Differential Predictors of Insulin Resistance in Nondiabetic Salt-Resistant and Salt-Sensitive Subjects

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Abstract—We studied the characteristics of insulin resistance in 19 normotensive and 25 hypertensive subjects who underwent an acute protocol for determination of salt-sensitivity of blood pressure. Hypertensive subjects were older and more obese, with higher creatinine, lipids, and aldosterone than normotensive volunteers. They also had higher glucose and insulin levels with a marked decrease in insulin sensitivity (HOMA2-S index). Once all participants were classified into salt-sensitive (SS) and salt-resistant (SR) groups, most of these differences were no longer present. In contrast, SS had classical characteristics of this phenotype (higher percentage of blacks, suppressed plasma renin, increased aldosterone-to-renin ratio, and blunted renin and aldosterone responses to changes in salt balance). Despite similar insulin levels, HOMA2-S was significantly lower in SS than SR. Salt-loading did not change HOMA2-S in SS or SR. In contrast, salt-depletion, by significantly increasing glucose and insulin of SR, decreased their HOMA2-S to the levels observed in SS. Correlates of insulin resistance in SR included age, triglycerides, body mass index, mean arterial pressure, aldosterone, and epinephrine. However, only body mass index and aldosterone remained as significant predictors in multivariate analyses. Correlates of insulin resistance in SS were mean arterial pressure, epinephrine, and norepinephrine, all remaining as significant predictors in multivariate modeling. Our data confirm that salt-sensitivity of blood pressure is associated with insulin resistance, suggest that salt restriction may be beneficial in SS but perhaps detrimental in SR subjects, and uncover possible differences in mechanisms of insulin resistance between SS and SR, with implications for pharmacological therapy. (Hypertension. 2013;61:707-715.)

Key Words: aldosterone ■ catecholamine ■ insulin action ■ insulin resistance ■ obesity ■ renin-angiotensin system ■ salt-sensitive
Methods
Normotensive volunteers and essential hypertensive patients were recruited into an Institutional Review Board-approved inpatient protocol to study effects of acute salt-loading and salt-depletion on BP. All of them provided informed consent. Of a total of 53 subjects, 5 were excluded for lack of insulin data and 6 for having diabetes mellitus; results for the remaining 42 are reported here.

We have previously described the protocol in detail. Briefly, after obtaining demographic information and routine laboratory data, hypertensive subjects discontinued therapy for 2 weeks. All subjects maintained their usual salt intake until admission to the hospital for an overnight stay. Baseline BP and heart rates were obtained by automated ambulatory monitors (Spacelabs 90207) from 7 to 8 AM the following morning, followed by salt-loading on the first day of study (160 mEq NaCl diet plus 2 L normal saline infused from 8 AM to 12 PM) and salt-depletion on the second (10 mEq NaCl diet plus 3 40 mg doses of oral furosemide). BP and heart rates were recorded throughout the study with the ambulatory monitors, every 15 minutes from 6 AM to 10 PM and every 30 minutes overnight. Average systolic BPs from noon (end of saline on the first day or second dose of furosemide on the second day) to 10 PM (bedtime) were used for classification of subjects into SS or SR groups; a fall of 10 mm Hg in systolic BP from salt-loading to salt-depletion was the cutoff. Body weights were recorded at baseline and daily at 7 AM, before interventions. Body mass index (BMI) was calculated as weight in kg divided by height in m2.

Blood samples for routine tests, plasma renin activity (PRA), aldosterone, insulin, and catecholamines (epinephrine and norepinephrine) were obtained at baseline (before saline-infusion of the first day) and on the mornings after the days of salt-loading and salt-depletion. PRA, aldosterone, and insulin were measured by radioimmunoassay and catecholamines by radioenzymatic assay.

Insulin sensitivity (S) and β-cell function (B) were assessed using the HOMA2 model with the paired fasting glucose and insulin levels of each day employing the HOMA2 Calculator v2.2 of the Diabetes Trials Unit, University of Oxford (www.dtu.ox.ac.uk).

Data are presented as mean±SEs of the mean. Skewed data were log transformed. Comparisons between groups were made with unpaired t tests. Changes in variables between periods of the protocol were analyzed with paired t tests. Differences between proportions were evaluated by χ² testing. Correlation coefficients were calculated with Pearson method, pooling the data for the 3 days of the protocol in each patient. These tests, single linear regressions and stepwise mixed multivariate analyses for model fitting, were performed with JMP software (version 3.0.2, SAS Institute). A probability < 0.05 was used to reject the null hypothesis.

Results
The 23 hypertensive and 19 normotensive subjects were 42.6±1.4 years old, 81% female and 38% black. Obesity (BMI>30 Kg/m2) was present in 64% of subjects. The prevalence of SSBP was somewhat higher in hypertensive patients than in normotensive subjects (43.5%) than in normotensive (36.8%) subjects, but its magnitude (assessed by the reduction in systolic BP from the salt-loading to the salt-depleted days) did not differ between SS (−13.5±1.9 versus −15.9±1.5 mm Hg), or SR (−2.2±1.2 versus −3.3±1.3), normotensive and hypertensive subjects.

The right columns of the Table show data after all subjects were reclassified into SS and SR groups. Several of the differences between normotensive and hypertensive subjects were no longer observed between SS and SR, because a similar percentage of hypertensive and normotensive subjects belonged to each of these groups. Hence, age, BMI, heart rate, creatinine, creatinine clearance, lipids, epinephrine, glucose, and insulin were similar between SS and SR.

In contrast, SS were characterized by larger percentage of black subjects, higher diastolic BP, lower PRA, higher aldosterone-to-renin ratios, and increased BP variability compared with SR. Despite similar insulin levels, SS had higher (not statistically significant) blood glucose levels, leading to significantly lower insulin sensitivity index (ie, greater insulin resistance) in SS than in SR.

Figure 1 shows effects of salt-loading (comparing baseline data with those after salt-infusion and high-salt diet) and salt-depletion (comparing data after salt-loading with those after low-salt diet and furosemide) on renin, aldosterone, and catecholamines in SS and SR. PRA was suppressed by the salt-loading and stimulated by salt-depletion in both groups, as expected, but the values of each day were lower in SS than in SR. Stimulation of PRA by salt-depletion in SS was blunted compared with that in SR (0.6±0.2 versus 1.3±0.3 ngA/L per second; P < 0.03). Aldosterone levels were suppressed by salt-loading and stimulated by salt-depletion in SR, whereas in SS, its suppression by salt was not significant and its stimulation by salt-depletion was of lesser magnitude than in SR (142±50 versus 268±48 pmol/L; P < 0.05). Aldosterone-to-renin ratios (not shown) did not change significantly in response to salt-loading in either group, consistent with concomitant suppression of PRA and aldosterone by salt-loading. In contrast, they were significantly diminished by salt-depletion in both groups, because of greater stimulation of PRA than of aldosterone by this intervention. Finally, in every phase of the experiment, aldosterone-to-renin ratios were higher in SS than SR subjects, reflecting the lower PRA of the former.

Plasma norepinephrine and epinephrine (Figure 1) did not differ between SS and SR on any day of the experiment. Salt-loading reduced the levels of both, but this change was significant for epinephrine in SS only. In contrast, both catecholamines were significantly stimulated by salt-depletion, to the same extent in SS and SR.

Figure 2 shows the effects of salt-loading and -depletion on metabolic parameters. Glucose, insulin levels, and β-cell function (estimated by HOMA2-B) were not significantly different between SR and SS during the baseline and salt-loaded days. However, slightly higher glucose in SS during those 2 days (about 0.47 mmol/L higher than those in SR) resulted in markedly diminished insulin sensitivity (HOMA2-S) compared with SR. After salt-depletion, significant increases in both glucose and insulin levels took place in SR, leading to a 24% decrease in insulin sensitivity in this group, reaching a level indistinguishable from that observed in SS during all periods of the study. Salt-depletion...
produced a modest significant increase in glucose in SS, but the slight further diminution of their HOMA2-S was not significant. In contrast to these changes in insulin sensitivity, HOMA2-B was not altered by salt-depletion in either group.

In other words, SS subjects were more insulin resistant, compared with SR, during baseline and after salt-loading,
but salt-depletion induced insulin resistance in SR subjects, equalizing HOMA2-S in both groups, without modifying β-cell function.

There was no correlation between the effects of salt-depletion on systolic BP (ie, the salt-sensitivity index) and the baseline insulin sensitivity of the patient. An apparent trend ($r=0.30; P=0.06$) was attributable to SS having larger falls in systolic BP and lower HOMA2-S, whereas the opposite was true in SR. However, there was no relationship between salt-sensitivity and insulin resistance when each group was analyzed separately.

Figure 3 depicts metabolic and renin–angiotensin system univariate correlates of HOMA2-S in SR (open circles) and SS (closed circles). Regression lines are plotted for the group with significant correlations only. Older age, magnitude of obesity, higher triglycerides, and higher log aldosterone correlated with greater insulin resistance (ie, lower HOMA2-S) in the relatively more insulin-sensitive SR group only. None of these variables correlated with insulin sensitivity in the more insulin-resistant SS subjects. Log PRA and log aldosterone-to-renin ratio did not correlate with HOMA2-S in either group (not shown).

Figure 4 depicts hemodynamic and catecholamine univariate correlates of HOMA2-S in SR and SS. Significant correlations are indicated by solid regression lines for SR and by dashed ones for SS. Higher mean arterial pressures (MAP) correlated with increasing insulin resistance in both groups, consistent with the observation that hypertensive subjects were more insulin resistant than normotensive ones (Table). The slope in SS was flatter than that of SR (0.51±0.20% reduction of HOMA2-S per each mm Hg increase in MAP in SS, versus 1.25±0.29% in SR, $P<0.02$). Hence, at the same BP level, if within the normal range, SS subjects were more insulin resistant than SR. In contrast, with high BP values, the
magnitudes of insulin resistance at any level of BP was similar in both groups.

Higher plasma epinephrine also correlated with increasing insulin resistance (lower HOMA2-S) in both groups, but the relationship was stronger (r value) in SS. The slopes were parallel (104±43% reduction of HOMA2-S per nmol/L increase in epinephrine in SS, and 98±32% in SR, ns), whereas the regression line for SS was shifted to the left (SS intercept, 50.73±3.64%; SR, 66.70±6.83%; P<0.03). This shift indicates that the effect of epinephrine on insulin resistance is enhanced in SS by 30% to 70%, depending on the absolute epinephrine value (the higher the epinephrine, the greater the percent reduction in HOMA2-S in SS compared with SR).

Higher heart rates correlated with insulin resistance in SR only. In contrast, higher plasma norepinephrine correlated with insulin resistance in SS only. Because levels of norepinephrine were about 20-fold higher than those of epinephrine in both groups, total catecholamines (norepinephrine plus epinephrine) also correlated with insulin resistance in SS only (r=0.30; P<0.04; not shown).

Within the SS group, the univariate correlates of HOMA2-S that cross-correlated with each other included epinephrine with norepinephrine, r=0.34, P<0.02, and MAP with norepinephrine, r=−0.27, P=0.05. In SR, there were many cross-correlations between the univariate correlates of HOMA2-S. Hence, MAP correlated with age (r=0.33; P<0.005), BMI (r=0.24; P<0.04), log aldosterone (r=0.60; P<0.00001), heart rate (r=0.44; P<0.0001), and epinephrine (r=0.25; P<0.04); heart rate with BMI (r=0.31; P<0.01), log aldosterone (r=0.50; P<0.00001), and epinephrine (r=0.47; P<0.0001); and log aldosterone with age (0.30; P<0.01) and epinephrine (r=0.29; P<0.02). Therefore, to assess the significant predictors of HOMA2-S in both groups, we used multivariate regression. In the model for SR, only BMI and log aldosterone remained as significant predictors of HOMA2-S, accounting for half of its variability: HOMA2-S=382.706–3.789*BMI–79.792*log_Aldo; R²=0.508; F=37.153; P<0.0001. In SS, the significant predictors were MAP, norepinephrine and epinephrine, with these catecholamines as separate variables having a greater predictive power than their sum as total catecholamines: HOMA2-S=115.928–0.575*MAP–0.362*Epi; R²=0.310; F=6.8893; P<0.001. The explanatory power of this model (31% of the variability of HOMA2-S) was less than that for SR, suggesting that in SS there might be contributors to variability of insulin resistance that we did not study in our subjects.

Discussion

We explored whether the characteristics of insulin resistance differ between SS and SR subjects, independent of BP (ie, in normotensive and hypertensive subjects). We first confirmed observations by others that hypertensive patients are, in general, more insulin resistant than controls. Two thirds of patients attending hypertension clinics exhibit abnormalities in glucose metabolism,11 and their reduced insulin sensitivity has been documented with euglycemic, hyperinsulinemic clamp,26,27 and HOMA techniques.14 In some28 but not all26 studies, normotensive offspring of hypertensive parents also had reduced peripheral glucose utilization. Because enhanced proximal tubular sodium reabsorption by insulin is preserved in hypertensive subjects27 and their offspring,28 it has been suggested that insulin resistance may precede and predict the development of essential hypertension, a contention supported by epidemiological studies of large populations.29 Insulin resistance increases with aging30 and our hypertensive subjects were somewhat older than our normotensive volunteers. However, it is unlikely that the 64% reduction
in insulin sensitivity in the former can be solely attributed to an age difference of less than a decade.

A relationship between SSBP and insulin resistance has been documented in Dahl-S rats\(^6\) and confirmed in humans. Steady-state glucose-to-insulin ratio during an insulin and glucose-infusion was twice as high in SS as in SR lean normotensive young subjects,\(^7\) a magnitude of insulin resistance remarkably similar to that in our normotensive SS participants, in whom HOMA2-S was 47% of that of SR. In hypertensive patients classified into SS or SR by dietary\(^4,10\) or acute\(^6\) protocols, use of euglycemic clamp techniques confirmed these observations. In 1 study,\(^10\) the relationship between SS and insulin resistance was independent of age, obesity, and hyperinsulinemia. We confirm this, because there were no differences in age, BMI, or insulin levels between our SS and SR subjects, indicating that insulin resistance in SS is not attributable to these confounding factors. Increased odd ratios for developing insulin resistance, SSBP, and lack of nocturnal dipping of BP (a feature of both SSBP and insulin resistance) have been linked to a polymorphism in the insulin–receptor–substrate type-1 (IRS-1) gene,\(^31\) suggesting that the relationship between SSBP and insulin resistance may be genetically determined.

Our protocol, with salt-loading and -depletion, allowed us to assess the effect of salt balance on insulin resistance, a highly controversial issue. An early study with an euglycemic clamp in normal subjects showed that a high-salt diet increased insulin resistance.\(^5,6\) Two other studies in controls\(^7,12\) and 1 in diabetic subjects\(^15\) failed to detect any effect of dietary salt on insulin resistance, employing either clamp techniques or steady-state glucose concentration during an insulin suppression test. The opposite observation, that is, increased insulin resistance by a low-salt diet, has been made in small studies of normal subjects (17% reduction in insulin-mediated glucose disposal),\(^13\) in a large group of normotensive participants of the HyperPath study (17% increase in HOMA insulin resistance index)\(^20\) and in normotensive diabetic subjects studied with a euglycemic clamp (12% reduction in insulin sensitivity).\(^32\) Stimulation of angiotensin II and catecholamines by a low-salt diet has been proposed as a mechanism for low-salt diet–induced insulin resistance.\(^15\) However, in the large HyperPath study the effect of low salt was independent of age, sex, BP, BMI, serum electrolytes, angiotensin II, PRA, aldosterone, and catecholamines.\(^20\) Only 2 studies assessed whether the effect of salt intake on insulin resistance depends on SSBP. In 1, a high-salt diet improved insulin sensitivity in SS normotensive men (not women) with a family history of hypertension,\(^22\) consistent with worsening insulin resistance by a low-salt intake, but in a sex- and SSBP-dependent manner. In the other, the conclusion was opposite, because glucose tolerance improved with salt restriction in healthy SS males, whereas it worsened in SR\(^23\).

Our study cannot be compared with the ones above because all of them used dietary changes in salt intake over several days, whereas ours used acute sodium balance manipulation and furosemide. However, our results agree with dietary studies showing worsened insulin resistance by salt-depletion, whereas we did not detect an effect of acute salt-loading. Furthermore, we show worsening of insulin resistance by salt-depletion only in the relatively insulin-sensitive SR subjects (attributable to 8% and 26% significant increases in glucose and insulin, respectively). In contrast, in the more severely insulin-resistant SS group, salt-depletion does not worsen it any further. This observation, if replicated in a dietary study without furosemide, would have obvious implications in terms of the controversy over recommended salt intake for hypertensive patients or normal populations. It would imply that salt restriction may be beneficial in SS subjects, reducing BP without worsening their already impaired metabolic status, whereas it may be detrimental in SR, not improving BP, while inducing or worsening insulin resistance.

Many clinical and biochemical correlates of insulin resistance have been described. The association of obesity with insulin resistance in normotensive\(^12\) and hypertensive\(^13\) subjects may be attributable to accumulation of diacylglycerol in adipocytes and skeletal myocytes. Diacylglycerol-stimulated PKC isoforms serine-phosphorylate IRS-1 and IRS-2, inactivating the downstream PI3-kinase needed for translocation of GLUT 4 to the cell membrane.\(^34\) A high salt intake may enhance this mechanism because it results in a 33% increase in plasma-free fatty acids.\(^35\) Indirect effects of obesity may include activation of sympathetic nervous system activity\(^33\) or inadequate suppression of aldosterone by salt.\(^36\) The association of hypertension with insulin resistance is probably attributable to decreased skeletal muscle blood flow (chronic vasoconstriction and capillary rarefaction) with marked decrease in peripheral glucose uptake\(^37\) and impairment in the normal skeletal muscle vasodilatory effect of insulin.\(^38\) Angiotensin II interferes with insulin signaling via effects of NO,\(^39\) NADPH oxidase,\(^40\) and the servoregulatory negative feedback loop by suppressor of cytokine signaling proteins, which is shared by angiotensin II and insulin signaling and results in inhibition of janus kinase/signal transducer and activator of transcription pathways.\(^41\) A relationship between PRA and insulin resistance was found in some studies in normotensive\(^12\) and hypertensive\(^13\) subjects but paradoxical improvement of insulin resistance by angiotensin II was shown by others.\(^42,43\) Aldosterone inhibits insulin signaling in rodents,\(^44\) isolated adipocytes, vascular smooth muscle,\(^45\) and skeletal muscle\(^46\) via effects of inflammation and NADPH oxidase. Its actions are mediated by mineralocorticoid\(^46,47\) or glucocorticoid\(^47\) receptors. Correlations between aldosterone and insulin resistance have been found in healthy subjects,\(^48\) hypertension\(^49\) and heart failure\(^50\) and its plasma levels predict development of insulin resistance in populations.\(^50\)

Regarding a link between the sympathetic nervous system and insulin resistance, the most likely mechanism for norepinephrine is diminution of skeletal muscle glucose uptake attributable to vasoconstriction.\(^51\) For epinephrine, increased lipolysis, hepatic gluconeogenesis, and decreased peripheral utilization of glucose\(^52,53\) predominate, as supported by epinephrine-induced insulin resistance in normal men at suppressor doses.\(^54\) Clinical studies have documented a relationship between heart rate and insulin resistance in normotensive and hypertensive subjects.\(^55\) Insulin can stimulate the sympathetic nervous system but the sequence of
events seems to be the opposite, that is, autonomic alterations preceding the development of insulin resistance.66,67

Our finding of multiple univariate correlates of insulin resistance is consistent with the studies above. The novel and striking finding is that they are different between SR and SS, an observation not made in the only other publication that assessed this issue in direct fashion.60 Univariate correlates of insulin resistance in our SR group (age, BMI, triglycerides, aldosterone, BP, heart rate, and epinephrine) are consistent with those described in normotensive and hypertensive patients not phenotyped for SSBP. Because of cross-correlations between these variables, we resorted to multivariate modeling, which indicated that BMI and aldosterone, although inter-related, are independent predictors of insulin resistance in SR. The reason by which these variables were not predictors in SS cannot be ascertained from our study. Although blunted aldosterone responses to salt balance in SS may diminish the role of aldosterone in determining insulin resistance in this group, circulating levels of plasma aldosterone were only slightly, but not significantly lower, in SS than SR.

In SS, significant predictors included BP and both catecholamines (epinephrine and norepinephrine), consistent with previously observed stronger relationship between catecholamines and insulin resistance in SS than SR.60 Their increased BP variability is consistent with reported relationships between insulin resistance and autonomic function.68 Whereas epinephrine correlated with insulin resistance in both groups, supporting participation of its metabolic actions in all subjects, the left shift of this relationship in SS suggests the presence of additional factors in this group. The exclusive correlation of norepinephrine with insulin resistance in SS strongly suggests exaggerated peripheral vasoconstriction with diminished skeletal muscle glucose uptake as a major contributor in this group. Alternatively, different predictors in SR versus SS may simply reflect greater severity of insulin resistance or vasoconstriction in the latter (ie, once established and severe, insulin resistance may depend on different mechanisms from those that operated at its onset). The decrease in the different magnitude of insulin resistance between groups as BP increased supports this possibility. Finally, it is noteworthy that we did not find relationships between PRA and insulin resistance in either group. Lack of this relationship in SS may be attributed to their blunted renin–angiotensin system but the reason in SR is less apparent, perhaps reflecting the conflicting effects of angiotensin II on insulin resistance quoted above.

Regardless of their reasons, different predictors suggest different underlying mechanisms for insulin resistance in SS versus SR. The obvious implication of this finding, if reproduced in larger populations with prolonged dietary protocols without use of furosemide, would be its applicability to selection of pharmacological therapy in hypertension. Whereas mineralocorticoid blockers could improve insulin resistance in SR, agents that suppress sympathetic activation should be more effective in SS.

In conclusion, our study confirms the presence of insulin resistance in hypertension and its greater severity in SS normotensive and hypertensive subjects compared with their SR counterparts. We also show differential effects of salt balance on and differential predictors of insulin resistance between groups, which may have implications for recommendations about salt restriction and pharmacological therapy in these 2 phenotypes.

Perspectives
We have shown that SS subjects have a high degree of insulin resistance compared with SR, and that acute salt-loading and salt-depletion do not further impair their insulin sensitivity. In contrast, SR are more insulin sensitive but when subjected to salt-depletion, their insulin sensitivity is reduced to the level observed in SS. In addition, our modeling analyses suggest that the predictors of insulin resistance are different between groups; that is, BMI and aldosterone levels in SS versus MAP and catecholamines in SR. We suggest that there are implications in terms of dietary recommendations for hypertensive patients or the population. Our findings predict that salt restriction will benefit SS by reducing their BP without modifying their metabolic status, whereas it may render SR insulin-resistant without benefit on their BP control. Also, different mechanisms for insulin resistance between these 2 groups may have implications for selection of pharmacological therapy in hypertension; for example, use of agents that block the renin–angiotensin–aldosterone system versus those that act on the sympathetic nervous system.

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Disclosures
None.

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### Novelty and Significance

**What Is New?**
- First, the demonstration that the effects of salt-depletion on insulin resistance are different in salt-sensitive and salt-resistant normotensive and hypertensive subjects. Second, the observation that the clinical and biochemical correlates of insulin resistance are also different between these 2 groups.

**What Is Relevant?**
- The different effects of salt-depletion on insulin resistance have implications for health policy initiatives that advocate reduction of salt intake for the population at large and for all hypertensive patients. The different correlates of insulin resistance in salt-sensitive and salt-resistant hypertensive patients may be relevant for selection of antihypertensive therapy, to achieve simultaneous improvement of blood pressure and insulin sensitivity.

### Summary

Salt-depletion is beneficial for reducing blood pressure of salt-sensitive subjects, which in the case of hypertension is the most prevalent phenotype. On the contrary, salt-depletion will not benefit salt-resistant hypertensive patients, and may have adverse effects on their insulin sensitivity. Blockers of the renin–angiotensin–aldosterone system may be efficacious agents for improvement of insulin sensitivity in salt-resistant subjects, whereas interventions that diminish sympathetic overactivity may be more efficacious in salt-sensitive ones.

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