Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Hypertension. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

Hypertension. 2018 December ; 72(6): 1272–1273. doi:10.1161/HYPERTENSIONAHA.118.11998.

Assessing the validity and utility of the Guyton model of arterial blood pressure control

Daniel A. Beard

Molecular and Integrative Physiology, University of Michigan

> "the criterion of the scientific status of a theory is its falsifiability, or refutability, or testability"
>
> Karl Popper[1]

Over the decades since its introduction, the so-called "Guyton Model" of the human cardiovascular system has attained an almost mythical or divine status, complete with adherents, detractors, and debates contentious and unresolved[2]. Many decades after its introduction, Kurtz et al.[3] put the model to the test, revealing crucial flaws in its ability to represent the human cardiovascular response to changes in chronic salt intake. As a disclosure, the author has found himself among the critics of Guyton's theories, questioning their very logical foundation[4]. Yet, leaving aside criticisms of Guyton's approach or conclusions, the model and modeling framework developed by Guyton and co-workers must be acknowledged for its innovative scope and ambition. In the 1960's, without the aid of programmable digital computers, Arthur Guyton, Thomas Coleman, and colleagues undertook to simulate the integrated workings of the mechanical, neural, and endocrine processes governing the operation of the cardiovascular system using models built as analog circuits. Eventually the analog computing approach gave way to digital computing, but the models remain rooted in analog circuit descriptions, as is evident in more recent adaptations and applications[5]. Whether or not one agrees with the assessment[6] that the many years of effort resulted in "the best, most complete, mathematical model of human physiology ever created", there is no doubt that the effort led by Dr. Guyton, in many ways ahead of its time, foreshadowed current initiatives aimed at capturing integrated physiological function via integrated computational modeling and simulation[7]. But was the effort more than just ambitious? Did it (does it) help us to understand important features of cardiovascular physiology?

Invoking the guiding axiom that "all models are wrong" [8], folks on both sides of the Guytonian Schism appreciate that no model is ever exactly correct in how it represents physiological and physical processes. A model as broadly encompassing as those of Guyton and co-workers is certain to be more wrong in some aspects and less wrong in others. In fact, such a model might have as much to teach us in what it gets wrong as in what it gets

Address for Correspondence: DA Beard, 2800 Plymouth Road, University of Michigan, Ann Arbor, MI 48109, phone: 734-763-8040, beardda@umich.edu.

Disclosures

None

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

right. Thus, appreciating its wrongness as not necessarily a limitation, and recognizing that the core of the various instantiations of the Guyton model is the relationship between arterial pressure and renal fluid and salt handling, and understanding that these models have been broadly used to support the argument that the arterial pressure is uniquely determined by renal fluid and salt handling[9], we might ask the Guyton model to illuminate the fundamental processes governing the cardiovascular-neural-humoral response to changes in sodium intake. In doing so, ultimately, we would want to know how the model components underlying the physiological response to changes in sodium intake were identified and validated. And we would want to know if and how these pathways and mechanisms were independently tested experimentally in humans and/or animal models? Finally, we could try to determine what gaps in knowledge are revealed by missing features of the model(s) and failures of simulations to match experimental observations. However, before getting to those questions and applications, the study by Kurtz et al.[3] illustrates that there is an even more fundamental question about the Guyton modeling paradigm that has remained largely unasked: what does the model get right? The (perhaps) astounding answer, in terms of the cardiovascular response to salt loading, is: essentially nothing.

That is an important conclusion, but, I will argue, not necessarily an entirely damning one. The evidence for the conclusion is in the simulations of two relatively recent derivations of the Guyton model (QCP-2005 and HumMod-3.0.4) and a reconstruction of the 1972 Guyton model, compared to data on arterial pressure, sodium retention, cardiac output, hematocrit, and plasma protein levels following changes in salt intake in normal salt-resistant humans reported by Schmidlin et al.[10]. The result is, frankly, a wholesale failure of the models to qualitatively or quantitatively represent the observed responses. Furthermore, for unknown reasons the models failed in markedly different ways, as detailed by Kurtz et al.[3]

It has been demonstrated[4] that fundamental conclusions that Guyton and his colleagues drew from their analysis of blood pressure control were tautological truisms that are not even wrong. In contrast, in demonstrating the failure of the available versions of Guyton's models to capture the physiological responses to changes in salt intake, Kurtz et al. show that these models do not suffer from the same fundamental flaws as do Guyton's broader theories. Instead of being not even wrong and thereby conferring no meaning or insight, these models are just plain wrong. And in being just plain wrong, they are useful. Indeed, in demonstrating that these models do not effectively capture the physiological response to salt loading, Kurtz et al.[3] diplomatically conclude that "these findings raise major questions about the validity of the hypotheses inherent in Guytonian models." I might offer a stronger conclusion: Kurtz et al. have shown that the hypotheses represented by these models are false. This falsification should be interpreted as nothing more or less than a successful execution of the scientific method. Successfully falsified, the models and the ideas that they represent should now be rethought, revised, or even discarded.

Given the large role the Guyton model has played in the field of hypertension research, this simple and even mundane conclusion might strike some readers as taboo. Proponents of Guyton's concepts may be mollified in remembering that "the great tragedy of Science" is "the slaying of a beautiful hypothesis by an ugly fact"[11]. Ugly or beautiful, the study of Kurtz et al. represents forward progress—progress that would not have been possible

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

without access to (at least) one generally agreed on instantiation of the Guyton model. Thus the contributors to the various versions of the Guyton model are to be credited along with Kurtz and colleagues with facilitating this progress. Given the surely huge effort involved in assembling and disseminating these models, which are reported to encompass thousands upon thousands of variables and parameters, one hopes that there is more utility that they can offer in the future. Built over decades, and invoking such an enormous number of variables and interactions, the computer codes and circuit diagrams of the Guyton models potentially represent a rich resource of accumulated knowledge. And in their enlightening demonstration that the "most complete…model…ever" is, maybe by definition, the most wrong model ever, Kurtz et al. may be saving this resource from the interpretations of its creator. The Guyton model has long suffered under a cloud of unsound claims inspired by the sometimes histrionic prose of Professor Guyton. (C.f., "Nevertheless, an event occurred in 1966 that like a flash of lightening, caused my colleagues and myself to focus our attention on the extreme importance of a single characteristic of one of the pressure control mechanisms."[12]) In showing that it is simply a model with some crucial bugs that need to be sorted out, the study of Kurtz et al. may prove to be an inspiring step toward setting the Guyton model free from the unrealistic and inappropriate influence it has had on the field of arterial pressure regulation. The Guyton model and its descendants are intriguing, flawed, ambitious in scope, wrong, and—who knows?—maybe still useful. They do not represent a canon against which all efforts and ideas are to be judged.

In conclusion, the hope is that moving forward we can continue to build a predictive, mechanistic, theoretical understanding of the integrated workings of the cardiovascular, renal, autonomic, and endocrine systems. Several such efforts are underway, some of which are reviewed by Kurtz et al. Regardless of one's belief (or lack of belief) in the potential utility of the Guyton model in contributing to those efforts, Kurtz et al.'s study teaches that the Guyton model (in its various instantiations) and its interpretations should never be invoked as a barrier to disqualify theories and interpretations that criticize or even reject the Guyton model or its associated claims.

Acknowledgments

Funding

NIH grant HL139813

References

1. Popper KR. Conjectures and refutations; the growth of scientific knowledge. London: Routledge and K. Paul; 1963.
2. Evans RG, Bie P. Role of the kidney in the pathogenesis of hypertension: Time for a neo-guytonian paradigm or a paradigm shift? American journal of physiology. Regulatory, integrative and comparative physiology. 2016;310:R217–229
3. Kurtz TW, DiCarlo SE, Pravenec M, Jezek F, Kofranek J, Morris C, Jr. Testing computer models predicting human responses to a high salt diet: Implications for understanding mechanisms of salt sensitive hypertension. Hypertension. 2018 In Press
4. Beard DA. Tautology vs. Physiology in the etiology of hypertension. Physiology (Bethesda). 2013;28:270–271 [PubMed: 23997184]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

5. Montani JP, Van Vliet BN. Understanding the contribution of guyton's large circulatory model to long-term control of arterial pressure. Experimental physiology. 2009;94:382–388 [PubMed: 19286638]

6. Hummod origin story. Http://hummod.Org/originstory/ 2018;2018

7. Nickerson D, Atalag K, de Bono B, Geiger J, Goble C, Hollmann S, Lonien J, Muller W, Regierer B, Stanford NJ, Golebiewski M, Hunter P. The human physiome: How standards, software and innovative service infrastructures are providing the building blocks to make it achievable. Interface Focus. 2016;6:20150103 [PubMed: 27051515]

8. Box GEP. Science and statistics. Journal of the American Statistical Association. 1976;71:791–799

9. Guyton AC, Coleman TG, Cowley AW, Jr., Liard JF, Norman RA, Jr., Manning RD, Jr. Systems analysis of arterial pressure regulation and hypertension. Ann Biomed Eng. 1972;1:254–281 [PubMed: 4358506]

10. Schmidlin O, Forman A, Leone A, Sebastian A, Morris RC, Jr., Salt sensitivity in blacks: Evidence that the initial pressor effect of nacl involves inhibition of vasodilatation by asymmetrical dimethylarginine. Hypertension. 2011;58:380–385 [PubMed: 21788605]

11. Huxley TH. Critiques and addresses. London: MacMillan and Co.; 1873.

12. Guyton AC. The surprising kidney-fluid mechanism for pressure control--its infinite gain! Hypertension. 1990;16:725–730 [PubMed: 2246039]