How Does High Salt Intake Cause Hypertension?

Renal Dysfunction, Rather Than Nonrenal Vascular Dysfunction, Mediates Salt-Induced Hypertension

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Long-term high salt intake increases the risk for hypertension and associated cardiovascular and kidney disease, whereas modest reductions in salt intake significantly decrease blood pressure (BP) in many hypertensive subjects. However, the mechanisms of salt-induced changes in BP continue to be the subject of considerable interest and controversy.

Response by Morris et al on p 907

Salt in the context of this review refers to NaCl. In humans and experimental models, full expression of salt-sensitive hypertension depends on sodium and chloride. Although some studies suggest that sodium bicarbonate loading can raise BP and cause renal vasoconstriction in sensitive subjects, the BP effect is about half as great as with NaCl loading, and plasma volume is expanded much less by nonchloride sodium salts than by NaCl.

Hemodynamic events that initially accompany abrupt, large increases in salt intake in subjects who are considered to be salt resistant include positive sodium balance and increased extracellular fluid volume (ECFV), transient increased cardiac output (CO), and minimal changes in BP. Total peripheral vascular resistance (TPR) may initially decrease, perhaps as a result of reflex/hormonal mechanisms that cause vasodilation in response to volume loading, but within a few days, TPR returns to nearly normal levels. In salt-sensitive subjects, high salt intake also causes sodium retention (which has been reported to be similar or greater than that in salt-resistant subjects) and increases in ECFV and CO. In salt-sensitive subjects, however, high salt intake causes a gradual increase in BP followed by an increase in TPR.

Because BP is mathematically the product of CO and TPR, the rise in BP in salt-sensitive subjects has been attributed to increased TPR, or vasodysfunction. The basic idea is that salt-resistant subjects vasodilate during high salt intake, whereas salt-sensitive subjects vasoconstrict, thereby raising their BP. This simplistic view does not take into account the following: (1) Overwhelming experimental evidence indicates that kidney dysfunction is required for increased salt intake to raise BP chronically in all experimental and human forms of genetic or acquired salt-sensitive hypertension studied thus far; (2) there is little evidence of vasodilation in salt-resistant subjects after several days of increased salt intake because BP, CO, and TPR are not significantly different from values at normal salt intake; (3) vasoconstriction often follows, rather than precedes, increased BP in salt-sensitive hypertension; (4) physiological studies show that increased BP almost invariably initiates pressure-dependent functional and structural vascular changes that increase TPR; (5) vascular changes associated with hypertension regress with treatments that improve renal excretory function (eg, diuretics) and reduce BP; and (6) vasoconstriction of nonrenal blood vessels,
induced experimentally or by genetic mutations, has not been shown to increase salt sensitivity of BP.

In this review, I discuss evidence that kidney dysfunction is required for chronic increases in BP in subjects who are salt sensitive and that vasoconstriction of nonrenal blood vessels, although present in salt-induced hypertension, is insufficient to chronically increase BP in the absence of kidney dysfunction. Evidence that vasoconstriction during salt loading may be secondary to increased BP, serving to protect tissues from pressure or flow overload, is also reviewed.12,15

**Heterogeneity of BP Responses to Changes in Salt Intake: Salt Sensitivity and Salt Resistance**

There is considerable heterogeneity of BP responses to changes in salt intake in normotensive and hypertensive subjects. Kawasaki et al,10 in one of the first reports of BP salt sensitivity, studied hypertensive subjects on normal (109 mmol/d), low (9 mmol/d), and high (249 mmol/d) sodium intakes for 1 week at each level (Figure 1). The 9 subjects who had at least a 10% increase in BP during high compared with low salt intake were identified as salt sensitive, and the other 10 subjects were classified as non–salt sensitive. The salt-sensitive subjects retained more sodium and gained more weight on high salt intake than those who were non–salt sensitive.10 This and subsequent investigations in normotensive or hypertensive subjects indicate that salt sensitivity is a continuous phenotype, not bimodal as might be inferred from the terms salt sensitive and salt resistant.4,16

Assessment of BP salt sensitivity in clinical studies is challenging. Weinberger16 measured changes in BP after large amounts of salt/volume were infused or rapidly depleted from the body by salt restriction and administration of powerful diuretics. This method has provided mechanistic insights into BP salt sensitivity and appears to be somewhat reproducible.16

The critical role of kidney dysfunction in salt-induced hypertension is highlighted by the fact that the most reproducible and consistent forms of experimental salt-sensitive hypertension are induced by impairing kidney function in various ways that reduce glomerular filtration rate or increase tubular reabsorption. In addition, all known monogenic forms of salt-sensitive human hypertension are characterized by mutations that directly or indirectly increase renal NaCl reabsorption.21–23

The challenge of assessing BP salt sensitivity in humans has led investigators to examine various surrogate biomarkers such as plasma renin activity, atrial natriuretic peptide, genetic screens, proteomics, and urine exosomes.16,17 Although some biomarkers have shown promise in predicting BP salt sensitivity, most have not been widely adopted for clinical practice, and their accuracy is still uncertain. Many of these issues related to assessment of BP salt sensitivity have previously been reviewed.16,17

Salt sensitivity, in addition to being heterogeneous, is not a fixed phenotype. With aging, there is often an increase in salt sensitivity16 associated with a gradual loss of functional nephrons after 40 years of age, even in healthy persons.18 Thus, most of us are prone to becoming salt sensitive to some extent if we live long enough. With various pathophysiological conditions that cause more rapid loss of kidney function (eg, diabetes mellitus, hypertension), loss of functional nephrons is accelerated and salt sensitivity is amplified.1,4,16 Thus, phenotypes that are often associated with salt-sensitive BP include older age, diabetes mellitus, hypertension, obesity, kidney disease, and black ethnicity.1,16

There is also evidence that salt sensitivity worsens when high salt intake is maintained for long periods of time.1,19 This progressive increase in salt sensitivity likely reflects target organ injury, especially renal injury, through the damaging effects of high BP or other effects of high NaCl intake.1,19 BP salt sensitivity and the mechanisms involved therefore depend partly on how long changes in salt intake are maintained.

Although BP salt sensitivity is heterogeneous, all individuals with salt-induced chronic increases in BP have a common characteristic: They maintain salt balance at the expense of increased renal perfusion pressure.12,13 This renal dysfunction can be caused by genetic or acquired intrarenal and extrarenal neurohormonal disorders that impair the ability of the kidneys to maintain NaCl balance at normal BP.14,20 In some cases, kidney dysfunction causes sodium retention and transient increases in CO that are followed by elevated TPR as BP rises. In other instances, renal dysfunction occurs concomitantly with vasoconstriction and decreased vascular capacitance, and minimal NaCl retention is required to raise BP sufficiently to restore salt balance.

The critical role of kidney dysfunction in salt-induced increases in BP in sensitive subjects is highlighted by the fact that the most reproducible and consistent forms of experimental salt-sensitive hypertension are induced by impairing kidney function in various ways that reduce glomerular filtration rate or increase tubular reabsorption. In addition, all known monogenic forms of salt-sensitive human hypertension are characterized by mutations that directly or indirectly increase renal NaCl reabsorption.21–23

![Figure 1. Percent increase in mean blood pressure in salt-sensitive and salt-resistant patients with hypertension when their diet was changed from low sodium (9 mEq/d) to high sodium (240 mEq/d) for 1 week at each level. Data are from Kawasaki et al.](http://circ.ahajournals.org/lookup/suppl/doi:10.1161/01.HYP.0000742005.44013.78/-/DC1/fig-1.png)
The Renal–Body Fluid Feedback Mechanism for Long-Term BP Regulation

Figure 2 shows the basic conceptual framework for long-term control of BP by the renal–body fluid feedback proposed by Guyton and Coleman in the 1960s and subsequently expanded to include a large number of cardiovascular, neural and hormonal mechanisms for BP regulation.12–14 ECFV is determined by the balance between intake and renal excretion of salt/water. Even temporary imbalances between intake and output will change ECFV and potentially BP if cardiac and vascular functions are adequate. Although sodium can be stored in tissues such as skin, independently of volume retention, intake and output must eventually be balanced; otherwise, continued fluid/salt accumulation or loss could eventually lead to circulatory failure.

A key element of this feedback is the effect of BP on salt/water excretion, often called pressure natriuresis/diuresis.20,26 This feedback was predicted to play a dominant role in long-term regulation of BP and salt/water balance.24 For example, if BP is increased above the renal-pressure natriuresis set point because of increased TPR or increased cardiac pumping ability, NaCl/volume excretion would also increase, and as long as excretion exceeds intake, ECFV would decrease until BP returned to normal and fluid balance was re-established.27 An important prediction of this concept is that chronic hypertension cannot be sustained unless pressure natriuresis is shifted to higher BP; otherwise, elevated BP would provoke increased sodium excretion, which would reduce ECFV and CO until BP eventually returned to normal. Supporting this prediction is the finding that increases in vascular resistance that do not impair pressure natriuresis, such as closure of an arteriovenous fistula or coarctation of the aorta below the kidneys (aortic coarctation above the kidneys causes hypertension), induce only transient increases in BP followed by natriuresis, decreased plasma volume, and rapid normalization of BP.12

Another key aspect of this conceptual framework for chronic BP regulation is the important role of neurohormonal systems in modulating pressure natriuresis.28,29 For example, during high salt intake, decreased angiotensin II (AngII) and aldosterone formation enhance the effectiveness of pressure natriuresis, allowing sodium balance to be maintained with minimal changes in BP as long as the renin-angiotensin-aldosterone system (RAAS) is functioning normally.13,28 Excessive RAAS activation, however, reduces the effectiveness of pressure natriuresis, thereby necessitating greater increases in BP to maintain sodium balance.29

In salt-resistant subjects, multiple intrarenal and neurohumoral adjustments permit salt balance with minimal changes in BP during increases in salt intake over several days. In salt-sensitive subjects, elevated BP contributes to increased salt/water excretion during high salt intake through pressure natriuresis/diuresis.20,26,30 In addition to helping maintain salt/water balance, this mechanism attenuates changes in BP during nonrenal disturbances.

In all forms of human or experimental hypertension studied thus far, there is a shift of pressure natriuresis to higher BPs.12–14 This shift of pressure natriuresis can be caused by intrarenal disturbances that initially reduce glomerular filtration rate or increase tubular reabsorption or by extrarenal factors such as increased sympathetic nervous system activity, excessive antinatriuretic hormones, or deficit of natriuretic hormones that reduce the ability of the kidneys to excrete NaCl and water.29 As BP rises, the initial kidney dysfunction is offset by natriuretic/diuretic effects of increased BP, thereby returning NaCl excretion to match intake.

Is Abnormal Renal-Pressure Natriuresis a Cause or a Consequence of Hypertension?

The fact that hypertensive patients have normal NaCl excretion (equal to intake) despite increased BP indicates that pressure natriuresis is reset to higher BP. However, this resetting has been suggested to be secondary to increased BP rather than a major cause of hypertension.31,32 If BP truly has no long-term effect on NaCl/volume excretion, pressure natriuresis and the renal–body fluid feedback would be relatively unimportant in long-term BP regulation.
Therefore, a critical issue is whether BP has a long-term effect on NaCl/volume excretion or whether pressure natriuresis is mainly a short-term phenomenon with little role in chronic BP regulation. Although this issue has been difficult to test experimentally, several studies have confirmed that renal perfusion pressure has an important long-term effect on renal excretion and that pressure natriuresis plays a key role in maintaining salt balance in various experimental models of hypertension.13,20,33–39

Evidence That Pressure Natriuresis Is a Powerful Long-Term Controller of Salt Excretion and BP

We tested whether pressure natriuresis has a long-term effect on sodium/water excretion by using a split-bladder preparation to collect urine separately from each kidney and servo-controlling renal perfusion pressure in each of the 2 kidneys independently33 (Figure 3). Because the 2 kidneys in each animal were exposed to the same neurohormonal influences and blood composition, the long-term effects of small changes in renal perfusion pressure on electrolyte excretion and renal hemodynamics could be directly quantified. These studies demonstrated that small changes in BP cause large alterations in NaCl/water excretion that persisted as long as pressure was altered (12 days). Thus, the kidneys did not adapt their excretory function during chronic changes in perfusion pressure. In fact, the long-term effects of BP on NaCl excretion are considerably greater than observed during acute pressure changes.27,29

We also assessed the role of pressure natriuresis in maintaining NaCl/volume balance in several forms of experimental hypertension, including AngII, aldosterone, DOC-salt, norepinephrine, adrenocorticotropic hormone plus norepinephrine, and vasopressin hypertension.34–39 In each case, servo-controlling renal perfusion pressure at the normal level led to progressive sodium/water retention and continued increases in ECFV and systemic arterial pressure. In some cases, extreme salt/volume retention occurred when pressure natriuresis was prevented during the development of hypertension, leading to circulatory congestion and pulmonary edema in a few days.

These observations highlight the powerful role of renal-pressure natriuresis in long-term regulation of NaCl balance and BP. They also strongly support the basic premise of the renal–body fluid feedback concept that chronic hypertension, including salt-sensitive hypertension, cannot be sustained in the absence of kidney dysfunction, characterized by impaired pressure natriuresis.

If Kidney Function Is Impaired in Salt-Sensitive Hypertensive Subjects, Why Do They Sometimes Excrete Sodium as Rapidly as Normotensive Subjects?

Previous studies have shown that salt-sensitive hypertensive subjects often retain more sodium than salt-resistant subjects during increased sodium intake.10,40 Some reports suggest, however, that salt-sensitive humans may excrete a sodium load almost as rapidly as salt-resistant subjects and are cited as evidence that salt-sensitive hypertension is not caused by renal dysfunction.51 An important, but often forgotten, consideration is that the kidneys of hypertensive subjects are perfused at elevated BP. Because increased BP tends to
cause natriuresis, the finding that similar rates of excretion are observed in hypertensive and normotensive subjects implies that there is a defect in renal excretory capability. In the presence of high BP, the natriuretic handicap disappears, and renal excretory function appears to be normal, except that pressure natriuresis is shifted to higher BP.

**A Common Misconception: Impaired Renal-Pressure Natriuresis Should Always Cause Sodium Retention, Increased Blood Volume, and Increased CO**

Although ECFV and blood volume are important components of long-term BP regulation, via the renal-body fluid feedback (Figure 2), BP is not a function of blood volume per se but of volume in relation to vascular capacity. This concept is sometimes referred to as effective blood volume.1 When vascular capacity increases (eg, large varicose veins), greater blood volume is needed to maintain normal BP. Conversely, with vasoconstriction, less volume is required to maintain normal BP. When high concentrations of strong vasoconstrictors such as norepinephrine and AngII are present, the kidneys may actually undergo pressure-induced natriuresis, and ECFV may decrease, even though renin and AngII are present, the kidneys cause natriuresis, and pressure drop natriuresis to higher BPs by increasing renal sodium excretion.13,29,37 they also rapidly increase BP because of peripheral vasoconstriction. If BP increases above the renal set point, the elevated BP will initially cause natriuresis and decreased ECFV until BP stabilizes at the set point dictated by the renal-pressure relationship. In parallel, decreased vascular capacitance permits maintenance of high BP with a reduced blood volume. This overfilling of the circulation, relative to vascular capacity, is reflected by increased mean circulatory filling pressure in various forms of salt-sensitive hypertension.12

**Acquired Kidney Disorders That Cause Salt-Sensitive Hypertension**

A challenge in determining mechanisms of salt-induced hypertension is that primary causes of increased BP are often obscured by compensatory neurohormonal, renal, and cardiovascular changes. Experimental and clinical studies have shown, however, that several types of kidney-specific disorders increase BP salt sensitivity.12,27,29,42–56 (Table 1). These include (1) various types of kidney injuries that cause loss of functional nephrons or decreased glomerular capillary filtration coefficient, (2) patchy (nonhomogeneous) increases in preglomerular resistance, (3) the inability to modulate the RAAS appropriately, and (4) acquired or genetic disorders that directly or indirectly increase renal NaCl reabsorption, especially in the distal and collecting tubules. The many conditions that can cause these disorders of kidney function have been reviewed previously and are distinct from those that cause salt-resistant hypertension.12,29

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<thead>
<tr>
<th>CD-specific deletion of NOS1</th>
<th>Hyndman et al42</th>
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<td>CD-specific deletion of endothelin A and B receptors</td>
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<tr>
<td>CD-specific deletion of endothelin B receptors</td>
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<td>CD-specific knockout of endothelin-1</td>
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<td>CD-specific overexpression of renin</td>
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<td>Kidney intercalated cell-specific pendrin overexpression</td>
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<td>Increased renal medullary-specific oxidative stress</td>
<td>Cowley et al48</td>
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<td>Glomerulonephritis, IgA nephropathy</td>
<td>Konishi et al54</td>
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<td>Adenine-induced kidney injury</td>
<td>Nguy et al56</td>
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Table 1. Examples of Experimental Kidney-Specific Disorders That Cause Salt-Sensitive Increases in BP

**Kidney Injury and Decreased Functional Nephrons Cause Salt Sensitivity**

One of the most reliable experimental methods for creating salt sensitivity is to induce renal injury and loss of functional nephrons.12,51,56 Although surgical removal of up to 70% of kidney mass does not, by itself, cause marked hypertension, it greatly enhances BP salt sensitivity.51 Uninephrectomy or a long-term high-salt diet in young animals after completed nephrogenesis also causes salt-sensitive hypertension in adulthood.53 Hydronephrosis, partial kidney infarction, tubulointerstitial inflammation, immune cell infiltration of the kidneys, IgA nephropathy, and many other types of renal insults also cause BP salt sensitivity.27,52,54,55,57 In patients with chronic kidney disease, BP salt sensitivity increases exponentially as creatinine clearance decreases.58 Salt loading in patients with severe kidney disease causes much greater increases in BP and intravascular volume than in patients with moderate kidney disease.58 Thus, acquired renal injuries caused by aging, diabetes mellitus, hypertension, and various types of acute and chronic kidney injury, even when they are subtle, usually increase BP salt sensitivity.4,16,27,54

**RAAS-Mediated Kidney Dysfunction Causes Salt Sensitivity**

Increased activity of the RAAS or fixed low activity of the RAAS causes BP salt sensitivity28 (Figure 4). This is not surprising because the RAAS is the most powerful hormone
system for regulating renal NaCl excretion. When the RAAS is fully functional, the chronic renal-pressure natriuresis curve is steep, and NaCl balance can be achieved over a wide range of intakes with minimal BP changes. The mechanisms that mediate the potent effects of AngII on pressure natriuresis and salt-sensitive BP include direct and indirect effects that increase tubular reabsorption and renal hemodynamic effects. Although the BP effects of AngII have often been attributed to its actions on the brain, adrenal gland, and nonrenal blood vessels, activation of kidney angiotensin II type 1 (AT1) receptors is required for AngII to cause chronic hypertension. Crowley and colleagues found that AngII infusion in wild-type mice increased BP and caused cardiac hypertrophy and fibrosis. However, in wild-type mice that received transplanted kidneys from AT1 receptor knockout mice (ie, angiotensin-I receptors were present on the peripheral vasculature, brain, heart, and other organs but not in the kidneys), AngII infusion did not raise BP chronically or cause cardiac hypertrophy/fibrosis. In AT1 receptor knockout mice that received transplanted kidneys from wild-type mice (ie, AT1 receptors were present only in the kidneys and not in peripheral blood vessels, brain, heart, or other organs), AngII infusion caused chronic hypertension and cardiac hypertrophy/fibrosis. These observations indicate that the renal effects of AngII, instead of peripheral vascular or other nonrenal effects, mediate chronic increases in BP and cardiac hypertrophy in this salt-sensitive model of hypertension.

Although the kidney cell lineages responsible for the long-term BP effects of AngII have not been completely elucidated, proximal tubule AT1 receptors play an important role by augmenting sodium-hydrogen exchanger 3-dependent sodium reabsorption. Kidney vascular angiotensin-I receptors contribute to the pathogenesis of AngII-induced hypertension by reducing renal blood flow, which also enhances sodium retention. Thus, the long-term effects of AngII on BP and salt sensitivity are closely coupled to renal tubular and hemodynamic actions that cause salt/water retention.

Excessive activation of the mineralocorticoid receptor (MR) also increases NaCl reabsorption in the distal nephron and BP salt sensitivity while suppressing AngII formation. MR activation can occur as a result of increased circulating ligands such as aldosterone or because of other factors that activate MR even in the absence of increased levels of mineralocorticoids. For example, deficiency of 11β-hydroxysteroid dehydrogenase 2 can lead to activation of MR by glucocorticoids, as discussed later. Additional factors in salt-sensitive hypertension that have been suggested to activate renal tubular MR in a ligand-independent manner include increased reactive oxygen species and Ras-related C3 botulinum toxin substrate, a Rho family small GTPase. The molecular/cellular mechanisms linking these changes with increased renal tubular NaCl reabsorption and BP salt sensitivity have been reviewed previously.

Endothelin-Mediated Kidney Dysfunction Causes Salt-Sensitive BP

Although endothelin-1 is a potent vasoconstrictor, its renal actions, especially in the collecting ducts (CDs), are of unique importance in long-term BP salt sensitivity (Table 1). The CDs produce endothelin-1, which binds in an autocrine manner to endothelin A/B receptors, causing inhibition of salt/water reabsorption. Salt/volume loading stimulates CD endothelin-1 production through local mechanisms that sense salt delivery and shear stress when flow rate increases. Locally released endothelin-1 activates endothelin-B receptors and inhibits sodium reabsorption. The importance of these renal actions is demonstrated by the fact that CD-specific deletion of endothelin-B receptors increases BP salt sensitivity. CD-specific deletion of endothelin-1 production or deletion of endothelin A/B receptors in CDs produces even greater salt-dependent BP elevation than knockout of endothelin-B receptors alone. Blockade of endothelin-1 receptors also attenuates or abolishes hypertension in Dahl-salt sensitive rats and DOCA-salt hypertension.

These observations do not necessarily negate a potential role for extrarenal endothelin-1 or its receptors in BP salt sensitivity. Although endothelin-1 is a potent vasoconstrictor in many tissues, including the kidneys, and may stimulate sympathetic nervous system activity and regulate extracellular sodium storage, whether these extrarenal actions ultimately influence renal-pressure natriuresis and chronic BP regulation is unclear. What is clear is that the renal actions of endothelin-1, especially in the CDs, play a major role in protecting against salt-sensitive hypertension.
Genetic Kidney Disorders That Cause Salt-Sensitive Hypertension

Kidney Transplantation Attenuates or Abolishes Genetic Salt-Sensitive Hypertension in Rodents.

In Dahl salt-sensitive rats,69,70 Milan hypertensive rats,71 Prague hypertensive rats,72 and Okamoto spontaneously hypertensive rats,69,73 hypertension can be transferred with renal grafts from the hypertensive strain to normotensive histocompatible recipients. Conversely, renal grafts from normotensive control strains reduce or normalize BP in each of these genetically hypertensive rat strains. Thus, renal mechanisms have consistently been shown to play a key role in rodent models of genetic, salt-sensitive hypertension.

Although kidney dysfunction is clearly a major cause of increased BP in these rodent models of genetic hypertension, there is often little evidence of volume expansion or increased CO after hypertension is established. The most obvious abnormality is increased TPR. The mechanisms responsible for increased TPR have not been fully elucidated but in some cases likely occurs secondary to the increase in BP via pressure- or flow-dependent autoregulatory vasoconstriction.14 In other instances, neurohormonal or paracrine factors may contribute to increased TPR even though kidney dysfunction is required for hypertension to be sustained.

Volume expansion is required for increases in BP and TPR to be triggered in some forms of salt-sensitive hypertension. For example, servo-control of body weight to prevent volume expansion abolished increased BP when Dahl salt-sensitive or AngII-infused rats were placed on a high-salt diet.74,75 Regardless of whether increased BP is associated with measurable volume expansion, kidney dysfunction plays a critical role in genetic and acquired forms of salt-sensitive hypertension.

Kidney Dysfunction in Monogenic, Salt-Sensitive Human Hypertension.

Table 2 shows 7 monogenic disorders that share the common features of increased renal NaCl reabsorption and salt-sensitive hypertension.21–25 Although these disorders account for <1% of human hypertension, they provide additional examples of salt-sensitive BP associated with kidney dysfunction and impaired pressure natriuresis.

That these human monogenic forms of hypertension are effectively treated with appropriate diuretics that reduce renal NaCl reabsorption reinforces the importance of excessive renal salt/water reabsorption in the pathogenesis of increased BP. For example, pseudohypodaldosteronism type 2 (Gordon syndrome) is caused by mutations of genes that encode WNK1 and WNK4, 2 members of the WNK family of serine-threonine kinases expressed in the distal nphron.76 Mutations of WNK1 are large intronic deletions that increase WNK1 expression, whereas WNK4 mutations are missense and cause loss of function. Both mutations increase activity of thiazide-sensitive NaCl transporters in the distal nphron, and patients with these mutations are effectively treated with thiazide diuretics that lower BP chronically by inhibiting renal NaCl reabsorption.76

Liddle syndrome is caused by gain of function mutations of the β or γ subunits of the epithelial sodium channel (ENaC).21–23 This disorder causes increased sodium reabsorption, hypaldosteronism, and low plasma renin activity and is effectively treated with amiloride or triamterene, both of which block ENaC and inhibit CD reabsorption.21,22

Glucocorticoid-remediable aldosteronism, apparent mineralocorticoid excess (AME), congenital adrenal hyperplasia, familial hyperaldosteronism not remedial by glucocorticoids (familial hyperaldosteronism-III and -IV), and AME indicates apparent mineralocorticoid excess; BP, blood pressure; and MR, mineralocorticoid receptor. Vasodilators are generally ineffective in treating these disorders that are associated with increased renal tubular NaCl reabsorption.

Table 2. Monogenic Forms of Salt-Sensitive Hypertension and Therapies That Effectively Reduce BP in These Disorders

<table>
<thead>
<tr>
<th>Genetic Disorder</th>
<th>Treatment</th>
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<tr>
<td>Liddle syndrome</td>
<td>Amiloride, triamterene</td>
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<tr>
<td>Activating MR mutation exacerbated by pregnancy</td>
<td>Delivery of fetus, amiloride, triamterene</td>
</tr>
<tr>
<td>AME</td>
<td>MR antagonist, amiloride, triamterene</td>
</tr>
<tr>
<td>Gordon syndrome</td>
<td>Thiazide diuretic</td>
</tr>
<tr>
<td>Glucocorticoid remediable aldosteronism (familial hyperaldosteronism-I)</td>
<td>Glucocorticoids, MR antagonist, amiloride, triamterene</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>Adrenalectomy or MR antagonist</td>
</tr>
<tr>
<td>Familial hyperaldosteronism not remediable by glucocorticoids (familial hyperaldosteronism-III and -IV)</td>
<td>Adrenalectomy or MR antagonist</td>
</tr>
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AME indicates apparent mineralocorticoid excess; BP, blood pressure; and MR, mineralocorticoid receptor. Vasodilators are generally ineffective in treating these disorders that are associated with increased renal tubular NaCl reabsorption.

and with patients these mutations are effectively treated with thiazide diuretics that lower BP chronically by inhibiting renal NaCl reabsorption.76

Kurtz and colleagues11 questioned whether increased renal NaCl reabsorption can account for increased BP in monogenic salt-sensitive hypertension and opined that vasodysfunction may underpin hypertension. Their main argument is based on the observation that salt-induced BP increases are often associated with increased TPR, whereas nonhypertensive salt-resistant subjects may have normal or reduced TPR.11 It should be noted, however, that changes in CO and TPR have not actually been measured during salt-induced BP increases in these forms of monogenic hypertension. Additionally, primary vascular dysfunction has not been shown to play a causal role in initiating the hypertension and may occur secondarily to increased BP and pressure- or flow-dependent autoregulatory responses.14,15,82

A common misconception, illustrated in the review by Kurtz et al,11 is that autoregulatory increases in TPR require
increased CO to be activated. However, increased BP almost invariably evokes vasoconstriction, even in isolated blood vessels, with or without increases in CO or blood flow and may result from pressure-dependent structural changes during chronic increased BP.\textsuperscript{14,15,82} Neurohormone-mediated vasoconstriction may also occur concomitantly with kidney dysfunction and, if severe, may actually reduce plasma volume and CO even though kidney dysfunction is required for salt-induced BP increases to be sustained.

**Kidney Transplantation Attenuates or Abolishes Salt-Sensitive Hypertension in AME or Liddle Syndrome**

AME, a monogenic form of salt-sensitive hypertension, is caused by deficiency of 11β-hydroxysteroid dehydrogenase 2, which causes glucocorticoid activation of MR.\textsuperscript{84} Although cortisol can bind to MR with high affinity, renal epithelial cells are normally protected by 11β-hydroxysteroid dehydrogenase 2, which locally converts cortisol to cortisone, which does not avidly bind MR. Therefore, 11β-hydroxysteroid dehydrogenase 2 deficiency causes excessive MR stimulation by cortisol, which activates ENaC in aldosterone-sensitive distal nephrons, leading to impaired renal-pressure natriuresis and hypertension with characteristics similar to that caused by primary aldosteronism.\textsuperscript{85} After hypertension is established, most indexes of kidney function appear normal except for hypokalemia and impaired renal-pressure natriuresis, and multiple vascular abnormalities begin to appear as a consequence of increased BP.

Unambiguous evidence for kidney dysfunction in mediating this form of salt-sensitive hypertension comes from the finding that transplantation of normal kidneys into patients with AME caused complete remission of hypertension and electrolyte abnormalities.\textsuperscript{77,78} These observations indicate that hypertension in AME has a renal origin.

Similar results were obtained in a patient with the Liddle syndrome whose hypertension resolved after a kidney transplantation.\textsuperscript{79} The finding that BP remained normal for at least 5 years after kidney transplantation, even though potential extrarenal effects associated with this syndrome were still present, indicates that the kidney abnormalities played a critical role in the pathogenesis of hypertension.

Kidney dysfunction also occurs in salt-sensitive hypertension caused by excess MR activity in primary aldosteronism or glucocorticoid-remediable aldosteronism.\textsuperscript{86} Although vascular dysfunction may occur in rodent and human genetic salt-sensitive hypertension, to the best of my knowledge, there are no studies demonstrating that nonrenal vasoconstriction induced by MR activation causes salt-sensitive hypertension in rodents or humans. In addition, it is unclear whether increased TPR is directly related to vascular/endothelial MR activation or is secondary to NaCl/volume retention and pressure-dependent vasoconstriction in these forms of hypertension. On the other hand, there is substantial evidence that kidney dysfunction is necessary for increased BP in human and rodent genetic salt-sensitive hypertension.

**Human Primary Hypertension**

Curtis et al\textsuperscript{80} demonstrated in patients with primary hypertension that transplantation of kidneys from normotensive donors completely resolved their hypertension. After an average follow-up of 4.5 years, the patients were normotensive, without antihypertensive medication.\textsuperscript{80} BP normalization was associated with regression of vascular injury and left ventricular hypertrophy, indicating that these abnormalities occurred as a consequence of hypertension. If vascular dysfunction or nonrenal neurohumoral mechanisms were major causes of hypertension in these patients, then increased BP should have reappeared. However, all patients remained normotensive and had normal renal sodium handling in response to wide variations in sodium intake (between 9 and 300 mmol/d) even after several years of follow-up, indicating that kidney abnormalities underpinned their hypertension.\textsuperscript{80}

Guidi et al\textsuperscript{81} followed up 85 patients with hypertension and end-stage renal disease of different origins for an average of 8 years after renal transplantation. Recipients who were transplanted with kidneys from donors with a positive family history of hypertension needed more antihypertensive treatment to reach target BP than those transplanted with a kidney from a donor with a negative family history of hypertension.

Although limited human data are available, current evidence suggests that nonrenal vascular dysfunction often follows the hypertension rather than causing increased BP. As shown in Table 3, kidney-specific interventions attenuate or prevent salt-induced increases in BP in many models of salt-sensitive hypertension.\textsuperscript{62,63,70–73,78–80,84–88} These observations do not negate the importance of neurohormonal mechanisms in mediating vasoconstriction or hypertension by altering kidney function, but they do provide another proof-of-principle test of the concept that kidney dysfunction is an essential component of salt-sensitive hypertension.

**Diuretics Lower BP in Salt-Sensitive Hypertension by Reducing Renal Tubular Reabsorption**

Responses to diuretics provide additional insights into the mechanisms by which salt/volume changes influence BP regulation in salt-sensitive subjects. Although diuretics initially reduce renal NaCl and water reabsorption, balance between NaCl intake and output eventually occurs, BP decreases, CO is usually normal or slightly reduced, and TPR decreases.\textsuperscript{89} These responses, the reverse of what happens when salt intake is increased in salt-sensitive subjects, have led to speculation that diuretics lower BP by causing peripheral vasodilatation.\textsuperscript{90} However, diuretics have little long-term effect on BP unless they are able to increase renal NaCl/volume excretion; for example, thiazide diuretics do not significantly lower BP in patients with end-stage renal disease who cannot respond to
their natriuretic and volume-depleting effects.91 The hypotensive effects of furosemide also depend on natriuresis and diuresis.92

If direct vascular actions of diuretics cannot account for their chronic BP-lowering effects, why do diuretics lower TPR? Frohlich and colleagues89 showed that chlorothiazide administration initially reduced plasma volume and CO. With prolonged diuretic administration, TPR decreased in parallel with the decrease in BP. This sequence suggests that decreased TPR is secondary to volume depletion and decreased BP and again highlights the key role of kidney dysfunction in mediating salt-induced BP increases in salt-sensitive subjects.

### Kidney Disorders That Cause Salt-Resistant Hypertension

Although kidney dysfunction is necessary for hypertension to be sustained chronically, not all kidney disorders cause salt-sensitive hypertension. Generalized increases in preglomerular resistance caused by suprarenal aortic coarctation or constriction of 1 renal artery and removal of the contralateral kidney (1-kidney, 1-clip Goldblatt hypertension) cause salt-resistant hypertension.12,93 Immediately after constriction of the renal artery or aorta, glomerular filtration rate and sodium excretion decrease and renin secretion increases. As BP increases, most indexes of renal function return to nearly normal, including sodium excretion and pressure distal to the stenosis, if the constriction is not too severe.12,93

A major reason that high salt intake does not greatly exacerbate hypertension caused by increased preglomerular resistance is that after BP increases sufficiently to restore renal perfusion pressure and renin secretion to normal, the RAAS is fully capable of appropriate suppression during high salt intake.29 As discussed previously, the ability to effectively modulate RAAS activity is a key mechanism for preventing salt sensitivity of BP.

### Phosphodiesterase 3A Mutations Cause Increased Vascular Resistance and Salt-Resistant Hypertension

Autosomal-dominant hypertension with brachydactyly is caused by gain-of-function mutations in the gene encoding phosphodiesterase 3A (PDE3A) which catalyzes hydrolysis of intracellular second messengers, cAMP and cGMP.94 The mutated PDE3A causes vascular smooth muscle cell proliferation and vasoconstriction, leading to increased TPR and presumably increased renal vascular resistance. Sympathetic blockade and hydrochlorothiazide treatment were ineffective in reducing BP, whereas nitroprusside caused acute decreases in BP, consistent with an intrinsic vascular abnormality.95,96 Despite marked vasoconstriction and increased TPR, these patients are not salt sensitive and have normal renin, aldosterone, and norepinephrine.96

Thus, generalized vasoconstriction does not appear to increase BP salt sensitivity in the absence of kidney abnormalities that increase tubular reabsorption, decrease glomerular filtration coefficient, and/or reduce responsiveness of the RAAS. Renal preglomerular vasoconstriction can increase BP, but the hypertension is usually not salt sensitive.

### Is Increased TPR (Vasodysfunction) a Consequence Rather Than a Cause of Salt-Sensitive Hypertension?

Although kidney dysfunction clearly plays a causal role in salt-induced hypertension (Tables 1 and 3), sodium balance, plasma volume, and CO may not be markedly different than in normotensive subjects after hypertension is established. The most obvious abnormality is often increased TPR; even in hypertension that is clearly initiated by kidney dysfunction and salt loading, CO is usually normal and TPR is increased after a few days. What causes increased TPR in salt-loading hypertension?

It is important to remember that TPR is a recondite number derived from measurements of BP and CO. If BP increases and CO returns to normal, as occurs even when kidney dysfunction and salt/volume retention initiate the hypertension, increased TPR will be calculated. Unless the heart is weakened or the metabolic rate of the tissues is altered, CO is chronically regulated at a level that is nearly normal, and TPR increases in proportion to BP.
Why does CO return to nearly normal after transient increases during salt loading? This is easier to understand if one remembers that CO represents the total blood flow of the organs/tissues. The proper level of tissue blood flow is one of the highest priorities for homeostasis and is achieved by multiple short-term and long-term mechanisms, including local tissue controls. Short-term studies showed that active vasoconstriction occurs in most tissues when BP or blood flow is increased. When BP increases are sustained, gradual vascular remodeling and thickening of blood vessel walls occur. Blood flows in most tissues, and therefore CO, are ultimately maintained at a level appropriate for the tissue metabolic needs even with high salt/volume intake and increased BP. This process, often called autoregulation, involves pressure- and flow-dependent factors and almost invariably leads to increased TPR when BP increases. Moreover, when renal excretory function is improved (eg, by kidney transplantation or treatment with diuretics) and BP is reduced, TPR also decreases and vascular changes usually regress.

Is Increased TPR Required for the Development of Salt-Sensitive Hypertension?

In contrast to multiple studies showing that kidney dysfunction is required for salt-sensitive BP increases, to the best of my knowledge, no studies have demonstrated that increased TPR is required for salt-induced increases in BP or that primary increases in nonrenal vascular resistance can cause salt-sensitive hypertension. In fact, multiple studies have shown that increases in nonrenal vascular resistance are unable to make BP salt-sensitive in the absence of kidney dysfunction. Additional observations that question whether primary vascular dysfunction is required for salt-sensitive hypertension are that increased salt intake in various forms of salt-sensitive hypertension (eg, AngII hypertension) causes hypertension even after genetic deletion of nonrenal vascular effects. Also, decreasing TPR to normal by infusion of vasodilators or by opening an arteriovenous fistula did not prevent DOCA-salt hypertension.

Technical and Conceptual Challenges in Determining Mechanisms of Salt-Induced Hypertension From Measurements of CO and BP

In most clinical and experimental studies, BP and CO are measured for only a few minutes under resting conditions during a control period before an experimental manipulation such as increasing salt intake and then during the experimental period. TPR is calculated from BP and CO measurements, and inferences are made regarding whether changes in BP are due to changes in CO or TPR (Figure 5). A major limitation of this approach is that BP and CO change rapidly throughout the day with various activities and thus it is unlikely that casual measurements of these variables can adequately represent the average changes throughout the day or small, dynamic differences, especially when changes are transient such as during increased salt intake.

![Figure 5. Time course of changes in mean arterial pressure (MAP), systemic vascular resistance (SVR), and cardiac output (CO) when NaCl intake was raised from 30 to 250 mmol/d in salt-resistant (SR; ◊) and salt-sensitive (SS; •) subjects. Values are shown as percent change from baseline (average of day 5–7 of 30 mmol/d NaCl intake). Responses of MAP and SVR to NaCl loading differ significantly in SS and SR subjects from day 2. Responses of CO did not differ between groups, and CO was not significantly different from baseline values after 4 days. Note that SVR increased significantly in SS subjects vs baseline, only after MAP increased. Also note that SVR was not significantly different compared with baseline values in SR subjects after 6 days. Baseline values for SS and SR subjects were not provided in the article. Data are from Schmidlin et al.* P<0.01 and † P<0.05 vs low-salt period.](http://circ.ahajournals.org/)

Another limitation is the accuracy of CO measurements when CO is assessed with methods such as impedance cardiography, which may have a variability of 9% to 11% compared with more direct methods such an electromagnetic flowmeter. Studies that have assessed CO by impedance cardiography during salt loading in humans, including those by Schmidlin, Morris and colleagues, have generally found only transient increases in CO that are ≤10% (Figure 5). Moreover, increased TPR in these studies generally follows, rather than precedes, increased BP after a few days of salt loading. Unless CO is measured continuously and with great accuracy, small transient changes that occur with salt loading are difficult to discern.

More important, although CO or TPR may be elevated at various stages of salt-induced increases in BP, neither of these variables is a primary long-term controller of BP. Instead, CO and TPR are the effectors of a complex system in which the
set point is determined by intrarenal and extrarenal factors that ultimately influence renal-pressure natriuresis and ensure that salt and water balances are maintained. Unless the heart is weakened or the metabolic needs of the tissues are altered, CO is maintained relatively constant, despite kidney dysfunction or salt loading, and TPR usually follows BP. Hypertensive disorders associated with primary increases in vascular resistance (eg, PDE3A mutations) have not been shown to be salt-sensitive.

Changes in vascular resistance certainly play a crucial role in moment-to-moment BP regulation, especially in emergency circumstances such as severe hemorrhage. A minimal level of vascular resistance and adequate cardiac function are required for normal long-term BP regulation. However, primary changes in TPR that are not accompanied by changes in the relationship between BP and renal salt/water excretion (renal-pressure natriuresis/diuresis) have not been shown to cause salt sensitivity or to change the long-term level of BP.

Summary and Conclusions
Long-term high salt intake increases the risk for hypertension, and moderation of salt intake is an important strategy for preventing cardiovascular and kidney disease, especially in salt-sensitive subjects. BP salt sensitivity is a highly variable, continuous phenotype and may worsen with aging and kidney injury if high salt intake is maintained chronically.

Kidney dysfunction, characterized by impaired pressure natriuresis, has been demonstrated in all forms of experimental and human genetic or acquired salt-sensitive hypertension studied thus far. Experimental models and monogenic forms of salt-sensitive hypertension have abnormalities of kidney function that directly or indirectly increase NaCl reabsorption, decrease glomerular capillary filtration coefficient, or cause nephron injury/loss.

Vascular dysfunction may occur concomitantly or secondarily to increased BP in salt-sensitive hypertension, but increases in nonrenal vascular resistance have not been shown to increase BP salt sensitivity unless renal-pressure natriuresis is impaired. The mechanisms by which high salt intake increases TPR are not fully understood but may involve multiple factors, including pressure-dependent and flow-dependent autoregulation and neurohormonal factors that occur concomitantly with kidney dysfunction. The fact that hypertension-associated vascular changes usually regress when renal excretory function is improved and BP is reduced also suggests that increased TPR and vascular dysfunction are often secondary to hypertension. Although CO or TPR may be elevated in salt-sensitive hypertension, neither of these variables is a primary long-term controller of BP. Instead, CO and TPR are the effectors of a complex system in which the set point is determined by intrarenal and extrarenal factors that ultimately influence kidney function and ensure that salt/water balance is maintained.

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Disclosures
None.

References


Response to Hall

R. Curtis Morris, Jr, MD; Olga Schmidlin, MD, Anthony Sebastian, MD, Masae Tanaka, MD, Theodore W. Kurtz, MD

Dr Hall arbitrarily restricts the scope of vasodysfunction to vasoconstriction. He indicates that our vasodysfunction theory attributes initiation of salt-induced increases in blood pressure to vasoconstriction and increased total peripheral resistance. However, the actual theory that we presented holds that vasodysfunction, which we explicitly defined as a subnormal decrease in total peripheral resistance in response to increased salt intake (not as vasoconstriction or increased total peripheral resistance above baseline), is the hemodynamic abnormality that usually precedes and initiates salt-induced hypertension. Dr Hall presents no evidence contradicting this theory; rather, he argues against theories we have not advocated. In addition, he presents no evidence contradicting another core tenet of our vasodysfunction theory: In salt-sensitive subjects, substantial increases in salt intake initiate increased blood pressure usually without causing increases in sodium retention and cardiac output greater than those that occur in salt-loaded normal control subjects (salt-resistant subjects with normal blood pressure). Dr Hall asserts that we cited this lack of greater sodium retention in salt-sensitive subjects as evidence that salt-sensitive hypertension is not caused by renal dysfunction. In fact, we contend that renal dysfunction is involved in initiating salt-induced hypertension. However, such renal dysfunction does not usually initiate salt-induced hypertension by causing greater sodium retention in salt-sensitive subjects compared with salt-loaded normal control subjects. Rather, such renal dysfunction is characterized by a kind of vasodysfunction, that is, a subnormal decrease in renal vascular resistance in response to increased salt intake. This abnormal renal vascular resistance response to salt contributes to the abnormal total peripheral resistance response to salt that hemodynamically mediates the initiation of salt-induced hypertension.
Renal Dysfunction, Rather Than Nonrenal Vascular Dysfunction, Mediates Salt-Induced Hypertension
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