APRIL 2006
Volume 10, Issue 4

CardiologyRounds™
www.cardiologyrounds.org

AS PRESENTED IN THE ROUNDS OF THE CARDIOVASCULAR DIVISION
OF BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

The Role of Salt in Hypertension: Its Effects are Far More than to Increase Arterial Pressure

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… But his wife looked back from behind him, and she became a pillar of salt. – Genesis 19:26

The term "salt sensitivity" has been used for decades to suggest that increased ingestion of salt results in an elevated arterial pressure. This concept is supported by a tremendous body of epidemiological, experimental, and clinical literature demonstrating that increased arterial pressure is associated with dietary salt excess resulting in hypertensive disease.[1,2] These data have also demonstrated that the diets of unacculturated populations are strikingly low in salt and, hence, the prevalence of hypertension (defined as elevated arterial pressure) is significantly low.[3-9] In contrast, the diets of more acculturated populations have remarkably increased salt content and, consequently, there is a proportionately greater prevalence of hypertension.[9-15] To understand the role of salt in elevating arterial pressure, most specifically in patients with hypertension, salt-loading and deprivation studies have been widely reported.[16-18] However, it has become clear that not all patients with essential hypertension are "salt-sensitive" and, conversely, those whose pressures do not increase are said to be "salt-resistant." This concept has been strengthened experimentally by the controlled studies of Dahl who carefully genetically bred rats with "sodium-sensitive" and "sodium-resistant" hypertension.[19,20] Subsequently, his pioneering work was confirmed in compelling epidemiological, experimental, and clinical literature.

This issue of *Cardiology Rounds* describes the pathophysiological mechanisms behind the relationship between salt-excess and hypertension, our experimental studies into the effects of chronic salt-loading on the heart, aorta, and kidney, and our postulated pathophysiological mechanisms for the observation that salt-loading apparently both depresses and stimulates the renin-angiotensin-aldosterone system.

Supportive pathophysiological mechanisms

In support of the "cause and effect" relationship between salt-excess and hypertension, a number of physiological mechanisms have been proposed. Early studies by Ledingham demonstrated increased arterial pressure in rats during the development of renal vascular hypertension. This was ascribed to increased cardiac output associated with an expanded extracellular fluid volume that was prevented (or attenuated) by a pressure-associated renal diuresis.[21] This concept was strengthened further by two lines of studies. In the first, the Borsts demonstrated that licorice from Holland (containing a substance that acts as a sodium-retaining mineralocorticoid) promoted sodium retention, increased cardiac output and, subsequently, arterial pressure.[22]

This more direct relationship between extracellular volume expansion and a consequent increased arterial pressure was first demonstrated by Selkurt, whose studies of renal perfusion demonstrated a direct relationship between renal perfusion and urine volume.[23] It was the subsequent system analysis studies by Guyton and his associates that demonstrated the same sequence of events, ie, expanded intravascular volume, increased cardiac output, and subsequent hypertension associated with increased total peripheral resistance.[24] These workers postulated that "salt-sensitive hypertension" was related to an altered renal regulatory response (ie, "whole body autoregulation") that reduced the kidney's ability to excrete salt and water at the expense of a proportional increase in arterial pressure. This explanation was further strengthened by cross-transplantation studies from Bianchi's group. When they transplanted kidneys from rats that were "salt-sensitive" into normal rats, they produced hypertension in the

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The editorial content of *Cardiology Rounds* is determined solely by the Cardiovascular Division of Brigham and Women's Hospital. This publication is made possible by an educational grant.

Cardiology Rounds **is approved by the Harvard Medical School Department of Continuing Education to offer continuing education credit**

normal rats; and, when a kidney was transplanted from a normal rat into one that was "salt-sensitive," arterial pressure was normalized.[25]

Tobian subsequently repeated Selkurt's studies and concluded that the increased renal arterial perfusion pressure in hypertensive salt-sensitive rats was necessary to excrete the same salt load observed in salt-resistant rats.[26] Thus, these and other studies demonstrated that salt-excess expands extracellular fluid volume and increases cardiac output and, with the participation of a renal autoregulatory response, increases arterial pressure to normalize the expanded fluid volume in "salt-sensitive" hypertension. These early studies provided a rational hypothesis to explain why salt-loading could promote development of a persistently elevated arterial pressure.

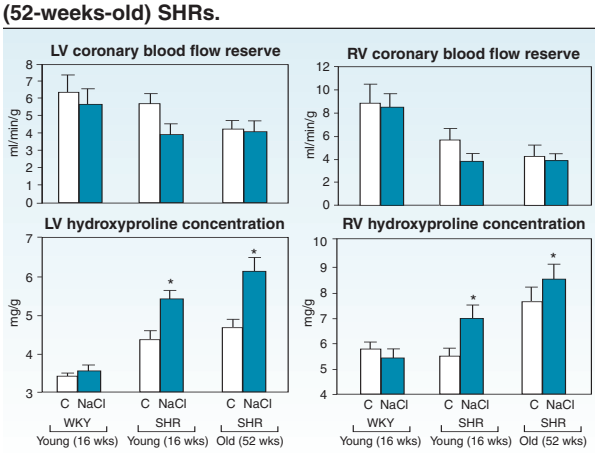
The clinical conundrum

There is a major troubling concern associated with this line of thinking – the frequent clinical observation that not all patients with essential hypertension (in fact, most patients) actually demonstrate "salt-sensitivity" – has perplexed this author over the ensuing years. Furthermore, early studies in which spontaneously hypertensive rats (SHR) were pretreated with one of several beta-adrenergic receptor blocking agents from conception, on to birth, and thereafter through weaning, demonstrated that prolonged reduction in cardiac output failed to prevent hypertension.[27] How then, can we reckon with the very strong epidemiological evidence that salt and hypertension are so inextricably related if most patients with hypertension are not "salt-sensitive"? Why then do most patients with hypertension demonstrate a normal response in arterial pressure to salt-loading? Could it be that salt-loading manifests not only as a rise in arterial pressure and that other manifestations of hypertensive disease occur following more chronic salt-loading? Our earliest studies in the 1970s and thereafter demonstrate that salt-loading (ie, 4% salt in food) in the SHR is associated with an increased cardiac mass even before arterial pressure increases.[28,29] These observations have been substantiated by others who demonstrated that increased ventricular mass is induced by salt in SHRs (given 8% salt in their food) and that these changes are associated with increased collagen deposition and fibrosis in heart and kidneys.[30]

Our hypothesis

The foregoing observations strengthened our hypothesis that salt-loading need not be expressed exclusively and solely by increased arterial pressure in hypertensive disease, especially in the target organs (eg, heart, aorta and large arteries, arterioles, and kidneys). Accordingly, we initiated a series of pathophysiological studies in the SHR (using the 8% salt-loading diet) model, reported so successfully by the Johnson group.[30] Our findings reinforced our postulated hypothesis that chronic salt-loading need not greatly elevate arterial pressure to exacerbate hypertensive disease and promote serious target organ disease (identical to that seen by patients with hypertension).[31-37] Indeed, our findings produced by long-term salt-loading, provide strong evidence to support current clinical observations in patients with essential hypertension, especially elderly patients with isolated systolic hypertension, patients with progressive cardiac failure manifested by impaired diastolic function associated with preserved systolic function, and patients with unrelenting end-stage renal disease.

Figure 1: Left (LV) and right (RV) ventricular coronary blood reserve and LV and RV hydroxyproline concentrations in control and salt-loaded young adult (16-weeks-old) normotensive WKY and SHRs and older adult (52-weeks-old) SHRs.



White bars represent those on control diets; Blue bars represent those receiving salt-loaded diets. C = control; NaCl = salt-loaded groups; * represents statistical significance between groups at least at the $p < 0.05$ confidence level.

The experimental model

The cardiac effects of salt-loading

In our studies, 2 groups of SHR rats were given 8% salt in food: one group of younger adult SHR rats received salt-loading starting at 8 weeks of age that continued until age 20 weeks; an older group of adult rats began salt-loading at 20 weeks that continued until age 52 weeks.[33] Most of the rats in both groups responded with concentric left ventricular hypertrophy (LVH) that was associated with impaired LV diastolic relaxation and a less impressive increase (only 17%) in arterial pressure (Figure 1). However, 25% of the younger adult SHR rats developed overt cardiac failure manifested by impaired LV systolic function, biventricular hypertrophy, increased LV diastolic diameter, pulmonary edema, or death. This latter response occurred only in the younger adult rats and, most surprisingly, none of the older adults. LV mass increased substantially in both groups, but more so in the younger rats versus the older rats (88% vs. 25%, respectively); and this increased ventricular mass correlated more closely with sodium intake rather than the magnitude of the rise in arterial pressure. This relationship between salt-loading and increased LV mass has also been demonstrated clinically in hypertensive patients,[38,39] as well as experimentally.[29,30] We confirmed that this increased LV mass was associated with a markedly increased fibrosis of the extracellular matrix, as well as perivascularly.[33-37]

This ventricular fibrotic response to salt-loading was also demonstrated in normotensive Wistar-Kyoto (WKY) control rats, although the increased pressure was not as great in this group of rats.[34] Moreover, ventricular fibrosis was not only demonstrated in the hypertrophied LV of these hypertensive rats, but also in the right ventricle, the chamber not exposed to the increased afterload of hypertensive disease.[34] Most impressively, fibrosis resulting from salt-loading, was reversed therapeutically.[36]

Fibrosis in LVH has also been repeatedly shown to occur in patients with essential hypertension without occlusive epicardial coronary arterial disease (CAD). It has also been

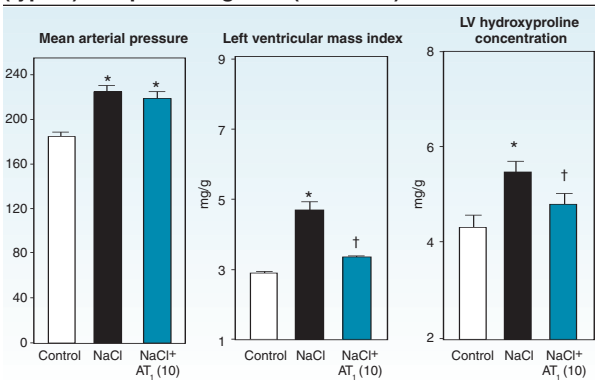
repeatedly demonstrated that fibrosis in LVH can be reversed therapeutically with angiotensin-converting enzyme (ACE) inhibitors[40-42] or a type 1 angiotensin II receptor (AT1) antagonist.[43] Furthermore, the magnitude of ventricular fibrotic response in hypertensive patients with LVH can be related quantitatively to the amount of a circulating carboxy-terminal propeptide of procollagen type I and carboxy-terminal telopeptide of collagen type I and this can be utilized as an extremely useful clinical marker of ventricular collagen turnover.[44,45] These findings, both experimentally and in patients with essential hypertension, provide strong evidence that the LV fibrosis that occurs in hypertension, is exacerbated by salt-loading and, subsequently, can be reversed therapeutically.

It is also extremely interesting to note that a salt-induced increase in LV mass is associated with functional impairment of the chamber. We demonstrated these structural and functional changes (diastolic, as well as systolic) in the SHR, as well as in normotensive rats echocardiographically, using Doppler technology.[46,47] This approach is extremely important since, if echocardiographic measurements are to be obtained longitudinally, excluding SHRs and normotensive WKY rats with congenital cardiac defects is essential to avoid drawing invalid conclusions. Pre-existing anatomic arteriovenous communications or cardiac defects occur frequently in the SHR.[48-50] Indeed, we have demonstrated that a significant proportion of both SHRs and normotensive WKY rats have arteriovenous communications that result in biventricular hypertrophy.[48-50]

In our recent studies, younger adult SHRs that developed overt cardiac failure demonstrated impaired LV systolic (fiber shortening rate), as well as diastolic functions that were associated with structural changes of the chambers.[34] Moreover, the younger, as well as the older adult SHRs, had markedly impaired diastolic function (eg, prolonged isovolumic relaxation times, reduced VE/VA ratios, and slower propagation velocities [VPs] of early ventricular filling) that were associated with further increased LV mass and hydroxyproline concentration. Although the relationship between salt excess and LV functional changes has been sparsely reported clinically, impaired LV diastolic filling has been correlated with sodium excretion and blood pressure sensitivity.[51] Thus, a reduction in the maximal early diastolic filling velocity (VE), as well as in the ratio of VE to the atrial filling velocity (VA) – the VE/VA ratio – have also been found in sodium-sensitive essential hypertensive patients, but not in sodium-resistant patients.[52] We were most surprised to find that none of the older adult SHRs had developed overt cardiac failure despite their significantly older age and longer history of hypertensive disease. Nevertheless, all the SHRs (in both adult groups) demonstrated impairment in each of the measured LV diastolic functions and these functional changes were associated with further increased LV mass and fibrosis.

The severe fibrosis of the extracellular matrix no doubt relates to measured abnormal diastolic functions, while perivascular fibrosis provides a sound structural explanation for the impaired ventricular coronary vascular hemodynamics (ie, reduced coronary flow and flow reserve and increased coronary and minimal coronary vascular resistance), which we also reported in the younger, as well as the older adult SHRs (Figure 1).[53] Thus, salt-loading has been shown both experimentally and clinically to exacerbate myocytic hypertrophy and perivascular and extracellular ventricular fibrillar collagen content and deposition. These changes may be related to

Figure 2: Responses of mean arterial pressure, LV mass index, and LV hydroxyproline concentrations in young adult control (white bars), salt-loaded (black bars), and salt-loaded diets with the addition of an angiotensin II (type 1) receptor antagonist (blue bars)



* represents statistically significant differences from the control groups at least at the p<0.05 confidence level.

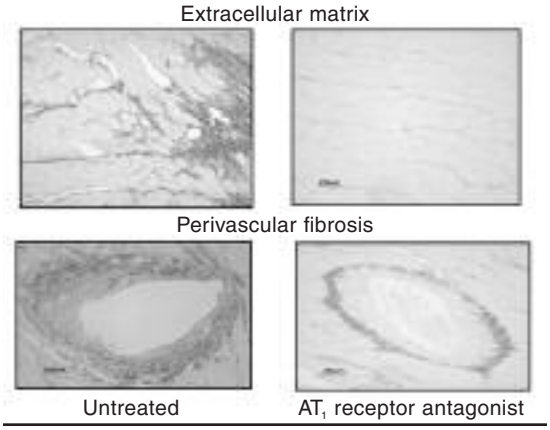
abnormal structural and altered systolic, as well as diastolic function. Since it is now feasible to relate the degree of LV fibrosis to levels of circulating biomarkers of collagen deposition,[44,45] it now seems eminently possible to clinically relate the degree of ventricular fibrosis with impaired LV function and mass. Moreover, the reversal of that fibrosis with various therapeutic interventions can also be followed clinically.

At the recent meeting of the Council for High Blood Pressure Research, we reported that when the adult SHR is treated with either a low (1 mg/kg) or high (10 mg/kg) dose of an AT1 antagonist (candesartan), this antihypertensive agent impressively diminished LV mass but, most surprisingly, it failed to lower arterial pressure in spite of the significant reductions in LV mass and hydroxyproline content (Figure 2).[26] This reduction in LV mass was associated with markedly improved LV diastolic function in these adult SHRs and, most impressively, it reversed LV extracellular and perivascular fibrosis (Figure 3). These pathophysiological changes strongly suggest that the local effects of salt-loading on the heart may be directly related to stimulation by the local cardiac renin-angiotensin system and/or indirectly (also) related to the participation of locally-produced aldosterone.[35]

Effects of salt-loading on the aorta and kidney

Associated with the foregoing changes associated with salt-loading on cardiac structure and function, we have also found that there are significant structural and functional changes in the aorta and kidney.[34] Salt-loading in the same adult SHRs increased aortic mass and decreased aortic distensibility, pulse-wave velocity, and propagation. In addition, there were profound renal changes. Thus, the same 8% salt-loading diet significantly increased serum creatinine and uric acid concentrations and produced massive proteinuria, changes that are consistent with severe nephrosclerosis in hypertensive patients with end-stage renal disease (ESRD). Moreover, these changes have already been shown to be associated with remarkably increased intrarenal fibrosis.[30] We have also demonstrated (as yet unpublished data) that these changes were associated with markedly diminished renal blood flow, increased renal vascular resistance, and profoundly severe glomerular dynamic changes that were related to afferent and

Figure 3: The two left figures present high-power micrographs (using picrosirius red-stained tissue) demonstrating the extent of collagen deposition and fibrosis in the extracellular matrix and perivascular tissue surrounding a coronary arteriole of a left ventricle. The 2 figures on the right present the remarkable reversal of the collagen deposition and fibrosis in these 2 areas of the left ventricle following treatment with an angiotensin II (type 1) (AT1) receptor antagonist for 8 weeks.



efferent arteriolar constriction and increased glomerular hydrostatic pressure. These findings are also consistent with severe nephrosclerosis. Our current studies are presently focused on determining whether the changes provoked by the 8% salt-loading are also provoked by lesser salt-loads (eg, 4% and 6% salt-loads).

Postulated pathophysiological mechanisms

As suggested above, one mechanism is the postulated induction of a locally-generated cardiac renin-angiotensin-aldosterone system (RAAS).[54] This concept may, at first thought, be incompatible with the voluminous literature amassed over the years demonstrating that salt-loading suppresses the systemic RAAS. Consequently, salt-loading has been consistently associated with suppression of the release of renin from the juxtaglomerular apparatus of the kidney and, hence, a diminution in systemically-generated angiotensin II. However, in more recent years, the existence of a local cardiac RAAS has been established.[55,56] In addition, a second intrarenal RAAS has been suggested (and confirmed) that operates locally within the kidney.[57,58] Thus, it may very well be that, in addition to the classical endocrine RAAS that may be suppressible by salt-loading, other (local) RAASs are operating in other organs that may be stimulated by salt-loading. Indeed, this would explain the myocytic and fibrotic mitogenic angiotensin II (and/or aldosterone)-initiated effects that are promoted by salt-loading and even salt-withdrawal.[35]

It is not necessary to rely solely on the effects of the RAAS to explain the above observations (although we strongly believe that the RAAS plays a major role). Other systems have been implicated to be involved with salt-loading and restriction. For example, reducing salt intake has been shown repeatedly to modulate hemodynamic responses to catecholamines, thereby affecting adrenergic function.[37,59-65] Clinical medicine is replete with descriptions of the effects of salt-restriction or diuretic therapy on cardiovascular and renal responsiveness to norepinephrine or other pressor substances.[59,64,66] In addition, adrenergic function has also been shown to be enhanced with sodium-loading, although it may not necessarily increase circulating norepinephrine levels.[62,66] Salt-loading has also been demonstrated to initiate responses to growth-promoting hormones or factors. Thus, there may be the participation of locally, as well as systemically, generated components of the RAAS,[67] including endothelin,[68] TGF-beta,[30] and other mitogenic substances.

Conclusion

Over the millennia, salt has played an important role in the behavior, economy, and social discourse of mankind.[69] Notwithstanding this importance, the role of salt in health and disease has also been the subject of a considerable body of controversial epidemiological, experimental, and clinical literature. For the most part, these studies have incriminated diets with increased salt (or sodium) content, maintaining that they have adverse effects on cardiovascular, renal, endocrine, and other bodily functions. These effects have been associated with an exacerbation of hypertension, cardiac and renal failure, diabetes mellitus, and other common diseases frequently encountered in acculturated societies. It is intriguing and highly provocative to speculate that the longstanding salt-replete dietary habits in these societies not only result in elevating arterial pressure, but also impair cardiac and renal function in patients with hypertension and other diseases. However, because not all patients with hypertension demonstrate an increase in arterial pressure (eg, salt-sensitivity) with prolonged salt-loading, we have hypothesized that longstanding salt-loading not only elevates arterial pressure, but also provokes additional adverse effects on target organs.[31,32] Thus, although increased arterial pressure with prolonged salt-loading is observed in a minority of patients with essential hypertension, there is increasing evidence that there are other adverse effects on the target organs (eg, reduced aortic distensibility, cardiac, or renal failure) that are seen clinically with increasing frequency.

We therefore postulate that prolonged salt-loading, as demonstrated over and over again in acculturated societies, may also be expressed by evidence of disease in the aorta, heart, and kidneys. This may provide an explanation (at least, in part) for the unrelenting increase in the prevalence of:

- isolated systolic hypertension in the elderly
- impaired diastolic function (with preserved systolic function) in hypertensive, as well as normotensive, individuals
- cardiac failure in elderly patients
- end-stage renal disease.

The experimental studies described in this article provide compelling evidence that long-term salt-loading in the SHR increases arterial pressure; however, although this is possibly statistically significant, it may be minimally so. Equally important are the pathophysiological changes in structure and function in the heart, aorta, other vessels, and kidneys associated with deposition of collagen in these organs. In the aorta, changes in reduced elasticity are associated with reduced distensibility and pulse-wave velocity that may be expressed by isolated systolic hypertensive disease.[70-73] In the heart, salt-loading

may provoke overt cardiac failure but, in most instances, results in impaired diastolic, but preserved systolic function. Finally, in the kidney, salt-loading impairs structure, total renal and glomerular function, and leads to proteinuria changes that are consistent with ESRD. These structural and functional findings may be reversed with antihypertensive therapy, although such therapy may fail to reduce arterial pressure.

We therefore strongly believe the hypothesis that prolonged salt-loading need not be accompanied by exacerbation of overall hypertensive disease that manifests solely and exclusively by a further rise in arterial pressure. Salt-loading may also be expressed by impaired structural and functional derangements of the target organs, leading to clinical derangements in cardiac, vascular, and renal function such as those encountered in patients with longstanding hypertensive disease and, possibly, in aging patients who are normotensive.

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Disclosure: *Dr. Frohlich has no disclosures to declare in association with the enclosed CME questionnaire.*

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This publication is made possible by an educational grant from

Novartis Pharmaceuticals Corporation