

## Another Major Role for Dietary Sodium Reduction Improving Blood Pressure Control in Patients With Resistant Hypertension

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Resistant hypertension, defined as blood pressure (BP) above goal in spite of the current use of 3 antihypertensive agents of different classes, is a common problem in general medical practice as well as specialty hypertension clinics.<sup>1</sup> The prevalence of resistant hypertension is uncertain. Recent trials suggest a prevalence of 20% to 30%,<sup>2</sup> which might be an overestimate because of selection procedures and enrollment criteria. If one applies a prevalence of 10% to the estimated 65 million Americans with hypertension, then ≈6.5 million Americans have resistant hypertension. The cause of this condition is almost always multifactorial. Common factors include lifestyle factors (eg, excess sodium intake, obesity, high alcohol intake), drug-related causes (eg, non-narcotic analgesics, sympathetic agents), and secondary causes of hypertension (eg, obstructive sleep apnea, primary aldosteronism, chronic kidney disease, and renal artery stenosis). In contrast to most of these conditions, a high sodium intake is ubiquitous and provides an opportunity to improve BP control, even when other factors coexist.

Evidence linking salt (sodium chloride) intake with elevated BP is substantial and indisputable. Sodium reduction has been shown to lower BP in persons with prehypertension, untreated Stage 1 hypertension, and medication-treated hypertension.<sup>3</sup> The effects of sodium reduction in hypertensive individuals on multiple medications, with or without controlled BP, has received scant attention, probably because of challenges related to accrual of participants and ethical issues related to prolonged assignment to a high-sodium control condition. In this issue of *Hypertension*, Pimenta and colleagues document the benefits of sodium reduction in patients with resistant hypertension.<sup>4</sup>

Pimenta and colleagues are to be congratulated for designing and implementing this challenging but informative and likely influential study. One cannot overestimate the logistical difficulties of recruiting eligible and interested participants, feeding them every meal over an extended period, and collecting a plethora of measurements. In brief, Pimenta and colleagues conducted a 2-period, randomized, crossover feeding study that compared 2 levels of sodium intake (250 mmol

[5700 mg] per day versus 50 mmol [1150 mg] per day). Each feeding period lasted 1 week. Participants were 12 patients with resistant hypertension (50% black, 67% female, mean age of 55.5 years, mean body mass index of 32.9 kg/m<sup>2</sup>). At baseline, participants had mean office BP of 145.8/83.9 mm Hg on an average of 3.4 antihypertensive medications; baseline 24-hour urine sodium excretion was 194.7 mmol (4470 mg) per day.

The results were striking. Compared to the higher level of sodium intake, the lower level of sodium intake reduced mean (95% CI) office systolic BP by 22.7 mm Hg (11.8, 33.5) and office diastolic BP by 9.1 mm Hg (3.1, 15.1). Reductions in daytime, nighttime, and 24-hour ambulatory BP were virtually identical to reductions in office BP. The extent of BP reduction vastly exceeds corresponding levels of BP reduction observed in trials of hypertensive individuals not on medication (see Table for a comparison of trial results with corresponding data from untreated hypertensive individuals enrolled in the Dietary Approaches to Stop Hypertension-Sodium [DASH-Sodium trial]).<sup>5</sup>

The main limitations of the trial by Pimenta and colleagues are its size (only 12 participants) and the duration of feeding

**Table. Comparison of Two Trials of Sodium Reduction**

Feature	Trial by Pimenta et al <sup>4</sup> (n=12)	DASH-Sodium Trial (Subset of Participants With Untreated Hypertension) <sup>5</sup> (n=168)
% on antihypertensive medication	100%	0%
% black	50%	61%
% female	67%	63%
Mean±SD age, y	55.5±9.4	50.3±10.6
Mean±SD baseline sodium excretion, mmol/day	194.7±68.6	153.4±74.8
Highest and lowest sodium levels provided during feeding, mmol/day	250 vs 50	150 vs 50
Mean±SD baseline systolic BP, mm Hg	145.8±10.8	143.0±7.8
Mean±SD baseline diastolic BP, mm Hg	83.9±11.2	88.5±4.5
Mean (95% CI) systolic BP reduction, mm Hg	22.7 (11.8, 33.5)	8.3 (6.6, 10.0)
Mean (95% CI) diastolic BP reduction, mm Hg	9.1 (3.1, 15.1)	4.1 (3.3, 5.4)

Data taken from Trial by Pimenta et al<sup>4</sup> of patients with resistant hypertension and the DASH-Sodium Trial<sup>5</sup> of patients with untreated hypertension.

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(only 1 week per feeding period). Replication of the study is clearly warranted. Its strengths include superb implementation, which achieved the intended contrast in sodium intake (24-hour urine sodium excretion of 252.2 versus 46.1 mmol/d), and the large number of outcome variables, including ambulatory BP, pulse wave velocity measurements, and measurements of renin-angiotensin system activity. In the context of other human research on dietary sodium intake and BP, which has focused almost exclusively on individuals who were on no or few antihypertensive medications, these results extend the role of sodium reduction to an important but understudied population.

Were the large BP reductions expected? Perhaps. Some might anticipate that sodium reduction would lower BP substantially, because all participants were taking either an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Medications that block the renin-angiotensin system lead to increased salt sensitivity.

However, I was surprised by the extent of BP reduction, which was roughly the equivalent of adding 2 antihypertensive medications. First, trial participants were already taking a large number of antihypertensive medications (mean of 3.4 drugs per day). Subadditivity commonly occurs when multiple effective therapies are implemented simultaneously. Second, all participants were taking hydrochlorothiazide. In this setting, one might expect an attenuated effect from dietary sodium reduction given that participants were already on volume-reducing therapy. Nonetheless, participants must have still had some degree of volume expansion, likely quite large, given the pattern of findings—namely, higher plasma renin activity and reductions in weight, brain natriuretic peptide, and creatinine clearance when sodium intake was reduced. The relatively high level of nighttime BP compared to daytime BP (mean nighttime BP of 146.8 versus mean daytime BP of 152.3 mm Hg on the higher sodium level) also suggests a volume-expanded state. Third, despite the diagnosis of resistant hypertension, mean office systolic BP of 145.8 mm Hg was just above the treatment goal of 140 mm Hg, whereas the mean office diastolic BP of 83.9 mm Hg was well below the treatment goal of 90 mm Hg. In general, trials that enroll persons with lower levels of BP observe less BP reduction from active therapy than trials enrolling persons with higher levels of BP. Fourth, the background diet of the participants was rich in potassium (4100 mg [106 mmol] per day). The effects of sodium reduction on BP are commonly blunted in the setting of high potassium intake.

Another remarkable, perhaps expected, finding was the high baseline sodium intake, measured when the participants were eating food that they prepared or selected. Indeed, the mean 24-hour urinary sodium excretion of 194.7 mmol (4470 mg) per day at baseline is nearly double the recommended upper limit of 100 mmol (2300 mg) of sodium per day for the general population and nearly triple the corresponding limit of 65 mmol (1500 mg) per day for persons with hypertension.<sup>6</sup> Although one might be discouraged by the excessive levels of sodium intake in this high-risk population, such levels also provide a clear opportunity for intervention.

Given the documented benefits of reducing sodium in this high-risk population, a critical issue is how to accomplish

effective sodium reduction. Options include individual-based counseling, such as that provided by dietitians, and public health strategies designed to achieve population-wide reduction in the sodium content of the food supply. These strategies are not mutually exclusive. However, it will be impossible to reach an intake of 50 mmol per day without a major reduction in the sodium content of commercially prepared foods. Outside of the arcane environment of the feeding study, a sodium intake of  $\approx$ 50 mmol per day is rare in the United States. Fewer than 5% of adult men and women consume less than 65 mmol (1500 mg) of sodium per day.<sup>7</sup> Even with intensive behavioral counseling that focuses exclusively on sodium reduction, mean achieved levels of sodium intake are typically about 100 mmol (2300 mg) per day.<sup>8</sup> Comprehensive lifestyle interventions that include weight loss and improved dietary patterns commonly are less successful, likely because of the complexity of making multiple lifestyle changes and potential tradeoffs when there are multiple lifestyle goals. Hence, although long-term intensive counseling by dietitians has been shown to lower sodium intake<sup>9</sup> and reduce cardiovascular disease risk,<sup>10</sup> the vast scope of the BP epidemic argues for major changes in the food supply.

In the meantime, how should physicians manage patients with resistant hypertension? Of course, prescription of appropriate drug therapy is one pillar of therapy. Results from this trial document volume expansion on conventional doses of hydrochlorothiazide and therefore support recommendations that chlorthalidone, a thiazide diuretic with a long duration of action, be preferentially used rather than the shorter-acting thiazide diuretic, hydrochlorothiazide. As for diet recommendations, physicians should reinforce key messages related to the importance of reducing dietary sodium intake; provide basic information on common food sources of sodium; refer the patient, if possible, to a dietician for basic counseling; and advocate for policy changes that lead to a reduced sodium content of commercially prepared foods.

In summary, data presented by Pimenta and colleagues strongly suggest that persons with resistant hypertension are extremely sensitive to the BP-lowering effects of sodium reduction. The observed reductions in BP were huge—roughly equivalent to adding 2 antihypertensive medications. Although clinicians commonly focus on the next drug (eg, aldosterone blocking therapy) and sometimes a device (eg, Rheos systems that stimulate carotid baroreceptors), a renewed and aggressive emphasis on lifestyle modification, specifically sodium reduction, is warranted in patients with resistant hypertension and uncontrolled BP.

## Disclosures

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