



Published in final edited form as:

*Hypertension*. 2018 December ; 72(6): 1407–1416. doi:10.1161/HYPERTENSIONAHA.118.11552.

## Testing Computer Models Predicting Human Responses to a High Salt Diet: Implications for Understanding Mechanisms of Salt Sensitive Hypertension

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### Abstract

Recently, mathematical models of human integrative physiology, derived from Guyton's classic 1972 model of the circulation, have been used to investigate potential mechanistic abnormalities mediating salt-sensitivity and salt-induced hypertension. We performed validation testing of two of the most evolved derivatives of Guyton's 1972 model, QCP-2005 and HumMod-3.0.4, to determine if the models accurately predict sodium balance and hemodynamic responses of normal subjects to increases in salt intake within the real-life range of salt intake in humans. Neither model, nor the 1972 Guyton model, accurately predicts the usual changes in sodium balance, cardiac output, and systemic vascular resistance that normally occur in response to clinically realistic increases in salt intake. Furthermore, although both contemporary models are extensions of the 1972 Guyton model, testing revealed major inconsistencies between model predictions with respect to sodium balance and hemodynamic responses of normal subjects to short-term and long-term salt loading. These results demonstrate significant limitations with the hypotheses inherent in Guyton models regarding the usual regulation of sodium balance, cardiac output and vascular resistance in response to increased salt intake in normal salt-resistant humans. Accurate understanding of the normal responses to salt loading is a prerequisite for accurately establishing

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Disclosures  
None

abnormal responses to salt loading. Accordingly, the present results raise concerns about the interpretation of studies of salt sensitivity with the various Guyton models. These findings indicate a need for continuing development of alternative models that incorporate mechanistic concepts of blood pressure regulation fundamentally different from those in the 1972 Guyton model and its contemporary derivatives.

## Keywords

sodium chloride; dietary; salt; hypertension; blood pressure; kidney

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## Introduction

Major advances in computer hardware and software technology have enabled scientists to develop large scale mathematical models which simulate various complex physiologic functions of the human body.<sup>1</sup> The most useful computer-based models of integrative physiology are mathematical formulations of hypotheses about principles and mechanisms that govern physiologic variables and their interaction<sup>2</sup>, e.g., variables such as sodium balance, cardiac output, blood pressure, etc. Testing the validity of mathematical models, by assessing their ability to predict experimental outcomes, provides a useful way of determining the soundness of the mechanistic hypotheses inherent in the models.<sup>2</sup> In addition to validation testing, it is possible to compare the outputs of separate computer models to identify inconsistencies between the models, and thereby identify discrepancies between the hypotheses/concepts embodied in the different mathematical formulations.

The development of mathematical models for exploring hypotheses regarding mechanisms regulating cardiovascular function was pioneered by Guyton, Coleman, and colleagues at the University of Mississippi.<sup>3–6</sup> In 1972, Guyton and colleagues published a model of the cardiovascular system<sup>4</sup> that is said to incorporate more than 150 variables.<sup>1, 7</sup> This model, which was derived from an earlier version developed by Guyton and Coleman,<sup>8</sup> is referred to as “Guyton’s large circulatory model,”<sup>9</sup> or the “1972 Guyton model,”<sup>1</sup> and is said by Hall to be “the first large-scale model of the entire cardiovascular system.”<sup>10</sup> As noted by investigators at the University of Mississippi including Dr. Thomas Coleman, one of the main developers of the 1972 model, the model was used to test a variety of hypotheses “mainly focusing on acute and chronic blood pressure control and the role of the kidney in the long term regulation of blood pressure.”<sup>1</sup>

The 1972 Guyton model was revised and expanded by Guyton and colleagues over decades and has served as the foundation for development of much more complex models of human physiology that can be readily run on personal computers with Windows-based operating systems.<sup>1</sup> The most evolved derivative of the 1972 Guyton model is a large, multi-scale model called “HumMod” that includes a Windows-based graphical user interface.<sup>11, 12</sup> HumMod version 3.0.4 is said to contain over 8000 independent variables<sup>13</sup> and according to its developers from the University of Mississippi, is “the best, most complete, mathematical model of human physiology ever created.”<sup>14</sup>

In reviewing the literature on the 1972 Guyton model and the most evolved derivatives of the Guyton model, we could not find validation studies testing the capacity of the models to accurately predict sodium balance, cardiac output, and vascular resistance responses of normal subjects to increases in dietary salt within the real life range of salt intake in humans. Accurate quantitative characterization of the physiologic responses to salt loading in normal control subjects is a prerequisite for accurately determining which physiologic responses to salt loading are abnormal in salt sensitive subjects.

In the present studies, we performed validation testing of the most highly evolved version of the Guyton model, HumMod 3.0.4, and one of its closely related predecessors, Quantitative Cardiovascular Physiology (QCP 2005), with respect to their capacity to predict the usual sodium balance and hemodynamic responses of normal humans to increases in dietary salt within the real life range of salt intake in humans (clinically realistic increases in salt intake). We also compared simulations performed with the historical 1972 Guyton model to those performed with HumMod 3.0.4. Testing demonstrated that none of these models accurately predicts the usual changes in sodium balance, cardiac output, and systemic vascular resistance that occur in response to increased salt intake in normal salt resistant humans. Furthermore, although the contemporary models are held to be extensions of the same 1972 Guyton model,<sup>1</sup> testing revealed major inconsistencies between the predictions made by these models with respect to cardiovascular and sodium metabolic responses to acute and chronic increases in salt intake. These findings raise major questions about the validity of the hypotheses inherent in Guytonian models that pertain to the regulation of sodium balance and hemodynamic responses to changes in salt intake within the real-life range of salt intake in humans. The findings have implications for understanding the normal mechanisms usually involved in mediating salt resistance, and the abnormalities usually involved in the initiation and maintenance of salt-induced hypertension.

## Methods

The data supporting the findings of this study are available within the article and its Online Supplement, and from the corresponding author on appropriate request.

Details on study design, definitions of terms, sources of computer modeling software, methods of running the computer simulations, and the benchmark human studies used in the validation testing are provided in the methods section of the Online Supplement.

## Statistical Analysis

For validation testing, the predictions of the computer models were plotted against the human experimental data. A model was considered to fail validation testing when the salt-induced change predicted by the model fell outside the 95% confidence limits of the mean of the salt-induced changes observed in human studies. When comparing predictions between models, we applied criteria of  $\pm 25\%$  to the *changes* that occur with salt loading. Specifically, the predictions of HumMod 3.0.4 were considered to agree with those of another model when the changes predicted by the HumMod simulation were within  $\pm 25\%$  of those predicted by the other model.

## Results

### Contemporary Computer Models Fail to Accurately Predict Sodium Balance Responses to Short-Term Salt Loading in Normal Humans

With respect to predicting usual sodium balance responses to short-term increases in salt intake in normal humans (normotensive, salt resistant subjects), both computer models (HumMod 3.0.4 and QCP 2005) showed poor agreement with the results of the human studies and both models failed validation testing. Figure 1 shows that both model simulations vastly underestimate the cumulative amount of sodium that is usually retained in response to switching from a very low NaCl intake of ~ 30 mmol/70 kg body weight/day to a high salt intake of ~ 250 mmol/70 kg body weight/day in normal subjects (normotensive salt resistant subjects in the salt-loading protocol of Schmidlin et al).<sup>15</sup> Figure 2 shows that HumMod 3.0.4 also vastly underestimates the cumulative amount of sodium that is usually retained when switching from a moderately low NaCl intake of ~ 100 mmol/day to a high salt intake of ~ 275 mmol/day in normal subjects (salt-loading protocol of Ishii et al).<sup>16</sup> The QCP model provided a reasonable approximation of the usual amount of sodium retained in response to switching from a moderately low NaCl diet to a high NaCl diet for 5 days (Figure 2). Despite being extensions of the same 1972 Guyton model, the HumMod 3.0.4 and QCP 2005 models showed poor agreement with each other regarding the predicted trend in cumulative sodium balance over time as well as the predicted magnitude of sodium retention (Figures 1 and 2).

### Computer Model Predictions of Arterial Blood Pressure Responses to Short-Term Salt Loading in Normal Humans

In the study of Schmidlin et al,<sup>15</sup> switching from a very low salt diet to a high salt diet induced a 5% decrease in mean arterial pressure during the first 12 to 48 hours of salt loading, followed by a return of mean arterial pressure to baseline by the 5<sup>th</sup> day of salt loading (Figure 3). Neither QCP nor HumMod accurately predicted this reduction in mean arterial pressure that is transiently induced upon switching normal subjects from a very low salt diet (~ 30 mmol NaCl/70 kg body weight/day) to a high salt diet (~250 mmol NaCl/70 kg body weight/day) (Figure 3). Both models accurately predicted that in normal subjects, switching from a very low salt diet to a high salt diet for 5 to 7 days causes minimal increases in blood pressure above baseline (Figure 3). Both models also accurately predicted the results from the study of Ishii et al which showed that in normal subjects,<sup>16</sup> switching from a moderately low salt diet (~100 mmol NaCl/day) to a high salt diet (~275 mmol/day) for 5 days causes little or no increase in blood pressure. (data not shown).

### Contemporary Computer Models Fail to Accurately Predict Cardiac Output and Vascular Resistance Responses to Short-Term Salt Loading in Normal Humans

In model simulations of the changes in cardiac output and systemic vascular resistance that occur in response to short-term increases in salt intake, the predictions by both QCP and HumMod showed poor agreement with the experimental results and both models failed validation testing. The simulation results from HumMod 3.0.4 markedly overestimate the usual salt-induced increases in cardiac output (Figure 4), and markedly overestimate the usual salt-induced decreases in systemic vascular resistance (Figure 5). The simulation

results from the QCP model significantly underestimate the usual salt-induced increases in cardiac output and salt-induced decreases in systemic vascular resistance (Figures 4 and 5).

While both models fail to accurately estimate the magnitude of the changes in cardiac output and systemic vascular resistance usually induced by clinically realistic degrees of salt loading in normal subjects, both models appropriately reflect the general trends in these variables that normally occur in response to physiologic salt loading. Specifically, both models show that in normal subjects, non-extreme salt loading induces relatively little or no increase in blood pressure because normal subjects usually undergo robust vasodilation and reduce systemic vascular resistance sufficiently to offset the potential pressor effects of substantial salt-induced increases in cardiac output. These observations are consistent with the results of salt loading studies in normal salt resistant humans and in animals,<sup>15, 17</sup> These observations are also consistent with the vasodysfunction theory of salt sensitivity<sup>18, 19</sup> which holds that in response to salt loading, normal subjects undergo substantial decreases in systemic vascular resistance that offset potential pressor effects of salt-induced increases in cardiac output whereas salt sensitive subjects do not.

### **Comparing Predictions of HumMod 3.0.4 To Predictions of the Historical Guyton Model**

In simulations of subjects with normal kidney function, switching from a very low NaCl diet to a high salt diet induces far greater short-term and long-term increases in blood pressure in the original 1972 Guyton model than in HumMod 3.0.4 (Figure 6 and Figure S7). The 1972 Guyton model clearly overestimates the extent to which arterial pressure increases in response to salt loading in HumMod 3.0.4 and in normal humans (Figures S7 and S8). Thus, the default subject with normal renal function simulated by the 1972 Guyton model is not normal and is salt sensitive according to criteria recommended for identifying salt sensitivity by the expert panel of the American Heart Association, and by other scientists with experience investigating salt sensitivity in humans.<sup>20, 21</sup>

Throughout both the initiation and maintenance phases of salt loading, the greater salt sensitivity in the 1972 Guyton model simulation than in the HumMod simulation is a consequence of much greater levels of systemic vascular resistance in the 1972 Guyton model than in HumMod 3.0.4 (see Figures 6, Figure S7, and raw data in the online supplement). Throughout salt loading, the salt-induced increases in cardiac output and sodium balance are much smaller in the 1972 Guyton model than in HumMod 3.0.4, yet the salt-induced increases in blood pressure are much greater in the 1972 Guyton model (Figures 6, S7). The greater salt sensitivity in the 1972 Guyton model than in HumMod or normal humans is not initiated by greater levels of sodium retention and cardiac output (Figures 6, S9, S10), but rather by greater levels of systemic vascular resistance (Figures 6, S11).

### **Computer Simulations of Long-Term Salt Loading: Conflicting Results Between Contemporary Models**

Computer simulations of hemodynamic, sodium balance, and fluid volume responses to long-term salt loading also produced conflicting results between the contemporary models (see results in online data supplement). In addition, HumMod simulations of female subjects

yielded striking differences from those of male subjects (see results in online data supplement).

## Discussion

Arthur Clifton Guyton and colleagues pioneered the use of large-scale computer models to investigate potential physiologic abnormalities involved in the initiation and maintenance of salt-induced hypertension.<sup>4, 22</sup> It is axiomatic that accurate identification of abnormal physiologic responses to a high salt diet depends on an accurate understanding of the normal physiologic responses to a high salt diet. In the present study, two large-scale, contemporary mathematical models of human integrative physiology, HumMod 3.0.4<sup>12</sup> and QCP 2005<sup>23</sup>, both derivatives of the historical 1972 Guyton model of the circulation,<sup>4</sup> failed validation testing with respect to accurately predicting the changes in sodium balance, cardiac output, and vascular resistance that usually occur in normal subjects in response to clinically realistic increases in dietary intake of salt. Depending on the different variables and model tested, the responses predicted were outside the 95% confidence intervals of the means of actual experimental responses, or were not directionally appropriate, or both. In addition, the 1972 Guyton model greatly underestimates the levels of sodium balance, and greatly overestimates the levels of blood pressure and systemic vascular resistance that usually occur with initiation of clinically realistic degrees of salt loading in normal humans (salt resistant normotensive humans).

The lack of published validation studies of the historical Guyton model, or of its contemporary derivatives, with respect to predicting normal sodium balance and hemodynamic responses to salt loading is surprising and prompted the present investigation. Despite the lack of model validation studies in salt loaded normal controls, these models have been used for many years to probe hypotheses about the possible role of abnormalities in sodium excretion, cardiac output, and vascular resistance in mediating pressor responses to both short-term and long-term salt loading.<sup>5, 6, 13, 24, 25</sup> Also surprisingly,<sup>18, 19, 26</sup> neither Guyton and his colleagues, nor most other investigators searching for abnormalities mediating salt sensitivity, published studies of sodium balance, cardiac output, and systemic vascular resistance responses to salt-loading in normal humans or animals. Despite the lack of such studies in normal controls, many investigators advocate the view that abnormally large increases in renal sodium retention and in cardiac output are usually involved in the pathogenesis of salt sensitivity.<sup>27-33</sup> While increases in sodium balance and cardiac output occur in response to acute salt loading, the increases that occur in salt sensitive subjects are not greater than those that occur in salt resistant normal controls.<sup>18, 19, 26</sup>

In a recent effort to “test hypotheses of salt sensitivity,” Clemmer and colleagues at the University of Mississippi used HumMod 3.0.4 to simulate responses of cardiovascular, renal, and neurohormonal variables to massive degrees of salt-loading in normal subjects, and in subjects with various experimental manipulations.<sup>13</sup> However, these investigators did not perform or cite any validation studies that tested the ability of HumMod to accurately predict the responses of normal humans to the extreme increases in salt intake that were used to define salt sensitivity in their simulation studies. In the simulation studies performed by Clemmer and colleagues, salt sensitivity was defined according to blood pressure responses

to massive, clinically unrealistic increases in salt intake (> 30 fold increase in salt intake to 1000 mmol/day).<sup>13</sup> Thus, even if simulations with HumMod 3.0.4 were to accurately predict the sodium balance and hemodynamic responses of normal subjects to such extreme degrees of salt loading, the relevance of such findings to the usual human responses to clinically realistic degrees of salt loading would be questionable.

### **Inconsistent Predictions Between Two Closely Related Derivatives of the 1972 Guyton Model**

In addition to failing validation testing, the HumMod and QCP models predict vastly different results with respect to acute and chronic salt-induced changes in cardiac output, blood volume, interstitial fluid volume, plasma protein concentrations, and systemic vascular resistance. This is surprising because both models are viewed as “extensions” or “derivatives” of the same 1972 Guyton model of the circulation,<sup>1</sup> and both “are due in large parts to the efforts of Dr. Thomas Coleman, a primary contributor to the 1972 Guyton model.”<sup>1</sup> In the testing of HumMod, we also observed strikingly different results between simulations of salt loading in male subjects versus those in female subjects.

### **Comparing Predictions of the Original 1972 Guyton Model With Those of HumMod 3.0.4**

In subjects with normal renal function, the original 1972 Guyton model predicts the occurrence of much greater salt-induced increases in blood pressure than those predicted by HumMod 3.0.4, the most recent extension of the Guyton model. This raises the question: what hemodynamic mechanism accounts for greater salt sensitivity in the 1972 Guyton model than in HumMod 3.0.4? In simulations with the 1972 Guyton model, the salt-induced increases in cardiac output and sodium balance are much smaller than those in simulations with HumMod 3.0.4 (Figure 6 and Figure S7). The greater acute and chronic salt sensitivity in the 1972 Guyton model than in HumMod 3.0.4 is caused by strikingly greater levels of vascular resistance with salt loading in the 1972 model than in HumMod 3.0.4, not by greater levels of sodium retention and cardiac output (Figure 6, Figure S7, and raw data in online-only supplement). In the 1972 Guyton model, acute and chronic salt loading causes only a modest decrease in systemic vascular resistance, whereas in HumMod 3.0.4, salt loading causes very large decreases in systemic vascular resistance, acutely and chronically (Figure S7). These findings raise an additional question: During the derivation of HumMod 3.0.4 from the 1972 Guyton model, what changes were made that account for the much greater decreases in systemic vascular resistance, and the much greater increases in sodium balance and cardiac output, that occur with salt loading in HumMod 3.0.4 than in the 1972 Guyton model? While extensive follow-up studies will be required to answer this question in detail, a brief discussion of some key points related to this issue is provided below.

### **Do Modern Models of Blood Pressure Regulation Include the Main “Core” Features of the Original Guyton Model?**

According to a 2009 publication by Montani and Van Vliet, as the Guyton model evolved into more elaborate versions over the years, “the core of the model and the basic concepts remained untouched.”<sup>9</sup> Specifically, Montani and Van Vliet noted that the “pressure-natriuresis relationship” and “blood flow autoregulation” are main features of the 1972 Guyton model that “remained as core concepts” as the model evolved.<sup>9</sup> However, it appears

that neither one of these “core concepts” of the 1972 Guyton model is retained in HumMod 3.0.4.

### **The Phenomenon of “Blood Flow Autoregulation” Does Not Appear to be Retained in the Most Evolved Version of the 1972 Guyton Model**

According to the recent *Guyton and Hall Textbook of Medical Physiology*, the term “autoregulation” “means simply regulation of blood flow by the tissue itself. When increased blood volume increases the cardiac output, the blood flow increases in all tissues of the body, so this autoregulation mechanism constricts blood vessels all over the body, which in turn increases the total peripheral resistance.”<sup>32</sup> However, in HumMod simulations of subjects with normal renal function, salt loading causes very large, sustained increases in blood volume (Figure S4) and cardiac output (Figure S7) that are associated with almost equally large, sustained *decreases* in total peripheral resistance (systemic vascular resistance), not sustained increases in total peripheral resistance (Figure S7). This type of vascular resistance response to salt-induced increases in cardiac output is opposite to the type of vascular resistance response expected to occur with “blood flow autoregulation.”

In simulations with the 1972 Guyton model, switching from a low salt diet to a high salt diet, induced a greater than 50% increase in the variable “ARM” defined as “the vasoconstrictor effects of all types of autoregulation” (for the ARM data, see online data supplement file labeled “Guyton\_1972\_Fortran\_output”). In the 1972 Guyton model, this increase in the “vasoconstrictor effects of all types of autoregulation” could contribute to the failure of systemic vascular resistance to normally decrease in response to salt-induced increases in cardiac output. The large, sustained *decreases* in total peripheral resistance in the HumMod simulations suggest that the “core” feature of “blood flow autoregulation” in the 1972 Guyton model, has not been retained in HumMod 3.0.4 as a determinant of the systemic vascular resistance response to clinically realistic increases in salt intake in subjects with normal renal function (see the online supplemental material for a further discussion of autoregulation in the 1972 Guyton model).

This raises the question: has the core feature of early Guyton models that is held to mediate sustained salt-induced hypertension, i.e., the “pressure natriuresis relationship,” been retained in HumMod 3.0.4 ? This is a critical question because Guyton and colleagues have contended that for any given level of salt intake, the renal function curve (“pressure natriuresis relationship”) is the overriding determinant of long-term blood pressure control. 5, 32, 34

### **The Pressure Natriuresis Relationship Is Not Retained as a Determinant of Blood Pressure in the Most Evolved Version of the 1972 Guyton Model**

Although the “pressure natriuresis relationship” was incorporated as a critical determinant of blood pressure in early Guyton models of the circulation, investigators involved in the development of HumMod have recently stated that “In HumMod, there is no equation that describes the renal function curve or pressure natriuresis relationship per se.”<sup>13</sup> In addition, the investigators emphasize that in HumMod, renal function curves (pressure natriuresis curves) “are not artificially injected into the model but are the end result of the



simulations.”<sup>13</sup> These comments indicate that the renal function curve (pressure natriuresis relationship), the main “core” determinant of long-term blood pressure control in the early Guyton models, has not been retained in HumMod 3.0.4 as a driver of blood pressure outcomes in the simulations. Further, Osborn and colleagues<sup>35-37</sup> and Beard and colleagues<sup>38</sup> pointedly chose not to include the pressure natriuresis curve as the main controller of blood pressure in their modern models of arterial pressure regulation. It should also be noted that the Guytonian view on the dominant role of the pressure-natriuresis relationship in determining the chronic level of blood pressure, appears to be an expression of the three tautological “laws of long-term arterial pressure regulation” stated by Guyton and Coleman many years ago.<sup>39-42</sup> The omission of the pressure-natriuresis relationship as a driver of blood pressure outcomes in HumMod, and in other contemporary models,<sup>35-38</sup> agrees with Beard’s admonition to stop teaching and promoting physiologic concepts that are based on tautological thinking.<sup>39</sup>

### **Which Mathematical Calculations and Equations in the 1972 Guyton Model Have Been Retained in Its Contemporary Derivatives ?**

Because of the various ways in which the 1972 Guyton model and its derivatives are presented, it is difficult to discern how many of the mathematical calculations/equations from the early Guyton models are retained in the recent derivatives such as QCP and HumMod 3.0.4. As pointed out by Kofranek and colleagues, the 1972 Guyton model was originally presented as a diagram that appeared as some sort of “electrotechnical device,” the accompanying explicatory comments and reasoning behind the given formulas were “very brief,” and the model was disseminated in FORTRAN code.<sup>43</sup> With respect to the QCP model, the mathematical background of the model is hidden in source code written in C++.<sup>44</sup> With respect to HumMod, Kofranek and colleagues have noted that “the model description has been divided into thousands of XML files and more than a thousand directories” and “the entire structure of the model and following links and references are not easily identifiable.”<sup>44</sup> However, with the reimplementations of HumMod and other models in newer, more comprehensible software simulation environments like that provided by the Modelica modeling language,<sup>44-46</sup> it is hoped that opportunities for understanding differences in equations and structures between different models will improve.

### **Study Limitations**

One of the main goals of the current study was to perform validation testing of the capacity of large scale models of human integrative physiology to accurately predict sodium balance and hemodynamic responses to increases in salt intake. The current studies were limited because we could identify only two rigorously controlled studies for testing the capacity of the models to accurately predict the usual sodium balance responses to salt loading in normal salt resistant subjects, and only one study for testing accuracy in predicting the usual cardiac output responses to salt loading. Thus, the current study only tested the validity of the models in predicting responses to changes in salt intake under a small number of experimental conditions. However, none of these limitations undermines the main conclusions of the current study.

## Perspectives and Conclusions

In a discussion of the relevance of the 1972 Guyton model to modern cardiovascular physiology, Montani and Van Vliet state that “As Guyton pointed out, the most helpful contribution of the model is when it failed to correctly predict an empirical outcome, since that clearly indicated a limitation in our understanding of the system.”<sup>9</sup> Indeed, the results of the present studies indicate that the 1972 Guyton model, and its contemporary derivatives HumMod 3.0.4 and QCP 2005, reflect an incomplete understanding of the systems regulating sodium balance, cardiac output, and systemic vascular resistance in response to clinically realistic increases in salt intake. According to Dr. S. Randall Thomas and colleagues, the models developed by Guyton and his many collaborators led them to “profoundly reorient our understanding of the causes of hypertension.”<sup>7</sup> However, in light of the results of the current studies with the 1972 Guyton model and its derivatives, together with those of previous experimental studies in animals<sup>47–50</sup> and humans,<sup>15, 18, 51, 52</sup> the use of the models by Guyton and colleagues to “reorient understanding” of the causes of hypertension appears to have been overreaching.

The present findings underscore the value of validation testing of mathematical models to assess the accuracy of mechanistic hypotheses inherent in the models. It is hoped that these findings will motivate further revision of HumMod, and the continued development of alternative models<sup>36, 53</sup> that incorporate concepts of blood pressure control mechanisms different from those in the Guyton models. For example, we support the view of Osborn and colleagues<sup>35–37</sup> that future models include pathways involved in regulating vascular tone that are missing from, or inadequately developed in, the early Guyton model and its derivatives, e.g., pathways involved in regulating vascular resistance responses to changes in salt intake such as nitric oxide related pathways<sup>54</sup> and various neural-hormonal pathways.<sup>36, 38, 53, 55–57</sup> We believe that future models should follow the lead of HumMod 3.0.4 and other models<sup>35–38</sup> by not incorporating the tautological concept in the early Guyton models which holds that, for a given level of salt intake, the pressure-natriuresis relationship (curve) determines the chronic level of arterial pressure.<sup>39, 41</sup> We suggest that future models also avoid incorporating the concept embedded in Guyton models<sup>4, 22</sup> which holds that virtually all retained sodium distributes in the extracellular fluid volume. This concept has been open to question for many years,<sup>58–61</sup> and mounting evidence from the work of Heer and colleagues<sup>62</sup> and Titze and colleagues<sup>63, 64</sup> has cast further doubt on the concept. Finally, we would encourage investigators to develop new models, and evolve existing models, in open source, more comprehensible object-oriented modeling environments like Modelica, and make the code readily available so that other investigators can work freely to investigate and improve the models in a cooperative scientific fashion.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

Sources of funding

National Center for Research Resources, M0 RR-00079, US Public Health Service; National Institutes of Health/ National Heart, Lung and Blood Institute grant RO1-HL64230; Praemium Academiae award of the Czech Academy of Sciences to MP; and gifts from the Saw Island Foundation, the Antel Foundation, and the Maier Family Foundation.

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**Novelty and Significance****What Is New?**

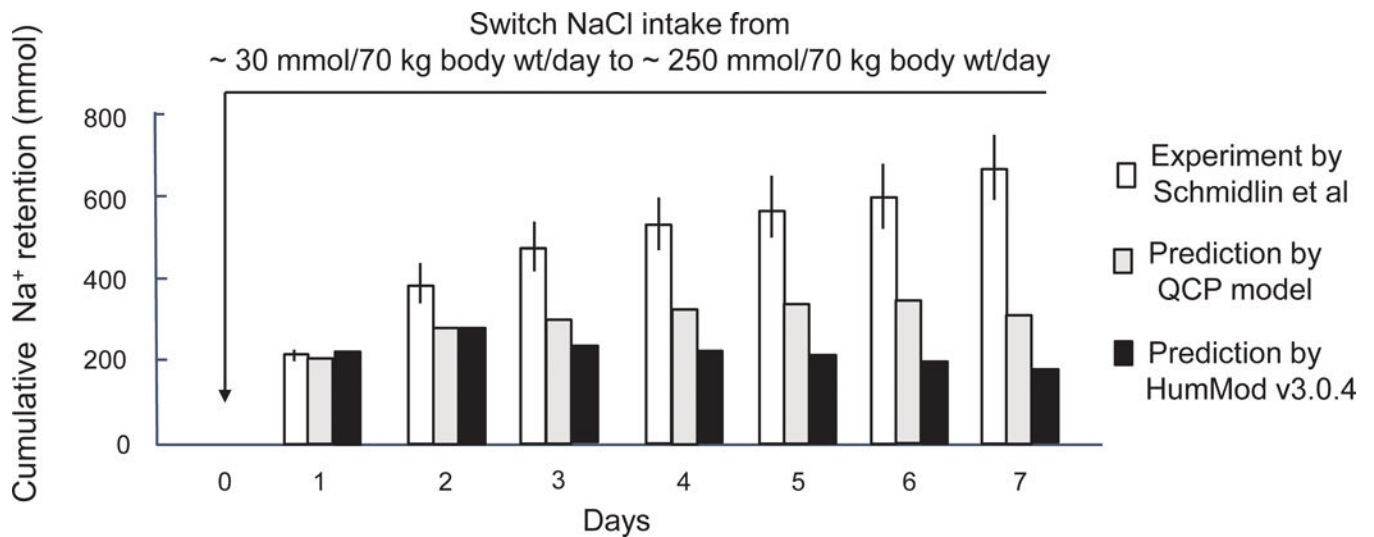
- Guyton's 1972 model of the circulation, and two large-scale models of integrative physiology recently derived from the 1972 Guyton model, HumMod 3.0.4 and QCP 2005, fail to accurately predict, or agree on, the usual changes in sodium balance, cardiac output, and systemic vascular resistance that occur in response to clinically realistic increases in salt intake in normal humans.

**What Is Relevant?**

- These findings are relevant for understanding the mechanisms that normally regulate blood pressure responses to clinically realistic increases in salt intake, and for recognizing the hemodynamic and renal abnormalities involved in the pathogenesis of salt-induced hypertension.

**Summary**

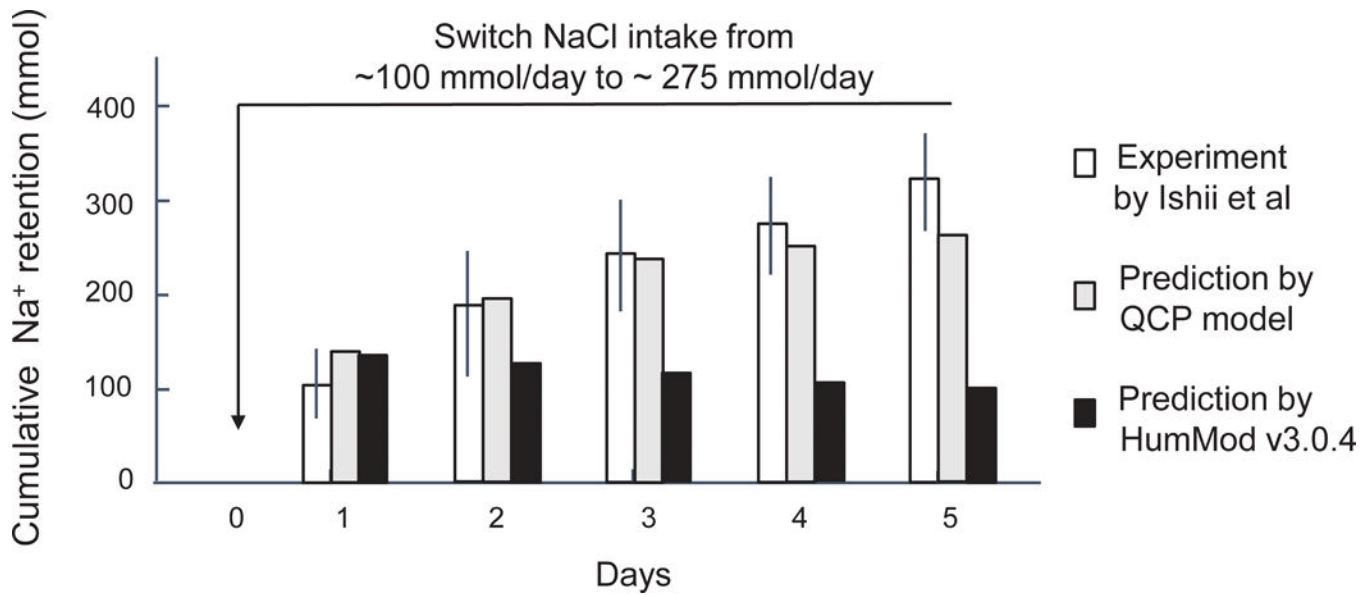
- The 1972 Guyton model of the circulation, and its contemporary derivatives, do not accurately represent the mechanisms normally involved in regulating blood pressure and sodium metabolic responses to realistic degrees of salt loading in humans.



**Figure 1.**

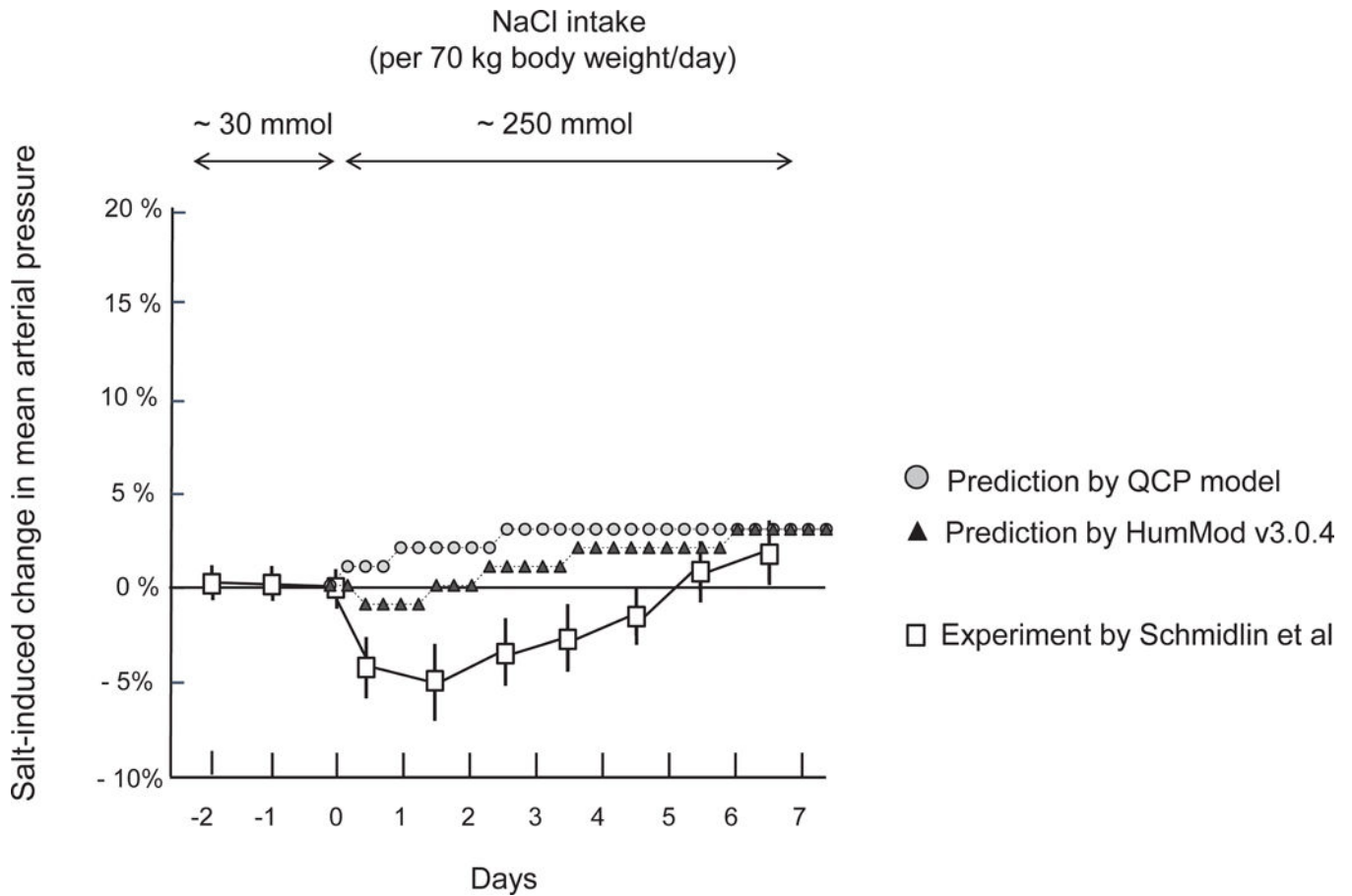
Experimental and predicted short-term effects on cumulative sodium balance induced by switching from a very low salt diet to a high salt diet. This figure shows cumulative sodium retention induced by switching NaCl intake from ~ 30 mmol/70 kg body weight/day to ~ 250 mmol/70 kg body weight/day according to the studies of Schmidlin and colleagues in normotensive salt resistant humans,<sup>15</sup> and according to the modeling predictions of HumMod 3.0.4 and QCP 2005. These results for both the human study and the model simulations were determined without including non-renal losses of sodium in the balance calculations (see online Data Supplement for details). Results of studies in humans are presented as means and 95% confidence intervals.





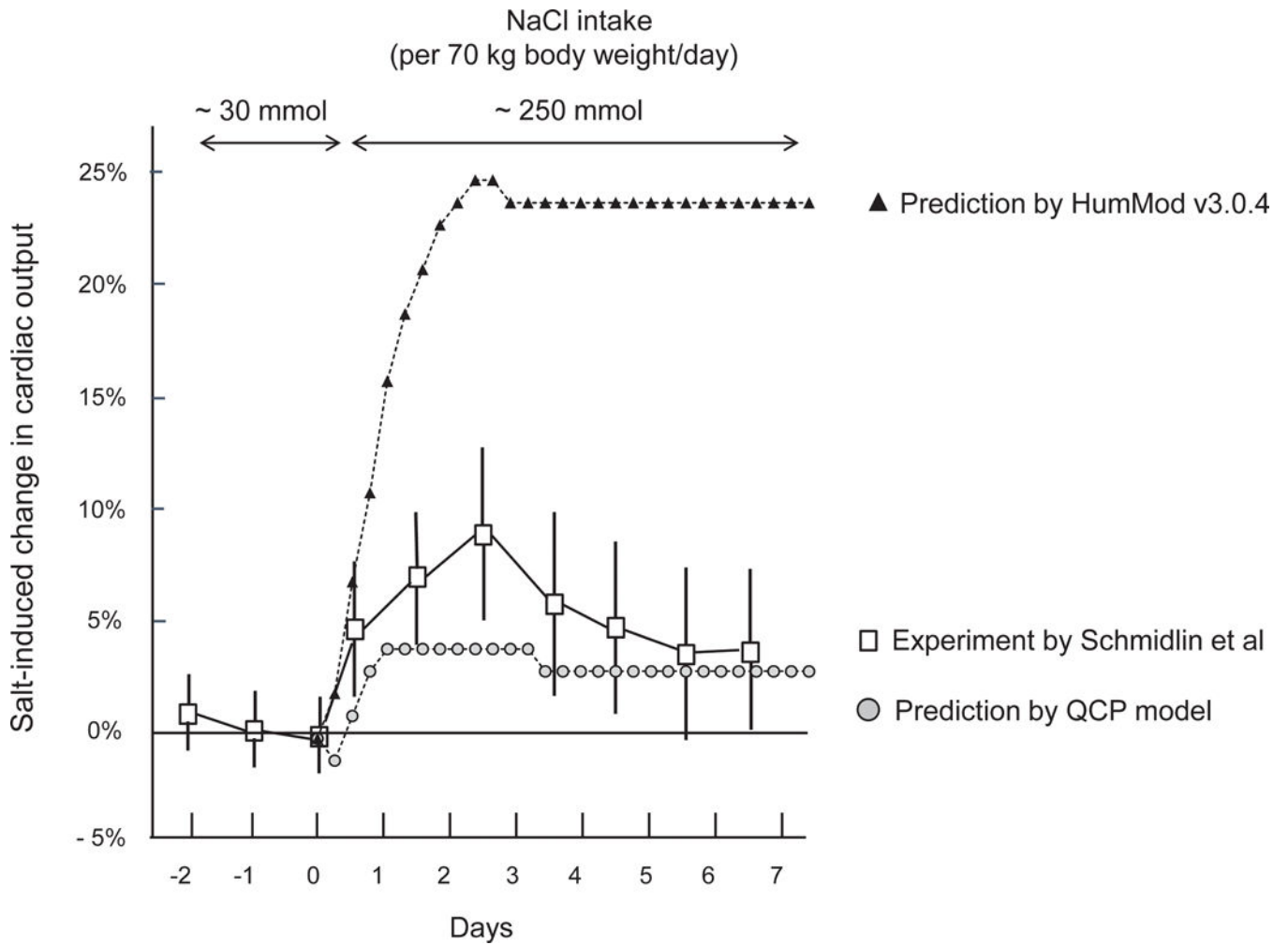
**Figure 2.**

Experimental and predicted short-term effects on cumulative sodium balance induced by switching from a moderately low salt diet to a high salt diet. This figure shows cumulative sodium retention induced by switching NaCl intake from ~100 mmol/day to ~275 mmol/day according to the studies of Ishii and colleagues in normotensive salt resistant humans,<sup>16</sup> and according to the predictions of HumMod 3.0.4 and QCP 2005. These results for both the human study and the model simulations were determined without including non-renal losses of sodium in the balance calculations. Results of studies in humans are presented as means and 95% confidence intervals.



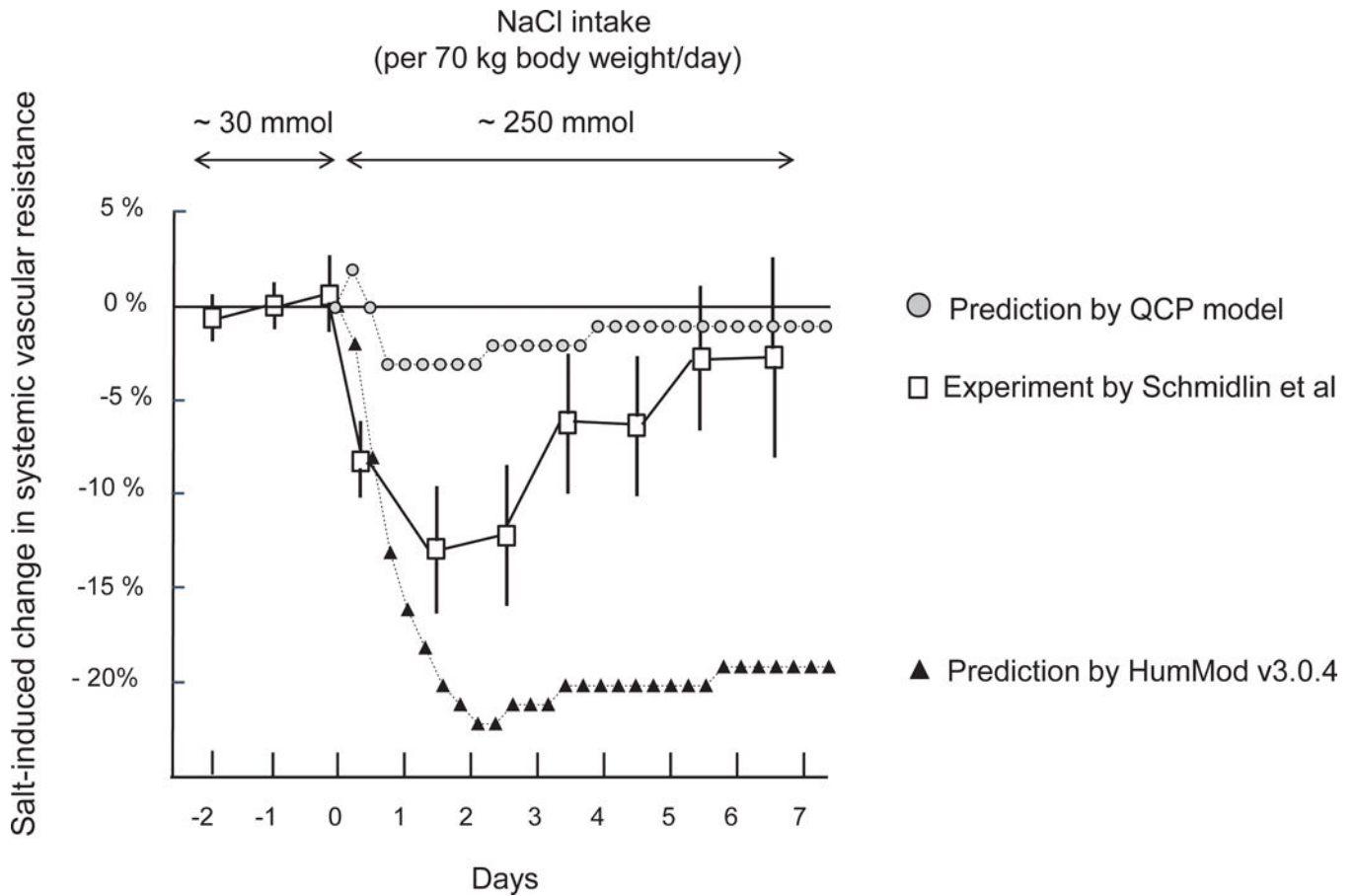
**Figure 3.**

Experimental and predicted short-term changes in blood pressure induced by switching from a very low salt diet to a high salt diet. This figure shows percent changes in mean arterial pressure induced by switching NaCl intake from ~ 30 mmol NaCl/ kg body weight/day to ~ 250 mmol/70 kg body weight/day according to the studies of Schmidlin and colleagues in normotensive salt resistant humans,<sup>15</sup> and according to the predictions of HumMod 3.0.4 and QCP 2005. Results of studies in humans are presented as means and 95% confidence intervals.



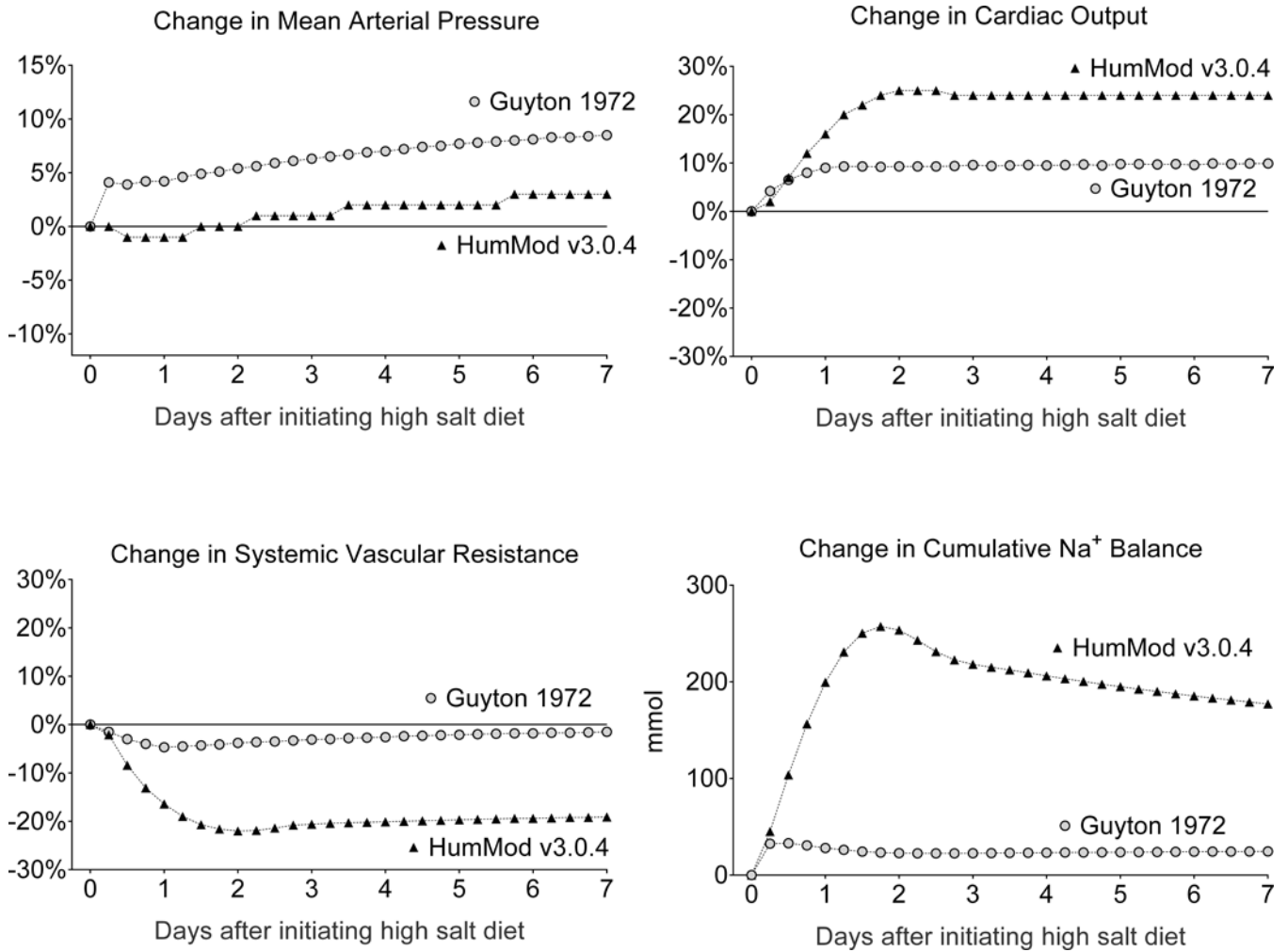
**Figure 4.**

Experimental and predicted short-term changes in cardiac output induced by switching from a very low salt diet to a high salt diet. This figure shows percent changes in cardiac output induced by switching NaCl intake from ~ 30 mmol/70 kg body weight/day to ~ 250 mmol/70 kg body weight/day according to the studies of Schmidlin and colleagues in normotensive salt resistant humans,<sup>15</sup> and according to the predictions of HumMod 3.0.4 and QCP 2005. Results of studies in humans are presented as means and 95% confidence intervals.



**Figure 5.**

Experimental and predicted short-term changes in systemic vascular resistance induced by switching from a very low salt diet to a high salt diet. This figure shows percent changes in systemic vascular resistance induced by switching NaCl intake from ~ 30 mmol NaCl/70 kg body weight /day to ~ 250 mmol/70 kg body weight/day according to the studies of Schmidlin and colleagues in normotensive salt resistant humans,<sup>15</sup> and according to the predictions of HumMod 3.0.4 and QCP 2005. Results of human studies are presented as means and 95% confidence intervals.



**Figure 6.**

Short-term sodium metabolic and hemodynamic responses to salt loading predicted to occur by HumMod 3.0.4 and the 1972 Guyton model in subjects with normal renal function. This figure shows the percent changes in mean arterial pressure, cardiac output, and total peripheral resistance (systemic vascular resistance), and the changes in cumulative sodium balance, predicted to occur in response to switching from a low NaCl intake of 30 mmol/day to a high NaCl intake of 270 mmol/day for 7 days. The changes predicted to occur with long-term salt loading are shown in Figure S7.