

RESEARCH ARTICLE | *Cardiovascular and Renal Integration*

Mechanisms of blood pressure salt sensitivity: new insights from mathematical modeling

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Clemmer JS, Pruett WA, Coleman TG, Hall JE, Hester RL. Mechanisms of blood pressure salt sensitivity: new insights from mathematical modeling. *Am J Physiol Regul Integr Comp Physiol* 312: R451–R466, 2017. First published December 9, 2016; doi:10.1152/ajpregu.00353.2016.—Mathematical modeling is an important tool for understanding quantitative relationships among components of complex physiological systems and for testing competing hypotheses. We used HumMod, a large physiological model, to test hypotheses of blood pressure (BP) salt sensitivity. Systemic hemodynamics, renal, and neurohormonal responses to chronic changes in salt intake were examined during normal renal function, fixed low or high plasma angiotensin II (ANG II) levels, bilateral renal artery stenosis, increased renal sympathetic nerve activity (RSNA), and decreased nephron numbers. Simulations were run for 4 wk at salt intakes ranging from 30 to 1,000 mmol/day. Reducing functional kidney mass or fixing ANG II increased salt sensitivity. Salt sensitivity, associated with inability of ANG II to respond to changes in salt intake, occurred with smaller changes in renal blood flow but greater changes in glomerular filtration rate, renal sodium reabsorption, and total peripheral resistance (TPR). However, clamping TPR at normal or high levels had no major effect on salt sensitivity. There were no clear relationships between BP salt sensitivity and renal vascular resistance or extracellular fluid volume. Our robust mathematical model of cardiovascular, renal, endocrine, and sympathetic nervous system physiology supports the hypothesis that specific types of kidney dysfunction, associated with impaired regulation of ANG II or increased tubular sodium reabsorption, contribute to BP salt sensitivity. However, increased preglomerular resistance, increased RSNA, or inability to decrease TPR does not appear to influence salt sensitivity. This model provides a platform for testing competing concepts of long-term BP control during changes in salt intake.

hypertension; kidney; renin-angiotensin system; angiotensin II; salt; cardiac output; vascular resistance

EXCESS SALT INTAKE increases blood pressure (BP) and the risk for cardiovascular disease. However, there is considerable variability in BP responses to changes in salt intake with some individuals being “salt sensitive,” whereas others are much less sensitive or “salt resistant.” Although salt sensitivity of BP, even in the absence of hypertension, is an important clinical phenotype that predicts increased mortality (56), assessment of BP salt sensitivity in clinical studies is challenging, and the mechanisms responsible for the heterogeneity of salt-induced increases in BP remain controversial. Mechanistic studies last-

ing more than a few days are rare and, in most cases, devoid of the hormonal, neural, renal, and hemodynamics changes that take place under more chronic conditions.

Neurogenic, vascular, hormonal, and kidney abnormalities have all been proposed to underlie salt sensitivity of BP. Averina et al. (2, 3) published a mathematical model that predicted salt-induced increases in BP may occur as a result of neurogenic or vascular dysfunction, independent of abnormal kidney function. The model of Averina et al. (2, 3), however, did not include the basic determinants of renal sodium excretion, glomerular filtration rate (GFR), and tubular sodium reabsorption, or many of the key neurohormonal factors that regulate GFR and renal sodium reabsorption. Another limitation of their model is that it was based on the premise that renal perfusion pressure has no long-term effect on sodium excretion, an assumption that is inconsistent with multiple experimental studies (17, 23, 26, 36). Therefore, there is a need for more realistic physiological models that permit analysis of the role of the kidney in causing salt-sensitive hypertension and that can address specific types of renal and neurohormonal abnormalities that may cause salt sensitivity.

Salt sensitivity has also been proposed to be caused mainly by failure to adequately reduce total peripheral vascular resistance (TPR) when salt intake is increased (37, 42). The main evidence supporting this hypothesis comes from the observation that increasing salt intake transiently reduces TPR to a greater extent in salt-resistant than in salt-sensitive subjects (37). However, in most clinical and experimental studies of salt sensitivity, BP and cardiac output (CO), the determinants of TPR, have been measured for only a few minutes during changes in salt intake. Moreover, calculations of TPR are often based on indirect methods for measuring BP (e.g., auscultatory method) and CO (e.g., impedance cardiography) (40, 41) that may not provide the precision needed to assess small transient changes in these variables that typically occur during changes in salt intake (23). Most importantly, no previous experimental studies have tested whether preventing TPR from decreasing during salt loading actually causes salt sensitivity. Thus whether a decrease in TPR is important for prevention of salt sensitivity is unclear. It is also unclear whether increases in TPR can cause salt-sensitive hypertension.

Kidney dysfunction and impaired renal-pressure natriuresis have also been proposed to play a critical role in salt-sensitive hypertension (11, 20, 29). For example, experimental forms of salt-sensitive hypertension are often initiated by insults to the kidneys or neurohormonal changes that increase renal sodium reabsorption (23). At least seven monogenic forms of salt-

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sensitive hypertension in humans share the common phenotype of increased renal sodium reabsorption (34, 38), and abnormal kidney function is an important causative factor in several genetic rodent models of salt-sensitive hypertension (23).

Although we previously summarized evidence that kidney dysfunction is a key component of BP salt sensitivity (23), a detailed analysis of the specific types of renal abnormalities and the associated hormonal, neural, and systemic hemodynamic changes that may contribute to salt-induced increases in BP has not been previously reported. One hormonal system that appears to be important in determining salt sensitivity of BP is the renin-angiotensin-aldosterone system (RAAS) through the renal effects of ANG II and aldosterone (17, 27). However, there have been no previous mathematical models, to our knowledge, that have included the various renal hemodynamic and tubular actions of ANG II and the resultant changes in CO, TPR, and BP during chronic changes in salt intake.

In the present study we used HumMod, a mathematical model that integrates a large number of hormonal, neural, and physical factors that influence renal hemodynamics, tubular reabsorption, electrolyte excretion, TPR, CO, and other potential determinants of BP salt sensitivity. HumMod is a complex model of human physiology developed by T. Coleman and described by Hester et al. (30) as an expansion of the large cardiovascular model initially established by Guyton and colleagues (20). HumMod includes over 8,000 independent variables that interact in a time-dependent manner to regulate multiple physiological systems, including the cardiovascular, renal, endocrine, metabolic, and sympathetic nervous systems (SNS). This model was not constructed specifically to simulate salt sensitivity of BP or hypertension but rather by incorporating empirical data and fundamental physiological principles to reflect multiple physiological and pathophysiological conditions.

We used HumMod to simulate physiological responses to chronic changes in salt intake under different conditions including normal renal function, low fixed plasma ANG II levels, high fixed plasma ANG II levels, bilateral renal artery stenosis, increased renal sympathetic nerve activity (RSNA), and decreased functional nephrons. We also conducted simulations to predict responses that are difficult to test experimentally, including the impact of changes in renal and nonrenal vascular resistance on BP salt sensitivity.

Our results suggest that specific types of kidney dysfunction associated with increased renal sodium reabsorption, reductions in the number of functional nephrons, or failure of the RAAS to function appropriately can cause BP to be highly salt sensitive, whereas BP sensitivity to salt intake is independent of changes in TPR and is not enhanced by increased preglomerular renal vascular resistance. HumMod provides a conceptual framework for testing other hypotheses and for understanding the complex cardiovascular, renal, and neurohormonal factors that determine whether BP will be salt sensitive or salt resistant.

METHODS

Model description. For all simulations we used the integrative mathematical simulator, HumMod, a well-established interactive physiological model composed of over 8,000 independent variables and ~2,000 parameters and mathematical relationships that have been developed over the past 40 years (30). HumMod integrates multiple

physiological systems, including the cardiovascular, renal, endocrine, metabolic, and SNS. HumMod and earlier versions have been used in several studies to provide a more complete understanding of physiological mechanisms in different clinical conditions (1, 46–50). The model is composed of mathematical expressions of the relationships between physiological variables based on well-documented principles of cell, tissue, and organ physiology. Details of the model structure are beyond the scope of this article, and earlier versions have been more extensively described (30). A brief summary of the model's elements of sodium and volume regulation, renal physiology, peripheral vasculature, and other relationships that are relevant to this study are provided as well as a link to download the entire model, structure code, and supplementary material including the raw data outputs for the experiments.

In HumMod, the body is divided into three general fluid spaces: intracellular, interstitial, and intravascular. The ratio of intracellular to extracellular volumes is influenced mainly by osmolarity of each fluid space. Water and electrolyte transport occurs between the interstitial and intravascular compartment via capillary filtration and reabsorption and lymph transport. In the model, lymph flow depends on increases in interstitial pressure (as valves prevent backflow (51), whereas capillary fluid filtration and reabsorption are determined by Starling forces (hydrostatic and colloid osmotic pressure gradients) across the capillaries and by the capillary filtration coefficients of the various tissues (see Fig. A1 in the APPENDIX).

There are two separate kidneys in HumMod. Each kidney is modeled as a nephron that contains multiple vascular and tubular components, and its total function is determined by the number of available filtering nephrons as well as by various local controls and neurohormonal factors. Blood flow through the afferent arterioles, glomeruli, and efferent arterioles is determined by the pressure gradients and resistances of the vascular segments which, in turn, are influenced by local and neurohormonal controls. A prominent regulator of afferent arteriolar resistance is tubuloglomerular feedback (TGF), which is influenced by macula densa sodium delivery, as well as ANG II, which increases TGF sensitivity to changes in sodium delivery. Myogenic responses, the SNS, and atrial natriuretic peptide (ANP) also influence afferent arteriolar resistance in the model. Efferent arteriolar resistance is modulated by ANG II and the SNS. GFR is determined by the Starling forces (hydrostatic and colloid osmotic pressure gradients) at the glomerular capillary and by the glomerular capillary filtration coefficient. Further information on these variables and the factors that influence them can be found in the APPENDIX (Fig. A2). Together, these factors interact to regulate renal arteriolar conductance, renal blood flow (RBF), GFR, as well as influence peritubular capillary dynamics and renal tubular reabsorption.

The tubular portion of each nephron is divided into proximal tubule, loop of Henle, macula densa, distal tubule, and collecting duct. Reabsorption of sodium and water is influenced by multiple physical factors as well as by the SNS and various hormones, including ANP, ANG II, and aldosterone. Another important factor influencing tubular reabsorption is glomerulotubular balance whereby increases in sodium and volume delivery to the tubules increases absolute sodium and volume reabsorption, although fractional reabsorption (the fraction of the sodium and volume delivered to the tubular segments that is reabsorbed) may be reduced (53). Reabsorption of sodium and water in the model occurs in the various components of the renal tubules, into an interstitial compartment, and ultimately into the peritubular capillaries. Details of the factors that influence sodium and water reabsorption in these nephron segments and peritubular capillaries are included in the APPENDIX (Fig. A3). Changes in GFR, filtered load, and tubular reabsorption ultimately determine excretion of water, electrolytes, and waste products in HumMod.

Additional components of the model that are important for the present study include kidney renin secretion, ANG II formation, aldosterone secretion by the adrenal cortex, and ANP secretion by the

heart. Details of the factors that regulate these systems in the model are included in the APPENDIX (Fig. A4).

The peripheral vasculature is composed of arterial, capillary, and venous circulations, and TPR is calculated from the inverse sum of all organ vascular conductances. Organs and tissues that make up the peripheral circulation in HumMod include skeletal muscle, gastrointestinal tract, liver, bone, brain, fat, skin, kidneys, heart, and lungs. Additionally, all tissue beds not mentioned are accounted for in an “other tissue” mass. The flow through these tissues is affected by the SNS and hormones such as ANG II, as well as local tissue factors such as oxygen levels (specifically P_{O_2}), which together regulate vascular tone and blood flow (Fig. A5).

HumMod’s entire code and user interface as well as supplementary material are available for academic download at <https://github.com/hummod/hummod-salt>.

Protocols. Each simulation was run for 1 wk (either at normal conditions or for the specified pathophysiological condition) to reach steady state. Salt intake was then changed to low, normal, and high intakes (30, 180, 500, and 1,000 mmol of sodium chloride/day) for 4 wk at each salt intake. At the end of each 4-wk period, the simulation was terminated and control conditions were once again established before commencing a new simulation at another level of salt intake.

The model simulations included changes in salt intake under the following conditions: normal renal function, fixed low ANG II, fixed high ANG II, high RSNA, partial nephrectomy (75% reduction in functional kidney mass), and moderate bilateral renal artery stenosis. For the low ANG II simulation, plasma ANG II was clamped at 2.9 pg/ml (compared with the normal level of 10 pg/ml) and was not allowed to vary with different levels of salt intake. For the high ANG II simulation, ANG II was clamped at 50 pg/ml. For the partial nephrectomy simulation, 75% of the nephrons were removed from each kidney, resulting in 25% of normal functioning nephrons. High RSNA was created by clamping RSNA at 4 Hz ($\sim 2.7 \times$ normal). Bilateral renal artery stenosis was created by increasing the right and left kidney preglomerular resistance 12-fold (but allowing the arterioles to respond normally), resulting in an initial drop of renal perfusion pressure from ~ 90 to 75 mmHg.

We also investigated the potential impact of changes in nonrenal TPR as a determinant of salt sensitivity by clamping organ vascular conductances during changes in salt intake with renal vascular resistance permitted to change. Simulations were run to reach steady state at normal salt intake (180 mmol/day) under three scenarios: 1) normal conditions with nonrenal TPR permitted to change as salt intake was increased; 2) nonrenal TPR fixed at the baseline level and unable to change as salt intake was increased; and 3) nonrenal TPR fixed at a high level and unable to change as salt intake was increased. In all cases, renal vascular resistance was permitted to change. Based on preliminary studies with the model, TPR changed the most when changing salt intake from 180 to 500 mmol/day. Therefore, salt intake was increased from normal to 500 mmol/day and the simulations were run for 4 wk. Acute and chronic responses of BP, CO, and other variables were observed.

RESULTS

Blood pressure, cardiac output, and peripheral vascular resistance responses. There were differences in baseline BP in some of the different pathophysiological conditions compared with the normal. High ANG II, high RSNA, renal artery stenosis, and 75% nephron loss all had increases in BP at the normal salt intake of 180 mmol/day, whereas low ANG II had reduced BP at baseline. MAP increased under all conditions as salt intake increased from 30 to 1,000 mmol/day (Fig. 1A). Salt sensitivity is a quantitative phenotype, and BP often rises to some extent even in normal subjects when salt intake is increased severalfold above normal (32, 35). We considered

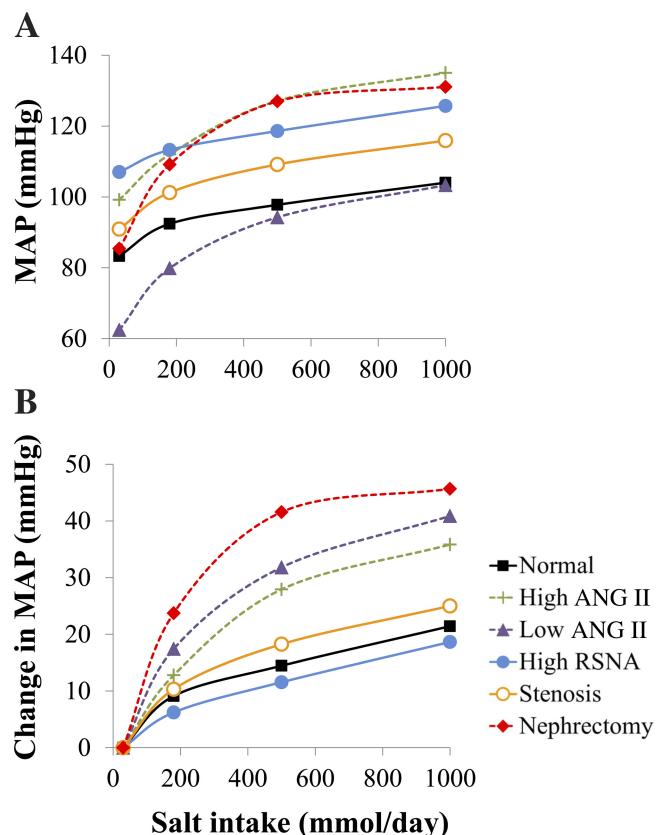


Fig. 1. Mean arterial pressure (MAP) during chronic changes in salt intake (30–1,000 mmol/day). A: MAP; B: changes of MAP for salt-sensitive (denoted by dotted lines) and salt-resistant (solid lines) simulations. ANG II, angiotensin II; RSNA, renal sympathetic nerve activity.

the BP responses in the model simulations to be salt sensitive if mean BP increased more than 30 mmHg when salt intake was increased over 30-fold. The simulations denoted by dashed curves demonstrated greater salt sensitivity, as shown by greater changes in MAP (>30 mmHg change at 1,000 mmol/day) compared with salt-resistant simulations, denoted by solid curves (Fig. 1B).

In each simulated case, there were transient increases in CO after increases in salt intake (not shown), but these values returned back toward normal after 4 wk. The steady-state CO increased in all simulations as salt increased from 30 to 180 mmol/day but remained relatively constant as salt intake increased above 180 mmol/day (Fig. 2). Although the partial nephrectomy and low ANG II simulations revealed a slightly reduced baseline CO, when salt intake was increased these two conditions showed the greatest increases in CO (Fig. 2B), extracellular fluid, volume, and blood volume. There was no association of BP salt sensitivity and CO under steady-state conditions.

In general, TPR increased in parallel with BP when salt intake was raised from normal to high levels in all simulations. Increases in TPR and BP were greater in salt-sensitive than in salt-resistant conditions during increases in salt intake (Fig. 3, A and B). There were also small increases in TPR compared with normal, when salt intake was reduced to the low level in all groups, except when ANG II was fixed and unable to increase as salt intake was reduced (Fig. 3B).

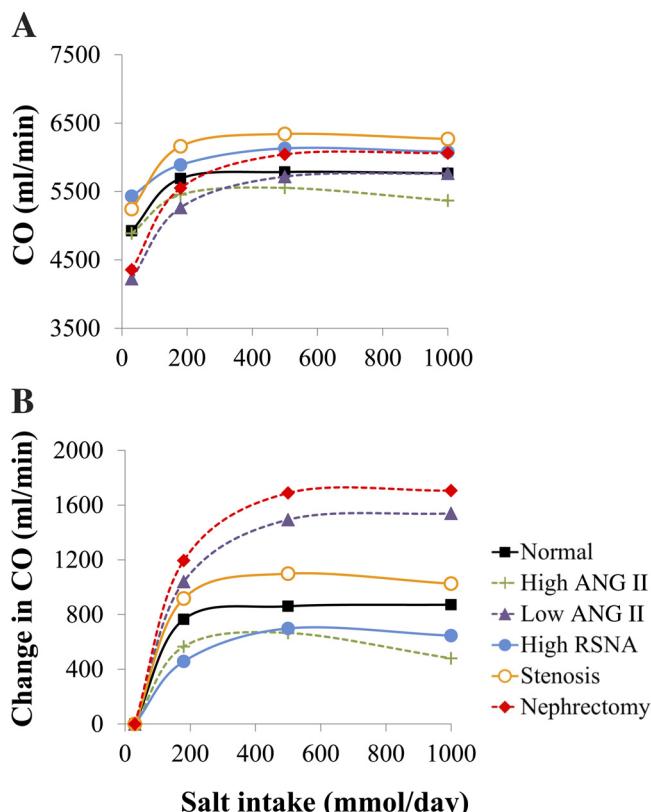


Fig. 2. Cardiac output (CO) responses during chronic changes in salt intake. A: absolute values for CO during each salt intake; B: changes in CO with baseline at 30 mmol/day.

GFR, renal blood flow, and renal vascular resistance. Baseline GFR was lower in the partial nephrectomy simulation compared with normal (Fig. 4A). GFR rose in all simulations as salt intake increased from low to high levels (Fig. 4A). At all salt intakes, the highest GFR was seen in the high RSNA and high ANG II simulations, whereas the lowest GFR was observed in the partial nephrectomy simulation (Fig. 4A). At high salt intake GFR increased substantially (~25–40 ml/min) in salt-sensitive simulations, whereas in salt-resistant simulations, smaller increases in GFR (<20 ml/min) were observed (Fig. 4B).

RBF also rose in all simulations as salt intake increased (Fig. 4C). The salt-resistant simulations had marked increases in RBF (>500 ml/min) at high salt intake (Fig. 4D). However, in the salt-sensitive simulations (fixed ANG II or partial nephrectomy), RBF increased to a lesser extent (~100–275 ml/min) during high salt intake (Fig. 4D).

Baseline afferent and efferent arteriolar resistances at normal sodium intake were increased in high ANG II, high RSNA, and partial nephrectomy compared with normal. In response to changing salt intake, there were variable responses in total renal vascular resistance due to changes in afferent (Fig. 4E) and efferent arteriolar resistances (Fig. 4F). At baseline and high salt, the highest renal vascular resistance was found in the partial nephrectomy, high ANG II, and high RSNA simulations.

Renin-angiotensin-aldosterone system. Plasma ANG II responses to changes in salt intake are shown in Fig. 5. As expected, at normal salt intake (180 mmol/day) both high ANG

II and high RSNA simulations had elevated plasma ANG II while partial nephrectomy and low ANG II simulations had decreased ANG II compared with the normal simulation (Fig. 5A). There were larger decreases in plasma ANG II at high salt intake in the salt-resistant simulations (>10 pg/ml) compared with the salt sensitive (<1 pg/ml change in ANG II) (Fig. 5B).

The high ANG II simulation had the highest plasma aldosterone concentration (Fig. 5C) and the lowest plasma potassium (not shown) at all salt intakes. Despite fixed ANG II levels, increased salt intake still decreased plasma aldosterone concentration, which highlights the important role of plasma potassium in controlling aldosterone secretion in this model, similar to experimental studies (27). There were larger decreases in plasma aldosterone at high salt intake in the salt-resistant simulations (>250 pmol/l) compared with the salt sensitive (~90–220 pmol/l decrease in plasma aldosterone) (Fig. 5D).

Tubular reabsorption of sodium. Renal proximal, loop of Henle, distal, and collecting duct sodium reabsorption in these simulations are expressed as absolute (total) sodium reabsorption. Proximal tubular sodium reabsorption had variable responses as salt intake increased from 30 to 1,000 mmol/day for the various simulations (Fig. 6A). As expected, the high ANG II and high RSNA simulations had the highest proximal tubule sodium reabsorption for any given sodium intake (Fig. 6A). Although the salt-resistant simulations were associated with marked decreases (>2 mmol/min) in proximal tubule sodium reabsorption, salt sensitivity was associated with smaller reductions in proximal tubule sodium reabsorption (<0.03 mmol/min) (Fig. 6B). The lowest absolute sodium reabsorption in each tubule segment was the partial nephrectomy simulation

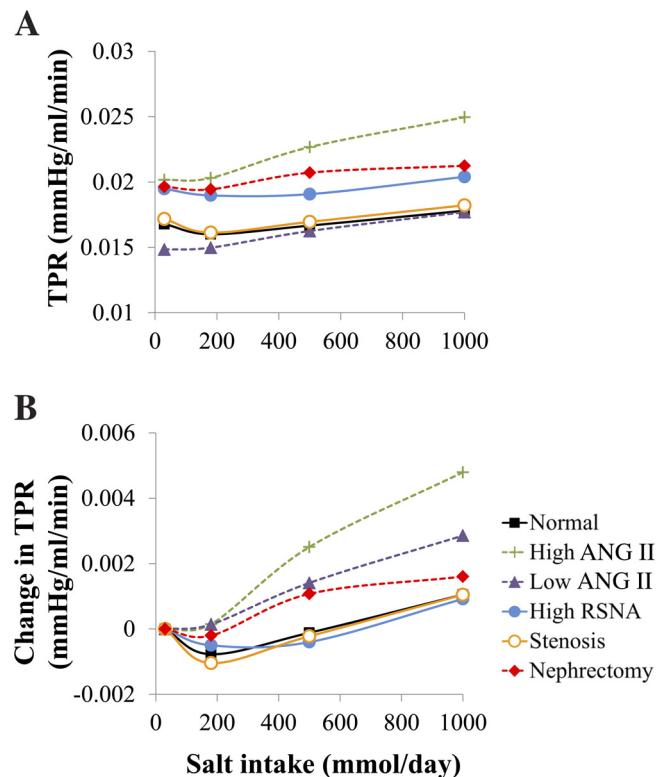


Fig. 3. Absolute values (A) and changes of total peripheral vascular resistance (TPR) (B) during changes in salt intake.

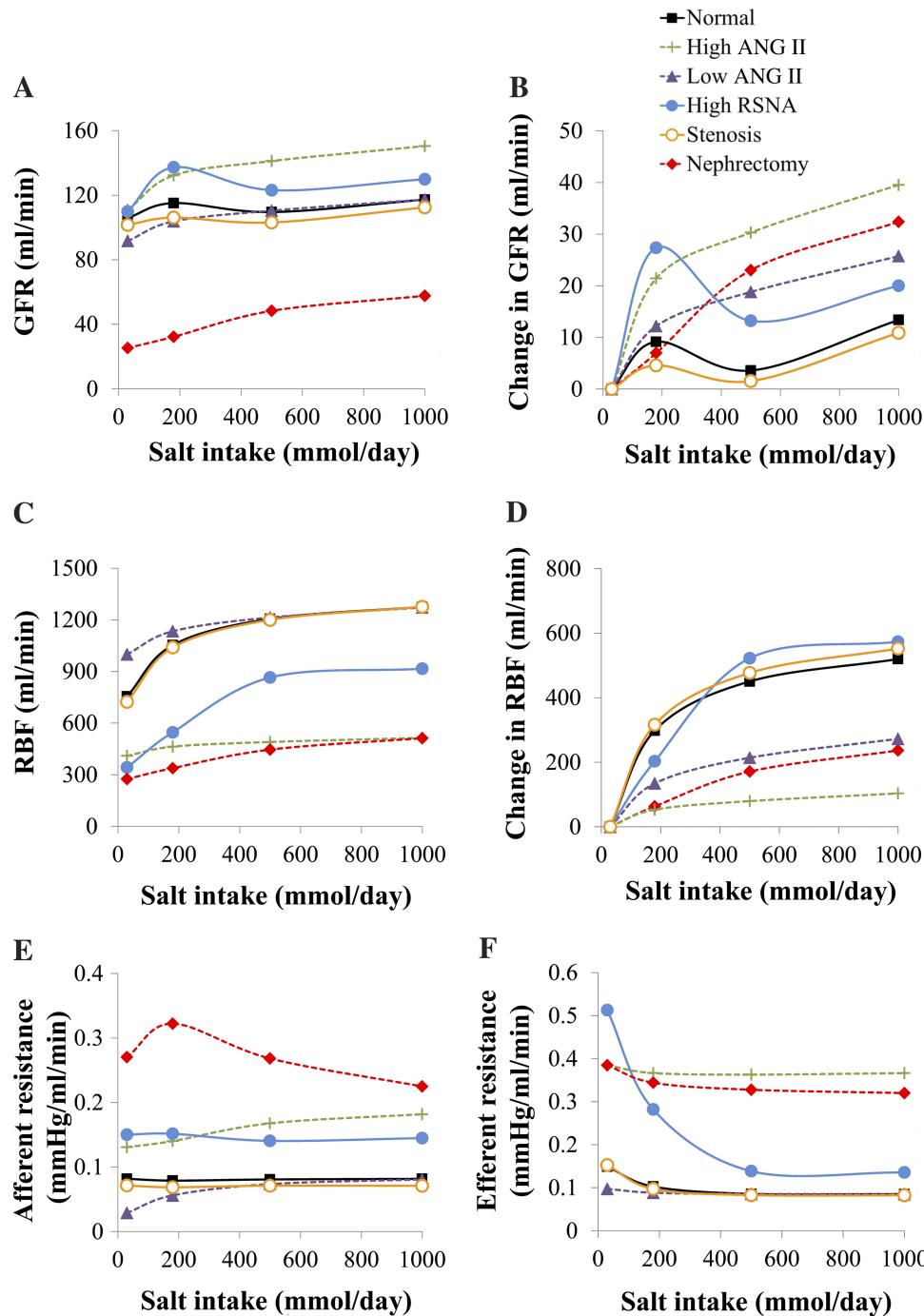


Fig. 4. Renal hemodynamics during changes in salt intake. Glomerular filtration rate (GFR) (A) and changes in GFR (B) from a baseline of 30 mmol/day, renal blood flow (RBF) (C), and changes in RBF (D), afferent arteriolar resistance (E), and efferent arteriolar resistance (F) during changes in salt intake from 30 to 1,000 mmol/day are shown.

as shown in Figs. 6 and 7, whereas it was also associated with the highest sodium delivery to the macula densa (Fig. 7B).

Besides the proximal tubule, increased sodium intake enhanced absolute (total) sodium reabsorption in each tubular segment in all simulations (Fig. 7, A–D) while decreasing fractional sodium reabsorption (not shown) in all tubular segments. Fractional sodium reabsorption of each tubular segment represents the fraction of the sodium delivered to that portion of the tubule that is reabsorbed. The increases in total reabsorption and decreases in fractional reabsorption of sodium were associated with increased sodium delivery to the proximal, loop of Henle, distal, and collecting tubular segments. The

total absolute sodium reabsorption in the kidney was increased in each simulation during high salt intake (not shown).

Sodium balance and extracellular fluid volume. Although there were small differences in baseline amounts of extracellular sodium and fluid volume, there were increases in blood volume, total extracellular sodium, and extracellular volume during increases in sodium intake in all simulations (Fig. 8); there were no major differences between the salt-sensitive and salt-resistant simulations in changes of these variables when sodium intake was increased above normal. However, at low sodium intake, total extracellular sodium and extracellular fluid volume were lower in the fixed low ANG II simulation (Fig. 8).

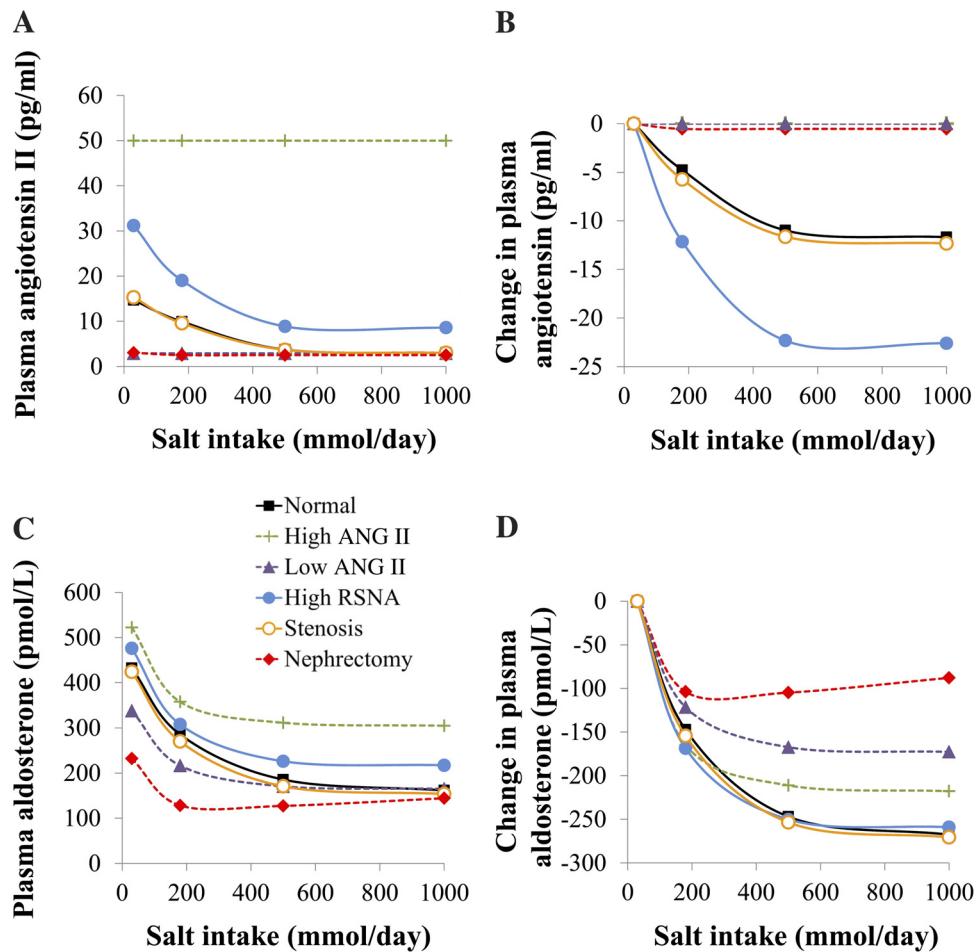


Fig. 5. Plasma ANG II and aldosterone in response to chronic changes in salt. Absolute values of ANG II (A) and changes in ANG II (B) and plasma aldosterone (C) and changes in plasma aldosterone (D) during changes in salt are shown.

Time-dependent changes in peripheral hemodynamics. From previous proposals that salt sensitivity is caused by vascular dysfunction, characterized by impaired vasodilation or excessive increases in TPR (37), and because our simulations revealed that salt sensitivity was associated with parallel increases in BP and TPR, we conducted additional simulations to determine whether increased TPR is necessary or sufficient for high salt intake to raise BP. Under normal conditions (Control), there were initially increases in organ vascular conductances in response to increasing salt intake, resulting in decreased TPR (Fig. 9A). However, within 1 wk there was an increase in TPR due to autoregulation of blood flows in the various organs, in parallel with the increased BP that persisted up to 4 wk (Fig. 9B). When salt intake was increased from 180 to 500 mmol/day, there was an initial increase in fluid retention (not shown) and CO, followed by a return of CO back toward normal as TPR increased (Fig. 9C). Clamping TPR at normal or high levels, however, had no substantial effect on long-term BP during high salt intake, although it did alter the time course of the BP increase (Fig. 9B).

DISCUSSION

Mathematical modeling has proved to be an important tool for understanding quantitative relationships among components of complex physiological systems and for testing competing hypotheses. Almost 50 years ago, Guyton and Coleman

used mathematical modeling and computer simulation to develop and test hypotheses of BP regulation, including the concept that renal abnormalities play a dominant role in causing chronic hypertension (19, 20). Although these early models were much larger than other available mathematical models of cardiovascular function at that time, the Guyton-Coleman model incorporated only ~450 variables. Despite limitations, their models advanced several major concepts of cardiovascular regulation and sparked many experimental studies to test the model predictions. The resulting experiments and additional clinical observations led to more complex models that have increasingly provided more realistic simulations of the cardiovascular, renal, and neurohormonal responses to many different physiological and pathophysiological perturbations.

HumMod represents our current and still evolving mathematical expression of integrative physiology, including over 8,000 variables and ~2,000 nonlinear, physiological relationships derived from human and animal data reported in the literature. HumMod has therefore advanced far beyond earlier versions and is able to illuminate with greater fidelity many complex physiological interrelationships that are difficult to comprehend and demonstrate experimentally or in a clinical setting. When compared with earlier models, HumMod includes additional cardiovascular components; two separate kidneys; a more detailed central nervous system with efferent sympathetic/parasympathetic control of the kidneys and car-

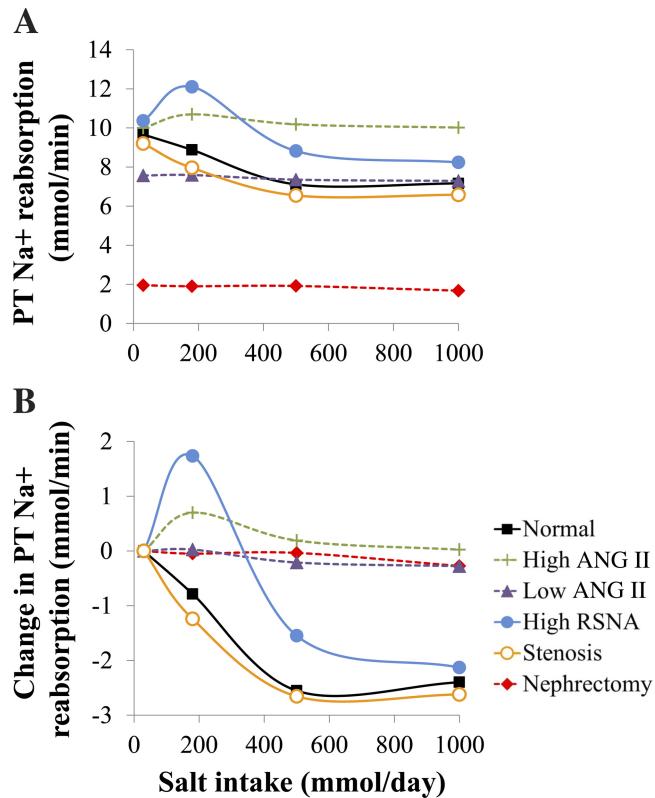


Fig. 6. Proximal tubular (PT) reabsorption of Na^+ as salt intake changed from 30 to 1,000 mmol/day are shown as absolute values (A) and changes in PT Na^+ reabsorption (B).

diovascular system; expanded endocrine system with many of the known hormones that regulate kidney, cardiovascular, and metabolic functions; additional torso water compartments; the major tubular segments with multiple transporters that regulate electrolytes; TGF with multiple factors such as ANG II and ANP that influence TGF sensitivity; glomerulotubular balance mechanisms; and the renal medulla with updated mechanisms for concentrating the urine and differentially regulating excretion of metabolic waste products (e.g., urea), electrolytes (e.g., sodium, potassium), and water. Many of these additional components are highly relevant to the current studies. To our knowledge, there are no other mathematical models currently available that contain the detailed neural, hormonal, renal, and cardiovascular mechanisms incorporated in HumMod and that can realistically simulate a wide range of cardiovascular disorders as well as the neuroendocrine, kidney, BP, and hemodynamic responses to chronic changes in salt intake. Even with this level of complexity, however, HumMod continues to be updated with new mechanisms added as additional clinical and experimental data become available.

Although HumMod was not designed specifically to simulate BP salt sensitivity, it provides a useful tool to address current controversies and explore the importance of various mechanisms that have been postulated to mediate the chronic BP responses to variations in salt intake. Important findings from our simulations include: 1) BP salt sensitivity was associated with specific differences in the GFR, RBF, and tubular reabsorption responses to changes in salt intake; 2) salt sensitivity of BP was associated with the inability to suppress the

RAAS during high salt intake; 3) excess salt and/or volume retention was not essential for salt sensitivity of BP; 4) peripheral vasoconstriction (increases in nonrenal vascular resistance) or inability to reduce TPR did not substantially influence salt sensitivity, and 5) increased preglomerular renal vascular resistance or increased RSNA caused hypertension but did not increase salt sensitivity of BP. The data from our simulations provide insights into debated physiological concepts of BP salt sensitivity.

Salt sensitivity is associated with altered renal hemodynamics and GFR. One important factor associated with salt sensitivity in our model was abnormal renal hemodynamics. For example, there were marked increases in RBF (>500 ml/min) at high salt intake in salt-resistant simulations, whereas the salt-sensitive simulations had attenuated increases in RBF (~ 100 –275 ml/min) compared with normal (Fig. 4D). Experimentally, salt-sensitive patients have been shown to have smaller increases in RBF in response to high salt diets compared with salt-resistant patients (7, 54, 57). As salt intake increases, the ability to vasodilate the efferent arteriole (due to the suppression of ANG II formation) and to increase peritubular capillary pressure and vasa recta flow are important factors that enhance the kidney's ability to excrete sodium and to maintain sodium balance without increasing BP (22).

Increases in renal vascular resistance at preglomerular sites (e.g., renal artery stenosis), however, did not increase salt sensitivity of BP. Thus the site of increased renal vascular resistance is an important factor in determining whether BP will be salt sensitive largely because of the impact on renal excretory capability rather than its effect of TPR. This finding contrasts with the hypothesis that "vaso-dysfunction," characterized by generalized increases in renal vascular resistance and TPR, can increase the salt sensitivity of BP.

Another important factor in salt sensitivity in our simulations was GFR. As discussed previously, increased salt intake raises GFR in experimental animals and in humans with normal kidney function (28, 39). Although the mechanisms for the salt-induced increase in GFR have not been fully elucidated, there is evidence from experimental studies (43) and from our computer simulations that reduced sensitivity of TGF may play an important role in this response. Our simulations also show that increases in GFR during high salt intake were greater in salt-sensitive models (Fig. 4B) and that this was irrespective of BP (Fig. 1A). These findings are consistent with studies showing that GFR responses to increased sodium intake may differ in salt-sensitive and salt-resistant subjects. For example, when sodium intake was increased to high levels, GFR increased more in salt-sensitive dogs with fixed high levels of ANG II compared with normal salt-resistant dogs despite the salt-sensitive animals having lower RBF (27), similar to the responses observed in our model. Moreover, in a study of salt-sensitive, normotensive males during high salt intake there were greater increases in GFR compared with the salt-resistant individuals (4). The differences in GFR responses between salt-sensitive and salt-resistant humans may be related, in part, to the inability to appropriately suppress ANG II (Fig. 5B) and its effects on efferent arteriolar resistance (Fig. 4F) and absolute proximal tubular sodium reabsorption (Fig.

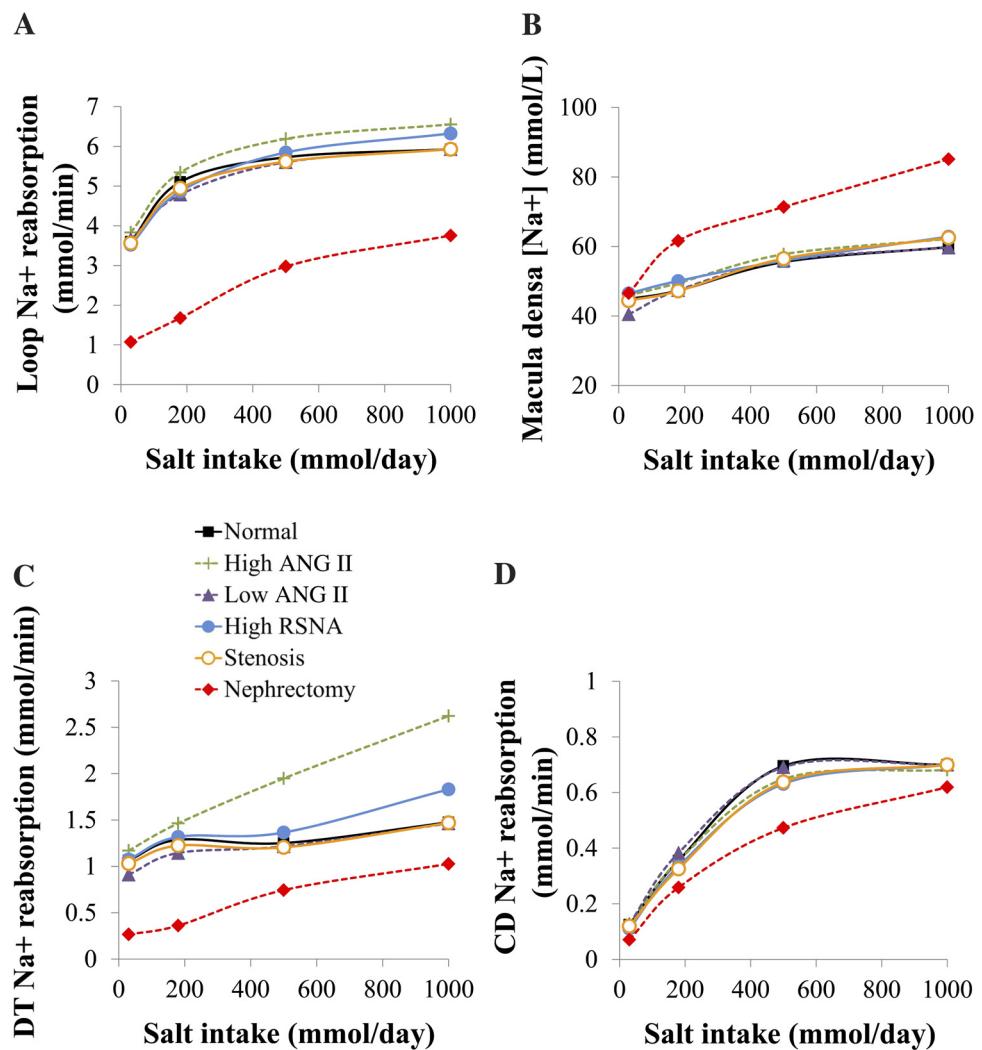


Fig. 7. Renal tubular handling of Na⁺ throughout different segments of the nephron. The Loop of Henle Na⁺ reabsorption (A), macula densa Na⁺ concentration (B), distal tubular (DT) Na⁺ reabsorption (C), and collecting duct (CD) Na⁺ reabsorption (D) as salt intake changed from 30 to 1,000 mmol/day are shown.

6B). With excessive increases in tubular reabsorption, greater increases in GFR are important for maintaining sodium excretion equal to sodium intake.

Changes in filtration fraction, the ratio of GFR to renal plasma flow (RPF), may also be associated with salt sensitivity of BP. Filtration fraction is importantly influenced by the vasoconstrictor effects of ANG II on efferent arterioles in HumMod as well as in experimental and clinical studies (21). At high salt intake, filtration fraction in the normal simulation was reduced in parallel with reductions in ANG II, whereas simulations with fixed levels of ANG II were associated with increased filtration fraction and salt-sensitive BP (not shown). Increased filtration fraction could contribute to increased tubular reabsorption and salt sensitivity, in part, by increasing colloid osmotic pressure of peritubular capillaries (21). In human studies, Bigazzi et al. (6) demonstrated that salt-sensitive essential hypertension was associated with significant increases in filtration fraction due to decreases in RPF, whereas salt resistance was associated with no change in filtration fraction due to the increased RPF.

Inability to suppress RAAS during high salt intake causes salt sensitivity of BP. In the current study, the partial nephrectomy, low fixed ANG II, and high fixed ANG II simulations

were salt sensitive, whereas bilateral renal artery stenosis and high RSNA simulations were associated with smaller changes in BP when subjected to high salt intakes. One important difference between the salt-sensitive and salt-resistant simulations was the ability to suppress the RAAS (both ANG II and aldosterone) during increased sodium intake. The fixed ANG II models obviously had no fluctuations in plasma ANG II and smaller changes in plasma aldosterone (Fig. 5D). These fixed ANG II simulations are consistent with experimental studies showing that inability of the RAAS to respond appropriately to changes in salt intake results in salt sensitivity of BP (27).

The partial nephrectomy simulation also revealed attenuated changes in ANG II during variations in salt intake (Fig. 5B). After partial nephrectomy, sodium delivery to the macula densa is elevated in hyperfiltering remnant nephrons (Fig. 7B). In HumMod, a major controller of renin release is sodium chloride delivery to the macula densa, with renin being suppressed as a result of increased macula densa sodium chloride delivery. Thus, through macula densa feedback, suppression of renin secretion in the partial nephrectomy simulation would be expected at all sodium intakes

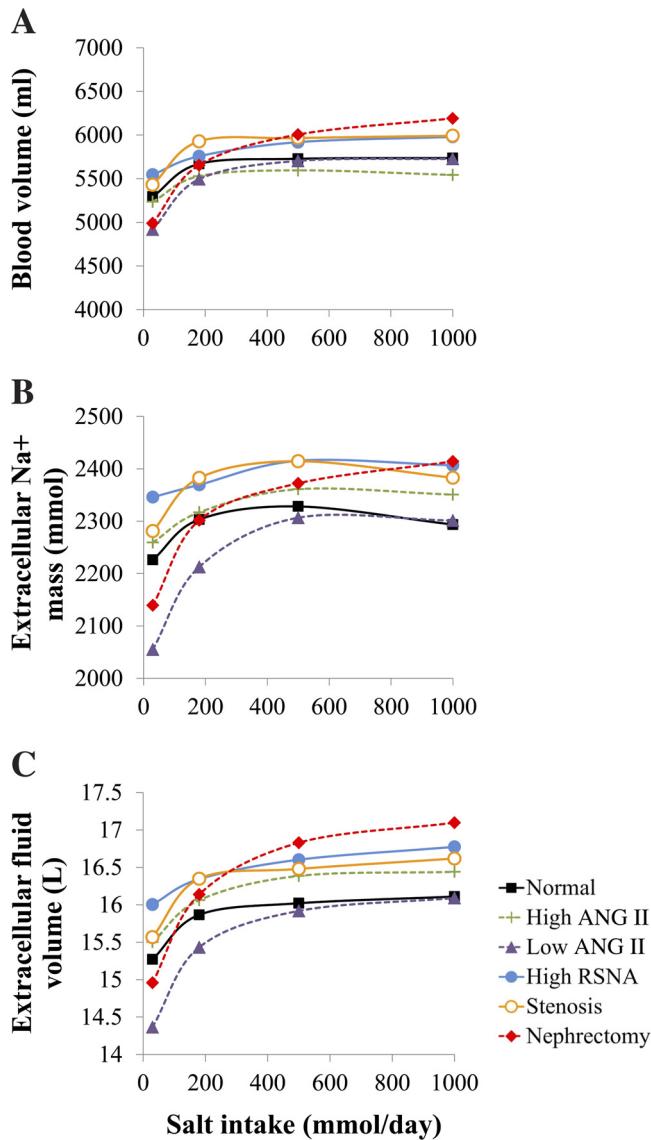


Fig. 8. Na^+ and volume retention during different salt intakes. A: blood volume; B: extracellular Na^+ mass; C: extracellular fluid volume.

thereby attenuating further suppression of renin release as sodium intake is increased.

Clinically, the ability to appropriately modulate the RAAS has been shown to play an important role in preventing salt sensitivity. In both normotensive and hypertensive salt-sensitive humans, there is often lower plasma renin activity and aldosterone at normal salt intakes (45). As these individuals increase their salt intake, their ability to further suppress RAAS is therefore diminished and could contribute to salt sensitivity. Likewise, in patients treated with RAAS blockers (e.g., angiotensin-converting enzyme inhibitors) or in patients with fixed ANG II and aldosterone (e.g., primary aldosteronism with fixed high aldosterone and completely suppressed renin) BP is highly salt sensitive (23, 26).

Salt sensitivity is associated with altered renal tubular reabsorption. Although it is often assumed that sodium balance is achieved mainly by reductions in renal sodium reabsorption when sodium intake is increased, our simulations as well as

experimental studies indicate that there is an increase in absolute (total) sodium reabsorption during chronic increases in sodium intake, although fractional sodium reabsorption is reduced (28, 39). This rise in absolute sodium reabsorption is mediated via glomerulotubular balance mechanisms whereby increases in sodium load to the tubules causes increased sodium reabsorption through mechanisms that are still poorly understood (53). The primary reason for increased sodium delivery to the tubules during increased salt intake is increased GFR and consequently increased filtered sodium load. The mechanisms responsible for increased GFR when salt intake is chronically elevated are unclear, although the results of our modeling suggest that resetting of TGF plays an important role.

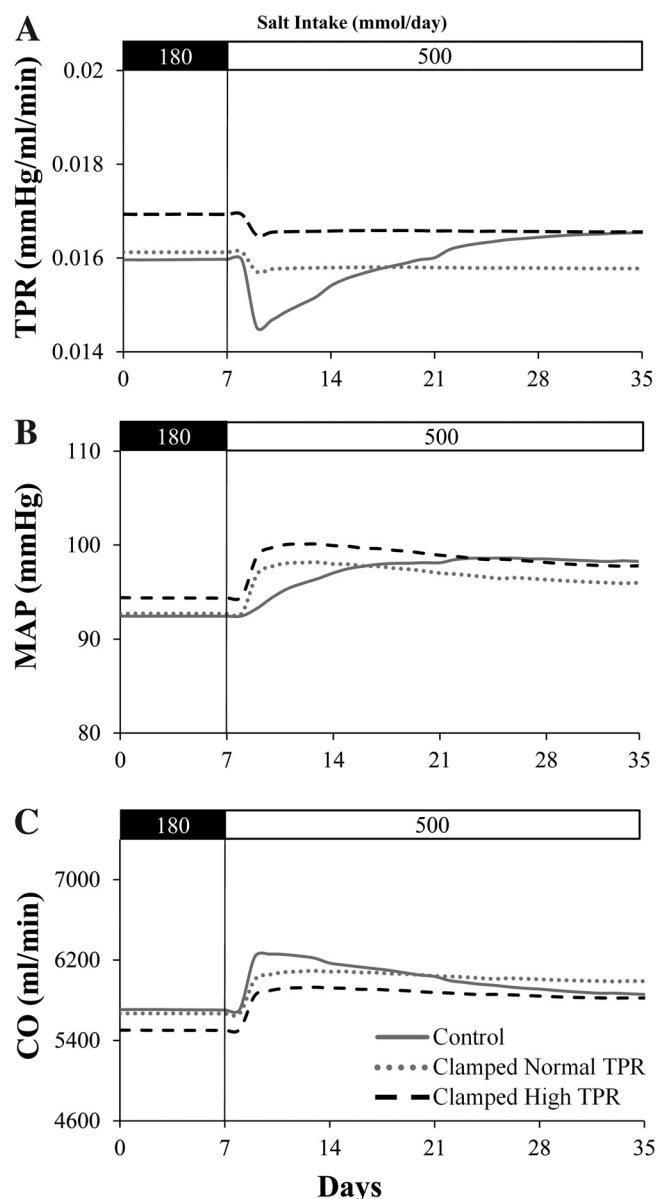


Fig. 9. Effect of increasing salt intake from 180 to 500 mmol/day during normal conditions in which TPR could change (Control) and after clamping nonrenal TPR, either at high (Clamped High TPR) or normal values (Clamped Normal TPR). TPR (A), MAP (B), and cardiac output (CO) (C) are presented as baseline values for 1 wk with subsequent increases in salt intake for 4 wk.

This TGF resetting in HumMod is based on experimental studies that show reduced feedback sensitivity in animals placed on high salt intake (43).

While changes in sodium reabsorption in the different segments of the tubule have not been well characterized in humans during changes in salt intake, a few studies have used lithium clearance as a surrogate for proximal/distal sodium reabsorption during sodium intake changes. Roos et al. (39) found that increasing sodium intake from 20 to 200 mmol/day for 5 days in normotensive healthy humans caused an increase in GFR from 103 to 119 ml/min as well as parallel increases in absolute (total) sodium reabsorption, proximal tubular reabsorption, and distal nephron reabsorption, although fractional sodium reabsorption decreased in these tubular segments (39). These experimental results are similar to the results of our simulations. Barba et al. (4) also demonstrated in normotensive men that a high salt intake increased absolute distal nephron sodium reabsorption while reducing fractional sodium reabsorption in distal tubular segments. Interestingly, absolute proximal tubular sodium reabsorption increased only in the most salt-sensitive individuals, whereas fractional sodium reabsorption in proximal tubules decreased in everyone (4). Hall et al. (28) also reported that absolute sodium reabsorption increased while fractional sodium reabsorption decreased when salt intake was raised chronically in normal dogs and in dogs with an impaired RAAS, similar to the results of our simulations.

Bilateral renal artery stenosis or high renal sympathetic nerve activity increased blood pressure but did not increase salt sensitivity. The two salt-resistant simulations (in addition to “normal”) included renal artery stenosis (increased preglomerular resistance) and increased RSNA. Our findings agree with experimental studies showing that bilateral renal artery stenosis or homogeneous increases in preglomerular resistance cause salt-resistant hypertension (17). Also, genetic disorders that cause homogeneous increases in renal vascular resistance cause hypertension that is not salt sensitive (17, 44). After an increase in preglomerular resistance and a fall in renal perfusion pressure, GFR and sodium excretion initially decrease and the RAAS is activated. Subsequently, BP and renal perfusion pressure increase as sodium and water are retained, restoring renin secretion and sodium excretion to nearly normal if the increased resistance is not too severe (26). When salt intake is subsequently increased, renin secretion and ANG II formation can then be adequately suppressed, thereby preventing salt sensitivity (26). Thus the renal artery stenosis simulation resulted in a salt-resistant form of hypertension in which there were similar decreases in ANG II, aldosterone, and proximal tubular sodium reabsorption when salt intake was raised compared with normal.

Increased RSNA (over twofold above normal) was also simulated and found to cause an increase in BP that was relatively salt resistant (Fig. 1B). Clinically, primary hypertension is commonly associated with increased RSNA, particularly when obesity is present (15, 25). Although there are no human studies, to our knowledge, focusing on the impact of RSNA on salt sensitivity, there have been some studies of obesity and salt sensitivity. Obese humans have increased sympathetic tone in multiple organs (52), including the kidneys which contributes to increases in renin

secretion and renal tubular sodium reabsorption as well as hypertension (24).

There are surprisingly few studies that have assessed salt sensitivity in obese subjects, independent of other disorders that often accompany obesity, such as diabetes and chronic kidney disease. However, available studies suggest that before the development of kidney injury and nephron loss, obesity causes salt-resistant hypertension through increases in RSNA (13, 14, 25, 31). For example, obese hypertensive individuals under the age of 45 were not salt sensitive and had similar BP responses to high salt intake compared with lean individuals (14).

Using HumMod, we showed that high RSNA increases plasma ANG II and aldosterone at baseline, but both ANG II and aldosterone were suppressed at high salt intakes (Fig. 5). Our observations are consistent with the idea that increased RSNA may cause hypertension in part by activation of the RAAS and increased sodium reabsorption, but that the RAAS remains fully functional and can respond appropriately to changes in chronic salt intake. In fact, when sodium intake was reduced to a low level in the high RSNA simulation, ANG II increased even higher than normal, helping to minimize net sodium loss. Further investigations of the impact of salt intake on development of hypertension during obesity and the role of RSNA in salt sensitivity are warranted.

Excess salt and volume retention are not required for salt sensitivity. Another point of controversy is whether salt-sensitive hypertension is highly dependent on sodium and volume retention. Figure 8 shows that in all simulations, including normal and other salt-resistant simulations, sodium and volume retention occurred with increased salt intake, with no major differences between salt-sensitive and salt-resistant conditions. This finding is consistent with experimental studies showing that salt-sensitive individuals have initial increases in extracellular fluid volume that are similar to those observed in salt-resistant subjects (41). In salt-sensitive subjects, however, the salt retention is followed by slow increases in BP and subsequent increases in TPR (42). It is important to note that the rise in TPR in salt-sensitive subjects occurred after the increases in BP and CO, both of which are able to cause an autoregulatory increase in vascular resistance in multiple organs (17, 23, 26). Thus the rise in TPR in salt-sensitive individuals does not appear to be caused by vascular dysfunction, but instead represents a normal autoregulatory process of many vascular networks throughout the body responding to increased BP (10, 23). This finding contrasts with the “vasodysfunction” concept of salt sensitivity (37) which does not recognize that increases in BP elicit secondary autoregulatory increases in vascular resistance, even independent of increased CO (8, 10), and that increases in TPR follow rather than precede the rise in BP as shown in our simulations as well as experimental studies (23, 42).

In the nephrectomy and low ANG II simulations there was greater than normal sodium retention when salt intake was raised. Conversely, when ANG II was fixed at a high level, there was less than normal salt retention during high salt intake. These results are consistent with previous studies demonstrating that high levels of potent vasoconstrictors such as ANG II or norepinephrine reduce vascular capacity so that less volume is required to raise BP sufficiently to maintain sodium balance via renal pressure natriuresis (17, 23). With decreased

ANG II, vascular capacity is increased and greater sodium retention is required to raise BP. Thus, although extracellular fluid volume and blood volume are important components of long-term BP regulation, BP is not a direct function of blood volume per se but of volume relative to vascular capacity.

Increased nonrenal peripheral vascular resistance does not cause salt sensitivity. The role of peripheral and renal vascular resistance in salt sensitivity continues to be controversial. While there are considerable data on the important roles of the kidney and RAAS in salt-sensitive hypertension, some investigators have proposed that vascular dysfunction characterized by an exaggerated increase, or a failure to decrease, systemic vascular resistance can drive salt sensitivity (37, 40, 42). Schmidlin et al. (40) observed that salt loading caused an initial decrease in TPR followed by a steady increase in TPR and BP in salt-sensitive humans. Salt-resistant subjects, however, had a substantial decrease in peripheral resistance during the first 3 days followed by a return of TPR to normal in the next few days (40). Based on these findings, Morris, Kurtz, and colleagues (37) proposed that “vasodysfunction” (both peripheral and renal), characterized by inadequate reductions in TPR, plays a major role in salt sensitivity of BP. However, reductions in TPR after increases in salt intake occur only transiently and may be secondary to baroreflexes or other mechanisms that are activated to transiently buffer increases in BP and have little importance in long-term BP regulation (12, 23).

Our simulations of various salt-sensitive conditions showed greater increases in TPR and BP during high salt intake compared with salt-resistant conditions (Fig. 3B). These observations could be interpreted as evidence that increased TPR, in response to salt loading, may cause an increase in BP in salt-sensitive conditions, whereas salt-resistant subjects are protected from increased TPR and hypertension. Thus additional simulations were run to test the importance of changes in peripheral vascular resistance in the acute and chronic phases of salt-induced hypertension. Nonrenal TPR was clamped at either normal or high levels and then compared with the normal control simulation where TPR could change due to autoregulation or other inputs as salt intake was raised. In the normal simulation, a high salt intake caused a rapid decrease in TPR due to volume expansion and baroreceptor activation (not shown), followed by a modest, slow rise in BP (Fig. 9) that was accompanied by an increase in TPR to ~4% above baseline (Fig. 9A). However, when peripheral organ vascular conductances (besides renal) were fixed at low or normal values (corresponding to high or normal nonrenal TPR), the BP responses to a high salt intake were altered only in the acute phase (<1 wk). After 1 wk there were no major differences in the BP responses to high salt intake in control, high fixed TPR, or fixed normal TPR simulations (Fig. 9). These simulations are consistent with the concept that nonrenal vascular responses to increased salt intake do not play a major role in determining chronic salt sensitivity of BP.

As previously mentioned, transient decreases in TPR were not sustained when salt intake was raised from normal to high levels in the control salt-resistant simulation (Fig. 9). This finding agrees with results of experimental studies that demonstrate salt-resistant humans have only a transient reduction in TPR during salt loading (42). Thus a “subnormal” decrease in TPR cannot be a major mechanism for protecting against chronic salt-sensitive hypertension, as suggested by the vasodysfunction concept of salt sensitivity (37), since there is no sustained decrease in TPR in salt-resistant subjects, either in experimental studies in humans or in our simulation results. The transient fall in TPR during high salt intake in our simulations was mainly due to baroreflex mechanisms rather than “vasodysfunction.”

There was a chronic reduction in TPR when salt intake was raised from a low to normal (30 to 180 mmol/day) in the simulations in which the RAAS was functional. The decreased TPR was due mainly to suppression of ANG II rather than vasodysfunction; when ANG II was fixed at a low or high level there were no reductions in TPR when salt intake was increased chronically.

Experimental studies have shown that increasing TPR or CO without affecting kidney function does not cause sustained increases in BP (11, 17). For example, in several pathophysiological conditions (i.e., beriberi, arterial-venous shunts, limb amputation, hypothyroidism), TPR can be much higher or lower than normal but these patients generally have normal BP (26). However, when increases in TPR are also associated with increased renal vascular resistance, hypertension does develop, although BP may not be salt sensitive (17, 23). Here we show in our simulations that high RSNA and high preglomerular resistance (stenosis) caused salt-resistant hypertension. Thus these data and experimental evidence suggest that increases in renal vascular resistance when occurring predominately in preglomerular vessels do not affect the salt sensitivity of BP.

Renal function curve. Based on computer simulations, Guyton predicted that long-term changes in arterial pressure can occur only as a result of changes in the pressure-natriuresis relationship or changes in salt intake (17). As a way of illustrating this important new concept, he introduced salt-loading renal function curves (17). These curves were based on empirical data, rather than computer simulations, and reflected the chronic steady-state relationship between BP and sodium excretion under various physiological conditions and disorders that lead to hypertension. The renal function curves were based on the assumption that arterial pressure has a long-term effect of renal salt and water excretion. If arterial pressure does indeed have a chronic effect on salt and water excretion, an assumption supported by many experimental studies (11, 17, 23, 26, 36), the intersection of the

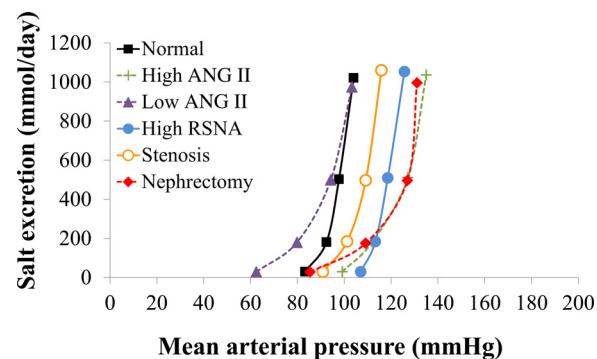


Fig. 10. Renal function curve (pressure natriuresis curve) for each simulation is displayed as the MAP for a given salt excretion (or salt intake, since each data point is after 4 wk and represents a simulation that is in salt balance). Simulations with larger fluctuations in MAP during changes in salt intake are designated salt sensitive (dotted lines). These curves represent the steady-state MAP associated with each sodium intake and sodium excretion load for the various conditions.

renal function curve and the salt intake/output is the only level of arterial pressure at which sodium balance can occur. Thus the renal function curve must be shifted to higher BP to maintain salt and water balance in hypertension.

Renal function curves based on computer simulations from HumMod are illustrated in Fig. 10 (note that these curves are nearly identical to the data presented in Fig. 1 with the axis flipped). Each data point represents a 4-wk simulation at a specified level of salt intake. The curves show that salt-sensitive forms of hypertension have slopes that are less steep compared with control or salt-resistant conditions. In HumMod, there is no equation that describes the renal function curve or pressure natriuresis relationship per se; instead, this relationship is the result of many different elements in the model, including of the multiple factors that influence GFR, filtered sodium load, and sodium reabsorption in various tubular segments, which together ultimately determine sodium excretion.

GFR and tubular reabsorption, in turn, are influenced by local controls in the kidney, such as TGF and glomerulotubular balance, and by neurohormonal factors, BP, and other variables that influence cardiovascular and renal function. Thus the relationship between BP and sodium excretion (i.e., pressure natriuresis or renal function curve) is a complex function of many variables interacting in a time-dependent manner until balance between intake and output of sodium is reached (there was slight oscillation in sodium excretion in all simulations (Fig. 10)). The current HumMod simulations produced results that are similar to those constructed from empirical data by Guyton more than 35 yr ago, although BP in the current normal simulation is somewhat more salt sensitive than the original curves presented by Guyton (18). It should be reemphasized that these curves are not artificially injected into the model but are the end result of the simulations and a proof of concept that demonstrates emergent behavior. The renal function curves can be an important tool to understand mechanisms that lead to salt sensitivity as well as hypertension.

Limitations. The current study tested only a few types of cardiovascular and renal abnormalities that have been proposed to contribute to salt-sensitive hypertension. Yet, the results of our multiple simulations are consistent with a large body of experimental and clinical studies of BP salt sensitivity. For example, nephron loss associated with normal aging can cause BP to be salt sensitive (5). Common pathologies in the aging population, such as long-term obesity, diabetes, and kidney disease, can accelerate and worsen salt sensitivity (55). Other experimental and clinical forms of salt-sensitive hypertension include dysfunction of the renal endothelin and nitric oxide systems (16, 33), Liddle Syndrome, and primary aldosteronism (9). Many of these forms of salt-sensitive hypertension may involve some of the same general mechanisms that contributed to salt sensitivity in our simulations, such as loss of functional nephrons, inability to suppress components of the RAAS, and inadequate reductions in sodium reabsorption during salt loading. Further studies are needed to test these concepts as well as emerging new mechanisms of BP regulation and salt sensitivity.

Although the current model simulations provide insights into potential mechanisms of BP salt sensitivity, we recognize that HumMod, like all mathematical models, is a theory that can be improved and become more robust as additional experimental and clinical data become available. Regardless of their complexity, mathematical models have limitations and should be rigorously tested until they ultimately fail to accurately simulate a physio-

logical or pathophysiological condition. When this occurs, the theory (i.e., model) should be revised to incorporate new mechanisms and tested again. Despite these limitations, mathematical modeling provides an important means of integrating complex experimental and clinical observations into a conceptual framework that can be tested. Indeed, the continued back-and-forth between integrative mathematical modeling, experimental studies, and clinical observations is a powerful approach to enhance the understanding of complex physiological systems.

Perspectives and Significance

Complex mathematical models such as HumMod offer insights that can guide further experimental studies. Although it was not specifically designed for studies of hypertension or salt sensitivity, HumMod is able to accurately simulate a large number of acute and chronic physiological and pathophysiological perturbations that lead to increased salt sensitivity and thus far has provided results that are consistent with many experimental and clinical studies.

These simulations demonstrate the important role of abnormal kidney function and the renal actions of the RAAS in determining salt sensitivity of BP. Increased BP salt sensitivity was associated with loss of functional nephrons, inability of ANG II to appropriately respond to changes in salt intake, smaller changes in RBF, greater increases in GFR, and greater increases in proximal tubular sodium reabsorption. However, there was no clear impact of changes in TPR, preglomerular vascular resistance, or increased RSNA on salt sensitivity of BP.

HumMod is a robust mathematical modeling tool that reveals key relationships in salt-sensitive hypertension and new insights of cardiovascular regulation. Although some of the renal responses to chronic changes in salt intake have been previously demonstrated in humans (and were instrumental in validating the current simulations), HumMod has provided novel insights that, to our knowledge, have never been investigated or validated. For example, there have been no experimental studies that have directly tested the “vascular dysfunction” hypothesis by preventing reductions in TPR during chronic changes in salt intake. Likewise, no previous studies have assessed renal arteriolar and proximal/distal tubular reabsorption responses to chronic changes in salt intake during high RSNA, clamped ANG II, or renal artery stenosis.

Salt-sensitive hypertension is a heterogeneous disorder and may not be fully represented by any single simulation that we have presented. However, many forms of experimental and clinical hypertension that are salt sensitive share common pathophysiological features that were examined with our model, including loss of functional nephrons (e.g., normal aging, chronic kidney disease, diabetic nephropathy) and inability to adequately modulate the RAAS (e.g., low renin and high renin hypertension, primary aldosteronism). Likewise, several clinical and experimental types of hypertension that are salt resistant share pathophysiological characteristics examined in our simulations, including renal artery stenosis (e.g., renovascular hypertension) and increased RSNA (e.g., obese subjects without nephron loss). Other forms of experimental and clinical salt-sensitive hypertension associated with renal and neurohormonal abnormalities that were not specifically examined in our simulations must await further development and testing of HumMod.

APPENDIX

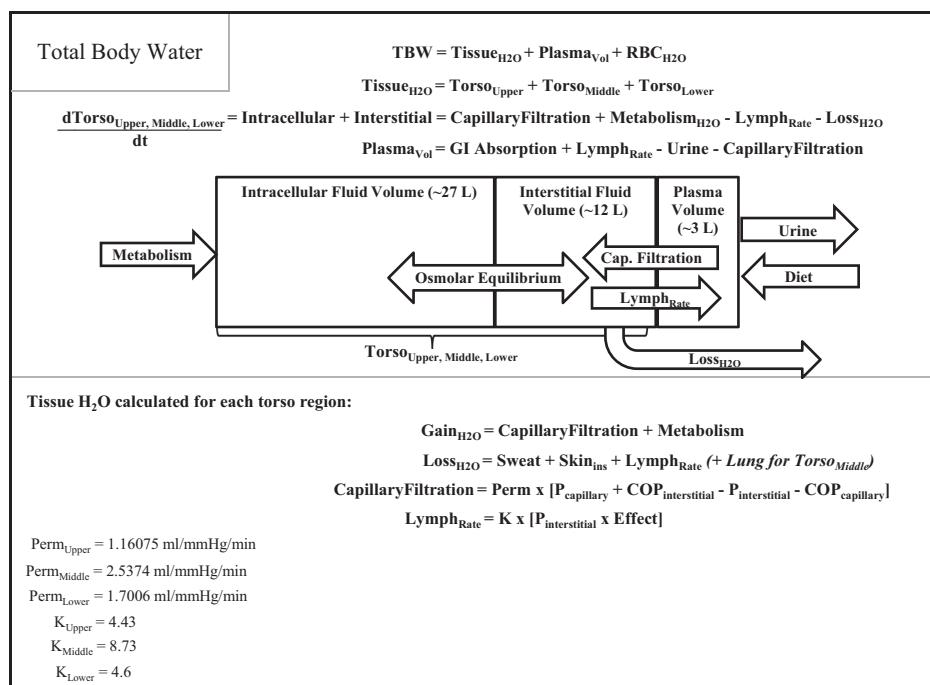


Fig. A2. Control of renal vascular resistance and GFR. Dependent variables are displayed in the left column, whereas factors and effects that impact the dependent variables are listed in the middle column, along with their effect range and input variable that determines the effect. TGF, tubuloglomerular feedback; ANP, atrial natriuretic peptide; FF, filtration fraction; SNGFR, single nephron glomerular filtration rate; PT, proximal tubule; PC, capillary hydrostatic pressure; PBC, Bowman's capsule hydrostatic pressure; P_{osm} , capillary colloid osmotic pressure.
 *Indicates a negative relationship

Indicates a negative relationship.

	Effect Range	Input	Afferent Arteriole Conductance	
			TGF Effect*	Sympathetic Effect*
	0.35 - 4	TGF Vascular Signal		
	0.3 - 1.2	α_1 Receptor Activity		
	0.8 - 1.2	Interlobular Pressure		
	0.9 - 3	[ANP]		
Baseline conductance (ml/min/mmHg/g) = 0.080883				
Efferent Arteriole Conductance	Effect Range	Input		
			ANG II Effect*	Sympathetic Effect*
	0.1 - 1.2	[ANG II]		
	0.3 - 1.2	Renal α Receptor Activity		
Baseline conductance (ml/min/mmHg/g) = 0.06218				
GFR	Effect Range	Input		
			Colloid Osmotic Pressure	Bowman's Capsule Pressure
			calculated	calculated
		Plasma Osmotic Pressure / (1 - FF)		
		Pelvis Pressure + (SNGN / PT conductance)		
		(RBF / Efferent Conductance) + Renal Venous Pressure		
			calculated	
$GFR = P_C - P_{BC} - P_{osm}$				

Proximal Tubule Fractional Sodium Reabsorption	ANG II Effect	0.8 - 1.2	[ANG II] Renal α Receptor Activity [ANP] Interstitial Fluid Pressure
	Sympathetic Effect	0.6 - 1.5	
	ANP Effect*	0.6 - 1.2	
	IFP Effect*	0.3 - 1.4	
Baseline fractional reabsorption = 0.58			
Loop of Henle Fractional Sodium Reabsorption	Load Effect*	0.9 - 2	Proximal Tubule Sodium Outflow GFR [Aldo]
	Flow Effect*	0.75 - 3	
	Aldosterone Effect	0.7 - 1	
Baseline fractional reabsorption = 0.75			
Distal Tubule Fractional Sodium Reabsorption	Load Effect*	0.75 - 3	Loop of Henle Sodium Outflow [Aldo]
	Aldosterone Effect	0.5 - 3	
Baseline fractional reabsorption = 0.75			
Collecting Duct Fractional Sodium Reabsorption	Load Effect*	0.75 - 3	Distal Tubule Sodium Outflow [Aldo]
	Aldosterone Effect	0.5 - 3	
Baseline fractional reabsorption = 0.75			

Fig. A3. Control of sodium reabsorption in the nephron. Dependent variables are displayed in the left column, whereas factors and effects that impact the dependent variables are listed in the middle column, along with their effect range and input variable that determines the effect. ANG II, angiotensin II; ANP, atrial natriuretic peptide; IFP, renal interstitial fluid pressure; GFR, glomerular filtration rate; Aldo, aldosterone. *Indicates a negative relationship

Macula Densa - TGF Vascular Signal	Sodium Effect ANG II Effect ANP Effect*	Effect Range 0.1 - 3 0.4 - 8 0.8 - 1.2	Input Sodium delivery to Macula Densa [ANG II] [ANP]
Basic Signal = 1			
Macula Densa - TGF Renin Signal	Sodium Effect ANG II Effect ANP Effect	Effect Range 0 - 3 0.8 - 5 0.8 - 2.7	Input Sodium delivery to Macula Densa [ANG II] [ANP]
Basic Signal = 1			
Renin Synthesis	TGF Effect* Sympathetic Effect	Effect Range 0.3 - 10 0.5 - 4	Input TGF Renin Signal Renal β Receptor Activity
Base synthesis = 160 GU/min			
Renin Synthesis = TGF Effect * Sympathetic Effect * Renal Mass% * Base			
Renin Secretion	TGF Effect* Sympathetic Effect	Effect Range 0.5 - 8 0.5 - 4	Input TGF Renin Signal Renal β Receptor Activity
Renin Mass = Renin Synthesis - Renin Secretion			
Renin Secretion = TGF Effect * Sympathetic Effect * Renin Mass * K			
ANG II Formation			Clearance = K * Renin Renin = Renin Secretion - Clearance PRA = Renin / (ECFV * VD) [ANG II] = PRA * ACE _{Activity} / 3
VD = 0.6 K = 0.0161 ACE _{Activity} = 30 pg/GU			
K = 0.00165			
Aldosterone Secretion	ANG II Effect [K+] Effect ACTH Effect	Effect Range 0.4 - 4 0.3 - 3 0.67 - 3	Input [ANG II] [K+] [ACTH]
Aldo Secretion = ANG II Effect * [K+] Effect * ACTH Effect * Base			
Base = 200 / G			
Aldosterone Formation			Clearance = K * [Aldo] * Hepatic Vein Flow + D * Mass Mass = Aldo Secretion - Clearance [Aldo] = Mass / TBW
D = 0.0007 K = 0.78			
Aldo Secretion = ANG II Effect * [K+] Effect * ACTH Effect * Base			
ANP Secretion	RAP Effect LAP Effect	Effect Range 0 - 10 0 - 10	Input Right Atrial Pressure Left Atrial Pressure
[ANP] = Mass/ECFV Mass = ANP Secretion - Clearance Clearance = K * Mass Secretion = Left Base * LAP Effect + Right Base * RAP Effect			
Left Base = 22 pmol/min Right Base = 31 pmol/min			

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.S.C., W.A.P., J.E.H., and R.L.H. developed the concept and design of the research; J.S.C. performed experiments and analyzed data; J.S.C., W.A.P., J.E.H., and R.L.H. interpreted results; J.S.C. prepared figures; J.S.C. drafted manuscript; J.S.C., W.A.P., T.G.C., J.E.H., and R.L.H.

edited and revised the manuscript; J.S.C., W.A.P., J.E.H., and R.L.H. approved final version of manuscript.

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		Effect Range	Input
Skeletal Muscle Conductance	ANG II Effect*	0.5 - 1.05	[ANG II]
	Sympathetic Effect*	0.3 - 1.3	SM α_1 Receptor Activation
	Sympathetic Effect	0.5 - 1.75	SM β_2 Receptor Activation
	Delayed PO ₂ Effect*	0 - 1.2	SM PO ₂
	Acute PO ₂ Effect*	0.4 - 6	SM PO ₂
	ADH Effect*	0.1 - 1	[ADH]
	Metabolism Effect	1.0 - 3	Metabolic Oxygen Need
	Muscle Pump Effect	1.0 - 3	Intensity and Rate of Exercise
Baseline conductance (ml/min/mmHg/g) = 0.00029			
GI Tract Conductance	ANG II Effect*	0.5 - 1.05	[ANG II]
	Sympathetic Effect*	0.1 - 1.3	GI α_1 Receptor Activation
	Delayed PO ₂ Effect*	0.2 - 1.2	GI PO ₂
	Acute PO ₂ Effect*	0.2 - 2	GI PO ₂
	ADH Effect	0.1 - 1	[ADH]
Baseline conductance (ml/min/mmHg/g) = 0.00904			
Fat Conductance	ANG II Effect*	0.5 - 1.05	[ANG II]
	Sympathetic Effect*	0.1 - 1.3	Fat α_1 Receptor Activation
	ADH Effect*	0.1 - 1	[ADH]
	Delayed PO ₂ Effect*	0.8 - 1.2	Fat PO ₂
	Acute PO ₂ Effect*	0.4 - 2	Fat PO ₂
Baseline conductance (ml/min/mmHg/g) = 0.00019			
Bone Conductance	ANG II Effect*	0.5 - 1.05	[ANG II]
	Sympathetic Effect*	0.1 - 1.3	Bone α_1 Receptor Activation
	ADH Effect*	0.1 - 1	[ADH]
	Delayed PO ₂ Effect*	0.8 - 1.2	Bone PO ₂
	Acute PO ₂ Effect*	0.4 - 2	Bone PO ₂
Baseline conductance (ml/min/mmHg/g) = 0.00029			
Brain Conductance	Delayed PO ₂ Effect*	0.8 - 1.2	Brain PO ₂
	Acute PO ₂ Effect*	0.9 - 2.2	Brain PO ₂
	Acute PCO ₂ Effect	0.7 - 2.2	Brain PCO ₂
Baseline conductance (ml/min/mmHg/g) = 0.00597			
Skin Conductance	ANG II Effect*	0.5 - 1.05	[ANG II]
	Sympathetic Effect*	0.1 - 1.3	Other Tissue α_1 Receptor Activation
	Body Temp Effect	0.3 - 8	(Core Temp - 37 °C)
	Local Temp Effect	0.2 - 5	Skin Temp
	ADH Effect*	0.1 - 1	[ADH]
	Delayed PO ₂ Effect*	0.8 - 1.2	Skin PO ₂
	Acute PO ₂ Effect*	0.2 - 2	Skin PO ₂
Baseline conductance (ml/min/mmHg/g) = 0.00112			
Liver Conductance	Sympathetic Effect*	0.1 - 1.3	Hepatic Artery α_1 Receptor Activation
Baseline conductance (ml/min/mmHg/g) = 0.00187			
Other Tissue Conductance	ANG II Effect*	0.5 - 1.05	[ANG II]
	Sympathetic Effect*	0.1 - 1.3	Tissue α_1 Receptor Activation
	ADH Effect*	0.1 - 1	[ADH]
	Delayed PO ₂ Effect*	0.8 - 1.2	Tissue PO ₂
	Acute PO ₂ Effect*	0.2 - 2	Tissue PO ₂
Baseline conductance (ml/min/mmHg/g) = 0.00141			

Fig. A5. Control of organ vascular conductance. Dependent variables are displayed in the left column, whereas factors and effects that impact the dependent variables are listed in the middle column, along with their effect range and input variable that determines the effect. Conductance is calculated from the product of the effects and the baseline conductance. ANG II, angiotensin II; SM, skeletal muscle; PO₂, partial pressure of oxygen; ADH, antidiuretic hormone; GI, gastrointestinal; PCO₂, partial pressure of carbon dioxide; temp, temperature. *Indicates a negative relationship.

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