A model-based approach to investigating the pathophysiological mechanisms of hypertension and response to antihypertensive therapies: extending the Guyton model

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Hypertension is a complex disease with multiple underlying pathophysiological mechanisms that are incompletely understood and vary from patient to patient. The renin-angiotensin-aldosterone system (RAAS) plays a critical role in blood pressure regulation and is the target of multiple antihypertensive therapies, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), direct renin inhibitors (DRIs), and mineralocorticoid receptor (MR) antagonists. Nevertheless, optimal blood pressure control typically requires the use of concomitant therapies, such as RAAS blockers in combination with diuretics or calcium channel blockers (CCBs). While there are many treatments for hypertension, studies have shown that individuals are reproducibly more responsive to some classes of antihypertensive agents than others (10). The reason for these differential responses has not been elucidated but is likely related to interpatient differences in hypertension pathophysiology.

Computational models provide a tool for integrating the large body of available data on blood pressure regulation, hypertension pathophysiology, and the effects of antihypertensive therapies into a consistent mechanistic framework. Computational approaches to modeling long-term blood pressure regulation, pioneered by Arthur Guyton and colleagues (16) in the early 1970s, established the foundation for our quantitative understanding of the role of the kidney in blood pressure regulation. Key aspects of this model include the infinite-gain pressure-natriuresis relationship and the role of blood flow autoregulation. The original Guyton model has been continuously updated and adapted to reflect new advances in the field (8). The fundamental role of the kidney presented in the Guyton model has been a point of contention (32, 41), with some arguing that an alternative model formulation that stresses the role of sympathetic nervous activity in long-term blood pressure regulation is needed. This criticism was partially addressed by Karaaslan et al. (25), who published an updated version of Guyton’s model that incorporates the influence of renal sympathetic nerve activity (RSNA) on the synthesis and release of renin and on tubular sodium reabsorption.

While the RAAS plays a critical role in blood pressure regulation and is the target of many antihypertensive therapies, its representation in the Guyton model is relatively simplistic. Recently, attempts have been made to more accurately model the RAAS (14, 29, 52) and its effects on the cardiovascular system (20). Here we describe how the Guyton/Karaaslan model has been extended to incorporate a more detailed model of the RAAS pathway (29), allowing simulation of the blood pressure response to different classes of RAAS-targeting therapies. Additional changes include refinement of the physiological effects of angiotensin and aldosterone, incorporation of the renal preglomerular vasculature, an accounting for the number of functioning nephrons, improvements in the representation of renal autoregulation, and incorporation of the mechanisms of
action of CCBs and diuretics. We then use the model to explore the impact of pathophysiological mechanisms of hypertension on the blood pressure response to different classes of antihypertensive agents.

MODEL FORMULATION

Updates to the Guyton/Karaaslan Model

A schematic of the model is shown in Fig. 1. While the source of the basic model structure and equations is the revision of the Guyton model by Karaaslan et al. (25), several novel updates have been incorporated (see below). Equations describing portions of the model that have been updated, including the RAAS submodel, renal hemodynamics and filtration, effects of angiotensin (AT1)-bound ANG II and aldosterone, and antihypertensive therapy effects, are included. Equations for portions of the model that are unchanged from the model of Karaaslan et al., including tubular sodium and water handling, fluid volume calculation, and cardiac and vascular function, are not repeated (see APPENDIX). An attempt has been made to remain consistent with the notation of Karaaslan et al. Normal steady-state values for newly introduced or changed model parameters are shown in Table 1. Values for parameters not listed here were taken from Karaaslan et al.

Incorporation of the RAAS submodel. Here, we briefly describe the key equations of the RAAS submodel and how it is linked with the larger model of blood pressure regulation. Lo et al. (29) provide a detailed description of the equations, parameter estimation, and validation of the submodel.

The two models are linked through renin secretion (an input from the blood pressure regulation model into the RAAS submodel) and angiotensin bound to the AT1 receptor (AT1-bound ANG II, an input from the RAAS model into the blood pressure regulation model). The renin secretion rate (Rsec), described by Eqs. 1–4, is a function of the equilibrium renin secretion rate (Nsec), an effect of sodium sensing by the macula densa (Nmd-sod), an effect of RSNA (Nrsna), and an effect of AT1-bound ANG II. Sodium flow through the macula densa (ΦMD-sod) and RSNA are described in the APPENDIX. AMD-renin,

Fig. 1. Model schematic, adapted from Karaaslan et al. (25). Top: biomechanical functioning of kidney (glomeruli and tubules), heart, and vasculature. Bottom: neurohormonal feedback mechanisms in the model, including nodes representing the biophysical drivers and effects of these neurohormonal mechanisms. P_oncotic, oncotic pressure; P_Bower’s, pressure in Bowman’s space; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; RSNA, renal sympathetic nerve activity; ANP, atrial natriuretic peptide; ADH, antidiuretic hormone.
The equilibrium level of AT1-bound ANG II (AT1-bound ANG IIEQ) were calculated from the equilibrium solution of the RAAS subsystem model with all feedback signals equal to 1, as described by Lo et al. (29)

\[
B_{\text{AT1-renin}} = 10^{\log_{10}(\text{AT1-renin})} 
\]

In the Guyton/Karaaslan model, the only factors affecting renin secretion are macula densa sodium sensing and RSNA. However, we found that these mechanisms alone are not sufficient to account for the rise in renin that occurs with therapeutic blockade of the RAAS (37). Since ANG II has been shown to directly inhibit renin secretion by juxtaglomerular cells (7), an additional direct negative feedback of AT1-bound ANG II on renin secretion was added.

Plasma renin concentration (PRC) is described by the rate of renin secretion and the rate of renin clearance, with a half-life of hrenin (Eq. 5). A typical renin concentration of 28 ng/ml was
used as the initial condition for PRC; $h_{\text{renin}}$ in the circulation was set to 12 min (51)

$$\frac{d(PRC)}{dt} = R_{\text{sec}} - \frac{\ln(2)}{h_{\text{renin}}} \times PRC$$  \hspace{1cm} (5)

Plasma renin activity (PRA) is related to PRC by a fixed constant $X_{\text{PRA-PRA}}$ (Eq. 6). $X_{\text{PRA-PRA}}$ was determined from the ratio of PRA to PRC in normotensive subjects in the absence of RAAS-blocking therapies (36, 37)

$$\text{PRA} = \text{PRC} \times X_{\text{PRA-PRA}}$$  \hspace{1cm} (6)

Plasma angiotensinogen is produced at a constant rate ($k_{\text{AGT}}$), converted to ANG I (by definition, PRA is the rate of conversion of angiotensinogen to ANG I), and cleared with a half-life of $h_{\text{ANGI}}$ (Eq. 7)

$$\frac{d[\text{ANGI}]}{dt} = k_{\text{AGT}} \times \text{PRA} - \frac{\ln(2)}{h_{\text{ANGI}}} \times [\text{ANGI}]$$  \hspace{1cm} (7)

Similarly, ANG I is generated by conversion of angiotensinogen to ANG II by ACE and chymase with rate constants $c_{\text{ACE}}$ and $c_{\text{chym}}$, respectively, converted to ANG-(1–7) by nephrilysin with a rate constant of $c_{\text{nep}}$, and cleared with a half-life of $h_{\text{ANGIV}}$ (Eq. 8)

$$\frac{d[\text{ANG I}]}{dt} = \text{PRA} - (c_{\text{ACE}} + c_{\text{chym}} + c_{\text{nep}}) \times [\text{ANG I}] - \frac{\ln(2)}{h_{\text{ANGIV}}} \times [\text{ANG I}]$$  \hspace{1cm} (8)

ANG II, in turn, is converted to ANG-(1–7) by ACE2 with a rate constant $c_{\text{ACE2}}$ and to ANG IV with a rate constant $c_{\text{ANGII-ANGIV}}$. It also binds to the AT1 and AT2 receptors with rate constants $c_{\text{AT1}}$ and $c_{\text{AT2}}$, respectively, and cleared with a half-life of $h_{\text{ANGII}}$ (Eq. 9)

$$\frac{d[\text{ANG II}]}{dt} = (c_{\text{ACE}} + c_{\text{chym}} + c_{\text{nep}}) \times [\text{ANG II}] - c_{\text{ACE2}} \times [\text{ANG II}] - c_{\text{ANGII-ANGIV}} \times [\text{ANG II}] - \frac{\ln(2)}{h_{\text{ANGII}}} \times [\text{ANG II}]$$  \hspace{1cm} (9)

ANG-(1–7) is produced by conversion of ANG I or ANG II and is cleared with a half-life of $h_{\text{ANG-(1–7)}}$ (Eq. 10). ANG IV is produced by conversion of ANG II and is cleared with a half-life of $h_{\text{ANGIV}}$ (Eq. 11)

$$\frac{d[\text{ANG-(1–7)}]}{dt} = c_{\text{nep}} \times [\text{ANG I}] + c_{\text{ACE2}} \times [\text{ANG II}] - \frac{\ln(2)}{h_{\text{ANG-(1–7)}}} \times [\text{ANG-(1–7)}]$$  \hspace{1cm} (10)

$$\frac{d[\text{ANG IV}]}{dt} = c_{\text{ANGII-ANGIV}} \times [\text{ANG II}] - \frac{\ln(2)}{h_{\text{ANGIV}}} \times [\text{ANG IV}]$$  \hspace{1cm} (11)

The AT1-bound ANG II complex is formed by binding of ANG II to the AT1 receptor and is cleared with a half-life of $h_{\text{AT1}}$ (Eq. 12). Similarly, the AT2-bound ANG II complex is formed by binding of ANG II to the AT2 receptor and is cleared with a half-life of $h_{\text{AT2}}$ (Eq. 13)

$$\frac{d[\text{AT1-bound ANG II}]}{dt} = c_{\text{AT1}} \times [\text{ANG II}] - \frac{\ln(2)}{h_{\text{AT1}}} \times [\text{AT1-bound ANG II}]$$  \hspace{1cm} (12)

$$\frac{d[\text{AT2-bound ANG II}]}{dt} = c_{\text{AT2}} \times [\text{ANG II}] - \frac{\ln(2)}{h_{\text{AT2}}} \times [\text{AT2-bound ANG II}]$$  \hspace{1cm} (13)

The key output of the RAAS submodel is the amount of AT1-bound ANG II. It is the binding of the peptide to the receptor, rather than the concentration of ANG II, that drives its physiological effects. Therefore, ANG II in the Guyton/Karaaslan model equations has been replaced with AT1-bound ANG II.

Changes to the structural representation of the renal vasculature. In the Guyton/Karaaslan model, renal vascular resistance included the afferent and efferent arteriolar resistances only, and contributions from other parts of the renal vasculature, such as the interlobar, arcuate, and cortical radial arteries, were not distinguished. However, changes in the larger renal vasculature may play a role in the development and treatment of hypertension. Thus the current model accounts for the vascular resistance of these preglomerular arteries.

In addition, Guyton/Karaaslan modeled the kidney as one single representative nephron. However, through disease or aging, nephrons can be lost to fibrosis and/or glomerulosclerosis, contributing to the development of hypertension. The current model represents the kidney as a network of nephrons in parallel, allowing explicit evaluation of the impact of nephron loss.

For arterioles in parallel, if each arteriole has a resistance $r$, and there are $N$ arterioles, then

$$\frac{1}{R} = \frac{1}{r_1} + \frac{1}{r_2} + \cdots + \frac{1}{r_N}$$  \hspace{1cm} (14)

where $R$ is the equivalent resistance of the network. If all arterioles have the same resistance, $r$, it follows that

$$R = \frac{r}{N}$$  \hspace{1cm} (15)

For simplicity, it is assumed that the afferent and efferent arterioles of all functioning nephrons have the same resistances, $r_a$ and $r_e$, respectively, and the arterioles of all non-functioning nephrons have infinite resistance.

Thus the total renal vascular resistance ($R_r$) is the total preglomerular resistance ($R_{\text{preglom}}$) plus the sum the single-afferent and single-efferent resistances divided by the number of functioning nephrons ($N_{\text{nephrons}}$)

$$R_r = (r_a + r_e)/N_{\text{nephrons}} + R_{\text{preglom}}$$  \hspace{1cm} (16)

The single-afferent arteriole resistance has a nominal value, $r_{a,0}$, and is modulated by effects of RSNA activity ($B_{\text{RSNA}}$), tubuloglomerular feedback [$TGF(\Sigma_g)$], and AT1-bound ANG II ($\Psi_{\text{AT1,aa}}$) (Eq. 17). It also exhibits a myogenic response to changes in glomerular pressure ($\Sigma_{\text{myo}}$). The single-efferent arteriole resistance has a nominal value, $r_{e,0}$, and is modulated...
by the effect of AT1-bound ANG II ($\Psi_{AT1-ea}^\text{1}$) (Eq. 18). For each, the nominal resistance value was determined from the typical total afferent or efferent resistance in a healthy human (30 or 50 mmHg·min$^{-1}$·l$^{-1}$, respectively) multiplied by the typical number of nephrons in a healthy human ($2 \times 10^9$). $\Psi_{AT1-aa}$, $\Psi_{AT1-ea}$, and $\sum_{\text{myo}}$ are defined later; $\beta_{\text{RSNA}}$ and $\sum_{\text{TGF}}$ are given by Karaaslan et al. (25).

$$r_{aa} = r_{aa,0} * \beta_{\text{RSNA}} * \sum_{\text{TGF}} * \Psi_{AT1-aa} * \sum_{\text{myo}} \quad (17)$$

$$r_{ea} = r_{ea,0} * \Psi_{AT1-ea} \quad (18)$$

$R_{\text{preglom}}$ is the nominal preglomerular resistance ($R_{\text{preglom}, 0.15}$ mmHg·min$^{-1}$·l$^{-1}$) modulated by the effect of sympathetic nervous activity, AT1-bound ANG II, and $\sum_{\text{myo}}$ (Eq. 19).

$$R_{\text{preglom}} = R_{\text{preglom}, 0.15} * \beta_{\text{RSNA}} * \Psi_{AT1-\text{preglom}} * \sum_{\text{myo}} \quad (19)$$

Renal hemodynamics are modeled as described by Karaaslan et al. (25), except preglomerular resistance and the number of functional nephrons are included in the calculation of glomerular pressure. Briefly, renal blood flow ($\Phi_{rb}$) is mean arterial pressure (MAP) divided by $R_c$ (Eq. 20), and pressure in the renal vein is assumed to be negligible. The hydrostatic pressure in the glomerulus ($P_{gh}$) is MAP minus the pressure drop across the preglomerular arteries and afferent arterioles, which is a function of renal blood flow, preglomerular resistance, and the individual afferent resistance divided by $N_{\text{nephrons}}$ (Eq. 21).

According to Starling’s law, single-nephron glomerular filtration rate (SNGFR) is single-nephron glomerular hydraulic conductance ($K_f$) times net filtration pressure, which is glomerular pressure minus pressure in Bowman’s space ($P_b$) and net glomerular oncotic pressure ($P_{go}$) (Eq. 22), and total glomerular filtration rate (GFR) is SNGFR times the number of functional nephrons (Eq. 23).

$$\Phi_{rb} = \text{MAP} / R_c \quad (20)$$

$$P_{gh} = \text{MAP} - \Phi_{rb} (R_{\text{preglom}} + r_{aa} / N_{\text{nephrons}}) \quad (21)$$

$$\text{SNGFR} = K_f (P_{gh} - P_b - P_{go}) \quad (22)$$

$$\text{GFR} = \text{SNGFR} * N_{\text{nephrons}} \quad (23)$$

Myogenic autoregulation of glomerular pressure. To better account for the autoregulation of glomerular pressure, a mechanism for the myogenic vascular response to changes in renal arterial perfusion pressure (in addition to the existing TGF mechanism) was incorporated. The myogenic component has been proven to exist independently of TGF (30) and contributes 50% of total renal autoregulation (23). It works through activation of a vascular sensor element that regulates vascular smooth muscle tone and changes microvessel diameters in response to alterations in arterial wall tension (5). The myogenic response has been observed in cortical radial and arcuate arteries and afferent arterioles, but not in efferent arterioles, in in vitro experiments and animal studies (35).

The myogenic autoregulation signal $\sum_{\text{myo}}$ is determined by comparing $P_{gh}$ with its normal value $P_{gh, \text{nom}}$ (60 mmHg) and is normalized to $\sim 1$ (Eq. 24); $c_{\text{GP,autoreg}}$ represents the gain of the feedback. This signal then feeds back to the afferent and preglomerular arterioles (Eqs. 17 and 19).

$$\sum_{\text{myo}} = c_{\text{GP,autoreg}} \times \left( \frac{P_{gh}}{P_{gh, \text{nom}}} - 1 \right) \quad (24)$$

Refinement of downstream effects of AT1-bound ANG II and aldosterone. The functional form of the physiological effects of AT1-bound ANG II on the renal vasculature and of aldosterone on tubular sodium handling was adapted to better fit human clinical data on the blood pressure response to antihypertensive agents, as described later. In Eqs. 25–27, $\Psi_{AT1-ea}$, $\Psi_{AT1-aa}$, and $\Psi_{AT1-\text{preglom}}$ are the effects of AT1-bound ANG II on efferent, afferent, and preglomerular resistance, respectively. AT1-bound ANG II is the output of the RAAS submodel, and $A$, $B$, and $C$ are fitting constants for each effect.

$$\Psi_{AT1-ea} = A_{AT1-ea} + B_{AT1-ea} * \text{AT1-bound ANG II} \quad (25)$$

$$\Psi_{AT1-aa} = A_{AT1-aa} + B_{AT1-aa} * \text{AT1-bound ANG II} \quad (25)$$

$$\Psi_{AT1-\text{preglom}} = A_{AT1-\text{preglom}} + B_{AT1-\text{preglom}} * \text{AT1-bound ANG II} \quad (26)$$

In Eqs. 28 and 29, $\Psi_{\text{aldo-DT}}$ and $\lambda_{\text{aldo-CD}}$ are the effects of aldosterone on distal tubule and collecting duct rate of sodium reabsorption, respectively. $C_{\text{aldo}}$ is the plasma concentration of aldosterone, and $A$ and $B$ are fitting constants for each effect. (For full equations describing sodium handling in the tubules, see Eqs. A2–A10).

$$\Psi_{\text{aldo-DT}} = A_{\text{aldo-DT}} * C_{\text{aldo}} \quad (28)$$

$$\lambda_{\text{aldo-CD}} = A_{\text{aldo-CD}} * C_{\text{aldo}} \quad (29)$$

Modeling effects of antihypertensive therapies. The effects of antihypertensive therapies that target different components of the RAAS, as well as therapies that target other biological processes, are represented in the model. When sufficient pharmacology data were available, an $E_{\text{max}}$ model for target inhibition was used to describe the percent target inhibition as a function of dose (Eq. 30).

$$\text{pct_target_inhibition} = \frac{E_{\text{max}} * \text{dose}}{\text{dose} + \text{ED}_{50}} \quad (30)$$

This is the case for aliskiren and eplerenone. For therapies with insufficient data to calibrate an $E_{\text{max}}$ dose-response relationship, the percent target inhibition is defined directly through a specific parameter value for each dose of the drug. Parameter values for each therapy incorporated in the model are shown in Table 2.

The pharmacodynamic effect of the therapy is incorporated by multiplying the target value by $1 - \text{pct_target_inhibition}$. The different RAAS-blocking agents act at different points along the RAAS pathway (Eqs. 31–34), although they ultimately induce their pharmacodynamic effects through the multiple downstream actions of AT1-bound ANG II and aldosterone. $c_{\text{ACE,nom}}$ and $c_{\text{AT1,nom}}$ are the typical rate constants for conversion of ANG I to ANG II by ACE and for binding AT1 to the AT1 receptor, respectively. $N_{\text{aldo}}$, the normalized aldosterone secretion rate, is described elsewhere (25).

$$\text{PRA} = \text{PRC} * X_{\text{PRC-PRA}} * (1 - \text{pct_target_inhibition}_{\text{DRI}}) \quad (31)$$

$$C_{\text{ACE}} = C_{\text{ACE,nom}} * (1 - \text{pct_target_inhibition}_{\text{ACE}}) \quad (32)$$

$$C_{\text{AT1}} = C_{\text{AT1,nom}} * (1 - \text{pct_target_inhibition}_{\text{ARB}}) \quad (33)$$
Table 2. Therapy parameter values

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Parameter</th>
<th>Dose</th>
<th>Value</th>
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</thead>
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<tr>
<td>Eplerenone</td>
<td>$E_{\text{max}}$</td>
<td>All</td>
<td>99%</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>$E_{\text{D50}}$</td>
<td>All</td>
<td>45 mg</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>$E_{\text{max}}$</td>
<td>All</td>
<td>99%</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>$E_{\text{D50}}$</td>
<td>All</td>
<td>20 mg</td>
</tr>
<tr>
<td>Valsartan</td>
<td>$pct_{\text{target}<em>{\text{inhibition}</em>{\text{ARB}}}}$</td>
<td>160 mg</td>
<td>92%</td>
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<tr>
<td>Valsartan</td>
<td>$pct_{\text{target}<em>{\text{inhibition}</em>{\text{ARB}}}}$</td>
<td>320 mg</td>
<td>94.70%</td>
</tr>
<tr>
<td>Losartan</td>
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<td>100 mg</td>
<td>93.70%</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>$pct_{\text{target}<em>{\text{inhibition}</em>{\text{ARB}}}}$</td>
<td>150 mg</td>
<td>89%</td>
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<tr>
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<tr>
<td>Ramipril</td>
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<td>94%</td>
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<tr>
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<td>56%</td>
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<tr>
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<td>26%</td>
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<tr>
<td>Amlodipine</td>
<td>$pct_{\text{target}<em>{\text{inhibition}</em>{\text{CCB}_{ea}}}}$</td>
<td>5 mg</td>
<td>26%</td>
</tr>
<tr>
<td>Amlodipine</td>
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<td>5 mg</td>
<td>26%</td>
</tr>
<tr>
<td>Amlodipine</td>
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<td>70%</td>
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<td>Amlodipine</td>
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<td>70%</td>
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<tr>
<td>Amlodipine</td>
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<td>Amlodipine</td>
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<td>32.80%</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>$pct_{\text{target}<em>{\text{inhibition}</em>{\text{CCB}_{sa}}}}$</td>
<td>10 mg</td>
<td>32.80%</td>
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<td>HCTZ</td>
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<td>50%</td>
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<tr>
<td>HCTZ</td>
<td>$pct_{\text{target}<em>{\text{inhibition}</em>{\text{HCTZ}}} }$</td>
<td>25 mg</td>
<td>65%</td>
</tr>
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</table>

\[ C_{\text{aldo}} = N_{\text{aldo}} * 85 \text{ ng/l} * (1 - pct_{\text{target}_{\text{inhibition}_{\text{MR}}}}) \]

Other drugs are represented directly through their postulated pharmacodynamic effects. CCBs are modeled through reducing afferent, pregglomerular, and, to a lesser extent, efferent and systemic vascular resistance (depending on the type of calcium channel that is blocked) (17) (Eqs. 35–38). Thiazide diuretics act by inhibiting sodium reabsorption in the distal tubules (Eq. 39). A hypothesized direct effect on renin secretion is also included (Eq. 40)

\[ r_{\text{sa}} = r_{\text{sa}_{-ss}} * \beta_{\text{RSNA}} * \sum_{\text{TGF}} * \Psi_{\text{AT1-sa}} * \sum_{\text{myo}} * (1 - pct_{\text{target}_{\text{inhibition}_{\text{CCB}_{sa}}}}) \]

Table 3. Simulated model outputs using baseline parameterization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Min</th>
<th>Max</th>
<th>Value</th>
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<tbody>
<tr>
<td>MAP</td>
<td>mmHg</td>
<td>80</td>
<td>135</td>
<td>83</td>
</tr>
<tr>
<td>GFR</td>
<td>ml/min</td>
<td>60</td>
<td>170</td>
<td>99</td>
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<tr>
<td>Urinary sodium excretion</td>
<td>mcg/min</td>
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<td>0.15</td>
<td>0.126</td>
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<tr>
<td>Extracellular fluid volume</td>
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<td>15</td>
</tr>
<tr>
<td>Daily urine flow</td>
<td>l/day</td>
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<td>3.2</td>
<td>2.1</td>
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<tr>
<td>Sodium concentration</td>
<td>mcg/l</td>
<td>140</td>
<td>145</td>
<td>143.3</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>l/min</td>
<td>4</td>
<td>7</td>
<td>3.15</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>l/min</td>
<td>0.6</td>
<td>1.15</td>
<td>0.9</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>mmHg·min⁻¹</td>
<td>70</td>
<td>172</td>
<td>86</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>ratio</td>
<td>0.15</td>
<td>0.28</td>
<td>0.19</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>mmHg·min⁻¹</td>
<td>12</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>Aldosterone concentration</td>
<td>pg/ml</td>
<td>30</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>PRA</td>
<td>fmol·ml⁻¹·h⁻¹</td>
<td>290</td>
<td>3,700</td>
<td>350</td>
</tr>
</tbody>
</table>

Simulated model outputs using baseline parameterization fall within the typical clinically observed range for key measurements of cardiovascular and renal function and neurohormonal status in normo- to hypertensive individuals. MAP, mean arterial pressure; GFR, glomerular filtration rate.

\begin{align*}
R_{\text{preglom}} &= R_{\text{preglom}_0} * \Psi_{\text{AT1-preglom}} * \sum_{\text{myo}} * (1 - pct_{\text{target}_{\text{inhibition}_{\text{CCB}_{preglom}}}}) \\
r_{\text{ea}} &= r_{\text{ea}_0} * \Psi_{\text{AT1-ea}} * (1 - pct_{\text{target}_{\text{inhibition}_{\text{CCB}_{ea}}}}) \\
R_a &= R_{a_0} * e_{\text{aum}} * (1 - pct_{\text{target}_{\text{inhibition}_{\text{CCB}_{sys}}}}) \\
\eta_{\text{DT-sodred}} &= n_{\eta \text{dr}} * \Psi_{\text{aldo-dr}} * (1 - pct_{\text{target}_{\text{inhibition}_{\text{thiazide}}}}) \\
R_{\text{sec}} &= N_{r_s} * v_{\text{MD-sod}} * v_{\text{RSNA}} * v_{\text{AT1-ANGII}} * (1 + pct_{\text{target}_{\text{stimulation_{thiazide}}}})
\end{align*}

where $R_a$ is systemic arterial resistance.

Modeling Software

Model building and creation of virtual patient cohorts were conducted in Entelos PhysioLab software. Model calibration, validation, and simulations were conducted in SBToolbox2 (www.sbtoolbox2.org) (50).

RESULTS

Evaluation of Physiologically Feasible Model Behavior

To ensure that the model produces physiologically reasonable outputs, the simulated steady-state model behavior using the baseline model parameterization was compared with key clinical measurements of cardiovascular and renal function and neurohormonal status. Table 3 shows the typical range of values for these measurements in normo- to hypertensive individuals, as well as the simulation results. For steady state, all simulated variables fell within observed ranges.

Evaluating Individual Pathophysiological Mechanisms of Hypertension

Hypertension is a heterogeneous disease with a number of potential underlying causes, including increased systemic and/or renal vascular resistance, alterations in renal sodium handling, pathological changes in the glomerular filtration membrane, tubular fibrosis leading to nephrin loss, upregulation of components of the RAAS, and overactivity of the sympathetic nervous system. To evaluate the effect of each of these potential hypertensive mechanisms on the transition from
normal blood pressure to hypertension, model parameters associated with each mechanism were varied individually over a wide range, and the effects on MAP and total peripheral resistance (TPR) were evaluated after a new steady state was achieved. Results are summarized in Fig. 2. Changes in TPR had little effect on long-term MAP, in agreement with previous simulations by Guyton (15). On the other hand, each of the other hypertensive mechanisms resulted in sustained changes in MAP and TPR. Blood pressure is particularly sensitive to increases in preglomerular and afferent resistances and to increases in sodium reabsorption along the tubules, especially at the collecting duct. These mechanisms not only affect MAP, but they also cause compensatory changes in TPR.

Generating a Cohort of Hypertensive Virtual Patients

Individually, each of the hypertensive mechanisms described above causes, at best, a moderate rise in blood pressure. In most cases, however, hypertension likely arises from some combination of pathological mechanisms. Moreover, the specific mechanisms involved may differ from patient to patient. To capture this heterogeneity and variability in essential hypertensive patients, a virtual cohort of hypertensive patients was generated.

A hypertensive virtual patient is defined as one unique set of model parameters that produces model outputs consistent with the clinically observed ranges for key cardiovascular, renal, and neurohormonal measurements. Consider a multidimensional space, where each mechanistic parameter in Fig. 2 corresponds to one axis of this space. Each point (or set of parameter coordinates) in this multidimensional space represents a possible hypertensive virtual patient. However, each point is considered a valid virtual patient only if the associated parameters produce model outputs that fall within the physiological ranges defined in Table 3. This approach was used to generate and screen thousands of potential virtual patients for physiological feasibility. Only the virtual patients with valid outputs were utilized in the model.

The resulting virtual patient cohort incorporates a range of underlying variability in the pathophysiological mechanisms (Fig. 3). The specific combination and severity of mechanisms vary among the virtual patients. In addition, the virtual patient cohort covers the range of observed clinical values for key functional measurements (Fig. 4). Thus the resulting virtual patient cohort is considered to represent the mechanistically and phenotypically diverse essential hypertensive population.

Model Calibration and Validation

Data sources for model calibration and validation. PRA, PRC, and MAP data from published placebo-controlled clinical trials of various antihypertensive agents were used for model calibration and validation. The data sources are summarized in Table 4. The goal was to model the steady-state response of plasma biomarkers and blood pressure to therapy, rather than acute changes. Thus only studies with a treatment duration of ≥4 wk were used. Placebo-adjusted PRA and PRC changes from baseline with therapy were obtained from studies in normotensive subjects and/or essential hypertensive patients. When available (for aliskiren and various ARBs and ACEi monotherapies), blood pressure data from the systematic reviews of the Cochrane Collaboration were used. In all other cases [eplerenone, amlodipine, hydrochlorothiazide (HCTZ), and various dual-RAAS and RAAS + non-RAAS combinations], placebo-adjusted MAP change from baseline was obtained from studies in essential hypertensive patients only. When data points from multiple studies for a given drug-dose combination were available, a composite weighted mean change from baseline was calculated.

Process overview. Model calibration and validation were conducted as a step-wise process. First, neurohormonal feedbacks and therapy effects within the RAAS submodel were
calibrated to fit data on changes in PRA and PRC in response to different classes of antihypertensive therapies. This portion of the model calibration was then validated by simulation of the PRC response to dual-RAAS therapy. Next, blood pressure data from RAAS-blocking agents were used to calibrate the downstream physiological effects of AT1-bound ANG II and aldosterone (the main outputs of the RAAS submodel) by relating the model-predicted changes in these receptor-bound peptides to the observed MAP response for each drug. Parameters governing the physiological effects were fit to minimize the error between the model-predicted MAP response and the observed mean data. Through this process, the MAP response for each RAAS therapy was also calibrated. In addition to RAAS-blocking antihypertensive agents, blood pressure responses to the CCB amlodipine and the diuretic HCTZ were calibrated.

Because of the multiple interactions between the RAAS and the blood pressure regulatory system, calibration of the model is necessarily an iterative process of identifying parameters that reduce the error between simulated and observed data for RAAS biomarkers and blood pressure. After iteration, the final resulting model parameterization presented here accurately reproduces the PRA, PRC, and blood pressure response to all RAAS-targeting and non-RAAS therapies tested. To validate the model, the PRC response and the blood pressure response to combination therapies (dual-RAAS, as well as RAAS + non-RAAS) were simulated with the final model and compared with reported levels of PRC increase and MAP reduction.

Since the underlying mechanism of hypertension impacts the blood pressure response to different classes of therapies (10), simulating the therapy response in any single hypertensive virtual patient may produce results that are biased by that virtual patient’s underlying pathophysiology. In addition, most available data on the blood pressure response to antihypertensive agents are from clinical trials (typically 8 wk in duration) in populations of essential hypertensive patients encompassing distinct etiologies and different drivers of disease. To mimic these clinical trials, calibration and validation were carried out by simulation over the entire hypertensive virtual patient cohort for 8 wk.

Final parameter values governing the system behavior, estimated during the model calibration, are given in Table 1. Parameter values describing the effects of antihypertensive therapies are shown in Table 2.

Calibration of feedbacks on renin secretion. The degree of the reactive rise in renin observed with therapies targeting various physiological mechanisms was used to separate out the relative contribution of different feedback mechanisms on renin secretion. Agents that reduce AT1-bound ANG II (ARBs, ACEi, and DRIs) cause a severalfold increase in renin secretion (2, 21, 36), while agents that are primarily diuretic, e.g., HCTZ, cause a moderate rise in renin (22, 49, 57, 58), and vasodilators, such as CCBs, cause a very mild and inconsistently observed rise in renin (33, 44, 54).

First, consider the renin response to diuretics. Initial simulations using the feedbacks on renin secretion as originally

![Fig. 3. Distribution of parameters associated with hypertensive mechanisms in the generated cohort of hypertensive virtual patients (VPs). PT, proximal tubule; DT, distal tubule; CD, collecting duct; Kf, single-nephron hydraulic conductance; norm, normal; norm, normalized.](http://ajpregu.physiology.org/doi/abs/10.1152/ajpregu.00039.2013)
calibrated in the Guyton/Karaaslan model substantially under-predicted the rise in renin with eplerenone and HCTZ. Given that some antihypertensive agents such as CCBs produce blood pressure reduction similar to or greater than diuretics with little or no sustained rise in renin, it is unlikely that pressure baroreceptors or renal sympathetic activity is responsible for the renin rise with these compounds, since these feedbacks would also be similarly affected by CCBs. This suggests that sodium sensing by the macula densa is a major contributor to renin stimulation by diuretics. However, even among different classes of diuretics, there are differences in the level of renin activation. MR antagonists, such as eplerenone, stimulate only a 20–45% rise in plasma renin, while HCTZ stimulates a 70–100% increase. There is some evidence that thiazide diuretics may exert an additional effect on renin secretion, mediated through cyclooxygenase 2 and prostaglandins (24).

We hypothesize that the rise in renin observed with eplerenone primarily reflects feedback from macula densa sodium sensing, and data on the renin response to eplerenone were used to recalibrate and strengthen the effect of macula densa sodium sensing on renin secretion in the model. Briefly, an $E_{\text{max}}$ curve (Eq. 30) fit to data from de Gasparo et al. (9) was used to represent the dose-dependent in vivo inhibition of MRs with eplerenone (see parameter values in Table 2). Parameters governing the effect of macula densa sodium flow on renin secretion (Eq. 2) were then determined by fitting the PRA dose response to eplerenone (49, 58).

We then hypothesize that the rise in renin observed with HCTZ includes both macula densa sodium sensing and an added effect on renin secretion that implicitly represents effects mediated by prostaglandins. Data on the renin response to HCTZ were then used to fit a direct effect of HCTZ on renin secretion (Eq. 40), in addition to its indirect effects through macula densa sodium sensing.

Next, consider the renin response to other RAAS-blocking agents. Even with the increased effect of macula densa sodium sensing on renin secretion, the model initially greatly underpredicted the large reactive increases in renin levels in response to ARBs, ACEi, and DRI. ANG II is known to inhibit renin secretion by acting on AT$_1$ receptors in the juxtaglomerulus, and the large increases in renin with RAAS blockade are likely due to negative feedback when AT$_1$-bound ANG II is suppressed. Thus negative feedback of AT$_1$-bound ANG II on renin secretion was added in the model (Eqs. 1 and 4).

The form and magnitude of feedback of AT$_1$-bound ANG II on renin secretion were determined from relative changes in PRA and PRC with the direct renin inhibitor aliskiren. Inhibition of renin activity causes a reactive rise in total (active and inactive) plasma renin (measured as PRC). Data from Nussberger et al. (36, 37) can be used to determine the percent renin inhibition from the values for PRA and PRC at baseline and at the end of the study (EOS), as in Eqs. 41 and 42. Here, $X$ is the ratio of PRA to PRC in the absence of renin inhibition [at baseline (BL)]. Then the percent renin inhibition is 1 minus the actual PRA after treatment (PRA$_{\text{EOS}}$) divided by the PRA that would be expected in the absence of treatment for the value of PRC measured at the end of the study (given by PRC$_{\text{EOS}}$ * $X$)
An Emax dose-response curve for the inhibition of renin with aliskiren was fit to the data (see parameter values in Table 2). AAT1-renin and BAT1-renin from Eq. 4 were then estimated, such that the error between the observed and predicted PRA and PRC responses was simultaneously minimized for each dose of aliskiren.

After aliskiren data were used to calibrate the feedback of AT1-bound ANG II on renin secretion, parameters describing the inhibition of the AT1 receptor with several common ARBs (valsartan, losartan, irbesartan, and candesartan), as well ACE inhibition with two common ACEi (enalapril and ramipril), were estimated by minimizing the error between observed and simulated reactive rise in PRC with these therapies.

Validation of the RAAS submodel with the PRC response to dual-RAAS therapy. After the effect of various feedback mechanisms on renin secretion, as well as target inhibition for each drug class and treatment dose as described above, was validated, the response to dual-RAAS inhibition with the DRI aliskiren and the ARB valsartan was simulated. The model was able to effectively capture the nonlinear reactive rise in PRC with this combination therapy.

Figure 5 compares the simulated PRA and PRC response to therapy of the final calibrated model with the observed responses to various monotherapies and combination therapies. The model captures the suppression of PRA with the DRI aliskiren, as well as the compensatory rise in active renin that accompanies suppression at any point along the RAAS pathway downstream of renin (Fig. 5A). The model also captures the reactive rise in PRC that results from inhibition at any point along the RAAS pathway, including direct renin inhibition (Fig. 5B).

Calibration of downstream effects of aldosterone and AT1-bound ANG II on blood pressure. With incorporation of the RAAS pathway into the Guyton/Karaaslan model, the current model now predicts RAAS therapy-induced changes in AT1-bound ANG II and aldosterone, entities that are not easily determined in vivo but are the ultimate effectors of blood pressure control via the RAAS. Model-predicted inhibition of these receptor-bound peptides can then be related to the observed blood pressure response, and the resulting relationship is used to determine the magnitude of the downstream physiological effects of these entities.

The effects of aldosterone receptor antagonism were considered first, since the blood pressure response with MR antagonists results primarily from a reduction of MR-bound aldoste-

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**Table 4. Data sources for model calibration and validation**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reference Number</th>
<th>PRA/PRC MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibration</td>
<td></td>
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</tr>
<tr>
<td>DRI</td>
<td></td>
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</tr>
<tr>
<td>Aliskiren</td>
<td>36, 37, 40</td>
<td>34</td>
</tr>
<tr>
<td>ARBs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>2, 31, 42</td>
<td>19</td>
</tr>
<tr>
<td>Losartan</td>
<td>2, 6, 12, 31</td>
<td>19</td>
</tr>
<tr>
<td>Valsartan</td>
<td>2, 26, 31, 40</td>
<td>19</td>
</tr>
<tr>
<td>ACEi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>21, 37, 42</td>
<td>18</td>
</tr>
<tr>
<td>Ramipril</td>
<td>55</td>
<td>18</td>
</tr>
<tr>
<td>MR blocker</td>
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<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>49, 58</td>
<td>49, 58</td>
</tr>
<tr>
<td>Diuretic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCTZ</td>
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<td>46, 57</td>
</tr>
<tr>
<td>CCB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>33, 45, 54</td>
<td></td>
</tr>
<tr>
<td>Validation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren + valsartan</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Aliskiren + ramipril</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Aliskiren + HCTZ</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Aliskiren + amlodipine</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Valsartan + HCTZ</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Valsartan + amlodipine</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

Responses of PRA, PRC, and MAP to different antihypertensive therapies were obtained from published, randomized, placebo-controlled clinical trials (reference numbers listed). Data on response to monotherapy were used for model calibration, and the model was validated by fitting to data for combination therapies. DRI, direct renin inhibitor; MR, mineralocorticoid.

\[
X = \frac{\text{PRA}_{BL}}{\text{PRC}_{BL}} \quad (41)
\]

\[
\% \text{ renin inhibition} = 1 - \frac{\text{PRA}_{EOS}}{\text{PRC}_{EOS} * X} \quad (42)
\]

![Fig. 5. Simulations with the final calibrated model fit the clinically observed PRA (A) and plasma renin concentration (PRC, B) response to a range of antihypertensive monotherapies. As validation, the calibrated model accurately predicts the nonlinear rise in PRC with the combination of aliskiren and valsartan. See Table 2 for data sources for observations. HCTZ, hydrochlorothiazide.](http://ajpregu.physiology.org/doi/10.1152/ajpregu.00039.2013)
rone alone, while the blood pressure reduction with other RAAS agents results from a decrement in AT₁-bound ANG II and aldosterone (through a reduction of ANG II-stimulated aldosterone). In simulating the blood pressure response to eplerenone (49, 58), changes in distal tubule sodium reabsorption alone were not able to account for the observed changes in blood pressure. Thus an additional effect of aldosterone on collecting duct sodium reabsorption rate was added to the model (Eqs. 29 and A8). The fitting constants in Eqs. 28 and 29 were estimated by minimizing the error between the simulated and observed MAP response to eplerenone.

Aldosterone suppression accounts for a portion of the blood pressure response to other RAAS blockers (DRI, ARBs, and ACEi) as well. The remaining bulk of the blood pressure reduction is due to reduction of AT₁-bound ANG II. Model-predicted reductions of AT₁-bound ANG II with RAAS-blocking agents were correlated with clinically observed MAP reductions (Fig. 6A), indicating that the level of AT₁-bound ANG II suppression achieved with therapy determines the magnitude of the blood pressure response, independent of the specific therapeutic target. AT₁-bound ANG II exerts its downstream physiological effects through vascular and tubular mechanisms. We found that increasing the strength of the effect on proximal tubule sodium reabsorption beyond that reported by Karaaslan et al. (25) resulted in unphysiological behavior; specifically, it caused a hemodynamic fall in GFR with RAAS therapy (driven by TGF) beyond that observed in hypertensive patients in the absence of kidney disease. This occurred even when autoregulation was strengthened by addition of the myogenic component. Therefore, the tubular effects of the RAAS, although significant, were assumed to be at the maximum level, and the blood pressure response was fit by reestimating the vascular effects of AT₁-bound ANG II. The fitting constants for AT₁-bound ANG II on efferent, afferent, and preglomerular resistances (Eqs. 14–16) were estimated by minimizing the error between the observed and the simulated MAP response to each therapy and dose.

**Calibration of the blood pressure response to amlodipine and HCTZ.** In addition to RAAS-targeting agents, the model can be used to simulate the response to other non-RAAS antihypertensive agents, with the assumption that the physiological mechanism of action is known. The CCB amlodipine, which blocks L- and N-type calcium channels, exerts a strong vasodilatory effect on the afferent and preglomerular vasculature and a weaker effect on efferent vessels (17). HCTZ is a diuretic that exerts its effects by inhibiting sodium reabsorption in the distal tubule. The magnitude of vasodilatation with amldipine (Eqs. 35–38) and the magnitude of distal tubule sodium reabsorption inhibition with HCTZ (Eq. 39) were calibrated to obtain a clinically observed blood pressure-dose response to these therapies.

**Validation through simulation of the MAP response to dual-RAAS and RAAS + non-RAAS combination therapies.** As validation, the blood pressure responses to several different combinations of therapies were simulated and compared with reported levels of MAP reduction. The model accurately predicted the MAP response to dual-RAAS combinations (aliskiren + valsartan and aliskiren + ramipril) and RAAS-non-RAAS combinations (aliskiren + amlodipine, aliskiren + HCTZ, valsartan + amlodipine, and valsartan + HCTZ). Figure 6B compares the simulated MAP response to therapy of the final calibrated model with the observed responses to various monotherapies and combination therapies and shows that the model is able to accurately reproduce the blood pressure response across a range of therapy classes and combinations.

**Model Application: Effect of Underlying Pathophysiology on the Response to Different Classes of Antihypertensive Therapies**

Using the final validated model, we explored the effect of underlying disease pathology on the response to different classes of antihypertensive therapies. For each hypertensive mechanism (γ-axis in Fig. 2), two virtual patients were created: one with a normal value for the associated parameter and one with a pathological high/low value. All other parameters were unchanged. Each virtual patient was then simulated on each of several classes of antihypertensive therapies for 8 wk. To determine whether a specific mechanism impacts the response to a particular therapy, the change in MAP from baseline to the end of the 8-wk simulation was determined and compared for...
each pair of virtual patients. The resulting matrix of simulations is summarized in Fig. 7.

The response to all therapies was greater in virtual patients with increased afferent resistance and decreased glomerular hydraulic conductance than in virtual patients with normal values. On the other hand, systemic vascular resistance did not impact the magnitude or response to any of the therapies tested. Increased preglomerular and afferent resistance resulted in a much greater responsiveness to RAAS-blocking agents and, to a lesser extent, CCBs than to diuretics. Increased proximal reabsorption also increased responsiveness to RAAS blockers, while increasing proximal tubule or collecting duct sodium reabsorption resulted in lower responsiveness to the diuretics HCTZ and eplerenone. Nephron loss increased responsiveness to all classes of therapy except CCBs. As would be expected, high-baseline renin secretion results in a greater response to RAAS blockers and a weaker response to diuretics than low-baseline renin secretion. Increased aldosterone also decreased responsiveness to HCTZ and MR blockers. Increasing RSNA significantly decreased responsiveness to RAAS blockers and CCBs but improved responsiveness to diuretics.

**DISCUSSION**

We have presented the development, calibration, and validation of an extension of the previously published Guyton/Karaaslan model of blood pressure regulation that incorporates a detailed submodel of the RAAS. This allowed explicit modeling of antihypertensive therapies that target different parts of this pathway and provides the capability to evaluate the response to combinations of these therapies. Literature data on plasma RAAS biomarker and blood pressure responses to different classes of therapies were used to refine and calibrate physiological effects of AT\(_1\)-bound ANG II and of aldosterone on renin secretion, renal vascular resistance, and sodium reabsorption. After the model was calibrated with data from individual therapies, it was shown to accurately predict the RAAS biomarker and blood pressure response to combinations of dual-RAAS agents, as well as RAAS therapies in combination with diuretics or CCBs.

**Impact of Individual Pathophysiological Mechanisms on Hypertension**

The model was used to evaluate the individual effect of underlying pathological mechanisms on the transition from normal physiology to hypertension. While increased vascular resistance is a common characteristic of hypertensive patients, a direct increase in systemic vascular resistance did not result in sustained blood pressure elevation in the model, because, as Arthur Guyton argued, an increase in peripheral resistance alone does not shift the infinite-gain pressure-natriuresis curve (15). While increasing vascular resistance acutely increases blood pressure, it also increases renal perfusion pressure, which results in increased natriuresis. With higher excretion of sodium and water, blood volume is reduced, and blood pressure returns to previous levels over time.

The association of increased vascular resistance with hypertension may, instead, be secondary to other hypertensive mechanisms that do alter the renal pressure-natriuresis curve. In particular, mechanisms such as increased renal vascular resistance, increased tubular sodium reabsorption, and RAAS or renal sympathetic activation contribute to sodium and water retention and, at least initially, to increased blood volume. With higher blood volumes, the associated rise in cardiac output temporarily increases blood flow to body tissues and

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**Fig. 7.** Simulated effect of underlying hypertension pathology on response to different antihypertensive therapies. White, black and hatched boxes indicate the degree to which the mechanism shown at left affected the MAP drop in response to the therapy shown at top. White, <25% difference in MAP reduction in VP with or without mechanism present; black, >25% larger reduction in MAP when mechanism was present; hatched, >25% larger reduction in MAP when mechanism was absent; *, 2-fold larger reduction in MAP.
organs, which respond by constricting, through local tissue autoregulatory mechanisms, to restore blood flow to normal levels. This vasoconstriction increases systemic vascular resistance, which further elevates blood pressure and returns cardiac output toward normal. At the same time, the rise in blood pressure increases the renal perfusion pressure and induces a further natriuretic/diuretic response. Thus the long-term effect of these pathophysiological changes is an elevation of blood pressure and peripheral resistance with only a slight increase in blood volume.

On the other hand, simulations showed that blood pressure is particularly sensitive to changes in preglomerular and afferent renal vascular resistance and, to a lesser degree, to damage to the glomerular capillary membrane (as modeled by increases in $K_0$). Increased renal vascular resistance may be caused by increased sympathetic nervous activity, widespread atherosclerosis, or other factors leading to constriction of the renal artery/arterioles. Damage to the glomerular filtration surface, resulting in lower membrane permeability or reduced membrane surface area, can occur through a variety of factors, including glomerulosclerosis, inflammatory processes, damage from reactive oxygen species, and elevated glomerular pressure. Disruption of the glomerular filtration surface may be particularly common in diabetic hypertensive patients. With increased renal vascular resistance or sclerosis of the glomerular membrane, a higher pressure is needed to maintain glomerular filtration; thus the pressure-natriuresis curve is shifted to the right.

Blood pressure was also shown to be sensitive to changes in tubular sodium reabsorption. Defects in sodium reabsorption in the tubules have been noted in hypertensive patients. For instance, increased rates of sodium reabsorption in the proximal tubule may occur in diabetic patients, since sodium reabsorption in this portion of the tubule is linked with glucose reabsorption through sodium-dependent glucose transporters (56). Insulin or aldosterone can also contribute to overstimulation of tubular epithelial sodium channels in more-distal portions of the nephron (4, 47). Increased sodium reabsorption is another way in which the pressure-natriuresis curve can be shifted to the right. Simulations showed that long-term blood pressure is sensitive to several neurohormonal stimuli, including renin secretion, aldosterone secretion, and RSNA. Increased plasma renin levels have been observed in some hypertensive patients, although suppressed renin levels have been observed in other hypertensive patients, especially African American and elderly patients (1). Renin upregulation and, subsequently, increased circulating ANG II cause constriction of the renal and systemic vasculature, increased sodium reabsorption in the proximal tubule, and increased aldosterone secretion, resulting in sodium and water retention and increased blood pressure. Elevated levels of aldosterone may also occur in hypertension (44, 53). Aldosterone primarily increases sodium reabsorption in the distal tubules and collecting duct, resulting in sodium and water retention and increased blood pressure. Overactivity of renal sympathetic nerves can shift the pressure-natriuresis curve to the right by increasing afferent tone, renin secretion, and sodium reabsorption in the proximal tubule. The role of renal sympathetic hyperactivity in the pathophysiology of hypertension in some patients is illustrated by studies showing that renal denervation substantially reduces hypertension in resistant hypertensive patients (11).

While the cause of renal sympathetic hyperactivity in some hypertensive patients is not fully understood, dysfunction of arterial baroreceptor reflex mechanisms or a hyperactive response to mental stress has been suggested (13).

Blood pressure was also shown to be mildly sensitive to nephron loss. Nephron loss occurs gradually with age and may be accelerated by diabetes (3, 38). The number of glomeruli has been found to be significantly lower in patients with primary hypertension than in normotensive controls (26). The kidney is able to compensate for nephron loss to a large degree without increasing blood pressure, as evidenced by the observation that renal transplant donors typically do not develop hypertension. This may occur through augmentation of glomerular pressure (e.g., through RAAS stimulation) or through glomerular membrane hypertrophy within the remaining glomeruli, thus maintaining the total perfusion surface area and allowing the pressure-natriuresis relationship to be maintained. However, if enough nephrons are lost, the ability to compensate may be overwhelmed, and the pressure-natriuresis curve may be shifted to the right. As shown in Fig. 2, the model indicates that a 50% decrease in the number of nephrons will result in a relatively small rise in blood pressure. However, the effect of nephron loss may also be compounded when combined with other mechanisms of hypertension discussed here.

Model Application: Effect of Underlying Pathophysiology on the Response to Different Classes of Antihypertensive Therapies

Just as different pathophysiological mechanisms can contribute to hypertension, the underlying pathophysiological mechanisms may also impact a patient’s response to therapy. The final model was used to explore the impact of underlying pathophysiological mechanisms of hypertension on the blood pressure response to different classes of antihypertensive agents.

It is generally expected that mechanisms that cause a rise in blood pressure will also result in a stronger reduction of blood pressure with treatment, simply because of the higher baseline blood pressure. For some mechanisms, this was the case, regardless of the class of therapy (e.g., for increased glomerular hydraulic conductance). However, some interesting results emerge when the response is compared among the different therapy classes for a given mechanism. While some mechanisms greatly increase the response to one class of therapy, the same mechanism may result in a weaker response to another class. For instance, increased renin secretion increases the response to RAAS blockers, does not impact the response to CCBs, and actually reduces the response to HCTZ and MR blockers. These simulations also seem to show a divide between agents that are vasodilatory (ARBs, ACEi, DRIs, and CCBs) and agents that are primarily diuretic (HCTZ and MR blockers) in terms of the types of mechanisms for which they are most effective. The vasodilatory agents are predicted to be much more effective when renal vascular resistance, proximal or collecting duct sodium reabsorption, or renin or aldosterone secretion is increased. However, increased renal sympathetic activation negatively impacts their effectiveness. This is particularly interesting, since renal sympathetic activity has been associated with resistant hypertension and lack of responsiveness to antihypertensive therapies. Diuretics, on the other hand,
are predicted to be much more effective with increased renal sympathetic activity. These simulations provide insight into why combination therapy is often needed to control blood pressure. In real patients, multiple mechanisms likely contribute to hypertension, and each of these mechanisms may impact the degree of response to each class of therapy.

**Model Limitations**

Several limitations of this model should be noted. 1) The model considers only steady-state trough levels of plasma biomarkers and blood pressure and does not attempt to account for differences in pharmacokinetics between different therapies. 2) The model assumes that the downstream effect of RAAS blockers is driven by AT1-bound ANG II and aldosterone alone and does not account for potential effects through other mechanisms, such as ANG-(1-7) or AT2-bound ANG II, since these mechanisms remain poorly understood. However, levels of ANG-(1-7) and AT2-bound ANG II are simulated as part of the RAAS pathway submodel; therefore, the model provides the possibility to test hypotheses linked to their downstream effects.

There are also inherent limitations in modeling a hypertensive population. To eliminate any potential bias due to assumptions of underlying hypertensive pathophysiology, all calibration simulations were carried out over the entire hypertensive virtual patient population, which includes virtual patients that cover a range of disease pathologies and severities. Still, some bias may persist, because our virtual population cannot mimic the true distribution of hypertensive mechanisms and also likely does not include all possible mechanisms. In addition, the model incorporates variability only for the specified hypertensive mechanisms and does not account for other natural individual variability. As our understanding of the underlying causes of hypertension improves, additional correlations, prevalences, and interindividual variability may need to be taken into account.

**Perspectives and Significance**

The model presented here is not a static and completed work but is, instead, a tool for data integration and hypothesis testing. In addition to testing hypotheses around the pathophysiological mechanisms of hypertension and their effect on therapeutic response, the model may also be used to evaluate the potential of therapies with novel mechanisms of action. For drugs with complex or incompletely understood mechanisms of action, the model can be used to test various hypotheses based on these the mechanisms of actions of therapies to see which scenarios are consistent with observed clinical responses. Furthermore, just as this model builds on previous models, it can continue to be extended and refined as additional data become available and our understanding of the pathophysiology of hypertension and the mechanisms underlying antihypertensive drugs advances. It also provides a backbone on which additional pathology can be incorporated. For example, we are currently extending this model to capture the pathophysiological changes that occur with chronic kidney disease and the effects of RAAS-dependent and -independent therapies on renal protection.

**APPENDIX**

The equations linking MAP to GFR through the renal vasculature are described in MODEL FORMULATION and RESULTS. Here, we provide the main additional equations needed to link GFR with sodium and water reabsorption in the tubules, fluid balance and extracellular volume, systemic hemodynamics, and determination of MAP. The full list of equations is available elsewhere (25).

The filtered sodium load \( (\Phi_{\text{f,lod}}) \) is determined as GFR times the plasma sodium concentration \( (C_{\text{sod}}) \)

\[
\Phi_{\text{f,lod}} = \text{GFR} * C_{\text{sod}} \quad (A1)
\]

As described by Karaaslan et al. (25), the fractional proximal sodium reabsorption rate \( (\eta_{\text{Pt-sodreab}}) \) is the nominal rate \( (n_{\text{Pt-sodreab}}) \) modulated by the effects of filtered sodium load \( (\text{GFR}) \), AT1-bound ANG II \( (\gamma_{\text{AT1-ANGII}}) \), and RSNA \( (\gamma_{\text{RSNA}}) \). \( \gamma_{\text{AT1-ANGII}} \) and \( \gamma_{\text{RSNA}} \) are empirical relationships defined by Karaaslan et al. Then the absolute proximal sodium reabsorption rate is the product of the filtered sodium load and the fractional proximal sodium reabsorption rate

\[
\eta_{\text{Pt,sodreab}} = n_{\text{Pt-sodreab}} * \gamma_{\text{AT1-ANGII}} * \gamma_{\text{RSNA}} \quad (A2)
\]

\[
\Phi_{\text{Pt,sodreab}} = \Phi_{\text{f,lod}} * \eta_{\text{Pt,sodreab}} \quad (A3)
\]

Sodium flow through the macula densa \( (\Phi_{\text{MD-sod}}) \) is the difference between the filtered sodium load and the proximal sodium reabsorption rate

\[
\Phi_{\text{MD-sod}} = \Phi_{\text{f,lod}} - \Phi_{\text{Pt,sodreab}} \quad (A4)
\]

The fractional distal sodium reabsorption rate \( (\eta_{\text{DT-sodreab}}) \) is the nominal rate \( (n_{\text{DT-sodreab}}) \) modulated by the effect of aldosterone \( (\Psi_{\text{aldo-DT}}) \), and the absolute distal sodium reabsorption rate \( (\Phi_{\text{DT-sodreab}}) \) is the product of the macula densa sodium flow rate and the fractional distal sodium reabsorption rate. The form of \( \Psi_{\text{aldo-DT}} \) has been changed from that in the model of Karaaslan et al., as described in MODEL FORMULATION

\[
\eta_{\text{DT,sodreab}} = n_{\text{DT-sodreab}} * \Psi_{\text{aldo-DT}} \quad (A5)
\]

\[
\Phi_{\text{DT,sodreab}} = \Phi_{\text{MD-sod}} * \eta_{\text{DT,sodreab}} \quad (A6)
\]

Distal tubule sodium outflow \( (\Phi_{\text{DT-sod}}) \) is the difference between the sodium flow through the macula densa and the absolute distal sodium reabsorption rate

\[
\Phi_{\text{DT-sod}} = \Phi_{\text{MD-sod}} - \Phi_{\text{DT-sodreab}} \quad (A7)
\]

The fractional collecting duct sodium reabsorption rate \( (\eta_{\text{CD-sodreab}}) \) is the nominal rate \( (n_{\text{CD-sodreab}}) \) modulated by the effect of distal tubule sodium outflow \( (\lambda_{\text{CD-sod}}) \), atrial natriuretic peptide (ANP) concentration \( (\lambda_{\text{ANP}}) \), and aldosterone \( (\lambda_{\text{aldo-CD}}) \). \( \lambda_{\text{ANP}} \) and \( \lambda_{\text{aldo-CD}} \) are empirical relationships defined by Karaaslan et al.; \( \lambda_{\text{aldo-CD}} \) is defined in MODEL FORMULATION

\[
\eta_{\text{CD,sodreab}} = n_{\text{CD-sodreab}} * \lambda_{\text{DT}} * \lambda_{\text{ANP}} * \lambda_{\text{aldo-CD}} \quad (A8)
\]

\[
\Phi_{\text{CD,sodreab}} = \Phi_{\text{DT,sod}} * \eta_{\text{CD,sodreab}} \quad (A9)
\]

The urinary sodium excretion rate \( (\Phi_{\text{u,sod}}) \) is the difference between the distal sodium outflow and the collecting duct sodium reabsorption rate

\[
\Phi_{\text{u,sod}} = \Phi_{\text{DT-sod}} - \Phi_{\text{CD-sodreab}} \quad (A10)
\]

As described by Karaaslan et al., the tubular water reabsorption rate \( (\Phi_{\text{wreab}}) \) is given by an empirical function of GFR, aldosterone concentration \( (\mu_{\text{aldo}}) \), and antidiuretic hormone (ADH) concentration \( (\mu_{\text{adh}}) \). \( \mu_{\text{aldo}} \) and \( \mu_{\text{adh}} \) are empirical relationships described by Karaaslan et al. The urinary flow rate \( (\Phi_{u}) \) is the difference between GFR and the tubular water reabsorption rate

\[
\Phi_{\text{u}} = 0.0251 - \frac{0.0011}{\mu_{\text{aldo}} * \mu_{\text{adh}}} + 0.8 * \text{GFR} \quad (A11)
\]
\[ \Phi_u = \text{GFR} - \Phi_{\text{creat}} \] (A12)

Water intake (\( \Phi_{\text{win}} \)) is an empirical function of ADH concentration. Sodium intake (\( \Phi_{\text{sod}} \)) is fixed to a constant \( R_{\text{sod}} \) (taken to be 0.126 meq/min under normal sodium intake conditions)

\[ \Phi_{\text{win}} = \frac{0.0081}{1 + 1.822(C_{\text{ADH}})^{-1.807}} - 0.00531 \] (A13)

\[ \Phi_{\text{sod}} = R_{\text{sod}} \] (A14)

The total sodium amount (\( M_{\text{sod}} \)) is determined by the time integral of the rate of sodium intake and rate of sodium excretion, with an initial condition of 2,160 meq. The extracellular fluid volume (\( V_{\text{ECF}} \)) is determined by the time integral of the rate of water intake and the urinary flow rate, with an initial condition of 15 liters. The plasma sodium concentration (\( C_{\text{sod}} \)) is then the total sodium amount divided by the extracellular fluid volume

\[ \frac{d(M_{\text{sod}})}{dt} = \Phi_{\text{sod}} - \Phi_{\text{u-sod}} \] (A15)

\[ \frac{d(V_{\text{ECF}})}{dt} = \Phi_{\text{win}} - \Phi_{\text{u}} \] (A16)

\[ C_{\text{sod}} = \frac{M_{\text{sod}}}{V_{\text{ECF}}} \] (A17)

As described by Guyton (15), blood volume (\( V_b \)) is an empirical function of \( V_{\text{ECF}} \)

\[ V_b = 4.56 + \frac{2.43}{1 + e^{-(V_{\text{ECF}}-18.1)/0.474}} \] (A18)

The mean filling pressure (\( P_{\text{mf}} \)) is an empirical relationship of blood volume, modulated by the autonomic multiplier effect (\( \epsilon_{\text{aum}} \)). Equations for \( \epsilon_{\text{aum}} \) are described in detail by Karaaslan et al. (25)

\[ P_{\text{mf}} = (7.436V_b - 30.18)\epsilon_{\text{aum}} \] (A19)

Venous return (\( \Phi_{\text{v}} \)) is then defined as the difference between \( P_{\text{mf}} \) and right atrial pressure (\( P_{\text{ra}} \)), divided by resistance to venous return (\( R_{\text{v}} \)), and cardiac output (\( CO \)) equals venous return

\[ \Phi_{\text{v}} = \frac{P_{\text{mf}} - P_{\text{ra}}}{R_{\text{v}}} \] (A20)

\[ \Phi_{\text{CO}} = \Phi_{\text{v}} \] (A21)

Right atrial pressure is an exponential function of CO

\[ P_{\text{ra}} = 0.279e^{0.228\Phi_{\text{aum}}} \] (A22)

Arterial resistance (\( R_a \)) is inversely related to vascularity (\( \text{vas} \), defined as an average measure of the number and diameter of blood vessels in the body) with a constant of proportionality \( K_{\text{bar}} \) and is modulated by autonomic activity

\[ R_a = \frac{K_{\text{bar}}}{\text{vas}\epsilon_{\text{aum}}} \] (A23)

The vascularity term is defined in detail in Karaaslan et al. Briefly, vascularity is the time integral of the vascular formation and destruction rates. The formation rate is an empirical function of CO, and the destruction rate is a constant fraction of vascularity.

Resistance to venous return (\( R_{\text{v}} \)) is an empirical function of arterial resistance and venous resistance (\( R_{\text{v}} \), assumed constant), and total peripheral resistance (\( R_{\text{tp}} \)) is the sum of arterial and venous resistance

\[ R_{\text{v}} = (8R_{\text{vs}} + R_{\text{a}})/31 \] (A24)

\[ R_{\text{tp}} = R_{\text{v}} + R_{\text{bv}} \] (A25)

MAP is then CO times total peripheral resistance

\[ \text{MAP} = \Phi_{\text{CO}} \times R_{\text{tp}} \] (A26)

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K.M.H., A.L., J.B., M.R., A.S., Y.X., S.E., S.F., H.d.L., A.G. contributed to the model building and calibration of the various components; H.S., as the author of the model against clinical datasets; R.W., J.B., M.R., R.S. were essential contributors to the hypothesis generation, background information, and data review; K.M.H., A.S., Y.X. carried out a number of different validation studies.

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