Sodium and Its Multiorgan Targets
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Case Presentation: A 66-year-old retired man presented to his physician with complaints of shortness of breath and weight gain over 1 week’s time during a recent cruise. He was not short of breath in the supine position, although his neck veins were distended. The blood pressure was 196/104 mm Hg; his heart rate was 92 bpm; and his cardiac rhythm was normal. He had a large habitus and was 76 in tall and 248 lb, which was 27 lb heavier than when he was evaluated 6 weeks previously in the office. The lungs revealed fine crackling rales bilaterally and posteriorly, but no wheezes or other sounds were noted. A fourth heart sound was heard at the apex. The ECG revealed left atrial abnormality and left ventricular hypertrophy with a normal sinus rate and rhythm. The echocardiogram confirmed left ventricular hypertrophy, increased left atrial size, and evidence of impaired diastolic function, and the left ventricular ejection fraction was 32%. Pulse wave velocity and aortic distensibility were impaired. There was severe 4+ bilateral edema of both lower extremities to the knees. Although the hemogram was normal, his blood urea nitrogen and creatinine concentrations were 28 and 1.2 mg/dL, respectively. The urinalysis revealed 4+ proteinuria, and a 24-hour urine collection for sodium content (at the time when his appointment was made) was >13 g.

Brief Commentary
The patient had been a long-time patient of ours, with well-controlled hypertension (receiving an angiotensin II receptor blocker, a calcium antagonist, a β-adrenergic receptor blocker, furosemide, spironolactone, and a statin). He controlled his diet at home, but always was tempted by the cuisine on his frequent vacation cruises. His dietary indiscretion actually produced his 27-lb weight gain within the first 3 days of his cruise and was lost 2 days after his office visit after a temporary increase in the dose of furosemide and spironolactone. This clinical experience was not at all unusual over the years that we followed him up, despite maintaining a workable therapeutic program designed for him. He had reduced his body weight from 293 to 260 lb on a calorie- and sodium-restricted diet, but over these many years of follow-up, his dietary indiscretions always took a holiday, and its toll. He always apologized to me and his wife, but never to himself. He fully understood the basis of the development of heart failure and cardiovascular disease and the potential for end-stage renal disease, vowing not to let this gain happen again.

His is one of the major health problems of our society, prompting repeated recurrences of heart failure, and is the basis of many revisions of the dietary recommendations by the American Heart Association, the Institute of Medicine, and the National High Blood Pressure Education Program. Despite his awareness of dietary indiscretions, he knew our recommendations and followed them when at home. What is necessary is our continued patience and education, coupled with careful attention to nutritional guidelines. When reasonable dietary programs were established recently for obese children and adults to reduce calories, industry not uncommonly added additional salt to processed and prepared foods to overcome the altered taste associated with reduced fat content.

Overview
Interest in the salt and hypertension relationship has escalated to a new level after resurgence of the dietary salt content controversy, the relationship of increased dietary salt intake...
with cardiovascular outcomes and healthcare costs, and the recently issued new guidelines by the American Heart Association. Each of these issues has been based on the prevalence of hypertension and the propensity of salt and body weight to elevate blood pressure. However, many other important issues, including cardiovascular and renal complications of sodium excess in hypertension, have not been considered adequately. Thus, over the years, epidemiological reports have focused primarily on the elevated blood pressure that would be expected in salt-sensitive individuals in response to short-term salt-loading studies. However, only a small percentage of patients with hypertension are, in fact, salt sensitive in terms of blood pressure response. Less well recognized are the more subtle adverse end points of dietary salt excess on the structural and functional damage to the target organs of hypertensive disease (Table 1). Evidence for the other adverse influences of salt excess is derived from short- and long-term experimental studies and clinical pathophysiological investigations, but only a few longer-term studies, including 1 extremely important long-term multicenter clinical trial.

This report emphasizes the very serious consequences of prolonged dietary salt excess on the major target organs of hypertensive disease and its very real potential for harm in normotensive individuals. Awareness of this vital information is necessary, because we not only must be concerned with the response of arterial pressure, but also need to recognize the lethal and costly effects of salt responsible for the progression of cardiovascular and renal diseases and failure. Double-blind randomized trials may no longer be feasible for ethical reasons.

It was not until the third report of the National High Blood Pressure Education Program on Nonpharmacological Treatment of Hypertension (later called lifestyle modifications) that the pathogenesis of salt risk was discussed extensively, and specific recommendations were provided. Since then, arguments and controversy have remained, and the role of salt in altering the structure and function of the vital organs (ie, heart, large arteries and kidneys) continues to be relatively unrecognized and underemphasized.

### Toward Enlightened Understanding of Hypertensive Disease

Part of the problem with the consequences of dietary salt overload relates to the need to appreciate the overall concept of hypertension as a specific disease entity. First and foremost, salt excess does not just raise arterial pressure. One must be aware of the broader concept of hypertensive disease and that its interaction with salt is not simply a trivial consequence. Hypertensive disease occurs in >60 million Americans and >2 billion people worldwide and involves progressively impaired structure and function of the heart, large arteries, and kidneys until eventually their end-stage failure supervenes. These are the most common causes of hospitalization and healthcare costs in elderly populations of all industrial societies, whether hypertensive or normotensive.

Cardiac failure continues to be the most common cause of hospitalization in elderly patients, whether they are normotensive or hypertensive. Moreover, end-stage renal disease has not diminished at all since the introduction of antihypertensive therapy. Furthermore, deaths from stroke have not decreased since the earlier reports that demonstrated control of arterial pressure and dramatic reduction of deaths from stroke. And most surprising, until 1 recent large and compelling controlled, multicenter clinical trial, no effective preventive measures by dietary salt restriction had been clearly demonstrated.

### Pathophysiology

#### Experimental Evidence

To support the above assertions, one must first obtain evidence in controlled experimental studies and animal models, including genetic breeding, to demonstrate salt sensitivity or salt resistance, salt loading with or without added steroidal substances, extirpation of as much as 70% renal mass with additional salt loading, and treatment with nephrotoxic substances. In our studies spanning >3 decades, we have exclusively used the genetically bred spontaneously hypertensive rat, which was not developed to be salt sensitive, but rather to develop a natural model of hypertension similar to essential hypertension in humans. These studies have consistently demonstrated an elevated arterial pressure (from birth) associated with progressive end-stage cardiovascular and renal structural and functional derangements that closely mimic common hypertensive complications in patients with essential hypertension. Moreover, currently used antihypertensive therapy to suppress the systemic renin-angiotensin-aldosterone system (RAAS) (including angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, or both agents) in conjunction with dietary salt loading in these spontaneously hypertensive rats confers cardiovascular and renal protection (Table 2). Thus, severe structural and functional damage of heart, large vessels, and kidney in the spontaneously hypertensive rat was markedly and significantly prevented (or attenuated) by the same pharmacological interventions that have been used.

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**Table 1. Clinical and Experimental Manifestations of Angiotensin II–Mediated Dysfunction**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Manifestations</th>
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<tbody>
<tr>
<td>Cardiac</td>
<td>Diastolic dysfunction with normal systolic function</td>
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<tr>
<td></td>
<td>Systolic dysfunction</td>
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<tr>
<td></td>
<td>Perivascular fibrosis</td>
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<td>Large arteries</td>
<td>Arterial distensibility</td>
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<tr>
<td>Kidneys</td>
<td>Proteinuria</td>
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<td></td>
<td>Abnormal renal structure</td>
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<td></td>
<td>Impaired renal function</td>
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<td></td>
<td>End-stage renal disease</td>
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</tbody>
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**Table 2. Hypertensive Disease Targets**

- Cardiovascular disease
- Renal disease
- Neurological disease
- Cardiovascular and renal structural and functional damage

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**References:**

1. Frohlich and Susic Multiorgan Na⁺ Targets

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clinically to prevent cardiac remodeling and end-stage renal disease.7,13,16

These adverse changes were produced experimentally primarily with an 8% dietary salt overload, but similar cardiac and renal changes were also obtained in our initial studies with 4% salt loading17 and later by 4%, 6%, or 8% salt loading.11–15 These later studies produced severe proteinuria associated with end-stage renal disease, confirmed by renal physiological micropuncture and histological evidence identical to changes that occur in patients with essential hypertension with end-stage renal disease.13–15 The cardiac data revealed severely impaired left ventricular diastolic function associated with preserved systolic function in older adult spontaneously hypertensive rats that was also associated with severe systolic cardiac failure in 25% of younger adult spontaneously hypertensive rats.12,14 Furthermore, their large arteries demonstrated diminished distensibility indexes of stiffer vessels,12 and the experimental pathophysiological and histological alterations were similar to those in patients with end-stage cardiac and renal diseases.13–15,17–20 All these salt-induced adverse effects occurred with only minimal elevation of arterial pressure.

Postulated Mechanisms of Treatment of Local RAAS
We may wonder why RAAS inhibition may be beneficial in preventing structural and functional impairment produced by long-term salt overload when it is well known that this therapy inhibits the adverse effects of the RAAS. Clearly, the angiotensin II type 1 receptor blockers in our studies did, in fact, act on the angiotensin II receptors in target organs, although apparently not through its classic endocrine action. We and others have suggested that angiotensin-converting enzyme inhibitors and/or angiotensin II type 1 receptor blockers antagonized the adverse effects on salt-stimulated local RAAS receptors in heart, large arteries, and kidneys,7,17–20 The mechanisms of these actions have been achieved by antagonizing angiotensin II–stimulated mitogenesis of cardiomyocytes, accumulation of fibrillar collagen within the extracellular matrix and surrounding arterioles, apoptosis, and other possible local pathological events in heart, vessels, kidneys, and other organs (Table 1).19,20

Short-Term Clinical Evidence
The changes of diastolic dysfunction and large vessel disease with salt excess have similarly been demonstrated clinically in patients with essential hypertension and renal disease and in elderly normotensive patients.17,19,20 Hence, these clinical findings in patients with essential hypertension with cardiac, large-vessel, and renal diseases with salt loading were very similar to the structured and functional changes that occurred experimentally with salt loading.17,19,20

Long-Term Clinical Studies
The 1 large, well-controlled epidemiological study (ie, the Trials of Hypertension Prevention [TOHP] study) involved prehypertensive patients who were divided into 2 groups: 1 group agreed to pursue a salt-restricted diet, whereas the second was permitted to continue their usual daily salt-loaded (25%–35% greater sodium intake) diet. The latter group developed severely significant cardiovascular end points, confirming the foregoing experimental and shorter-term clinical studies. A few earlier clinical studies demonstrated similar findings,8 but certain differences raised by the TOHP investigators were not considered confirmatory in support of their study.8

Early Evidence From Great Britain
In the United Kingdom, preliminary reports have emerged that a population-wide reduction in the dietary intake of salt of 10% was achieved within 4 years without affecting sales of food products.21

Clinical Implications and Trials
The clinical implication is that long-term salt loading does not simply elevate blood pressure. Evidence from experimental and clinical studies is abundantly clear that salt loading induces local pathophysiological changes in the target organs of hypertensive disease that adversely affect cardiovascular and renal functional and structural derangement, which promote cardiovascular morbidity and mortality. But, should these findings obtained with lifetime dietary salt excess occur only in patients with prehypertension? We know that these end points of cardiovascular derangements occur not only in hypertensive patients, but also in normotensive subjects. Hospitalization records of all industrialized societies confirm this concept.9 Furthermore, we have known for years that end-stage renal disease occurs more frequently in patients with hypertension and in those patients who are elderly and have demonstrated progression of benign nephrosclerosis.22 The conclusion is clear: A lifetime of salt excess produces the identical pathological and physiological alterations that we cite here.

Conclusions
Dietary salt excess has repeatedly been demonstrated epidemiologically to elevate arterial pressure. Underemphasized, however, have been the far more subtle and lethal effects of salt on the vital organs affected by hypertensive disease and exacerbated by excess dietary salt. Severe structural and functional cardiovascular and renal changes produced by salt excess have been demonstrated experimentally and clinically in patients with essential hypertension. Moreover,
these pathophysiological changes have been prevented or ameliorated experimentally by agents that inhibit the local RAAS in heart, large arteries, and kidneys. The time has come for us to follow our recent national recommendations beyond the statement that simply pronounces dietary restriction means to reduce sodium to <1500 mg/d and labeling of the sodium content of food on containers. We in the United States should join with Great Britain in requiring a 10% reduction of the sodium content of foods. Within a short period of time, disease end points in Great Britain have already been reduced without negatively affecting the cost of foods containing lesser amounts of salt. The time has come for the United States to implement this important healthcare undertaking and to serve this vital role in world health leadership.

Disclosures

None.

References

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