A mathematical model of long-term renal sympathetic nerve activity inhibition during an increase in sodium intake

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Karaaslan F, Denizhan Y, Hester R. A mathematical model of long-term renal sympathetic nerve activity inhibition during an increase in sodium intake. Am J Physiol Regul Integr Comp Physiol 306: R234–R247, 2014. First published November 27, 2013; doi:10.1152/ajpregu.00302.2012.—It is well known that renal nerves directly affect renal vascular resistance, tubular sodium reabsorption, and renin secretion. Inhibition of renal sympathetic nerve activity (RSNA) decreases renal vascular resistance, tubular sodium reabsorption, and renin secretion, leading to an increase in sodium excretion. Although several studies show that inhibition of RSNA promotes sodium excretion during an acute blood volume expansion, there is limited research relating to the importance of RSNA inhibition that contributes to sodium homeostasis during a long-term increase in sodium intake. Therefore, to dissect the underlying mechanisms of sodium excretion, a mathematical model of a cardiovascular system consisting of two kidneys, each with an independent RSNA, was developed. Simulations were performed to determine the responses of RSNA and sodium excretion to an increased sodium intake. In these simulations, RSNA in the left kidney was fixed at its normal steady-state value, while RSNA in the contralateral kidney was allowed to change normally in response to the increased sodium intake. The results demonstrate that the fixed-RSNA kidney excretes less sodium than the intact-RSNA collateral kidney. Because each kidney is exposed to the same arterial pressure and circulatory hormones, the impaired sodium excretion in the absence of RSNA inhibition supports the hypothesis that RSNA inhibition contributes to natriuresis in response to a long-term increase in sodium intake.

IT IS WELL ESTABLISHED that inhibition of renal sympathetic nerve activity (RSNA) is important for acute blood volume regulation (13). An increase in blood volume activates arterial and cardiac baroreceptors, giving rise to neural signals that inhibit RSNA (9, 17). Suppression of RSNA decreases renal vascular resistance (8, 34, 35), tubular sodium and water reabsorption (45, 52), and renin secretion (60). These responses promote sodium excretion during a short-term increase in blood volume (2, 14, 46, 50, 53).

Although some studies have demonstrated that inhibition of RSNA increases sodium excretion during an acute blood volume expansion, few studies have determined the contribution of the renal nerves to sodium homeostasis during chronic increases in body fluid volume. Jacob et al. (32) showed that a 10-fold increase in sodium intake over 10 days resulted in no significant difference between sodium excretion from the bilaterally denervated and bilaterally innervated kidneys. This finding suggests that suppression of RSNA does not promote sodium excretion during an increase in sodium intake. However, it is possible that several compensatory mechanisms (changes in arterial pressure and hormonal secretion) may be activated to provide sodium balance in the absence of the renal nerves. Therefore, these compensatory mechanisms may mask the RSNA effect on sodium excretion in response to a long-term increase in sodium intake (41).

To address these confounding effects, Lohmeier et al. (41) used a split-bladder preparation to permit separate 24-h urine collections from an innervated and a denervated kidney. This preparation is powerful tool for analysis of the physiological effects of the renal nerves, because both kidneys, innervated and denervated, are exposed to the same arterial pressure and circulating hormones. Thus any differences in sodium excretion must be due to differences in RSNA between the kidneys. Lohmeier et al. showed that, during 5 days of increased sodium intake, sodium excretion increased to a greater extent in the intact than the denervated kidney.

A cardiovascular model proposed by Karaaslan et al. (33) integrates components extracted from models developed by Guyton et al. (23, 25), Coleman and Hall (10), and Uttamsingh et al. (58). This model introduces additional mechanisms of RSNA that directly affect tubular sodium reabsorption and renin secretion. The aforementioned model, which includes a single kidney functionally equivalent to two kidneys, was specifically built to predict the effects of RSNA on blood volume regulation. An increased sodium intake in this one-kidney model resulted in the expected physiological responses, such as inhibition of RSNA, increase in arterial pressure, decrease in renin secretion, and increase in sodium excretion. On the basis of this one-kidney model, the effect of RSNA inhibition on sodium excretion during a long-term increase in sodium intake was examined by fixing RSNA at its normal steady-state value, allowing no response to the increase in sodium intake. Here, the assumption was that the difference in sodium excretion between intact- and fixed-RSNA conditions would demonstrate the influence of RSNA inhibition on sodium excretion. However, no difference in renal sodium excretion could be observed between the intact- and fixed-RSNA conditions. The observation of a higher arterial pressure under fixed- than intact-RSNA conditions led to the hypothesis that, in the one-kidney model, the higher arterial pressure under the fixed-RSNA condition masked the influence of RSNA inhibition on sodium excretion. Therefore, no conclusion could be drawn as to whether RSNA inhibition has an effect on sodium excretion during a long-term increase in sodium intake.

To understand the effect of RSNA inhibition on sodium excretion during a long-term increase in sodium intake, our previous model was changed by splitting the single kidney into...
two kidneys. Additionally, to develop a more inclusive model, three new mechanisms were introduced: nitric oxide (NO) (27, 35, 47, 51), the myogenic response (10, 18, 21), and the effect of angiotensin II on afferent arteriolar resistance (12). Thus the work presented here is a more detailed cardiovascular model with two kidneys.

The principal contribution of this new model is that it demonstrates simultaneous sodium excretion from intact- and fixed-RSNA kidneys during chronic changes in sodium intake. Thus this new model allows testing of the hypothesis that RSNA inhibition contributes to natriuresis in response to a long-term increase in sodium intake.

SIMULATION RESULTS AND DISCUSSION

The approach used in this model resembles the approaches of Guyton et al. (23, 25), Coleman and Hall (10), and Uttamsingh et al. (58). Experimental findings collected from medical literature are combined with functions borrowed from the models of Guyton, Coleman, and Uttamsingh and their colleagues to build a fully integrative closed-loop model (feedback mechanisms shown in Figs. A1 and A2). The block diagrams of the model (see Figs. A1 and A2), which show the qualitative relationships between variables, can be helpful for understanding the simulation results.

The computer model is designed to simulate human responses; thus, during development of the model, human data have been used whenever possible. However, because some variables cannot be measured in humans, mammalian data from the literature have been used after they were scaled, such that they are consistent with estimated human values.

To validate our model, we first compared it with the experimental study of He et al. (29). We chose the study of He et al. as a basis of comparison for our model for two reasons. 1) Our aim was to determine the effect of RSNA inhibition on sodium excretion during an increase in sodium intake. However, during sodium loading, to provide sodium balance, several mechanisms (e.g., blood pressure and hormones) were activated. So it was necessary to check whether the model had proper mechanisms to provide sodium balance during long-term sodium loading. 2) The experimental study of He et al. considered a 5-day increase and a subsequent 5-day decrease in sodium intake (i.e., perturbations in opposite directions). If the model has good compensatory mechanisms for sodium intake changes, it must give responses that are in accordance with this experimental study. So, before proceeding to analysis of the RSNA inhibition effect on sodium excretion, the model was tested using the experimental study of He et al.

Varying sodium intake in healthy subjects. He et al. (29) conducted an experiment in which sodium intake was raised from a normal to a high level (208% of normal), at which it was maintained for 5 days before it was dropped to a low level (13% of normal), at which it was maintained for 5 days. He et al. reported the expected decreases in plasma renin and aldosterone concentrations and a small increase in plasma sodium concentration during increased sodium intake. During the subsequent 5 days of sodium intake reduction, they found an increase in plasma renin and aldosterone concentrations and a small decrease in plasma sodium concentration.

In the present study, sodium intake was changed in accordance with the experimental study of He et al. (29) (Fig. 1A). Plasma renin activity (Fig. 1B) and plasma aldosterone concentration (Fig. 1C) decreased and plasma sodium concentration increased slightly (Fig. 1D) during the 5 days of increased sodium intake. After the 5 days of increased sodium intake, when sodium intake was decreased for another 5 days, plasma renin activity and aldosterone concentration increased and
plasma sodium concentration decreased slightly, consistent with the experimental data (29). These results demonstrate that the model presented here yields results similar to those of He et al.

He et al. (29) did not measure glomerular filtration rate (GFR); they measured serum creatinine levels on day 5 of sodium loading and then sodium restriction. To estimate GFR changes in real data, we used an equation that estimates GFR from serum creatinine level (40). In the experimental study, GFR estimated from the serum creatinine value was ~3% above the control value on day 5 of sodium loading and ~2% below the control value on day 5 of sodium restriction. Correspondingly, GFR in the model increased by ~2% and decreased by ~5%. So the difference in GFR between the model and the experimental study is <3%.

Renal sympathoinhibition during long-term increase in sodium intake. Lohmeier et al. (41) evaluated the contribution of the renal nerves to sodium homeostasis during an eightfold increase in sodium intake for 5 days following unilateral renal denervation and surgical division of the urinary bladder to allow separate 24-h urine collection from the denervated and innervated kidneys. They demonstrated a greater, sustained increase in sodium excretion from the innervated than the denervated kidney.

To test the hypothesis that RSNA inhibition contributes to natriuresis as a response to a long-term increase in sodium intake, RSNA of the left kidney was fixed at its normal steady-state value, while the collateral kidney could respond normally to sodium intake. The goal was to determine the effect of RSNA inhibition on sodium excretion during sodium loading, rather than the effect of renal denervation [as in the experiment of Lohmeier et al. (41)]. Renal denervation and fixing of RSNA at its normal value exhibit functional similarity, in that RSNA cannot respond to an increase in sodium intake in either case (31, 33). Because of this similarity, the simulation results were compared with the experimental results reported by Lohmeier et al.

Sodium intake. In the simulation, sodium intake was increased eightfold for 5 days and then returned to control levels similar to the experiment of Lohmeier et al. (41) (Fig. 2A).

Mean arterial pressure. When sodium intake is increased, a slight increase in mean arterial pressure is observed, similar to the finding of Lohmeier et al. (41) (Fig. 2B). In the simulation, during an eightfold increase in sodium intake for 5 days, the pressure natriuresis mechanism helps maintain sodium balance. The increase in sodium intake leads to an increase in blood volume and mean arterial pressure. Elevation of mean arterial pressure causes an increase sequentially in renal arterial pressure, afferent arteriolar pressure, and glomerular hydrostatic pressure and, hence, an increase in net filtration pressure. Therefore, GFR increases. GFR is incompletely autoregulated. This increase in GFR contributes in part to the increase in sodium excretion and, therefore, helps provide sodium balance.

Renal sympathetic nerve activity. To determine the effect of RSNA inhibition on sodium excretion during a chronic increase in sodium intake, as discussed above, RSNA of the left kidney was fixed at its normal steady-state value, preventing any change in RSNA, while RSNA of the right kidney was allowed to change in response to the increase in sodium intake. Because RSNA of the left kidney was fixed at its normal value, it could not respond to an increase in sodium intake (Fig. 2C). Consequently, any difference in sodium excretion between the intact-RSNA right kidney and the fixed-RSNA left kidney can be attributed to the effect of RSNA on sodium excretion. In the simulation, a sustained RSNA inhibition is seen during the chronic increase in sodium intake, leading to an increase in blood pressure. This result is in accordance with an experimental study by Barrett et al. (3), who observed a sustained RSNA inhibition in response to increased blood pressure.

Afferent arteriolar resistance. In this model, RSNA directly affects afferent arteriolar resistance (described in Block 2 in the APPENDIX and in more detail in Ref. 33), inducing a change in the same direction (i.e., increasing RSNA causing increased afferent arteriolar resistance and decreasing RSNA causing decreased afferent arteriolar resistance). In the simulation, short- and long-term increases in afferent arteriolar resistance in both kidneys are observed during increased sodium intake (Fig. 2D). Several studies have demonstrated that an increase in arterial pressure initiates tubuloglomerular feedback and the myogenic response, causing afferent arteriolar constriction (leading to an increase in afferent arteriolar resistance) to prevent an increase in GFR above the physiological range (18, 24, 48, 59). Thus these studies support the simulation results related to afferent arteriolar resistance over the short term. The model also predicts a higher afferent arteriolar resistance in the fixed- than intact-RSNA kidney over the long term. It is well known that RSNA stimulation increases afferent arteriolar resistance (38, 49). It is expected that a decrease in RSNA leads to vasodilation, resulting in a decrease in afferent arteriolar resistance. In the simulation, increased sodium intake causes an increase in blood pressure (Fig. 2B). During a long-term increase in sodium intake, this increase in blood pressure leads to a sustained decrease in RSNA, because RSNA does not reset over a long period of increased blood pressure (Fig. 2C). RSNA of the left kidney is fixed at its normal steady-state value; therefore, it cannot respond to the increase in sodium intake in the same way as the intact kidney. Hence, RSNA of the left kidney does not have a decreasing influence on the afferent arteriolar resistance, while a decrease in the intact kidney’s RSNA has a decreasing effect on afferent arteriolar resistance. Consequently, afferent arteriolar resistance is less in the intact-than fixed-RSNA kidney (Fig. 2D).

Myogenic response. It is known that an increase in pressure in the afferent arteriole causes a myogenic response. Renal arterial pressure is the same in both kidneys, while glomerular hydrostatic pressure (Fig. 2E) is higher in the intact-
fixed-RSNA kidney. This, in turn, is due to lower afferent arteriolar resistance in the intact- than fixed-RSNA kidney (Fig. 2D). Calculation of afferent arteriolar pressure using Eq. A12 \([\text{renal arterial pressure} + \text{glomerular hydrostatic pressure}/2]\) shows higher afferent arteriolar pressure in an intact- than a fixed-RSNA kidney (Fig. 2F). Therefore, the myogenic response is greater in the intact- than fixed-RSNA kidney (Fig. 2G).

**Efferent arteriolar resistance.** In the model, efferent arteriolar resistance is controlled by angiotensin II (28). An increase in plasma angiotensin II concentration increases efferent arteriolar resistance, and a decrease in plasma angiotensin concentration decreases efferent arteriolar resistance. It should be noted that efferent arteriolar resistances of intact- and fixed-RSNA kidneys decreases identically, because plasma angiotensin II concentration decreases during an increase in sodium intake, affecting efferent arteriolar resistance in both kidneys in the same manner (Fig. 2H).

**Renal vascular resistance.** Renal vascular resistance was modeled as the sum of afferent arteriolar resistance and efferent arteriolar resistance (see APPENDIX, Block 2). In the simulation, an increase in sodium intake decreases the intact kidney’s RSNA as well as plasma angiotensin II concentration. The change in angiotensin II concentration affects efferent arteriolar resistance in both kidneys in an identical manner. As previously mentioned, afferent arteriolar resistance is lower in the intact- than fixed-RSNA kidney during an increase in sodium intake. Since renal vascular resistance is calculated as the sum of afferent and efferent arteriolar resistance and the efferent arteriolar resistances of both kidneys decrease identically in response to the decrease in angiotensin II, the resulting renal vascular resistance is lower in the intact- than fixed-RSNA kidney (Fig. 2I). Leonard et al. (39) demonstrated that a short-term increase in blood volume causes no increase in blood flow in the denervated kidney, while it does lead to an increase in blood flow in the intact kidney. Thus it could be postulated that renal vascular resistance is higher in the denervated than intact kidney during a short-term volume increase. Therefore, it can be accepted that the study of Leonard et al. supports our simulation results regarding the renal vascular resistance of intact- and fixed-RSNA kidneys over the short term.

**Renal blood flow.** Although indirect measurements suggest that RSNA has some effect on renal blood flow in humans, such an effect is controversial in dogs (43). In dogs, RSNA is generally known to have no effect on renal blood flow, but the reverse has also been demonstrated (42). When the blood pressure changes were prevented and the left atrium was simultaneously stimulated, renal blood flow increased in the innervated kidney, but there was no change in renal blood flow in the denervated kidney (42).

In the simulation, blood flow is higher in the intact- than fixed-RSNA kidney, because renal vascular resistance is lower in the intact kidney (Fig. 2F). Leonard et al. (39) published data about the blood flow of bilaterally innervated and bilaterally denervated kidneys during an acute increase in blood volume. An acute increase in blood volume causes an increase in blood flow in innervated, but not denervated, kidneys (39). The experimental study of Leonard et al. supports this short-term simulation result. The model also shows greater blood flow in the intact- than fixed-RSNA kidney over the long term (Fig. 2J).

**Nitric oxide.** As expected, simulation results show greater NO release from the afferent arteriole in the intact- than fixed-RSNA kidney. This is a result of higher blood flow in the intact- than fixed-RSNA kidney (Fig. 2K). The derivation of equations about NO release and its effect on afferent arteriolar resistance is given in Block 4 in the APPENDIX.

**Glomerular filtration rate.** In the study of Lohmeier et al. (41), there were no differences in GFR between the denervated and intact kidneys in response to the increase in sodium intake. However, in the simulations, GFR increased in the intact-RSNA kidney, while it decreased slightly, \(-5\%\), in the fixed-RSNA kidney (Fig. 2L). In the fixed-RSNA kidney, the afferent arteriolar resistance is elevated (Fig. 2D), leading to a decrease in calculated glomerular hydrostatic pressure and, thus, a small decrease in GFR.

**Filtered sodium.** Because GFR is higher in the intact- than fixed-RSNA kidney, in the simulation the filtered sodium is higher in the intact- than fixed-RSNA kidney (Fig. 2M).

**Fractional proximal sodium reabsorption.** In the model, RSNA directly affects sodium reabsorption from the proximal tubule in the same direction; i.e., an increase or a decrease in RSNA leads to an elevation or a drop in fractional proximal sodium reabsorption, respectively. The equation expressing the relationship between RSNA and proximal sodium reabsorption is presented in Block 9 and Fig. A2 in the APPENDIX (for details of the equation and related assumptions see Ref. 33). In this simulation, the intact-RSNA exhibits sustained inhibition in response to a long-term increase in sodium intake (Fig. 2C). A decrease in RSNA leads to a decrease in the intact kidney’s fractional proximal sodium reabsorption during a long-term increase in sodium intake. Fractional proximal sodium reabsorption is less in the intact- than fixed-RSNA kidney, because there is no RSNA inhibitory effect on the fractional proximal sodium reabsorption in the fixed-RSNA kidney (Fig. 2N).

**Absolute proximal sodium reabsorption.** While fractional proximal sodium reabsorption is lower in the intact- than fixed-RSNA kidney, absolute proximal sodium reabsorption is higher (Fig. 2O). The reason for this is the higher filtered sodium in the intact kidney.

**Macula densa sodium flow.** Because macula densa sodium flow was modeled as the difference between filtered sodium load and absolute proximal sodium reabsorption [sodium reabsorption from the loop of Henle was lumped into proximal reabsorption, similar to the model of Coleman and Hall (10)], macula densa sodium flow is higher in the intact- than fixed-RSNA kidney (Fig. 2P).

**Renin secretion.** A brief description of the effect of RSNA and macula densa sodium flow on renin secretion in the model is given in Block 36 and Fig. A2 in the APPENDIX. RSNA directly affects renin secretion from the kidney (juxtaglomerular complex) as follows: an increase in RSNA raises renin secretion, while a decrease in RSNA leads to inhibition of renin secretion. On the other hand, macula densa sodium flow also directly affects renin secretion from juxtaglomerular cells, but in an inverse manner: when macula densa sodium flow decreases, renin secretion increases, and vice versa (for detailed derivation of these equations see Ref. 33).

In the model, an increase in arterial pressure (Fig. 2B) caused by a long-term increase in sodium intake leads to a decrease in the intact kidney’s RSNA (Fig. 2C). RSNA has been found to exhibit sustained inhibition, because it does not
have an adaptation mechanism (no resetting), and experimental studies show that a decrease in RSNA inhibits renin secretion (60). Therefore, in this model, renin secretion from the intact-RSNA kidney is expected to be less than that from the fixed-RSNA kidney during increased sodium intake, because reduction of the intact kidney’s RSNA has an inhibitory effect on its renin secretion. In addition, it is known that an increase in macula densa sodium flow decreases renin secretion (27). In the current two-kidney model, macula densa sodium flow (Fig. 2P) during increased sodium intake is higher in the intact- than fixed-RSNA kidney. Thus less renin secretion is expected as a result of macula densa sodium flow from the intact- than fixed-RSNA kidney. As a combination of these two effects (higher macula densa sodium flow and RSNA inhibition), the model demonstrates less renin secretion during a long-term increase in sodium intake from the intact- than fixed-RSNA kidney (Fig. 2R).

**Tubuloglomerular feedback signal.** In the employed model, the tubuloglomerular feedback signal was modeled as a function of macula densa sodium flow. When macula densa sodium flow increases, the tubuloglomerular feedback signal increases. In contrast, a decrease in macula densa sodium flow leads to a decrease in the tubuloglomerular feedback signal. This relationship between macula densa sodium flow and the tubuloglomerular feedback signal is described in an equation in Block 7 in the *Appendix* and in Fig. A2 (for more detailed information about building this equation see Ref. 33). Because macula densa sodium flow is higher in the intact- than fixed-RSNA kidney during the chronic increase in sodium intake in this simulation, the tubuloglomerular feedback signal is higher in the intact- than fixed-RSNA kidney (Fig. 2S).

**Sodium excretion.** More sodium was excreted from the intact- than fixed-RSNA kidney; results are qualitatively similar to those of Lohmeier et al. (41) (Fig. 2T). Lohmeier et al. did not find a difference between the GFRs of the intact and denervated kidneys during an increase in sodium intake; therefore, they explained the difference in sodium excretion between the intact and denervated kidneys on the basis of differences in tubular sodium reabsorption. However, a difference between GFRs of the fixed- and intact-RSNA kidneys is observed in the simulations. In the model, GFR is higher in the intact- than fixed-RSNA kidney. Simultaneously, during the increase in sodium intake, a higher fraction of the sodium was reabsorbed by the fixed- than intact-RSNA kidney (Fig. 2U). Consequently, the model demonstrates that GFR is higher in the intact- than fixed-RSNA kidney, resulting in more filtered sodium and less fractional tubular sodium reabsorption. These differences (higher GFR and less tubular sodium reabsorption) lead to a higher sodium excretion from the intact kidney during increased sodium intake in this simulation (Fig. 2T).

**Sodium balance.** In the simulation, total sodium excretion (Fig. 2V), the sum of the intact- and fixed-RSNA kidney sodium excretion, reaches the level of sodium intake after 1 day. Therefore, the sodium balance (Fig. 2Y) is similar to that observed by Lohmeier et al. (41).

**Mean arterial pressure and total urinary sodium excretion.** Finally, in this simulation, when sodium intake is returned to a normal value, mean arterial pressure and urinary sodium excretion return to normal values, similar to the study of Lohmeier et al. (41).

Although the experimental findings reported by McBryde et al. (44) lead to the conclusion that RSNA is not inhibited during a long-term increase in sodium intake, the model employed in this study shows that RSNA is inhibited during an eightfold chronic increase in sodium intake. However, McBryde et al. recorded RSNA for 15 min at 120-min intervals for 6 days under a fivefold increase in sodium intake, and they noted that RSNA inhibition may have been missed because of lack of continuous RSNA recording over the 6 days. The presented model predicts RSNA inhibition of only ~10% during an eightfold increase in sodium intake. McBryde et al. increased sodium intake to five times the normal value, so on the basis of the present model, we would predict a <10% RSNA inhibition in their study. Consequently, it is not possible to determine whether their experimental results are contrary to the simulation results.

As discussed previously, to clarify the effect of RSNA inhibition on sodium excretion during sodium loading, Lohmeier et al. (41) cut the renal nerve to eliminate its inhibition effect on sodium excretion. On the other hand, in the simulations, to investigate the RSNA inhibition effect, RSNA was fixed at its normal steady-state value in the model. This created a condition functionally similar to that in the experiment of Lohmeier et al., in that RSNA cannot respond to sodium loading. When Lohmeier et al. increased sodium intake, it was determined that sodium excretion from the denervated and intact kidney increased, but sodium excretion from the innervated kidney was greater than that from the denervated kidney. In this model, when sodium intake was increased in a similar way to the experiment of Lohmeier et al., sodium excretion from both kidneys increased, but sodium excretion was greater from the intact- than fixed-RSNA kidney, which is a behavioral similarity. In the experiment of Lohmeier et al., the denervated kidney excreted 20% less sodium than the intact kidney, whereas in this simulation, the difference is ~60%. This quantitative difference is probable, in that the renal nerve was fixed at its normal value in this simulation during sodium loading, but Lohmeier et al. cut the renal nerve. It is expected that renal denervation activated some unmodeled mechanisms that affect sodium excretion (56, 57).

A limitation in the employed model is that RSNA affects sodium reabsorption only from the proximal tubule, although it is known that it actually affects sodium reabsorption from all tubular segments. This simplification has been made taking into consideration the experimental studies (4, 5, 13, 15), which show that RSNA primarily influences sodium reabsorption from the proximal tubule.

Another restriction of this model is related to a general challenge in mathematical modeling: mathematical modeling requires that we specify the phenomenon of interest and concentrate on the dynamics at the time scale of this phenomenon. In addition, biological systems are time-varying systems (where system parameters change with time), and the effects of time on these system parameter changes are even more pronounced under pathological conditions. Because an attempt was made to simulate physiological situations, it was assumed that system parameters did not change within 10 days. In time-variant systems, when the same input is applied to the system at different times, the output of the system changes with time. However, in time-invariant systems, when the same input is applied, the output of the system will stay the same (30). Assume that sodium intake is increased (independent of the
experiment of Lohmeier et al.) for 5 days and then returned to its normal value for 5 days. Then assume that this exact process occurs a second time. The model will give the same result for both periods of sodium increase, because the model is assumed to be a time-invariant system. Therefore, in the first and second periods of sodium loading, the kidney response stayed the same. In reality, the human body is a time-variant system. Therefore, it is expected that the kidney response to sodium loading in the second period will be slightly different from that in the first period. This difference would be attributed to adaptation and aging in the human body. It is probable that any difference would be negligible over such a short period. Consequently, the performance of our model will deteriorate when experiments induce large changes that are comparable to pathological conditions. This limitation of the model should be kept in mind, particularly when extreme experiments are carried out over a longer period. Future improvements in the model can address this issue.

It is known from experimental studies that renin secretion is sensitive to decreases in renal arterial pressure (19, 55). Because the direct pressure effect on renin secretion is not included in the model, the model has the limitation of renin secretion during decreasing renal arterial pressure. However, the lack of the direct pressure effect on renin secretion in the model does not mean that the model completely ignores the effects of changes in renal arterial pressure on renin secretion. Changes in renal arterial pressure in the model affect renin secretion indirectly by changing macula densa sodium flow. Additionally, it is not clear in published studies (19, 55) whether renin release was controlled by the direct baroreceptor effect or the macula densa effect or both. There was no discrimination between these two mechanisms in these studies (19, 55). Because only renal arterial pressure was decreased in these studies, renin release was probably controlled by the direct baroreceptor effect and the macula densa effect.

Another limitation of the model is that it combines sodium reabsorption from the loop of Henle with reabsorption from the proximal tubule. It is clear that this assumption prevents us from analyzing the dynamics in the proximal tubule and the loop of Henle separately. After sodium is filtered, it enters the proximal tubule and loop of Henle, where it is reabsorbed; from there, it flows through the macula densa region. The macula densa senses sodium flow/concentration, and its main function is control of GFR and renin secretion according to this sodium flow/concentration. Because GFR and renin secretion in the model are close to the real values (29), lumping sodium reabsorption from the Loop of Henle into proximal tubule sodium reabsorption [as in the model of Coleman and Hall (10)] seems not to affect the GFR and renin secretion results in our simulations.

Although the simulation results obtained from the employed model exhibit quantitative differences from the results reported by Lohmeier et al. (41) related to urinary sodium excretion from the intact- and fixed-RSNA kidneys, they are qualitatively similar.

Conclusion. The acute effects of RSNA on kidney function are well described in the medical literature; however, the chronic effects of RSNA on kidney function remain relatively unknown because of the technical difficulties involved in continuous chronic recording of renal nerve activity. Therefore, it is clear that long-term mathematical models of the cardiovascular system can be used to understand the influences of RSNA on renal functions by predicting the responses of those variables that are difficult to measure experimentally.

Karaaslan et al. (33) attempted to predict the effect of RSNA inhibition on sodium excretion by creating a cardiovascular model, including a single kidney functionally equivalent to two kidneys. Since simulations based on this model did not exhibit a difference in sodium excretion between intact- and fixed-RSNA kidneys during a chronic increase in sodium intake, no conclusion could be reached as to whether RSNA inhibition has an effect on sodium excretion.

In the present study, the mathematical model of Karaaslan et al. (33) has been expanded. One of the major modifications is the use of two separate kidneys. This new model has been used to test the hypothesis that RSNA inhibition helps sodium excretion during a chronic increase in sodium intake. RSNA of the left kidney was fixed at its normal steady-state value, while RSNA of the collateral kidney was allowed to respond normally to an increase in sodium intake. It has been observed that the fixed-RSNA kidney excretes less sodium than the intact kidney. In the employed model, each kidney is exposed to the same arterial pressure and hormones during the increase in sodium intake; as a result, any difference in sodium excretion between the kidneys is due to the renal nerves. Thus the reason for less sodium excretion in the fixed- than intact-RSNA kidney is the absence of RSNA inhibition in the fixed-RSNA kidney. It can be concluded that this simulation result supports the hypothesis that RSNA inhibition contributes to natriuresis in response to a long-term increase in sodium intake. The employed mathematical model represents the first long-term model of the cardiovascular system, giving a detailed illustration of the effect of RSNA inhibition on kidney function during an increase in sodium intake.

Perspectives and significance. This study provides information about how inhibition of renal nerve activity contributes to natriuresis during a long-term increase in sodium intake. Several clinical studies have demonstrated that renal denervation reduces blood pressure in hypertensive patients (1, 16, 37). Some mechanisms related to renal denervation are known (56, 57); however, it is possible that several unknown mechanisms are also activated during and after renal denervation. The employed model can be improved by addition of the mechanisms that affect the simulation results of renal denervation. When these mechanisms are introduced into the model, the model may be used to analyze the effect of renal denervation on blood pressure in hypertensive patients.

APPENDIX

The cardiovascular model with two kidneys is an extension of our previous model (33) with a single equivalent nephron. In the present model, the basic assumptions of the previous model, except the single equivalent nephron, are maintained. Figure A1 shows the block diagram of the long-term, two-kidney cardiovascular model, while Fig. A2 gives the details of the related renal dynamics.

In this model, hormone concentration dynamics are modeled in the same way as in our previous model, which was adapted from the model of Guyton et al. (23). This model is based on the observations that 1) at steady state a hormone is destroyed at the same rate at which it is secreted, 2) at steady state the concentration of a hormone is proportional to its secretion rate (therefore, when the normalized steady-state secretion rate and the normalized steady-state hormone concentration are equal, both are unity), and 3) hormone concentration
exponentially converges to its steady-state value with a certain delay. As a consequence, the normalized hormone concentration (\(C_H\)) can be modeled as tracking the normalized secretion rate (\(S_H\)) with a delay of \(T\), as shown by a first-order differential equation (Eq. A1). If \(S_H\) is doubled, \(C_H\) will be also doubled with the given delay. Instead of the differential equation, the relation is shown in the integral form in the model in Eq. A2 [initial condition (IC)].

\[
\frac{dC_H}{dt} = \frac{1}{T} (S_H - C_H) \tag{A1}
\]

\[
C_H = IC + \frac{1}{T} \int_0^t (S_H - C_H) \, dt \tag{A2}
\]

The blocks shown in Figs. A1 and A2 are briefly explained below (for further detail see Ref. 33).

In the equations, units are not shown for the sake of brevity, and each variable is expressed in accordance with the respective unit (see Table S1 in Supplemental Material for this article available online at the Journal website).

**Block 1.** Because Barrett et al. (3) showed that a chronic increase in blood pressure results in a sustained decrease in RSNA, it was assumed that the RSNA response had no adaptation characteristic. Therefore, RSNA is represented as the product of the normalized RSNA (\(N_{rsna}\)), the effect of mean arterial pressure (\(P_{ma}\)) on RSNA (\(\alpha_{map}\)), and the effect of right atrial pressure (\(P_{ra}\)) on RSNA (\(\alpha_{rap}\)).

\[
\text{RSNA} = N_{rsna} \times \alpha_{map} \times \alpha_{rap} \quad N_{rsna} = 1 \tag{A3}
\]

\[
\alpha_{map} = 0.5 + \frac{1.05}{1 + e^{P_{ma} - 100/15}} \tag{A4}
\]

\[
\alpha_{rap} = 1 - 0.08 \times P_{ra} \tag{A5}
\]

**Block 2.** Renal vascular resistance (\(R_r\)) per kidney is calculated as the sum of the afferent arteriolar resistance (\(R_{aa}\)) and the efferent arteriolar resistance (\(R_{ae}\)) per kidney. \(R_{aa}\) is modeled as the product of its normal steady-state value (\(R_{aa-ss}\)), the effect of RSNA on \(R_{aa}\) (\(\beta_{rsna}\)), the effect of the tubuloglomerular feedback signal on \(R_{aa}\) (\(\zeta_{gtf}\)), the effect of angiotensin II on \(R_{aa}\) (\(\zeta_{ata}\)), the effect of NO on \(R_{aa}\) (\(\zeta_{no}\)), and the effect of the myogenic response on \(R_{aa}\) (\(\zeta_{maa}\)). \(\beta_{rsna}\) can be represented as a function of RSNA given in Eq. A8. \(R_{ae}\) is modeled as the product of its normal steady-state value (\(R_{ae-ss}\)) and the effect of the angiotensin II concentration (\(C_{ata}\)) on \(R_{ae}\) (\(\zeta_{ata}\)). \(\zeta_{ata}\) and \(\zeta_{ata}\) are expressed as a function of \(C_{at}\) (see Eqs. A10 and A11).

\[
R_r = R_{aa} + R_{ae} \tag{A6}
\]

\[
R_{aa} = R_{aa-ss} \times \beta_{rsna} \times \sum_{tgf} \times \zeta_{gtf} \times M_{maa} \times \Omega_{NO} \tag{A7}
\]

\[
R_{aa-ss} = 63.34 \, \text{mmHg} \cdot \text{min}^{-1} \tag{A8}
\]

\[
\beta_{rsna} = 1.5 \times (RSNA - 1) + 1 \tag{A9}
\]

\[
\zeta_{ata} = 0.9432 + \frac{0.2069 + e^{3.108 - 1.785 \times \log_{10} C_{at}}}{0.1363} \tag{A10}
\]

\[
\zeta_{ata} = 0.9854 + \frac{0.03658}{0.2215 + e^{3.115 - 1.7864 \times \log_{10} C_{at}}} \tag{A11}
\]

**Block 3.** It is known that an increase in transmural pressure (difference between internal pressure and external pressure) in the afferent arteriole causes a myogenic response, a constriction of the
smooth muscle to reduce the diameter of the afferent arteriole (18, 21). With the assumption that external pressure is constant at its normal value, \( M_{\text{ace}} \) was modeled (Eq. 15) as a function of the change in afferent arteriolar pressure (\( P_{\text{aa}} \)) with some modification to the model of Coleman and Hall (10). Average afferent arteriolar pressure (\( P_{\text{aa}} \)) is approximated as \( \frac{\text{renal arterial pressure} (P_{\text{re}}) + \text{glomerular hydrostatic pressure} (P_{\text{gh}})}{2} \) in the model, as shown in Eq. A12. The calculation for adapted \( P_{\text{aa}} \) is shown in Eq. A13. \( P_{\text{ace}} \) is calculated as a function of SNO, as shown in Eq. A14. To our knowledge, the maximum duration of a myogenic response is not known. A review by Cowley (11) did not present data on the maximum duration of the myogenic response. We simply assumed that the afferent arteriolar myogenic response adapts over the long term with an adaptation time constant of 240 min.

Because the largest proportion of renal vascular resistance comprises afferent and efferent arteriolar vessels (27), kidney vasculature in the employed model is composed of afferent and efferent arterioles. For the sake of simplicity, the interlobar, arcuate, and interlobular arteries were lumped together into the afferent arteriole in the model. Thus \( P_{\text{aa}} \) is approximated as half of the summation of \( P_{\text{re}} \) and \( P_{\text{gh}} \).

\[
M_{\text{ace}} = 2.094 - \frac{8.355}{5.734 + e^{-\frac{P_{\text{re}} + 15.87}{24.66}}} \quad (A15)
\]

\textbf{Block 4.} It is known that an increase in blood flow leads to an increase in shear stress between the surface of the endothelial cells and blood flow. This stress causes an increase in NO synthesis in the endothelial cells of the vessel. After NO is produced, it diffuses out of the endothelial cells and enters the vascular smooth muscle cells, causing them to relax (27). The blood vessel relaxes, and its diameter increases. Therefore, the blood vessel’s resistance decreases. Renal blood flow (\( \Phi_{\text{rh}} \)) was modeled as a summation of afferent and efferent arteriolar blood flow. Because experimental studies show that the efferent arteriole is not sensitive to NO synthesis inhibition but \( R_{\text{aa}} \) is sensitive (47), it was assumed that NO is synthesized in the endothelial cells of the afferent arteriole. NO release from the afferent arteriole (\( S_{\text{NO}} \)) was modeled as a function of \( \Phi_{\text{rh}} \), as shown in Eq. A16. As \( \Phi_{\text{rh}} \) increases, \( S_{\text{NO}} \) increases (35, 51). \( \Omega_{\text{NO}} \) is calculated as a function of \( S_{\text{NO}} \), as shown in Eq. A17. This released NO decreases \( R_{\text{aa}} \) (47).

\[
\Omega_{\text{NO}} = -0.3 \times S_{\text{NO}} + 1.3 \quad (A17)
\]

\[
S_{\text{NO}} = 1.228 - \frac{0.04802}{0.1079 + e^{-\frac{\Phi_{\text{rh}}-0.8661}{0.115}}} \quad (A16)
\]

Fig. A2. Detailed block diagram of renal mechanisms per kidney. Blocks show how output variables depend on input variables. Continuous and dotted arrows represent stimulatory and inhibitory effects, respectively.

\[
P_{\text{aa}} = \frac{P_{\text{re}} + P_{\text{gh}}}{2} \quad (A12)
\]

\[
P_{\text{aa}}(t) = \frac{1}{240} \int (P_{\text{aa}} - P_{\text{aad}}) \, dt \quad (A13)
\]

\[
P_{\text{ace}} = P_{\text{aa}} - P_{\text{aad}} \quad (A14)
\]
Block 6. GFR per kidney ($\Phi_{\text{gfn}}$) is represented as the product of the net filtration pressure ($P_f$) and the glomerular capillary filtration coefficient ($K_{\text{gcf}}$) per kidney. $P_f$ is the difference between $P_{\text{gh}}$ per kidney and the sum of Bowman hydrostatic pressure ($P_B$) and glomerular osmotic pressure ($P_{\text{os}}$) per kidney, $P_{\text{gh}}$ is calculated as the difference between $P_{\text{ma}}$ and the mean $P_{\text{aa}}$ per kidney. The latter is calculated as the product of $\Phi_{\text{fb}}$ and $R_{\text{ma}}$. $P_B$ and $P_{\text{os}}$ have been assumed to remain constant at their normal steady-state values.

$$\Phi_{\text{gfn}} = P_{\text{gh}} \times K_{\text{gcf}} \quad (A19)$$

$$P_f = P_{\text{gh}} - (P_B + P_{\text{os}}) \quad (A20)$$

$$P_{\text{gh}} = P_{\text{ma}} - (\Phi_{\text{fb}} \times R_{\text{ma}}) \quad (A21)$$

Block 7. It is known that the tubuloglomerular feedback signal is mainly activated by changes in sodium chloride concentration at the macula densa (54). There is a positive correlation between loop of Henle NaCl concentration and macula densa chloride concentration in isolated nephron studies (54). It was assumed that changes in sodium concentration at the macula densa region are also positively related to loop of Henle perfusion rate. Because of this positive correlation and because of the complicated nature of calculating sodium concentration at the macula densa region, for the sake of simplicity, the tubuloglomerular feedback signal was modeled as a function of macula densa sodium flow ($\Phi_{\text{md-sod}}$), as in the model of Coleman and Hall (10) and shown in Eq. A22.

$$\sum_{\text{tgf}} = 0.3412 + \frac{0.06296}{0.07079 + e^{2.045 \times \Phi_{\text{md-sod}}}} \quad (A22)$$

Block 8. Filtered sodium load per kidney ($\Phi_{\text{fil-sod}}$), which represents the amount of sodium filtered from the glomerulus to the proximal tubule per unit time, can be expressed as the product of $\Phi_{\text{gfil}}$ and sodium concentration ($C_{\text{sod}}$).

$$\Phi_{\text{fil-sod}} = \Phi_{\text{gfil}} \times C_{\text{sod}} \quad (A23)$$

Block 9. Absolute proximal sodium reabsorption rate per kidney ($\Phi_{\text{pt-sodreab}}$) is modeled as the product of $\Phi_{\text{fil-sod}}$ and the fractional proximal sodium reabsorption ($\eta_{\text{pt-sodreab}}$), which is represented as the product of its own normal value ($\eta_{\text{np}}$) and the effects of the filtered sodium load ($\gamma_{\text{fil-sod}}$), RSNA ($\gamma_{\text{rsna}}$), and the angiotensin II hormone ($\gamma_{\text{aum}}$). The effect of the filtered sodium load on the fractional proximal sodium reabsorption ($\gamma_{\text{fil-sod}}$) is modeled as a function of $\Phi_{\text{fil-sod}}$ given in Eq. A26. Similarly, the effect of the angiotensin II hormone on the fractional proximal sodium reabsorption ($\gamma_{\text{aum}}$) is modeled as a function of $C_{\text{sod}}$ given in Eq. A27. The effect of RSNA on the fractional proximal sodium reabsorption ($\gamma_{\text{rsna}}$) is calculated as a function of RSNA given in Eq. A28.

$$\Phi_{\text{pt-sodreab}} = \Phi_{\text{fil-sod}} \times \eta_{\text{pt-sodreab}} \quad (A24)$$

$$\eta_{\text{pt-sodreab}} = \eta_{\text{np}} \times \Phi_{\text{fil-sod}} \times \gamma_{\text{rsna}} \times \eta_{\text{pr}} \quad (A25)$$

$$\gamma_{\text{fil-sod}} = 0.7953 + \frac{2.167}{4.063 + e^{0.836 \times \Phi_{\text{fil-sod}}/4.663}} \quad (A26)$$

$$\gamma_{\text{aum}} = 0.95 + \frac{0.12}{1 + e^{2.66 \times 1.18 \times \log(C_{\text{aum}})} \times 4.448} \quad (A27)$$

$$\gamma_{\text{rsna}} = 1.1916 - \frac{0.4762}{1.064 + e^{-\gamma_{\text{rsna}} \times 0.50345 / 0.50345}} \quad (A28)$$

Block 10. $\Phi_{\text{md-sod}}$ is calculated as the difference between $\Phi_{\text{fil-sod}}$ and $\Phi_{\text{pt-sodreab}}$. Sodium reabsorption from the loop of Henle was lumped into proximal reabsorption, similar to the model of Coleman and Hall (10).

$$\Phi_{\text{md-sod}} = \Phi_{\text{fil-sod}} - \Phi_{\text{pt-sodreab}} \quad (A29)$$

Block 11. Absolute distal tubule sodium reabsorption rate per kidney ($\Phi_{\text{dt-sodreab}}$) is represented as the product of $\Phi_{\text{md-sod}}$ and the fractional distal tubule sodium reabsorption ($\eta_{\text{dt-sodreab}}$), while $\eta_{\text{dt-sodreab}}$ is expressed as the product of its normal value ($\eta_{\text{dt}}$) and the effect of aldosterone hormone concentration ($C_{\text{aal}}$) on fractional distal sodium reabsorption ($\eta_{\text{aal}}$). $\eta_{\text{aal}}$ is represented as a function of $C_{\text{aal}}$ given in Eq. A32.

$$\Phi_{\text{dt-sodreab}} = \Phi_{\text{md-sod}} \times \eta_{\text{dt-sodreab}} \quad (A30)$$

$$\eta_{\text{dt-sodreab}} = \eta_{\text{dt}} \times \gamma_{\text{aal}} \times \eta_{\text{aal}} = 0.5 \quad (A31)$$

$$\gamma_{\text{aal}} = 0.17 + \frac{0.94}{1 + e^{0.485 \times 1.2 \times \log(C_{\text{aal}})/0.85}} \quad (A32)$$

Block 12. Distal tubule sodium outflow per kidney ($\Phi_{\text{dt-sod}}$) is calculated as the difference between $\Phi_{\text{md-sod}}$ and $\Phi_{\text{dt-sodreab}}$.

$$\Phi_{\text{dt-sod}} = \Phi_{\text{md-sod}} - \Phi_{\text{dt-sodreab}} \quad (A33)$$

Block 13. Absolute collecting duct sodium reabsorption rate per kidney ($\Phi_{\text{cd-sodreab}}$) is modeled as the product of $\Phi_{\text{dt-sod}}$ and the fractional collecting duct sodium reabsorption ($\gamma_{\text{cd-sodreab}}$), which is expressed as the product of its normal value ($\eta_{\text{cd}}$) and the effects of $\Phi_{\text{dt-sod}}$ and atrial natriuretic peptide hormone concentration ($C_{\text{anp}}$) on $\gamma_{\text{cd-sodreab}}$.

$$\Phi_{\text{cd-sodreab}} = \Phi_{\text{dt-sod}} \times \eta_{\text{cd-sodreab}} \quad (A34)$$

$$\eta_{\text{cd-sodreab}} = \eta_{\text{cd}} \times \eta_{\text{cd-sod}} \quad (A35)$$

$$\lambda_{\text{dt}} = 0.796 + \frac{0.4778}{1.22 + e^{0.836 \times 0.8801 \times \Phi_{\text{dt-sod-reab}}}} \quad (A36)$$

$$\lambda_{\text{anp}} = -0.1 \times \lambda_{\text{aal}} + 1.1 \quad (A37)$$

Block 14. Urine sodium flow per kidney ($\Phi_{\text{u-sod}}$) is $\Phi_{\text{dt-sod}}$ reduced by $\Phi_{\text{cd-sodreab}}$.

$$\Phi_{\text{u-sod}} = \Phi_{\text{dt-sod}} - \Phi_{\text{cd-sodreab}} \quad (A38)$$

Block 15. Water intake rate ($\Phi_{\text{in}}$) is represented as a function of antidiuretic hormone concentration ($C_{\text{ah}}$).

$$\Phi_{\text{in}} = 0.01 \times \left[0.37 + \frac{0.8}{1 + e^{0.6 \times 3.5 \times \log(C_{\text{ah}})}}\right] - 0.0094 \quad (A39)$$

Block 16. Extracellular fluid volume ($V_{\text{ef}}$) is calculated as the time integral of the difference between $\Phi_{\text{in}}$ and the total urine output rate from both kidneys ($\Phi_{\text{tot}}$). The initial condition of $V_{\text{ef}}$ has been taken equal to its normal steady-state value.

$$V_{\text{ef}}(t) = V_{\text{ef}}(0) + \int_{0}^{t} \left[\Phi_{\text{in}} - \Phi_{\text{u-sod}}\right] \, dt \quad (A40)$$

$$V_{\text{ef}}(0) = 15 \text{ liters} \quad (A41)$$

Block 17. Blood volume ($V_{b}$) is represented as a function of $V_{\text{ef}}$.

$$V_{b} = 4.560227 + \frac{2.431217}{1 + e^{(-V_{\text{ef}}-18.11278)/2.10806}} \quad (A41)$$

Block 18. Mean filling pressure ($P_{\text{mf}}$) is expressed as a function of $V_{b}$ and the autonomic multiplier effect ($e_{\text{am}}$).

$$P_{\text{mf}} = (7.436 \times V_{b} - 30.18 \times e_{\text{am}}) \quad (A42)"
Block 19. Venous return ($\Phi_{vr}$) can be calculated by dividing the difference between $P_{ra}$ and right atrial pressure ($P_{ra}$) by resistance to venous return ($R_{vr}$).

$$\Phi_{vr} = \frac{P_{ra} - P_{ra}}{R_{vr}}$$  \hspace{0.5cm} (A43)

Block 20. Cardiac output ($\Phi_{co}$) is taken equal to $\Phi_{vr}$.

Block 21. Right atrial pressure ($P_{ra}$) is calculated as a function of $\Phi_{co}$.

$$P_{ra} = 0.2787 \times e^{0.2281 \times \Phi_{co}} - 0.879$$  \hspace{0.5cm} (A44)

Block 22. Vascularity is an average measure of the number and diameter of blood vessels in the body exhibiting a long-term autoregulatory behavior. The instantaneous value of vascularity (vas) can be calculated as the integral of the net vascularity increase rate, which is the difference between the vascularity formation rate ($vasf$) and the vascularity destruction rate ($vasd$); $vasd$ can be modeled as a constant variable ($a_{auto}$) directly related to $R_{ba}$; $vasd$ can be modeled as a constant fraction of the present value of vascularity, while $vasc$ can be expressed as a function of $\Phi_{co}$ (Eq. A46).

$$vas(t) = vas(0) + \int_{0}^{t} (vas_{t} - vas_{s}) d\tau$$

$$vas_{t} = \frac{11.312 \times e^{-\Phi_{co} \times 0.4799}}{100,000}$$  \hspace{0.5cm} (A45)

$$vas_{s} = vas \times K_{vd} \quad K_{vd} = 0.00001$$  \hspace{0.5cm} (A46)

$$R_{ba} = \frac{K_{bar}}{vas} \quad K_{bar} = 16.6 \text{ mmHg} \cdot \text{min}^{-1}$$  \hspace{0.5cm} (A47)

Block 23. Arterial resistance ($R_{a}$) is modeled as the basic $R_{a}$ ($R_{ba}$) modified by $e_{aum}$, where $R_{ba}$ is inversely proportional to $vas$.

$$R_{a} = R_{ba} \times e_{aum}$$  \hspace{0.5cm} (A48)

$$R_{ba} = \frac{K_{bar}}{vas} \quad K_{bar} = 16.6 \text{ mmHg} \cdot \text{min}^{-1}$$  \hspace{0.5cm} (A49)

Block 24. Guyton et al. (26) determined venous return by changing the $R_{a}$ and venous return experimentally. In a related theoretical study using the basic cardiovascular variables including arterial and venous resistances and capacitances (36), $R_{a}$ was calculated. Guyton et al. (23) combined the theoretical and experimental results and predicted $R_{vr}$ as a function of $R_{a}$ and basic venous resistance ($R_{hv}$), and it was used in the employed model.

$$R_{vr} = \frac{(8 \times R_{ba} + R_{a})}{31} \quad R_{hv} = 3.4 \text{ mmHg} \cdot \text{min}^{-1}$$  \hspace{0.5cm} (A50)

Block 25. Total peripheral resistance ($R_{tp}$) is calculated as the sum of $R_{a}$ and constant $R_{hv}$.

$$R_{tp} = R_{a} + R_{hv} \quad R_{hv} = 3.4 \text{ mmHg} \cdot \text{min}^{-1}$$  \hspace{0.5cm} (A51)

Block 26. $P_{ma}$ is calculated as the product of $\Phi_{co}$ and $R_{tp}$.

$$P_{ma} = \Phi_{co} \times R_{tp}$$  \hspace{0.5cm} (A52)

Block 27. $e_{aum}$ is modeled as the sum of chemoreceptor ($a_{chemo}$) and baroreceptor ($a_{baro}$) activities, which depend on an intermediate variable ($a_{auto}$) directly related to $P_{ma}$; $a_{baro}$ exhibits an adaptation behavior with a time constant of 2,000 min (Eq. A56).

$$e_{aum} = a_{chemo} + a_{baro}$$  \hspace{0.5cm} (A53)

$$a_{chemo} = 3.079 e^{-\tau_{ma}^{0.011}}$$  \hspace{0.5cm} (A54)

$$a_{baro} = \frac{1}{4} a_{auto}$$  \hspace{0.5cm} (A55)

$$a_{auto}(t) = \frac{3}{4} a_{auto} - \frac{1}{2,000} \int_{0}^{\tau} a_{auto}(\tau) - \frac{3}{4} d\tau$$  \hspace{0.5cm} (A56)

Block 28. The normalized antidiuretic hormone secretion rate ($\dot{S}_{adh}$) is mainly determined by $C_{sod}$, $e_{aum}$, and the effect of right atrial pressure ($\delta_{a}$) in an additive manner (Eq. A57). Since $C_{sod}$ contributes to the antidiuretic hormone secretion rate from a certain concentration level (taken as 141 meq/l) onward, in this block, $C_{sod}$ has been limited to values above this level. Similarly, the contribution of $e_{aum}$ in Eq. A57 is limited to values $>1$. For further explanation see Ref. 33. $\delta_{a}$ is related to right atrial pressure via a self-adaptation mechanism given in Eq. A58. The dynamics of the normalized $C_{sod}$ and $e_{aum}$ are expressed as an integral equation (Eq. A59) dependant on ($\dot{S}_{adh}$). $C_{sod}$ is calculated as the product of $C_{sod}$ and steady-state $C_{sod}$ ($C_{sod-ss}$).

$$\dot{S}_{adh} = \frac{1}{3} (C_{sod} - 141) + (e_{aum} - 1) - \delta_{a}$$

Valid for $C_{sod} > 141$ meq/l and $e_{aum} > 1$  \hspace{0.5cm} (A57)

$$\delta_{a}(t) = 0.0007 \times \int_{0}^{t} (0.2 \times P_{ra} - \delta_{a}) d\tau$$  \hspace{0.5cm} (A58)

$$C_{sod} = \frac{1}{3} \dot{S}_{adh} + a_{um}$$

$$C_{sod-ss} = 4 \text{ meq/l}$$  \hspace{0.5cm} (A59)

Block 29. Tubular water reabsorption rate per kidney ($\Phi_{w-reab}$) is calculated as a function of the effects of $C_{sod}$ and $C_{adh}$ ($\mu_{al}$ and $\mu_{adh}$, respectively) and the GFR ($\Phi_{gfr}$), as in Eq. A61.

$$\Phi_{w-reab} = \frac{1}{2} \left(0.025 - 0.001 \mu_{al} \times \mu_{adh} + 0.8 \times \Phi_{gfr} \right)$$  \hspace{0.5cm} (A61)

$$\mu_{al} = 0.17 + \frac{0.94}{1 + e^{0.48 - 1.7 \log_{10}([C_{sod}]/0.88)}}$$  \hspace{0.5cm} (A62)

$$\mu_{adh} = 0.37 + \frac{0.8}{1 + e^{0.6 - 3.7 \log_{10}(C_{adh})}}$$  \hspace{0.5cm} (A63)

Block 30. The urine flow rate per kidney ($\Phi_{u}$) is calculated as the difference between $\Phi_{gfr}$ and $\Phi_{w-reab}$.

$$\Phi_{u} = \Phi_{gfr} - \Phi_{w-reab}$$  \hspace{0.5cm} (A64)

Block 31. Total $\Phi_{u}$ ($\Phi_{u-tot}$) is calculated as the sum of $\Phi_{u}$ of the left and right kidneys ($\Phi_{u-left} + \Phi_{u-right}$).

$$\Phi_{u-tot} = \Phi_{u-left} + \Phi_{u-right}$$  \hspace{0.5cm} (A65)

Block 32. Total renal sodium excretion ($\Phi_{sod-tot}$) is calculated as the sum of sodium excretion from the left kidney ($\Phi_{sod-left}$) and sodium excretion from the right kidney ($\Phi_{sod-right}$).

$$\Phi_{sod-tot} = \Phi_{sod-left} + \Phi_{sod-right}$$  \hspace{0.5cm} (A66)

Block 33. Sodium intake ($\Phi_{sod-int}$) has been treated as an independent variable with a normal steady-state value of 0.126 meq/min.

$$\Phi_{sod-int} = \Phi_{sod-tot}$$  \hspace{0.5cm} (A67)

Block 35. $C_{sod}$ is expressed as the ratio of $M_{sod}$ to $V_{ecf}$.

$$C_{sod} = \frac{M_{sod}}{V_{ecf}}$$  \hspace{0.5cm} (A68)
Block 36. There are two main hypotheses about intrarenal mechanisms that cause renin secretion from the juxtaglomerular apparatus: 1) the macula densa hypothesis and 2) the baroreceptor pressure hypothesis. According to the macula densa hypothesis, changes in sodium concentration are sensed by the cells of the macula densa region. Changes in sodium concentration initiate renin release from the granular cells, which are located at the wall of the afferent and efferent arterioles (27). According to the baroreceptor hypothesis, there are pressure receptors in the afferent arterioles that sense the changes in Paa and then affect renin release directly (28). To determine the direct effect of Paa on renin secretion, glomerular filtration was blocked (nonfiltering kidney) by a combination of renal ischemia and ureteral ligation (6, 7). Hence, this experimental design eliminated the macula densa effect on renin secretion. As a result, it was observed that changes in renal arterial pressure affected renin secretion in the nonfiltering kidney. In a study to compare both hypotheses to determine which has a greater effect on renin secretion, Guyton and Hall (22, 28) showed a negligible direct influence of the baroreceptor mechanism compared with the effect of macula densa sodium flow on renin secretion. Additionally, when the studies by Blaine et al. (6) and Farhi et al. (20) are compared, it seems that macula densa control is more effective than Paa control on renin secretion during decreased renal arterial pressure. Therefore, the direct effect of pressure on renin secretion was not included in the model. Subsequently, renin secretion was modeled by the direct effects of RSNA and macula densa sodium flow on the juxtaglomerular complex to secrete renin. Renin secretion was not included in the model. Subsequently, renin secretion was modeled by the direct effects of RSNA and macula densa sodium flow on the juxtaglomerular complex to secrete renin. The dynamics of the normalized renin secretion rate (\(\hat{S}_{r-tot}\)) is obtained by normalizing the sum of the renin secretion rates from both kidneys by dividing it by the normal steady-state total renin secretion rate (\(S_{r-ss-tot}\)). The dynamics of the normalized renin concentration (\(\hat{C}_r\)) is expressed as an integral equation (Eq. A73) dependent on \(\hat{S}_{r-tot}\).

\[
\hat{S}_{r-tot} = \frac{S_{r-right} + S_{r-left}}{S_{r-ss-tot}} \quad S_{r-ss-tot} = 1,500 \text{ ng ANGI} \cdot \text{h}^{-1} \cdot \text{min}^{-1}
\]

\[
\hat{C}_r(t) = \hat{C}_r(0) + \int_0^t (\hat{S}_{r-tot} - \hat{C}_r)d\tau \quad \hat{C}_r(0) = 1, T_i = 15 \text{ min}
\]

Block 37. The normalized total aldosterone secretion rate (\(\hat{S}_{al}\)) is calculated as the product of the effects of the potassium concentration (\(C_\text{k}\))-to-\(C_{\text{ald}}\) ratio, \(P_{\text{ma}}\), and \(C_{\text{ald}}\) (\(\hat{C}_{\text{ald}}, \hat{\xi}_{\text{map}}\), and \(\hat{\xi}_{\text{al}}\), respectively). The dynamics of the normalized \(C_{\text{ald}}\) (\(\hat{C}_{\text{ald}}\)) are expressed as an integral equation (Eq. A79) dependent on \(\hat{S}_{al}\). \(\hat{C}_{\text{ald}}\) is calculated as the product of \(\hat{C}_{\text{ald}}\) and steady-state \(C_{\text{ald}}\) (\(C_{\text{ald-ss}}\)).

\[
\hat{S}_{al} = \xi_{k/sod} \times \hat{\xi}_{\text{map}} \times \hat{\xi}_{al}
\]

\[
\xi_{k/sod} = \frac{C_{\text{k}}}{C_{\text{ald}}} - 9
\]

\[
\hat{\xi}_{\text{map}} = \begin{cases} 69.03 \times e^{-0.0425 \times P_{\text{ma}}} & \text{if } P_{\text{ma}} \leq 100 \\ 1 & \text{if } P_{\text{ma}} > 100 \end{cases}
\]

\[
\hat{\xi}_{al} = 0.4 + \frac{2.4}{1 + e^{2.82 - 1.5 \times \log_{10}(\hat{C}_{\text{ald}}) / 0.8}}
\]

Block 38. \(C_{\text{ald}}\) is assumed to be proportional to \(\hat{C}_r\).

\[
C_{\text{ald}} = \hat{C}_r \times C_{\text{ald-ss}} \quad C_{\text{ald-ss}} = 20 \text{ ng/l}
\]

Fig. A3. Results of percent change in response of renin secretion from the right kidney to a 10% increase and decrease in glomerular capillary filtration coefficient in the right kidney (A), percent change in response of renin secretion from the left kidney to a 10% increase and decrease in glomerular capillary filtration coefficient in the right kidney (B), percent change in response of renin secretion from the right kidney to a 10% increase and decrease in Bowman hydrostatic pressure in the right kidney (C), and percent change in response of renin secretion from the left kidney to a 10% increase and decrease in Bowman hydrostatic pressure in the right kidney (D).
\( \hat{C}_{al}(t) = \hat{C}_{al}(0) + \frac{1}{T_{al}} \int_{0}^{t} (\hat{S}_{al} - \hat{C}_{al}) \, dt \quad \hat{C}_{al}(0) = 1, \ T_{al} = 60 \text{ min} \) 

(A79)

\( C_{al} = \hat{C}_{al} \times C_{al-ss} \quad C_{al-ss} = 85 \text{ ng/l} \) 

(A80)

Block 40. The normalized atrial natriuretic peptide concentration \( \langle \hat{C}_{nap} \rangle \) is calculated as a function of right atrial pressure.

\( \hat{C}_{nap} = 7.4052 - \frac{6.554}{1 + e^{(\hat{P}_{ra} - 3.762)}} \) 

(A81)

Block 41. Block 41 represents \( C_{ks} \), which in this model has been assumed to remain constant at its normal value (i.e., 5 meq/l).

The curve-fitting tool of MATLAB has been used to obtain nonlinear equations from the results presented in the literature in numerical or graphical form.

The employed cardiovascular system model has been implemented using MATLAB/Simulink. The Runge-Kutta numerical method with fixed step size of 0.5 min has been used to solve the nonlinear differential equations in this model.

Results of sensitivity analysis done by changing five parameters one at a time by \( \pm 10\% \) of their nominal values are shown in Table S2 (see Supplemental Material for this article). The resulting changes in the steady-state values of the 27 variables are, in general, small compared with the \( \pm 10\% \) parameter change. The parameter with the greatest sensitivity (17.03\%) is the rate of renin secretion from the left kidney in response to a 10\% decrease in steady-state Bowman hydrostatic pressure in the right kidney. It can be said that the employed model is quite robust with respect to parameter changes. Percent change in renin secretion in response to a 10\% increase and decrease in the glomerular capillary filtration coefficient and Bowman hydrostatic pressure is shown in Fig. A3.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

F.K., Y.D., and R.L.H. are responsible for conception and design of the research; F.K. performed the experiments; F.K. analyzed the data; F.K. and Y.D. interpreted the results of the experiments; F.K., Y.D., and R.L.H. prepared the figures; F.K. and Y.D. drafted the manuscript; F.K. and R.L.H. edited and revised the manuscript; F.K., Y.D., and R.L.H. approved the final version of the manuscript.

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