

ORIGINAL ARTICLE

A Quantitative Systems Physiology Model of Renal Function and Blood Pressure Regulation: Application in Salt-Sensitive Hypertension

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Salt-sensitivity (SS) refers to changes in blood pressure in response to changes in sodium intake. SS individuals are at greater risk for developing kidney disease, and also respond differently to antihypertensive therapies compared to salt-resistant (SR) individuals. In this study we used a systems pharmacology model of renal function (presented in a companion article) to evaluate the ability of proposed mechanisms to produce salt-sensitivity. The model reproduced previously published data on renal functional changes in response to salt-intake, and also predicted that glomerular pressure, a variable that is not easily evaluated clinically but is a key factor in renal injury, increases with salt intake in SS hypertension. We then used the model to generate mechanistic insight into the differential blood pressure and glomerular pressure responses to angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, and calcium channel blockers observed in SS and SR hypertension.

CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 393–400; doi:10.1002/psp4.12177; published online 23 January 2017.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Blood pressure salt-sensitivity (SS) is associated with increased kidney disease and differential responses to antihypertensive therapy. The mechanisms responsible for these phenomena are incompletely understood.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We utilized a systems model of renal function to evaluate hypothesized mechanisms of SS and the impact on glomerular hydrostatic pressure, a key driver of renal injury. We also explored the system behavior underlying differential responses to antihypertensive treatments.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ We demonstrated that reduced sensitivity to regulatory signals like RIHP and the RAAS can cause SS of both blood pressure and glomerular pressure. While BP reduction with ACE inhibition was predicted to be lower in SS subjects, glomerular pressure reduction was similar, suggesting that renoprotective effects of RAAS blockade are maintained.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

☑ A mechanistic understanding of SS hypertension, and the consequences for renal injury and response to therapy, may allow optimized use of existing therapeutics. This approach may also be applied to evaluate new therapies in the setting of SS hypertension.

In a companion article, we described a quantitative systems pharmacology (QSP) model of renal function and volume regulation. Here we utilized that model to investigate mechanisms contributing to blood pressure salt-sensitivity (SS), and the differential response to antihypertensive therapy in salt-sensitive hypertensive patients. SS refers to large changes in blood pressure in response to changes in sodium intake. In salt-resistant (SR) individuals (and animals), blood pressure changes minimally even with several fold changes in sodium intake, while in SS individuals, changes in sodium intake result in substantial blood pressure changes.^{1,2} SS status is more common in certain groups, including blacks^{3–6} and diabetics^{4,7}—groups who are also at increased risk for development of chronic kidney disease.⁸ It also impacts the response to antihypertensive therapies—SS individuals tend to demonstrate a weaker response to drugs targeting the renin angiotensin aldosterone system (RAAS).^{9,10}

In this study, we utilized a QSP model to evaluate hypothesized mechanisms of SS, to generate model-based hypotheses regarding the differential response to antihypertensive therapy, and to evaluate changes in glomerular hydrostatic pressure, a key driver of renal damage,^{12,13} in these two populations.

MATERIALS AND METHODS

QSP renal model

We utilized the mathematical model of renal function and systemic volume regulation presented in the companion article.¹¹

Evaluating mechanisms of salt-sensitivity

Simulation 1: Hypothesized mechanisms of salt-resistance/salt-sensitivity. Salt-sensitivity has been proposed to result from impairment in tubular sodium handling. Although the mechanisms have still not been completely elucidated,

tubular reabsorption of sodium is thought to be regulated by both intrinsic signals (e.g., renal interstitial hydrostatic pressure (RIHP),^{14,15} likely mediated by nitric oxide release^{16,17}) and neurohormonal signals like angiotensin and aldosterone.¹⁴ Impairments in these regulatory mechanisms have been proposed to lead to blood pressure salt-sensitivity.

In this study, we evaluated the impact of sensitivity to RIHP, as well as sensitivity to the RAAS, on the blood pressure and glomerular filtration rate (GFR) response to changes in salt intake over a physiologically relevant range. To evaluate the effect of RIHP-sensitivity, the magnitude of the effect of RIHP on tubular sodium reabsorption (S_{P-N} in Eq. 33 of the accompanying article) was varied from zero (no effect) to a value sufficient to maintain stable blood pressure and GFR over a wide range of sodium intake—from 20 to 200 mmol/day, or 0.5 to 4.3 g/day (for reference, 65 mmol or 1.5 g/day is the recommended sodium intake, although the average sodium intake in the US is 150 mmol or 3.4 g/day). For these simulations, all other parameters, including parameters describing physiologic effects of the RAAS, were held constant at values listed in the companion article. To evaluate the contribution of the RAAS, the simulations were repeated using the final value of S_{P-N} , but with parameters describing the strength of the physiologic response to the RAAS ($AT1_{preaff}$, $AT1_{aff}$, $AT1_{eff}$, $AT1_{pt}$, $AT1_{aldo}$) set to zero. Again, all other parameters were set to the values given in the companion article.

Simulation 2: Validation with clinical data. To confirm that the mechanisms modeled accurately reproduce differences in renal and cardiovascular function observed in salt-sensitivity, we utilized data from a study by Barba *et al.*¹⁸ In brief, in that study normotensive individuals with a habitual high-salt diet were placed on a salt-restricted diet for 3 days, and blood pressure, GFR, and tubular sodium handling (fractional sodium (Na) excretion (FENA), fractional proximal Na reabsorption (FPR) and fractional distal Na reabsorption (FDR)) were measured during both habitual (high-salt) and low-salt intake. Based on differences in blood pressure between diets, subjects were categorized as having low, medium, or high salt-sensitivity.

To simulate this study, we generated two virtual patients (VPs) to represent the low-sensitivity (salt-resistant, SR) and high-sensitivity (salt-sensitive, SS) groups in the study. Since plasma Na concentration, fractional PT, and distal (combined ALH, DCT, and CNT/CD) Na reabsorption, and sodium intake were directly measured, we set $C_{Na,0}$ (the plasma Na concentration setpoint), $\eta_{pt,0}$ (the nominal fractional rate of PT Na reabsorption), and $\Phi_{Na,in}$ (Na intake rate) to the values measured while on the low-salt diet (which we assume represents the “baseline” physiologic state). All other parameter values were set to values listed in the companion article. The parameter values given for distal rates of Na reabsorption ($\eta_{alh,0}$, $\eta_{dct,0}$, $\eta_{cnt/cd,0}$) produced a total fractional distal Na reabsorption rate that was consistent with the observed data, so these parameters were not changed. We then simulated an increase in sodium intake from low-salt to habitual salt diet (as reported in the study), and estimated the value for tubular pressure natriuresis strength (S_{P-N}) for each VP, using the observed

changes in mitogen activated protein (MAP) as the constraint. Predicted changes in other variables (GFR, FENA, plasma Na concentration, FPR, FDR) were then compared with the clinical data.

Simulation 3: Investigating effect of salt-sensitivity on response to antihypertensive therapies. In hypertension, salt-sensitive status is associated with differential responses to antihypertensive treatments.⁹ Among ethnic groups with higher prevalence of salt-sensitivity, such as those of African descent, blood pressure response to drugs targeting the RAAS is weaker, while response to diuretics is greater, and the response to calcium channel blockers is similar to groups with lower prevalence of salt-sensitivity.^{10,19,20} To determine whether the model can reproduce these observations, we generated two hypertensive VPs—a salt-sensitive and a salt-resistant VP.

The salt-sensitive hypertensive VP was created as in Simulation 2, by reducing sensitivity of tubular reabsorption to RIHP (S_{P-N} reduced from 3 to 1 for each tubular segment), and hypertension was induced by increasing Na intake to 200 mmol/day, thus increasing baseline MAP from 85 to 107 mmHg. All other parameters were fixed to values given in the companion article.

When sensitivity of tubular reabsorption to RIHP is strong, the model is salt-resistant, and an increase in Na intake has minimal effect on MAP. Thus, to produce a salt-resistant hypertensive VP with comparable MAP to the SS VP, we increased nominal preafferent and afferent vascular resistance by 40% each (R_{preaff} increased from 14 to 19.6 mmHg-L/min, afferent diameter d_{aff} decreased from 15 to 13.5 μm , resulting in 40% increase in R_{aff}). The myogenic responsiveness of these vessels ($S_{autoreg}$) was also assumed reduced from 0.5 to 0.1. These changes are reflective of a renovascular hypertensive phenotype,²¹ in which narrowing of the preglomerular arteries and arterioles leads to increased preglomerular vascular resistance and loss of myogenic responsiveness of these vessels, and were necessary to produce the same degree of hypertension as the SS VP. Na intake was increased to the same level as the SS VP (200 mmol/day), but the increase had minimal effect on the SR VP's baseline MAP. All other parameters were fixed to values given in the companion article.

The response of each VP to angiotensin converting enzyme (ACE) inhibition (ACEi), calcium channel blockade (CCB), and a thiazide diuretic was then simulated. We have previously described how the physiological effects of these antihypertensive therapies are modeled.²² In brief, ACE inhibition was modeled as a 90% reduction in ACE. A thiazide diuretic was modeled as an 80% reduction in DCT fractional Na reabsorption rate (η_{dct}). CCB was modeled as a 40% reduction in preafferent and afferent resistance (R_{preaff} and R_{aff}).

RESULTS

Simulation 1: Evaluating mechanisms of salt-sensitivity and salt-resistance

Figure 1a shows the simulated final steady-state MAP and GFR response to a step change in sodium intake over a

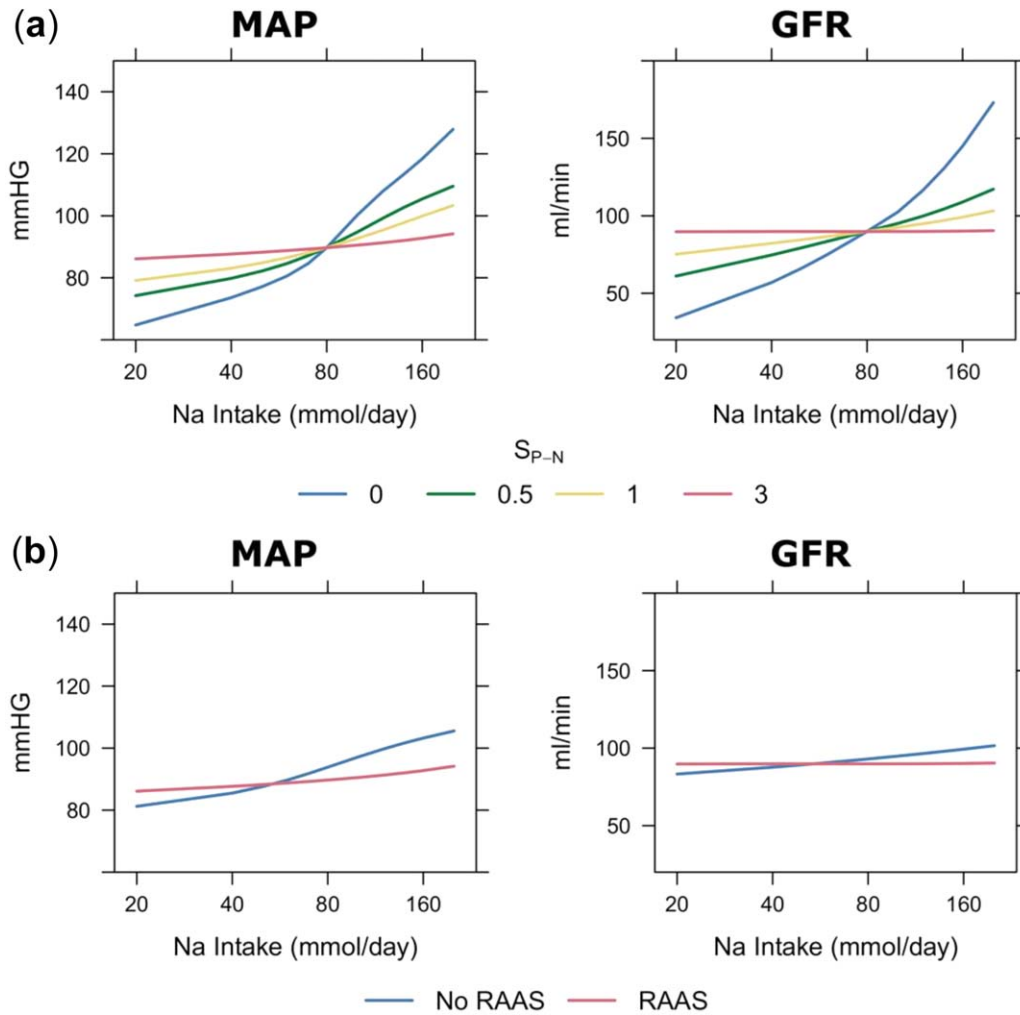


Figure 1 (a) Steady-state MAP and GFR over a 10-fold range of daily Na intake rates, for different strengths of the tubular pressure-natriuresis mechanism (S_{P-N}). The strength of this mechanism determines the stability of mean arterial pressure and GFR as salt-intake changes. In other words, impairment of this mechanism results in salt-sensitive MAP and GFR. For this simulation, all other parameters, including effects of the RAAS, were set to the values given in the companion article for this simulation. (b) Steady-state MAP and GFR over a 10-fold range of Na intake rates, with and without the physiologic effects of the RAAS included in the model. ($S_{P-N} = 3$ for these simulations, all other parameters set to values in companion article). Removal of RAAS results in moderate salt-sensitivity even when the tubular pressure-natriuresis mechanism is strong.

10-fold range (20–200 mmol/day), when the effect of RIHP on tubular Na reabsorption were varied, while the RAAS effects were held constant. When the effect of RIHP on tubular Na reabsorption was turned off ($S_{P-N} = 0$), the effects of RAAS alone were not sufficient to maintain stable MAP and GFR, and large changes in MAP and GFR were predicted. But as the RIHP effect increased, stable blood pressure and GFR were maintained over the physiologically relevant range of Na intake. **Figure 1b** shows the same simulation with S_{P-N} fixed to 3, with the effects of RAAS either included or turned off. When the effects of the RAAS were removed, again blood pressure and MAP were predicted to change substantially over the physiologic range. In other words, RIHP and the RAAS are both required to maintain stable MAP and GFR in the face of changing sodium intakes.

Another way of looking at these simulations is that impairment in these mechanisms—and particularly reduced sensitivity of tubular Na reabsorption to changes in RIHP—will result in blood pressure that is sensitive to sodium intake. In addition, these simulations suggest that changes in GFR will necessarily parallel changes in MAP in salt-sensitive subjects. In other words, when tubular Na reabsorption is not able to adapt sufficiently (in response to RIHP and RAAS signals) to match Na excretion to intake, then the necessary Na excretion required for Na balance will be achieved through increased filtration (GFR), driven by increased MAP.

Simulation 2: Validation with clinical data

Figure 2 shows the simulated response of an SS and SR VP to increased Na intake, compared with clinical data from Barba *et al.*¹⁸ S_{P-N} was set to 3 in the SR VP (the

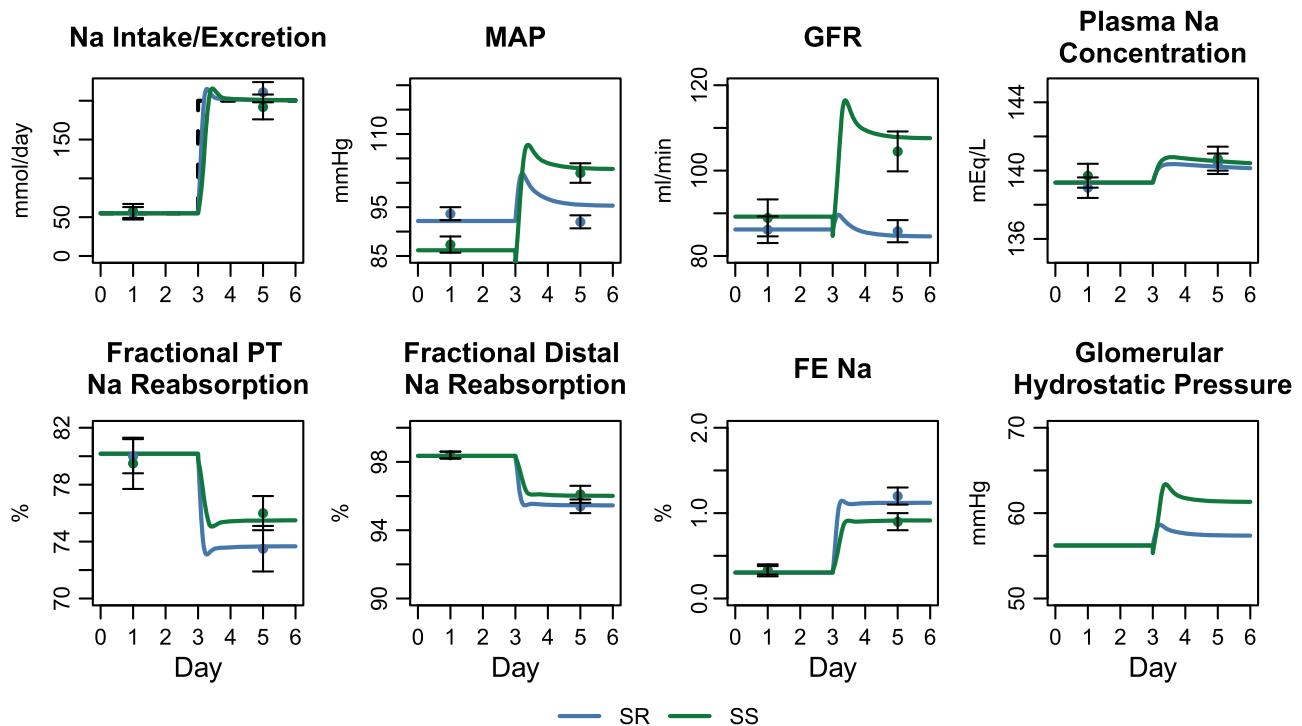


Figure 2 Comparison of simulated outputs and clinical data for several variables of renal function. SS and SR VPs were simulated on a low sodium diet (60 mmol/day) for 3 days, followed by habitual sodium intake levels observed in Barba *et al.* (200 mmol/day) for 3 days (panel 1, dashed black line). The tubular pressure natriuresis strength (S_{P-N}) was estimated for each VP, constrained by the observed changes in MAP (panel 2). Other variables (panels 3–8) were then simulated and compared with clinical data. Solid lines: simulation; points with error bars: data from Barba *et al.*¹⁸

normal case), and was estimated to be 1.1 in the SS VP, constrained by the clinically observed change in MAP. The model was then able to accurately predict observed changes in GFR, plasma Na, FPR, FDR, and FENA. As shown in the top left panel, Na balance was eventually returned (excretion matched to intake—the black dotted line) in both the SS and SR VP, although it returned more slowly in the SS VP. In the SR group, the study data actually showed a small mean decrease in MAP with higher salt intake, which the model could not reproduce. This reduction in MAP with increased salt-intake is an unexpected anomaly—other similar studies show constant blood pressure but not blood pressure (BP) reductions in SR subjects. Thus, we believe that the observed reduced MAP in this study is likely an artifact of BP cutoffs placed to classify patients as low-sensitivity (Δ MAP <3.9 mmHg).

The model also predicted a much greater increase in glomerular pressure with increased salt-intake in the SS VP than in the SR VP. Glomerular pressure is not easily determined clinically, but is an important driver of renal injury, and thus of interest in understanding differences in propensity for renal injury and disease in different patient groups.

Simulation 3: Investigating effect of salt-sensitivity on response to antihypertensive therapies

In hypertension, salt-sensitive status is associated with differential responses to antihypertensive treatments. **Figure 3** shows the simulated response of an SS and SR VP on three different therapies: ACEi, a thiazide diuretic, and a CCB. With

ACEi, the model predicted a smaller MAP reduction in the SS compared to SR VP (difference of -2.9 mmHg). With a thiazide diuretic, the model predicted the opposite: a larger MAP response in SS compared to SR (difference of $+7.5$ mmHg). And with a CCB, the model predicted similar blood pressure reductions in both (difference of -0.4 mmHg in SS compared to SR). These results are consistent with a meta-analysis that compared the response to common antihypertensives in whites and blacks (who have a higher prevalence of salt-sensitivity than whites).²⁰ This meta-analysis found that MAP reduction in blacks compared to whites was smaller (-3.5 mmHg [$-1.4, -5.0$]) with an ACEi, larger ($+2.2$ mmHg [$0.2, 4.2$]) with a diuretic, and similar ($+1.1$ [$-0.4, +2.0$]) with CCBs). Since the meta-analysis included two populations (white and black), each of which likely include a mix of individuals with different degrees of salt-sensitivity, while our simulation compares two single VPs and does not account for this variability and heterogeneity, the simulation and meta-analysis are not directly comparable. In addition, salt-sensitivity may not be the only determining factor for racial differences in therapy response.

The model also predicts changes in glomerular hydrostatic pressure—a key driver of kidney damage that is not easily experimentally measurable. For ACEi, the model predicts similar reductions in glomerular pressure in both VPs, even though the MAP reduction was larger in the SR VP. For diuretics, the reduction in glomerular pressure is larger in the SS than in SR VP. And for CCBs, the model predicts no sustained change in GP in either patient type.

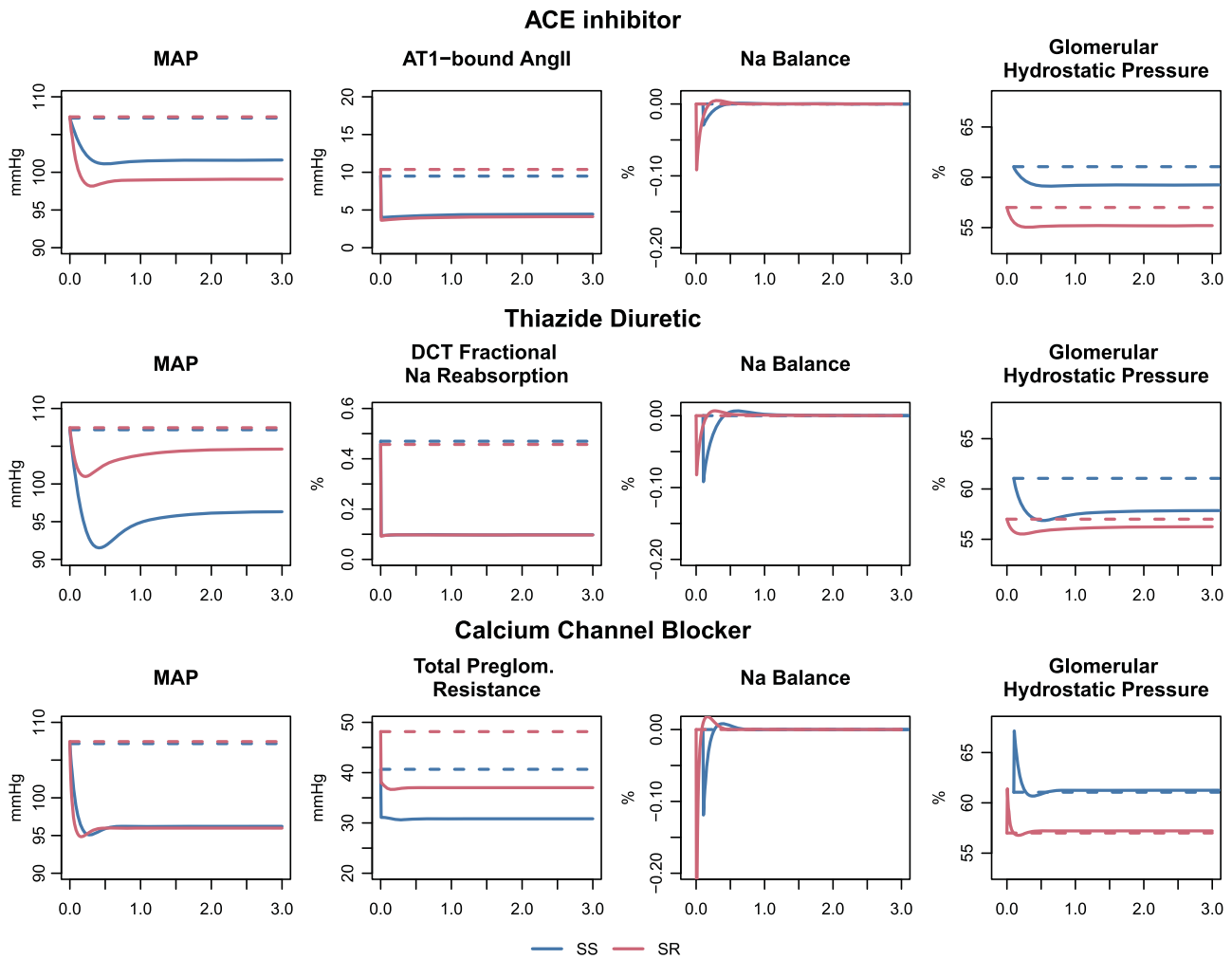


Figure 3 Simulated effect of salt-sensitive status on blood pressure reduction and other functional variables with common antihypertensive classes. The simulations predict lower MAP reduction with ACEi, greater MAP reduction with diuretics, and similar MAP reduction with CCBs in SS compared to SR. The model also predicts that both ACEi and diuretics will lower glomerular pressure (and degree of reductions with ACEi is not different between SS and SR), while CCBs will not affect steady-state glomerular pressure.

DISCUSSION

Evaluating mechanisms of salt-sensitivity and salt-resistance

The simulations in **Figure 1** demonstrate that regulation of tubular Na reabsorption in response to changes in RIHP can confer blood pressure salt-resistance, and that the actions of the RAAS complement this effect; or alternatively, that impairment in tubular sensitivity to regulatory signals—and particularly reduced sensitivity of tubular Na reabsorption to changes in RIHP—will result in blood pressure that is sensitive to sodium intake. In addition, these simulations suggest that following changes in Na intake, changes in GFR will necessarily parallel changes in MAP in salt-sensitive subjects.

To determine whether these trends are in line with reality, we replicated a study comparing the renal response in SS and SR subjects to a change in salt intake. As shown in **Figure 2**, the model was able to reproduce not only the blood pressure changes, but also the changes in tubular sodium handling (FPR, FDR, and FENA), plasma Na

concentration, and GFR observed clinically in salt-sensitive normotensive individuals. Thus, the predicted change in GFR with change in MAP is consistent with clinical data, as were the simulated differences in renal sodium handling between salt-sensitive and salt-resistance subjects.

Taken together, the data and simulations confirm that impaired ability of the tubule to adapt sodium reabsorption in response to regulatory signals like RIHP can produce salt-sensitivity. The simulations also shed light on the underlying dynamics of renal function responsible for this behavior. A basic principle of renal and cardiovascular physiology is that sodium balance must exist at steady-state; that is, sodium excretion must equal intake. If this were not the case, sodium and water would be either continuously lost or accumulated, until the body either dried up or exploded. This sodium balance is achieved by the kidney: as sodium and water content is increased, blood pressure and thus renal perfusion pressure rises, driving an increase in renal sodium excretion—the “pressure-natriuresis” phenomenon. It may seem obvious that increasing renal perfusion pressure would increase

excretion by increasing pressure-driven filtration. But in fact, in normal physiology, glomerular pressure is tightly regulated and GFR actually changes little with changes in Na intake or other perturbations of sodium balance. Instead, sodium balance is achieved primarily through adaptations in tubular reabsorption of sodium that match excretion to intake without changes in filtration. However, when tubular Na reabsorption is not able to adapt sufficiently to match sodium excretion to intake in response to regulatory signals, or when those signals are not generated appropriately, then Na balance must be achieved by another means. As seen in the top left panel of **Figure 2**, sodium balance is eventually returned in both the SS and SR VP, although it returns more slowly in the SS VP. How does this occur? Excretion is the net effect of filtration and reabsorption. The model demonstrates that when an Na imbalance persists for a period of time, Na and water are accumulated/lost, so that blood pressure rises/falls. This change in blood pressure is transmitted to the glomerulus, resulting in changes in glomerular pressure and GFR that ultimately return Na balance. Thus, hyperfiltration with increased Na intake is a *necessary* response to impaired regulation of tubular sodium reabsorption.

The model also predicts that this hyperfiltration is driven by an increase in glomerular hydrostatic pressure. Glomerular pressure is a key driver of renal damage, leading to glomerulosclerosis, podocyte damage, and subsequent proteinuria.^{12,13,23,24} The higher glomerular pressures with high salt intake in SS may explain why SS individuals develop chronic kidney disease at higher rates and progress more quickly.^{1,8,25} Since glomerular pressure is a key causative factor for proteinuria, it may also explain why a low-salt diet reduces proteinuria in SS subjects.^{3,26}

Effect of salt-sensitivity on response to antihypertensive therapies

To our knowledge, this is the first study to use a mathematical model to explore the effect of salt-sensitivity on response to antihypertensive therapy. It is well established that salt-sensitivity can affect the response to antihypertensive treatments. In particular, salt-sensitive individuals respond better to thiazide diuretics and calcium channel blockers than to treatments that target the RAAS. Blacks have been shown to have a much higher prevalence of salt-sensitivity than whites, and a meta-analysis has shown that they experience smaller blood pressure reductions with RAAS blockers, larger reductions with diuretics, and similar blood pressure reductions with calcium channel blockers.^{19,20,27,28} Simulation of these therapies in SS and SR VPs reproduced these trends (**Figure 3**).

In addition to reproducing the trends, further investigation of changes in model variables in these simulations provides some mechanistic explanation for these differences. The blood pressure reduction achieved is proportional to the area between the Na balance curve and zero. First consider ACE inhibition. ACE inhibitors act by suppressing AngII available to bind to the AT1 receptor, resulting in multiple physiologic effects that contribute to blood pressure lowering, including efferent (and afferent) arteriole dilation, reduced PT Na reabsorption, and reduced aldosterone secretion (which in turn reduces distal sodium reabsorption). Our simulations

suggest that the key to the differential effect on blood pressure reduction in SR vs. SS is the effect of these drugs on efferent arteriole dilation. When efferent resistance is reduced, more pressure is transmitted past the glomerulus to peritubular and medullary circulation and renal interstitial, increasing RIHP (even though glomerular pressure is initially unchanged, since both the efferent and afferent arterioles are dilated by RAAS blockade), and thus indirectly reducing tubular Na reabsorption (and increasing Na excretion) through the tubular pressure-natriuresis mechanism. In the SR VP, where the tubules are highly sensitive to changes in RIHP, there is a large reduction in tubular sodium reabsorption and a large negative Na balance (**Figure 3**, top row, panel 3), and thus a large reduction in blood pressure. The SS VP is less sensitive to the increase in RIHP, so there is a smaller decrease in tubular reabsorption, smaller negative Na balance, and smaller MAP reduction. Interestingly, though, the hemodynamic effect on glomerular pressure is similar in both patient types.

Now consider thiazide diuretics, which act by reducing sodium reabsorption in the distal convoluted tubule. Initially, there is a negative Na balance of similar magnitude in both SS and SR VPs (**Figure 3**, middle row, panel 3), causing MAP to fall. However, as blood pressure falls, the pressure transmitted to the glomerulus and then to RIHP also falls, resulting in an increase in tubular Na reabsorption that counters the decrease caused by the diuretic, driving Na balance back toward zero. Thus, the blood pressure reduction that can be achieved is limited by the feedback of RIHP on tubular sodium reabsorption. However, in SS subjects, where tubular Na reabsorption is less sensitive to changes in RIHP, the feedback is weaker, allowing larger reductions in MAP than in the SR subject.

Lastly, consider CCBs. They act by dilating the preafferent and afferent vasculature, without affecting efferent resistance. This initially increases glomerular pressure leading to increased GFR. In addition, RIHP is increased, resulting in reduced tubular Na reabsorption. Together, the increased filtration and reduced reabsorption lead to increased sodium excretion (negative Na balance) and blood pressure falls. The initial changes in glomerular pressure (and thus GFR) and RIHP are similar in the SR and SS VPs. But because tubular Na reabsorption is more sensitive to RIHP in the SR subject, the initial negative Na balance is much larger, causing MAP to fall more quickly. As MAP falls, both RIHP and glomerular pressure return back toward normal quickly, and thus GFR and Na balance return to normal quickly as well. In the SS subject, since the tubule is less sensitive to RIHP, the initial negative Na balance is smaller, and MAP falls more slowly. However, this means that glomerular pressure, and thus filtration, remain elevated longer, and the negative Na balance is maintained longer. Since blood pressure reduction is proportional to the area between the Na balance curve and zero, the blood pressure reduction is ultimately the same as in the SR subject. Thus, the primary mechanism of blood pressure reduction is different between SR and SS, with reduced tubular Na reabsorption contributing more in SR, and increased filtration contributing more in SS. But the blood pressure reduction achieved is the same.

The simulations also predict different effects of therapies on glomerular pressure—an important variable in renal function and injury, but one that is not readily measurable. Both ACEi and thiazide diuretics are predicted to cause sustained reductions in glomerular pressure, while CCBs have no sustained effect on glomerular pressure (although they increase it initially). Glomerular hypertension is believed to be a critical driver of renal damage and cause of podocyte damage and proteinuria. These predictions are consistent with studies that show the RAAS blockers and diuretics lower proteinuria and provide greater renoprotection than CCBs.²⁹

LIMITATIONS AND FUTURE DIRECTIONS

In this study, we considered two renal mechanisms of SS, but there may be many contributing factors to SS hypertension.² Sympathetic activity and, more recently, peripheral sodium storage have been proposed to play a role in sodium homeostasis.^{30,31} Future work should consider the role of sympathetic activity, as well as the potential effects of a third sodium compartment.

While we demonstrated the importance of the pressure-natriuresis phenomenon in salt-sensitivity, the mechanism itself was treated as a “black box.” We did not attempt to describe transmission of renal perfusion pressure to the interstitium, or how this pressure is ultimately sensed by tubular epithelial cells. While there is quite a body of data in the literature investigating pressure-natriuresis, its exact mechanisms have remained elusive, partially due to experimental challenges in measuring processes occurring inside the kidney. Thus, there are a plethora of hypotheses but little consensus. Going forward, we believe this model can be expanded to open this “black box” and couple the existing data with the physics of the kidney processes to evaluate these alternate hypotheses and propose experiments for validation. A better understanding of this critical mechanism and its impairment may also allow model-based evaluation of new targets for treating or preventing/reversing SS hypertension and associated renal damage.

Our analysis suggests that SS hypertension is associated with an increase in glomerular pressure. The model presented here could also be expanded to evaluate the renal hemodynamic and long-term consequences of increased glomerular pressure, particularly in the setting of diabetic kidney disease.³² For instance, we are currently utilizing the model, coupled with experimental and clinical data,^{33,34} to investigate the unexpected positive renal and cardiovascular benefits observed with inhibition of sodium glucose cotransporter 2 (SGLT2).³⁵

CONCLUSION AND IMPLICATIONS

Utilizing a QSP model of renal function and sodium homeostasis, in this study we demonstrated that regulation of tubular Na reabsorption by RIHP and the RAAS can confer blood pressure salt-resistance, and that reduced sensitivity to these mechanisms can result in salt-sensitivity. The simulations indicate that SS causes not only systemic blood

pressure but also glomerular hydrostatic pressure to be salt-sensitive, suggesting that high salt intake in SS subjects may contribute to renal injury. This could explain the increased risk of chronic kidney disease in diabetics and African Americans, two populations with high SS prevalence.

The analysis also provides insights into the differential response to antihypertensive therapies observed in SS compared to SR subjects. The simulations indicate that the degree of BP lowering achieved with a therapy in SS hypertensives may depend on the degree to which the therapy’s effect relies on sensitivity of tubular Na transporters to regulatory signals. While the BP reduction with ACE inhibition was predicted to be lower in SS subjects, the glomerular pressure reduction was similar, suggesting that the renoprotective effects of RAAS blockade may not be diminished in SS, even if the BP reductions are.

Acknowledgments. The authors thank Anna Georgieva, Gabriel Helmlinger, Yuan Xiong, Arthur Lo, Jeni Beh, Manoj Rodrigo, Volker Val-lon, Antoine Soubret, David James, and Wenping Wang for their contributions to this work over the years.

Conflict of Interest/Disclosures. Within the past 24 months, the authors have received funding from AstraZeneca Pharmaceuticals and Takeda Pharmaceuticals.

Author Contributions. K.M.H. wrote the article; K.M.H. designed the research; K.M.H. performed the research; K.M.H. and Y.G. analyzed the data; K.M.H. and Y.G. contributed new reagents/analytical tools.

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