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EDITORIAL COMMENT

Excessive Sodium Intake and Cardiovascular Disease

A-Salting Our Vessels*

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Salt is ubiquitous in food, and its consumption in large amounts is consequently widespread. Whereas for thousands of years salt was required as a food preservative (Neolithics extracted salt from springs in 6000 B.C., and the town of Salzburg built a thriving economy on salt production), canning and refrigeration have provided good alternatives for food preservation for the past several decades. Despite these technological advances, salt levels in foods remain high, and over 75% of daily sodium intake comes as salt hidden in processed foods (1). With the minority of salt actively added as seasoning, getting individuals to substantially reduce their intake is a considerable challenge.

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A coherent body of data from animal, human pathophysiology, and clinical trials leaves little doubt that the usual level of sodium intake in our diets (at 3,000 to 4,500 mg daily) has substantial and widespread adverse effects on the cardiovascular system (2). Chiefly, excess dietary sodium predisposes to clinically measured hypertension and especially to age-related increases in blood pressure (and thereby leading most likely to consequences such as stroke and heart failure). Furthermore, many studies indicate that excess sodium itself may have adverse health outcomes independent of its effects on blood pressure; such effects may include ventricular fibrosis, renal damage, gastric cancer, and even osteoporosis (via increased urinary calcium loss) (3).

One of the chief organ systems vulnerable to the adverse effects of excess sodium in the diet is the systemic vasculature. Endothelial dysfunction in particular is an early pathogenic event in hypertensive arteriopathy, developing before hypertension-related complications such as arterial stiffness and atherosclerosis. In this issue of the *Journal,* Jablonski et al. (4) provide novel insights into the vascular effects of controlled dietary sodium reduction in mildly hypertensive middle-aged and older adults.

In a small but elegant study, these investigators randomized 17 adults (systolic blood pressure: 130 to 159 mm Hg) to 4 weeks of reduced (1,200 to 1,500 mg) or usual (3,600 mg) sodium intake, verified by urinary sodium excretion and detailed food frequency measurement. The diets were otherwise closely matched. Systolic blood pressure fell by an average of 12 mm Hg, and endothelial function improved significantly in both the conduit (brachial) artery and the arterial microcirculation. There was a significant relationship between low sodium excretion and improved endothelium-dependent dilation in the large arteries.

In a series of mechanistic experiments, the investigators then demonstrated that low sodium intake was associated with a number of potentially beneficial changes in arterial biology in vivo: greater arterial nitric oxide release, restored bioactivity of tetrahydrobiopterin (an essential cofactor for the healthy operation of the enzyme nitric oxide synthase), and likely a local reduction in arterial "oxidative stress." Further study is required to determine whether these favorable biological effects will be sustained in the longer term if persistent dietary salt reduction can be maintained.

The current study, like a number before it, proposes blood pressure–independent effects of salt reduction as the mechanism by which the observed changes were achieved. Although this is certainly possible, and is supported by other literature (2), the methodology employed by Jablonski et al. (4) was not a good test of this hypothesis. Including individuals' blood pressure measurements in statistical models is a poor means of controlling for the effects of change in blood pressure because of the enormous moment-to-moment within-individual variability of blood pressure levels. This means that little of the effect of blood pressure is controlled for when models are fitted in this way, with alternate methods that use grouped data being required to properly explore the blood pressure–dependent versus blood pressure–independent effects of interventions (5).

Whether via blood pressure or not, however, excess dietary sodium clearly exerts a variety of adverse effects on the systemic vasculature. What would be the likely cardiovascular effects of reducing sodium intake to the level realized in the current study (4), or less?

For hundreds of thousands of years, humans evolved on a diet that contained just traces of sodium (6). The Yanomamo Indians of the Amazon basin, first studied by Western society in the 1950s, provide some insight into what can be achieved with salt consumption at physiological levels (7). When first studied in the middle of the last century, the Yanomamo were consuming an unacculturated diet that delivered just a fraction of a gram of salt each day. The most striking consequence of this diet was that blood

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pressure in the older Yanomamo was the same as that in the adolescents.

The right concept of "normal" is fundamental to understanding the potential benefits of salt reduction to society. Although "normal" sodium consumption around the world these days is on the order of 3,000 to 4,500 mg/day, the combined anthropologic, physiological, and epidemiological evidence suggests that "normal" salt intake for most of human evolution was about one-tenth of that. Likewise, although a generation of clinicians has learned that "normal" systolic blood pressure is approximately 100 mm Hg plus age, it is now evident that this is not the physiological norm either. Cardiovascular events rates are substantially elevated at these higher blood pressure levels but reduce to a minimum at about 100 mm Hg systolic—the levels seen in adult Yanomamo (8).

If optimal salt intake and blood pressure are much lower than the currently accepted norms, then most adults have higher-than-optimal levels and thereby potentially have adverse health effects as a consequence (9). This is likely causing an enormous burden of preventable disease but offers a large, mostly untapped, opportunity for disease prevention.

Whereas we cannot return to the ways of the Yanomamo, an "achievable" level of dietary salt reduction has been proposed in a series of studies examining the DASH (Dietary Approaches to Stop Hypertension) diet, which reduces dietary sodium intake by approximately 50%. This has proven achievable in research studies (10), but widespread implementation would require action by many stakeholders, including legislators, food companies, and retailers, as well as by consumers. The gains from such a strategy, however, could be substantial. In the United States alone, a reduction in sodium intake by 1,200 mg daily across the population could have the following health benefits: 60,000 to 120,000 fewer coronary events, 32,000 to 60,000 fewer strokes, and healthcare cost savings of $10 to $24 billion each year (11). Furthermore, because centrally implemented programs targeting salt in the food supply require rather few resources, they are also highly cost effective (12).

Large, acute changes in dietary sodium restriction produce adverse effects on measures such as sympathetic nerve activation, insulin sensitivity, and aldosterone secretion (13), and on this basis, some have expressed caution in proposing universal dietary sodium reduction (14). Nonetheless, and based on the totality of the available evidence, sodium-reduction strategies have been widely proposed (e.g., a 2010 "Call to Action" by the American Heart Association [2]). More than 30 countries now have some form of action plan for dietary salt reduction in place (15), and the World Health Organization recommends salt reduction to its members as a "best buy" (16).

Studies such as that by Jablonski et al. (4) remind us that a simple molecule such as sodium can assault our vessels in complex maladaptive ways. Our next challenge is to translate this knowledge derived from vascular biology into effective and appropriate public health strategy. A randomized, population-based salt-reduction trial would be lengthy and difficult but would provide clarity in this important area.

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