures. In addition to potential BP-independent effects of sodium/potassium intake on the vascular wall, it is possible that NaCl intake and central hemodynamics interact to exert deleterious effects on target organs. Under normal circumstances, renal autoregulation operates to preserve a relatively constant renal blood flow and glomerular filtration rate over a physiological range of perfusion pressures by at least 2 mechanisms: afferent arteriolar myogenic response (smooth muscle contraction with increasing stretch) and tubuloglomerular feedback (which translates flow-dependent changes in the composition of the tubular fluid at the macula densa into proportionate changes in afferent arteriolar resistance). Importantly, afferent arteriolar myogenic tone appears to be primarily responsive to systolic pressure, regardless of the level of diastolic or mean pressure, and may partially protect the nephron from barotrauma during hypertension. In some rat models, glomerular injury can result from the combination of systemic hypertension and impaired autoregulation that permits transmission of the elevated pressure into the glomerulus. Animal data suggest that a high-sodium diet reduces myogenic reactivity in preglomerular resistance vessels and autoregulatory responses of juxtaglomerular afferent arterioles. If similar mechanisms operate in response to NaCl intake in at least some individuals, dietary NaCl-induced impaired autoregulation may conspire with adverse central hemodynamics to promote an accelerated renal function decline. Parmer et al showed that black hypertensive subjects responded to an increase in dietary sodium with greater increases in glomerular filtration rate compared with white subjects despite similar increases in mean arterial pressure, a response associated with higher renal plasma flow and decreased renovascular resistance, consistent with afferent arteriolar vasodilation. NaCl may also potentiate the effects of adverse central hemodynamics on the heart. Animal, epidemiological, and clinical studies suggest that a high-sodium diet is associated with myocardial hypertrophy, independent of BP. In vitro, NaCl directly induces myocardial hypertrophy, and in at least 1 animal model, NaCl induces left ventricular hypertrophy even in the absence of hypertension, an effect that may be related to decreased myocardial expres-

Figure. Potential mechanisms by which sodium/potassium intake and central hemodynamics may interact to promote hypertensive target organ damage. SVR indicates systemic vascular resistance; NOS, NO synthase; LVH, left ventricular hypertrophy; WINKs, with-lysine kinases; Zc, characteristic impedance. The potential role of the skin interstitium in regulating sodium homeostasis and the effect of volume expansion on cardiac preload are not schematized.
tion of NO synthase.\textsuperscript{10} Finally, like the renal circulation, the cerebral vasculature is a low-resistance/low-impedance bed, and excessive central pulsatility with penetration into the brain small vessels has been proposed to play a role in microvascular disease.\textsuperscript{11}

The Figure summarizes potential causal relationships and mechanisms of the observed association among sodium/potassium intake, central hemodynamics, and target-organ damage. These remain highly speculative and should be addressed in future studies.

The novel results of Redelinghuys et al\textsuperscript{3} should be taken in the context of their limitations. Caution should be taken when attempting to generalize these results to other populations, because black populations are particularly susceptible to the effects of sodium on BP. As noted by the authors, the study does not demonstrate that central hemodynamic changes mediate the effect of sodium/potassium intake on cardiovascular risk. Indeed, a high-sodium diet may influence human health by several mechanisms other than (peripheral or central) BP. Although the relationship between urinary \( \text{Na}^+ / \text{K}^+ \) and pulsatile hemodynamics was modest, it should be recognized that many factors can affect central hemodynamics and that, despite careful design and technique, varying degrees of measurement accuracy are inevitable when one-time noninvasive assessments and urine collections are performed in large free-living populations. This is not accounted for when correlation coefficients are computed with linear regression, introducing the potential to understate relationships. Nearly one third of participants with hemodynamic data were not included because of lack of 24-hour urinary samples meeting prespecified quality-control criteria, and none of the study participants had carotid-femoral pulse wave velocity and sodium/potassium intake measured over 24 hours.

The lack of an association between carotid-femoral pulse wave velocity and sodium/potassium intake is surprising given previous data. Despite this finding, the urinary \( \text{Na}^+ / \text{K}^+ \) ratio was associated with greater forward wave amplitude, which is determined by the early systolic flow generated by the left ventricle and by proximal aortic characteristic impedance, which, in turn, depends on ascending aortic stiffness but is also highly sensitive to changes in aortic diameter. Therefore, these findings raise the possibility that \( \text{Na}^+ / \text{K}^+ \) intake correlates with aortic characteristic impedance, which, in turn, may suggest preferential stiffening of the proximal aorta or (more likely) a relationship with proximal aortic diameter. However, higher flow rates from greater cardiac preloading cannot be excluded. Analyses of aortic pressure-flow relations would have allowed a more precise assessment of hemodynamic patterns. Nevertheless, the study by Redelinghuys et al\textsuperscript{3} provides further evidence of the feasibility and importance of assessing central hemodynamics in clinical and epidemiological studies and suggests that these assessments should be an important component of salt-sensitivity studies in humans.

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