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ABSTRACT

The term "abnormal pressure natriuresis" refers to a subnormal effect of a given level of blood pressure (BP) on sodium excretion. It is widely believed that abnormal pressure natriuresis causes an initial increase in BP to be sustained. We refer to this view as the "pressure natriuresis theory of chronic hypertension." The proponents of the theory contend that all forms of chronic hypertension are sustained by abnormal pressure natriuresis, irrespective of how hypertension is initiated. This theory would appear to follow from "the three laws of long-term arterial pressure regulation" stated by Guyton and Coleman more than three decades ago. These "laws" articulate the concept that for a given level of salt intake, the relationship between arterial pressure and sodium excretion determines the chronic level of BP. Here we review and examine the recent assertion by Beard that these "laws" of long-term BP control amount to nothing more than a series of tautologies. Our analysis supports Beard's assertion, and also indicates that contemporary investigators often use tautological reasoning in support of the pressure natriuresis theory of chronic hypertension. Although the theory itself is not a tautology, it does not appear to be testable because it holds that abnormal pressure natriuresis causes salt-induced hypertension to be sustained through abnormal increases in cardiac output that are too small to be detected.

INTRODUCTION

As noted by Hall, Guyton, and others, the terms "pressure natriuresis"[1,2] and "pressure natriuresis mechanism"[3] refer to the "effect of arterial pressure on renal excretion of sodium."[1-3] It is contended that "in all forms of hypertension, including essential hypertension, pressure natriuresis is abnormal."[4] It is further contended that hypertension "cannot be sustained if pressure natriuresis is unaltered"[5] and that "in all forms of hypertension that have been studied, there is a shift of renal-pressure natriuresis that sustains the hypertension."[6] Recently, Crowley and Coffman have reviewed "evidence supporting the premise that an impaired capacity of the kidney to excrete sodium in response to elevated blood pressure (BP) is a major contributor to hypertension, irrespective of the initiating cause."[7] Few investigators question the idea that: chronic hypertension is sustained by abnormal pressure natriuresis regardless of the initial cause of the hypertension. Here we use the term "pressure natriuresis theory of chronic hypertension" to refer to the view that abnormal pressure natriuresis causes an initial increase in BP to be sustained.

Background on Pressure Natriuresis

Increases in systemic BP may directly increase sodium excretion by causing increases in renal arterial perfusion pressure.[8,9] However, even when increases in renal arterial perfusion pressure are experimentally prevented, salt-induced increases in systemic BP can be associated with increases in sodium excretion, and sodium balance (sodium output = sodium intake) can be attained through multiple mechanisms besides “renal-pressure” natriuresis.[10] During increases in salt intake, increases in

BP may be correlated with, but not necessarily causal of, alterations in the activity of a variety of factors that promote natriuresis.[9,10] Further, as emphasized by Bie,[11] and as also observed in studies by other investigators,[12] changes in arterial pressure are not necessary for the changes in natriuresis that occur with ordinary dietary increases in salt intake.

Distinguishing the "Pressure Natriuresis Concept" from the "Pressure Natriuresis Concept of Long Term Blood Pressure Control"

In the present analysis, we do not question the "pressure natriuresis concept" that in some circumstances, increased arterial pressure may contribute to an acute or chronic increase in sodium excretion. It is important to distinguish between the "pressure natriuresis concept" itself and the "pressure natriuresis concept of long term blood pressure control," that is, the concept that for a given level of salt intake, the pressure natriuresis relationship determines the chronic level of arterial pressure.[9,13,14] Here we question the logic of the "pressure natriuresis concept of long term blood pressure control," and we question the pressure natriuresis theory of chronic hypertension.

Is The Pressure Natriuresis Theory Of Chronic Hypertension Based On Tautological Thinking ?

The pressure natriuresis theory of chronic hypertension would appear to follow from what Guyton and Coleman called "the three laws of long-term arterial pressure

regulation."[13] These “laws” of long term arterial pressure regulation are shown in the Supplementary Information section and articulate the pressure natriuresis concept of long term BP control stated earlier. Recently, Beard published an editorial in which he asserts that these "laws" of long-term arterial pressure regulation amount to a series of tautologies.[15] Beard's assertion raises the possibility that for decades, many investigators in the field have continued to entertain, if not embrace, a theory for the pathogenesis of chronic hypertension that is based on tautological thinking. In the current analysis, we: 1) review and examine Beard's assertion that the Guyton-Coleman "laws" of long-term arterial pressure regulation are tautologies, 2) address logical issues with statements made in support of the pressure natriuresis theory of chronic hypertension, and 3) discuss whether the pressure natriuresis theory of chronic hypertension is a tautology and whether it can be tested.

Definition Of A Tautology

A proposition that must be true simply by definition of terms used in the proposition is a tautology.[16] For example, the following proposition is a tautology: “all men who have never been married are bachelors.” Of course, given the definition of the word bachelor, the proposition must be true. Consider another proposition: Condition X is present in all forms of chronic hypertension. This proposition would be a tautology, for example, if the presence of "condition X" is operationally defined as the maintenance of a beating heart together with chronic hypertension. In this case, it would be equivalent to merely stating that the maintenance of a beating heart together with chronic hypertension is present in all forms of chronic hypertension. However, if

one is not familiar with the operational definition of "condition X", the tautology would not be evident. While the proposition that condition X is present in all forms of chronic hypertension is true (given the definition of condition X, the statement must be true), tautological propositions are trivial; they do not further the understanding of the consideration at issue. As noted by Beard, tautologies are true merely by virtue of saying the same thing twice.[15] Beard contends that tautologies in physiology textbooks and in many articles have hampered progress in the field of hypertension.[15]

Analysis of Beard's Assertion That the Guyton-Coleman "Laws" of Long-Term Arterial Pressure Regulation Amount to a Series of Tautologies

Beard[15] recast the Guyton-Coleman "laws" of long term BP regulation by using algebraic symbols in place of the terms in the "laws," and mathematically demonstrated that each "law" is a tautology, i.e., each "law" merely states something that must be true based on the definition of terms used in the "laws." If Beard's analysis is correct, these Guyton-Coleman "laws," and the pressure natriuresis concept of long term BP control expressed by the "laws," are no more meaningful than the statement that "condition x is present in all forms of chronic hypertension" (when the term "condition x" is defined as the maintenance of a beating heart together with chronic hypertension). In the Supplementary Information section, we review and examine Beard's analysis in detail. Our analysis of the "laws" shows, as did Beard's, that each "law" is a tautology.

In light of Beard's analysis and conclusions, and our analysis which supports his conclusions, we next consider whether certain statements often made in support of the

pressure natriuresis theory of chronic hypertension involve tautologies and circular reasoning, and whether the theory itself is a tautology. To do this, it is necessary to first explicitly state the operational definition of "abnormal pressure natriuresis" in someone with chronic hypertension. Without knowing how the presence of “abnormal pressure natriuresis” is operationally defined, it is difficult to discern whether statements that include the term “abnormal pressure natriuresis” are tautologies.

How is the Term "Abnormal Pressure Natriuresis" Operationally Defined ?

The terms "abnormal pressure natriuresis," "shift in pressure natriuresis," "resetting of pressure natriuresis," "impaired pressure natriuresis," and "altered pressure natriuresis" are used interchangeably and generically refer to a putatively subnormal effect of a given level of BP on sodium excretion. Here we use the term "abnormal pressure natriuresis."

Although the term "abnormal pressure natriuresis" generically refers to the occurrence of a putatively subnormal effect of a given level of BP on sodium excretion, it is important to understand how abnormal pressure natriuresis in an individual with chronic hypertension is operationally defined in practice. One must have a way to operationally define the presence of "abnormal" and "normal" pressure natriuresis if one is to experimentally test whether "abnormal pressure natriuresis" is chronically present in an individual with hypertension. Because the current analysis is focused on the role of abnormal pressure natriuresis in causing hypertension to be chronically sustained, we discuss how the presence of abnormal pressure natriuresis is

operationally defined in chronic studies of pressure natriuresis in intact individuals with chronic hypertension.

Chronic Studies of Pressure Natriuresis in Intact Humans and Animals With Hypertension

In chronic studies of pressure natriuresis, intact humans or animals are subjected to different levels of salt intake and BP is measured at each level of salt intake.[13] For each level of salt intake tested, the measurement of BP is obtained after the subject is judged to have achieved a steady state with respect to both sodium balance (sodium output = sodium intake) and BP. It is important to recognize that these chronic studies of pressure natriuresis in intact hypertensive and normotensive subjects do not actually show the effects of increasing renal artery perfusion pressure per se on sodium excretion. Rather, they show the effects of increasing salt intake on sodium excretion and systemic BP. Nevertheless, investigators refer to graphical curves that display the results of these studies as "chronic pressure natriuresis curves,"[17] "pressure natriuresis curves,"[18] or even as "renal-pressure natriuresis curves"[9] (sometimes referred to as "chronic renal function curves").[19,20] Examples of "chronic pressure natriuresis curves" are shown and discussed in Figures 1 and 2. Note that "chronic pressure natriuresis curves" do not necessarily represent the effects of different levels of renal perfusion pressure on sodium excretion and could reflect the effects of other mechanisms that affect sodium excretion (Figure 2).

How Is Abnormal Pressure Natriuresis Operationally Defined in Chronic Studies of Pressure Natriuresis and Hypertension ?

In chronic studies of pressure natriuresis in intact subjects: 1) normal pressure natriuresis is operationally defined by the presence of sodium balance together with normal BP in a steady state, and 2) abnormal pressure natriuresis is operationally defined by the presence of sodium balance together with increased BP in a steady state.[4,5] Thus, in chronic studies of pressure natriuresis in intact hypertensive and normotensive subjects, the variable that distinguishes subjects with abnormal pressure natriuresis from normal control subjects (those with normal pressure natriuresis) is actually the level of BP, not the level of sodium excretion (because in these studies, everyone is in sodium balance and the subjects with abnormal pressure natriuresis are excreting the same amount of sodium as the normal subjects).[4,5] Note that simply *by operational definition* in these studies, "abnormal pressure natriuresis" *must* be present in individuals with sustained hypertension.

The operational definition of abnormal pressure natriuresis in subjects with chronic hypertension is encapsulated by the statement of Hall and colleagues that "In all forms of hypertension, including human hypertension, pressure natriuresis is abnormal *because* sodium excretion is the same as in normotension despite increased arterial pressure."[4] Hall and colleagues also state that "in all forms of chronic hypertension, the renal-pressure natriuresis mechanism is abnormal *because* sodium excretion is the same as in normotension despite increased blood pressure"[5] (italics added by current authors to both statements).

Tautological Statements Used In Support of the Pressure Natriuresis Theory of Chronic Hypertension

According to Granger and Hall, a "key finding" in studies of pressure natriuresis and hypertension is that "renal-pressure natriuresis is abnormal in all types of experimental and clinical hypertension."[6] It is also said that "direct support for a major role of renal-pressure natriuresis in long-term control of arterial pressure and sodium balance comes from studies demonstrating that pressure natriuresis is impaired in all forms of chronic hypertension."[1] What is the meaning of statements such as "pressure natriuresis is impaired (abnormal) in all forms of chronic hypertension"?[1] To understand the meaning of this kind of statement, we substitute the operational definition of abnormal pressure natriuresis used in chronic studies of pressure natriuresis[4,5] for the phrase "pressure natriuresis is abnormal" in the statement. With this substitution, the statement becomes (with the substitution shown in brackets): "[sodium balance together with increased blood pressure are present in a steady state] in all forms of chronic hypertension." Thus, the statement merely says that increased BP is present in a steady state in all forms of chronic hypertension. This kind of statement would seem to satisfy the definition of a tautology because the statement is true simply based on how the term “abnormal pressure natriuresis” (or "abnormal renal-pressure natriuresis mechanism") is defined in an individual with chronic hypertension. The proviso that sodium balance is also present in all forms of chronic hypertension is not helpful: In chronic studies of pressure natriuresis in which sodium excretion and BP

are in steady state conditions, everyone is in sodium balance regardless of whether or not they have chronic hypertension.

The Argument As To Why Hypertension Cannot Be Sustained if Pressure Natriuresis is Normal

Proponents of the pressure natriuresis theory of chronic hypertension do not contend that abnormal pressure natriuresis is required for all acute increases in BP. However, they do contend that when BP is initially (acutely) elevated, the increase in BP cannot become sustained without an impairment in pressure natriuresis[1,7] or in the renal-pressure natriuresis mechanism[4] - "because sodium excretion exceeds intake, thereby reducing extracellular fluid volume until blood pressure returns to normal and intake and output of sodium are balanced."[1,4] That is, the argument is made that when BP is initially increased, the hypertension cannot be sustained if pressure natriuresis is normal because sodium excretion would be in excess of sodium intake until arterial pressure returns to normal.[1,4] However, this contention seems to involve circular reasoning because it uses a tautology to make the argument. To consider this possibility, it is necessary to understand how "normal pressure natriuresis" is operationally defined in individuals in whom BP is initially (acutely) increased (because the argument holds that when BP is initially increased, the hypertension cannot be sustained if pressure natriuresis is normal).

The Definition of "Normal Pressure Natriuresis" in Individuals In Whom Blood Pressure Is Initially Increased

How do the proponents of the pressure natriuresis theory operationally define the presence of normal pressure natriuresis in individuals in whom BP is initially increased? Recall that in studies in subjects in a chronic, steady state with respect to sodium balance and BP, the presence of normal pressure natriuresis is operationally defined by the presence of sodium balance together with normal BP. However, in subjects who are not in a steady state with respect to sodium balance and BP, e.g., subjects with an initial, acute increase in BP, the presence of normal pressure natriuresis is operationally defined in a different manner: According to Hall and others, when BP is initially increased, i.e., before the occurrence of steady state hypertension, normal pressure natriuresis is operationally defined by the presence of sodium excretion in excess of sodium intake until BP returns to normal.[1,4] Note that by this definition, an individual with "normal pressure natriuresis" can have an acute increase in BP, but they *cannot* develop sustained steady state (chronic) hypertension.

The Logical Issue With the Argument Why An Initial Increase In Blood Pressure Cannot be Sustained if Pressure Natriuresis is Normal

The argument has been made that when blood pressure is initially increased, the hypertension cannot be sustained if pressure natriuresis is normal because sodium excretion would be in excess of sodium intake until arterial pressure returns to normal.[1,4] The tautological nature of this argument can be appreciated by substituting the operational definition of normal pressure natriuresis in someone with an initial (acute) increase in blood pressure for the phrase "pressure natriuresis is normal" in the argument. By making this substitution (with brackets used to identify the substitution),

the argument becomes: "When blood pressure is initially increased, the hypertension cannot be sustained if [sodium excretion is in excess of sodium intake until blood pressure returns to normal] because sodium excretion would be in excess of sodium intake until blood pressure returns to normal."

This argument constitutes circular reasoning because a tautology is used to make the argument. The argument is true simply based on the operational definition of "normal pressure natriuresis" in someone with acutely increased BP (acute hypertension). This argument is similar to stating that in an individual with acute hypertension, increased BP cannot be sustained if something happens that makes arterial pressure return to normal because something happens that makes arterial pressure return to normal. Such an argument has no meaning *irrespective* of whatever is believed to make arterial pressure return to normal.

Is The Pressure Natriuresis Theory of Chronic Hypertension A Tautology ?

The pressure natriuresis theory of chronic hypertension holds that abnormal pressure natriuresis *causes* an initial increase in BP to be sustained.[1,4,5] Because "abnormal pressure natriuresis" is operationally defined as the maintenance of sodium balance in someone with increased BP, the pressure natriuresis theory of chronic hypertension holds that it is the maintenance of sodium balance that *causes* an initial increase in BP to become sustained. Stated in this fashion, the theory does not simply say the same thing twice in different words; it is not a proposition that is true simply based on the definition of terms used in the proposition. Thus, the pressure natriuresis

theory of chronic hypertension itself is not a tautology, and it should not be deemed invalid because tautological statements and circular reasoning are used to promote the theory. However, if the critical tenets of the theory cannot be adequately tested, this would raise questions about its usefulness as a scientific theory.[21,22]

Can the Pressure Natriuresis Theory of Chronic Hypertension Be Tested?

Many if not most individuals with chronic hypertension, including essential hypertension and salt-dependent forms of chronic hypertension such as hyperaldosteronism, are hemodynamically characterized by increased total peripheral resistance (TPR).[23-25] This raises a critical and perplexing question, how does abnormal pressure natriuresis lead to the sustained increase in TPR that hemodynamically sustains the increased BP in many if not most cases of hypertension?

For example, in salt-induced hypertension, proponents of the pressure natriuresis theory contend[9,13,14,26] that abnormal pressure natriuresis causes increases in cardiac output (CO) that lead to sustained increases in TPR through the pathways shown in Figure 3. In salt-induced ("volume-loading") hypertension, it is contended that "it is the increased cardiac output that is basic to this type of hypertension, because without it the elevated total peripheral resistance itself cannot be maintained."[13] As noted by Cowley, "It is evident that neither blood volume nor cardiac output could theoretically return completely to normal or the stimulus for increased vascular resistance to flow would be abolished."[26]

Importantly, and in direct opposition to these statements, at no time during the initiation or maintenance of salt-induced hypertension has it been found that CO is greater in salt-loaded salt-sensitive subjects than in salt-loaded normal controls.[27] To address this fact, the proponents of the pressure natriuresis theory contend that the abnormal increases in CO are too small to detect.[9,13,14,28] For example, it is stated that: "The long term elevation in cardiac output is so slight that usual methods for measuring cardiac output are not adequate to prove that it is indeed elevated."[13] According to Guyton, Hall, and others, "it will be literally impossible to measure with any known techniques the slight changes in cardiac output that would be required to cause serious hypertension."[29] Recently, Hall has suggested[28] that greater salt-induced increases in cardiac output in salt-sensitive subjects than in salt-resistant normal controls are too small to detect even with impedance cardiography, a method that we have found[30] capable of detecting increases in cardiac output of 4 - 5%. Accordingly, in salt-induced hypertension, it would not seem possible to test the mechanism through which abnormal pressure natriuresis is theorized to cause sustained elevations in TPR and BP, because the abnormal increases in CO held to mediate these effects are said to be too small to detect.[9,13,14,28,29] Thus, the proponents of the pressure natriuresis theory of chronic hypertension appear to have advanced an un-testable theory.

Conclusion

The Guyton-Coleman "laws" of long-term arterial pressure regulation articulate the pressure natriuresis concept of long term BP control: For a given level of salt intake,

the pressure natriuresis relationship determines the chronic level of BP. We concur with Beard's assertion that these "laws" amount to a series of tautologies.[15] Further, by understanding how "abnormal pressure natriuresis" is operationally defined in individuals with chronic hypertension, it can be appreciated that tautologies and circular reasoning have been used to support the theory that abnormal pressure natriuresis *causes* an initial increase in BP to be sustained. Although this pressure natriuresis theory of chronic hypertension itself is not a tautology, it appears that the theory cannot be tested. The theory holds that abnormal pressure natriuresis causes sustained salt-induced hypertension by causing abnormal increases in cardiac output that are too small to be detected.[9,13,14,28] These observations add to growing concerns[15,27,31-37] about the pressure natriuresis theory of chronic hypertension. Accordingly, we anticipate that this theory, advanced through the pioneering efforts of Arthur Guyton and others,[4,5,13,38-42] will eventually be replaced by testable theories about the abnormalities that initiate hypertension and cause it to be sustained.

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FIGURE LEGENDS

Figure 1. Examples of "chronic renal function curves" plotted on the "pressure analysis diagram."[13,19] Note that "chronic renal function curves" are also referred to as "chronic pressure natriuresis curves"[17] or as "renal-pressure natriuresis curves"[9] even though the natriuresis is not necessarily being mediated by the renal-pressure natriuresis mechanism (e.g., see Figure 2). Such curves are typically generated by measuring the effects of changing salt intake on sodium excretion and systemic arterial pressure. The "chronic renal function curve" ("chronic pressure natriuresis curve") is defined by the mathematical relationship between steady state sodium output values (*y*) and arterial pressure values (*x*).[9,13,17-20] The arterial pressure and sodium output values are obtained after the subject is judged to have achieved a steady state with respect to both blood pressure and sodium balance (sodium output = sodium intake). Because non-renal losses of sodium are regarded as negligible, the levels of sodium intake and renal sodium output are considered to be identical in the steady state. Thus, these "pressure natriuresis curves" are drawn by plotting data for either chronic sodium intake or chronic sodium output against the data for chronic blood pressure.

For reasons that are not clear, sodium intake or sodium output values are customarily plotted on the dependent (y) axis and the systemic arterial pressure values are plotted on the independent (x) axis even though the arterial pressure levels and sodium output values are dependent on changes in salt intake in the experiment. Plotting data in this fashion may give the incorrect impression that changes in urine

sodium output (*y*) that are associated with changes in systemic arterial pressure (*x*) are being *caused* by the changes in systemic arterial pressure (*x*) or by changes in renal arterial perfusion pressure. This representation of "pressure-natriuresis curves" ("renal function curves") could confuse people into supposing that the curves depict effects of the renal-pressure natriuresis mechanism (the direct effect of arterial pressure on sodium excretion). In fact, the curves simply depict a mathematical relationship between two variables (systemic arterial pressure and sodium output). A mathematical relationship between the two variables (systemic arterial pressure and sodium output) does not establish a cause and effect relationship between the two variables.

An "equilibrium point" on this diagram is any point where the steady state level of sodium intake = sodium output (*y*) crosses a chronic renal function curve (chronic pressure natriuresis curve).[13] Such an "equilibrium point" on a "chronic renal function curve" simply depicts the chronic level of blood pressure for a given chronic level of salt intake in an individual in steady state sodium balance (sodium output = sodium intake). Four examples of "equilibrium points" are shown and labeled as "A", "B", "C", and "D". The horizontal dotted lines depict the steady state levels of sodium intake/sodium output crossing the renal function curves at these "equilibrium points." Guyton contended that an "equilibrium point depicts the arterial pressure that will *provide* equilibrium between output and intake"[13] (italics added be current authors). However, renal function curves and points on those curves do not establish that it is arterial pressure that accounts ("provides") for the equivalence ("equilibrium") between sodium output and sodium intake.

Figure 2. "Chronic pressure natriuresis curves" ("chronic renal function curves") do not necessarily represent effects of the renal-pressure natriuresis mechanism (the effect of renal arterial perfusion pressure on sodium excretion). Steady state urinary sodium output values are plotted against either steady state *renal arterial* pressure values (left panel, “chronic *renal-pressure* natriuresis curves”) or steady state *systemic arterial* pressure values (right panel, “chronic pressure natriuresis curves”) using results reported by Hall and colleagues in dogs with surgically reduced renal mass[10] and in normal dogs.[12] All dogs were studied when given either a low salt intake or a high salt intake. In the dogs with reduced renal mass, a servo control device was used to experimentally prevent changes in renal arterial perfusion pressure during increases in salt intake that caused increases in systemic arterial pressure.[10]

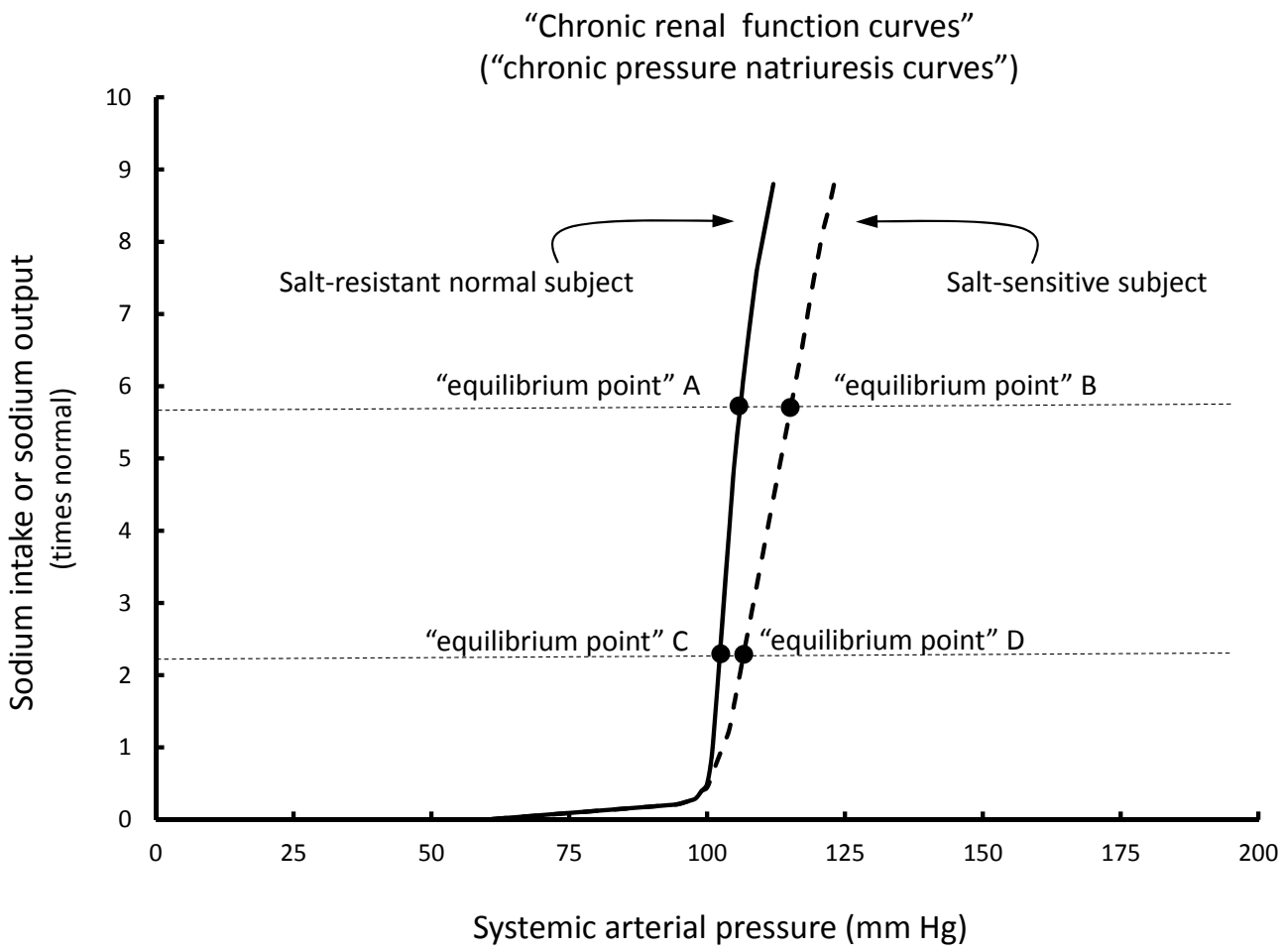
The *renal-pressure* natriuresis curves in the left panel show that with salt loading in reduced renal mass dogs as well as in normal dogs, substantial natriuresis occurs and sodium balance is attained in the absence of increases in *renal arterial* perfusion pressure.[10] Although increases in sodium excretion are associated with increases in *systemic arterial* pressure in the reduced renal mass dogs (right panel), the increases in sodium excretion are not being caused by increases in renal perfusion pressure (because no changes occurred in renal perfusion pressure as shown in the left panel). As noted by Hall and colleagues, even "in the absence of pressure natriuresis, other important control mechanisms can be recruited to maintain sodium and water balance." [10] These observations demonstrate that "chronic pressure natriuresis curves"

(e.g.,Figure 1) do not necessarily represent effects of the renal-pressure natriuresis mechanism and could reflect changes in natriuresis that are not caused by changes in either renal or systemic arterial pressure.

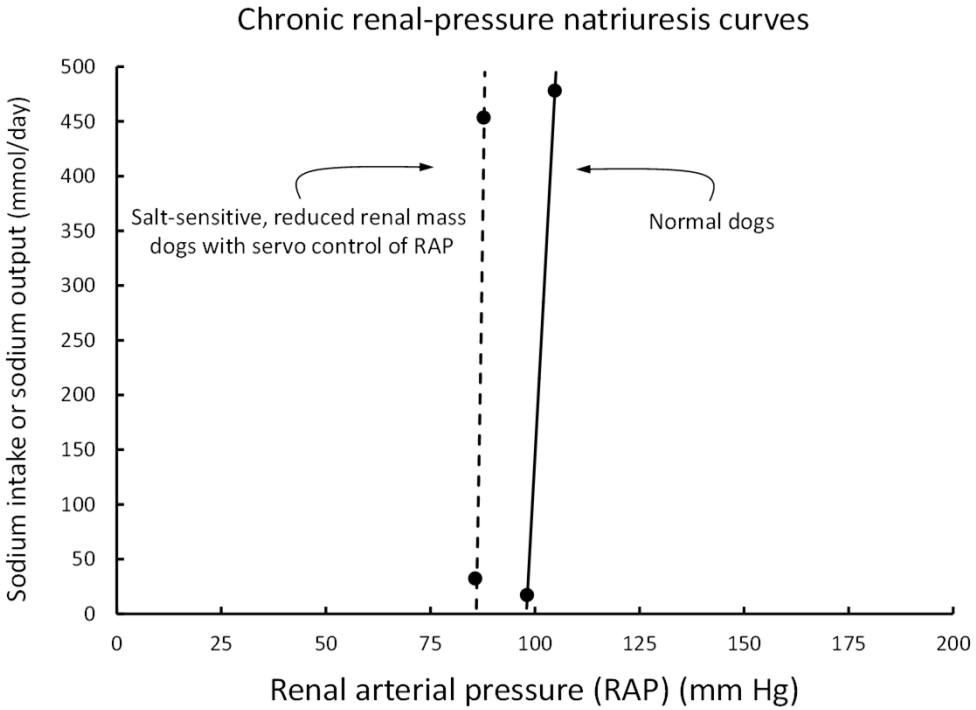
Figure 3. The mechanism whereby abnormal pressure natriuresis is said to cause sustained salt-induced increases in blood pressure (BP) and total peripheral resistance (TPR) (left panel),[9,13,14,26] and the mechanism whereby normal pressure natriuresis is said to prevent salt-induced increases in BP (right panel).[9,13,14,26] Abnormal pressure natriuresis is said to cause sustained salt-induced increases in BP and TPR by initiating and sustaining abnormally increased sodium balance and cardiac output.[9,13,14,26] The abnormally increased CO directly contributes to increased BP.[9,13,14,26] The abnormally increased CO is held to cause increases in TPR through several mechanisms, and the increases in TPR contribute to sustaining the increased BP.[9,13,14,26] Increases in CO are held to increase TPR through the process of "autoregulation" which involves "contraction of the smooth muscle in arteriolar walls"[14] evoked by CO-driven increases in tissue blood flow[14,26] and in transmural pressure.[26] Increases in CO are also said to cause increases in TPR by causing CO-initiated increases in BP that lead to structural changes (e.g., hypertrophy) of the blood vessel walls.[14,26] The diagram shows that for abnormal pressure natriuresis to cause sustained salt-induced increases in BP and TPR, the abnormal pressure natriuresis must both initiate and sustain abnormally increased CO. Note that when salt intake is initially increased, and before the occurrence of steady state sodium balance and hypertension, abnormal pressure natriuresis is said to cause sodium output to be less than sodium intake. Once steady state sodium balance

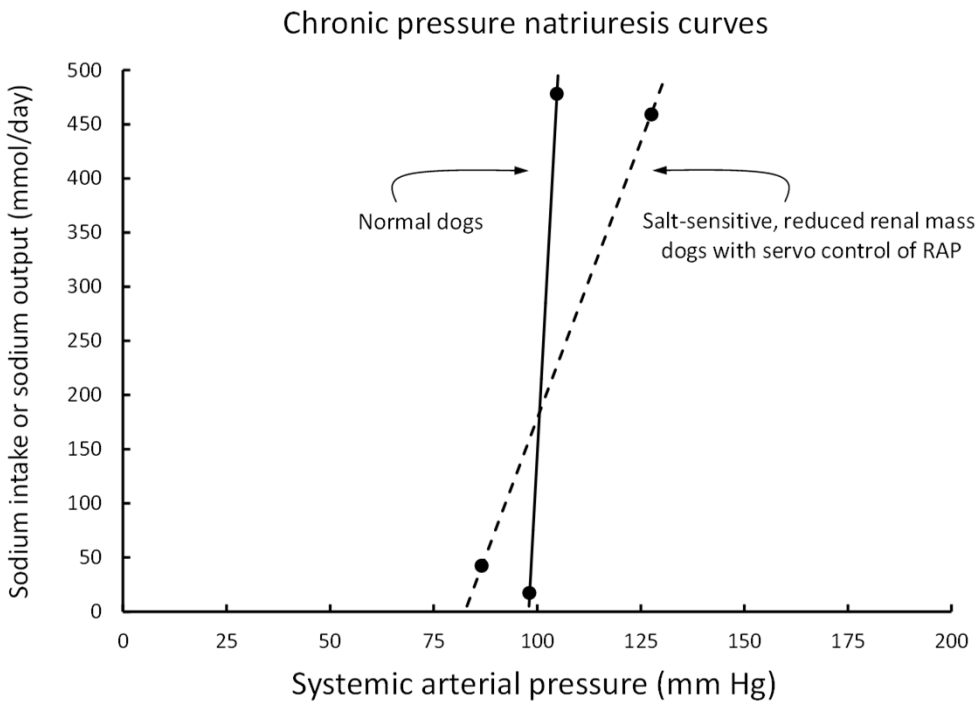
and hypertension have been attained, abnormal pressure natriuresis is said to maintain sodium balance by preventing the increased BP from causing sodium output to exceed sodium intake. In contrast, when salt intake is increased in an individual with normal pressure natriuresis, it is said that there is little or no increase in BP "because the kidneys rapidly eliminate the excess salt and blood volume is hardly altered."[9]

BW Figure 1

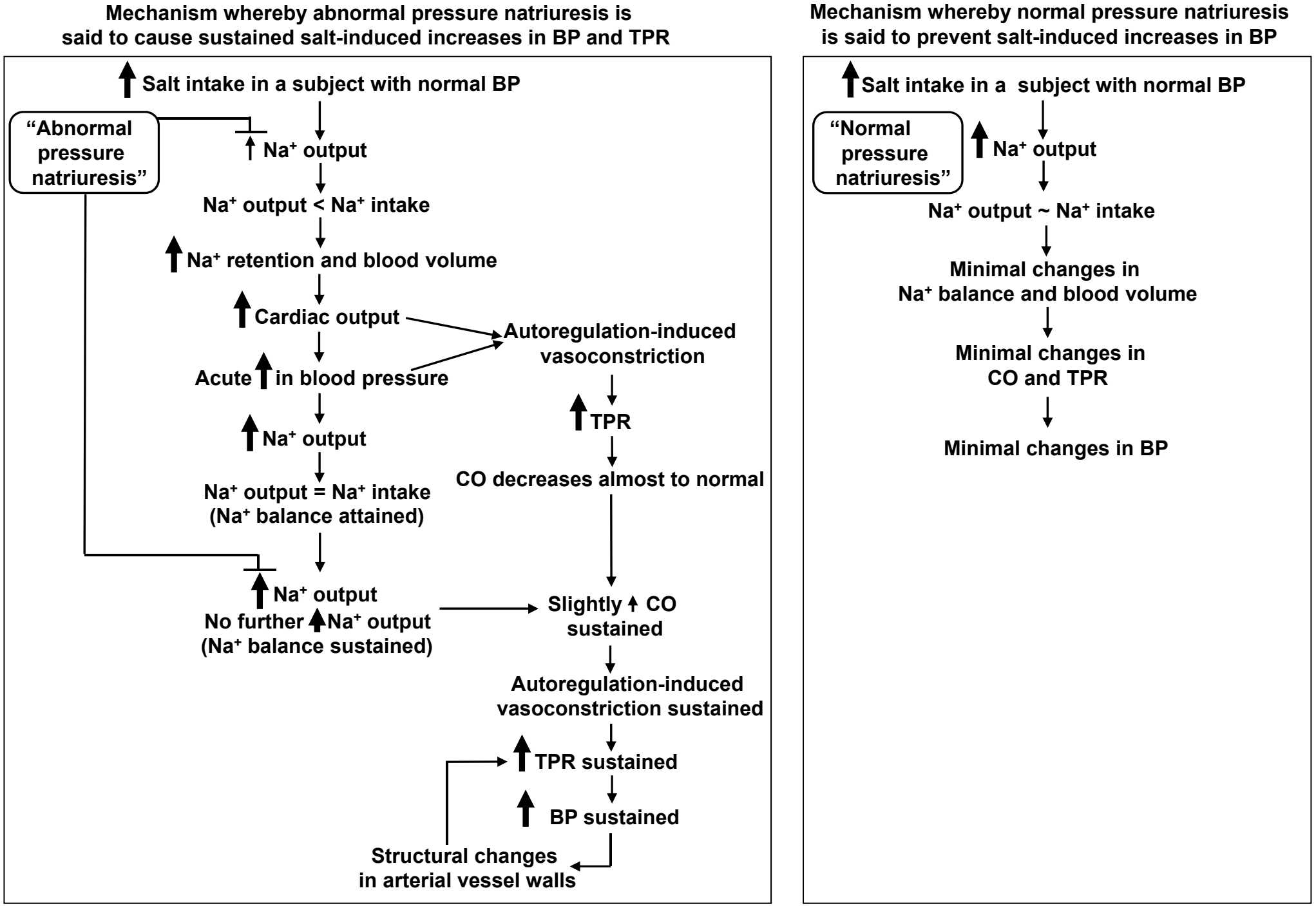

"Chronic renal function curves"
("chronic pressure natriuresis curves")
Sodium intake or sodium output
(times normal)
Systemic arterial pressure (mm Hg)
Salt-resistant normal subject
Salt-sensitive subject
"equilibrium point" A
"equilibrium point" B
"equilibrium point" C
"equilibrium point" D
0
1
2
3
4
5
6
7
8
9
10
0
25
50
75
100
125
150
175
200

BW Figure 2


Chronic renal-pressure natriuresis curves
Sodium intake or sodium output (mmol/day)
Renal arterial pressure (RAP) (mm Hg)
Salt-sensitive, reduced renal mass dogs with servo control of RAP
Normal dogs
0
50
100
150
200
250
300
350
400
450
500
0
25
50
75
100
125
150
175
200


Chronic pressure natriuresis curves
Sodium intake or sodium output (mmol/day)
Systemic arterial pressure (mm Hg)
Normal dogs
Salt-sensitive, reduced renal mass dogs with servo control of RAP
0
50
100
150
200
250
300
350
400
450
500
0
25
50
75
100
125
150
175
200

BW Figure 3


Mechanism whereby abnormal pressure natriuresis is said to cause sustained salt-induced increases in BP and TPR
Salt intake in a subject with normal BP
"Abnormal pressure natriuresis"
↑ Na+ output
Na+ output < Na+ intake
↑ Na+ retention and blood volume
↑ Cardiac output
Autoregulation-induced vasoconstriction
Acute ↑ in blood pressure
↑ TPR
↑ Na+ output
CO decreases almost to normal
Na+ output = Na+ intake (Na+ balance attained)
↑ Na+ output
No further ↑ Na+ output (Na+ balance sustained)
Slightly ↑ CO sustained
Autoregulation-induced vasoconstriction sustained
↑ TPR sustained
↑ BP sustained
Structural changes in arterial vessel walls
Mechanism whereby normal pressure natriuresis is said to prevent salt-induced increases in BP
Salt intake in a subject with normal BP
"Normal pressure natriuresis"
↑ Na+ output
Na+ output ~ Na+ intake
Minimal changes in Na+ balance and blood volume
Minimal changes in CO and TPR
Minimal changes in BP

SUPPLEMENTARY MATERIAL

Logical Issues With the Pressure Natriuresis Theory of Chronic Hypertension

Running title: Logical Issues With The Pressure Natriuresis Theory

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Consideration of the Assertion That the Guyton-Coleman "Laws" of Long-Term Arterial Pressure Regulation Amount to a Series of Tautologies

Here we consider the assertion of Beard[1] that the "three laws of long-term arterial pressure regulation" of Guyton and Coleman[2] amount to a series of tautologies. The "laws" of long term arterial pressure regulation as originally stated by Guyton and Coleman[2] are listed below. Note that these "laws" have also been stated by Guyton and other investigators in essentially the same way.[3-5] These "laws" are an expression of the pressure natriuresis concept of long term blood pressure control: for a given level of salt intake, the pressure natriuresis relationship determines the chronic level of blood pressure.

Law # 1: "If the long-term arterial pressure level changes, either the chronic renal function curve or the net intake curve, or both, must have changed."

Law #2: "If the equilibrium point in the pressure-analysis diagram changes to a new arterial pressure level, then the actual regulated arterial pressure will eventually also change to that new level."

Law #3: "The two sole determinants of the long-term arterial pressure level are: (1) the renal function curve and (2) the intake curve."

To understand whether these "laws" of long-term blood pressure regulation are tautologies, i.e., propositions that are true simply based on the definitions of terms used in the laws, it is necessary to understand how certain terms in the laws are defined by Guyton and Coleman.[2] Therefore, we first discuss how various terms in the

laws are defined. We then recast the laws by substituting algebraic symbols for the terms used in the laws.

Definition of "chronic renal function curve"

According to Guyton and Coleman, the "chronic renal function curve" is defined by a mathematical function *y(x)* in which the values of *x* and *y* used to derive the mathematical function are *x* = systemic arterial pressure and *y* = sodium output = sodium intake.[2] Examples of "chronic renal function curves" (also known as "chronic pressure natriuresis curves") are shown in Figures 1 and 2 in the main article.

Definition of "net intake curve"

As described by Guyton and Coleman, the "net intake curve" in normotensive and hypertensive subjects is simply equivalent to the steady state level of sodium intake (*y* = steady state sodium intake = "net intake curve").[2]

Definition of "equilibrium point in the pressure analysis diagram"

The "pressure analysis diagram" is the same diagram used to plot chronic renal function curves, i.e., a diagram in which systemic arterial pressure is plotted on the x axis and sodium output or sodium intake is plotted on the y axis (e.g., see Figure 1 in the main article). According to Guyton and Coleman, the location of an "equilibrium point in the pressure analysis diagram" is the point where the steady state level of sodium intake = sodium output (*y*) crosses the chronic renal function curve (*y(x)*).[2] Four examples of "equilibrium points" are shown in Figure 1 in the main article and are labeled as "A", "B", "C", and "D".

Based on how the various terms in the "laws" of long term blood pressure regulation are defined by Guyton and Coleman, algebraic symbols are assigned to the terms as follows:

x = steady state systemic arterial pressure

y = steady state sodium output = steady state sodium intake = the "net intake curve"

y(x) = the "chronic renal function curve."

Note: the "chronic renal function curve" is defined by the mathematical relationship between y and x where *y* (steady state sodium output) is a *mathematical function* of *x* (steady state arterial pressure) whether or not sodium output (*y*) is a *mechanistic function* of arterial pressure (*x*).

Having established how the terms in the "laws" are defined, and having assigned algebraic symbols to those terms, the "laws" can be recast using algebraic symbols as follows. Note that the following analysis is being made under the assumption that the chronic renal function curve (*y(x)*) is a monotonic function (where a monotonic function is defined as a function that is either entirely non-increasing or non-decreasing (http://mathworld.wolfram.com/MonotonicFunction.html)). This assumption would seem reasonable given that the chronic renal function curve as plotted by Guyton, Coleman, and others does appear to be monotonic over the intervals of blood pressure usually examined.[2,5-9]

Law #1: If *x* changes, then either *y(x)* or *y*, or both must have changed.

Law# 2: If *y* changes and or if *y(x)* changes, then *x* must change accordingly.

Law #3: The sole determinants of *x* are y(x) and *y*.

These substitutions reveal the "laws" of long-term blood pressure regulation as stated by Guyton et al[2,3] to be tautologies. Obviously, according to the definition of the "chronic renal function curve" (*y* is a monotonic mathematical function of *x*), if a value of *x* changes *on the diagram* and the mathematical function is not changed, then the value of *y* must change *on the diagram*; if a value of *x* changes *on the diagram* and the value *y on the diagram* determined by the mathematical function is not changed, then the mathematical function must change. The "laws" make statements about relationships between arterial pressure (*x*), sodium output or sodium intake (*y*), and the chronic renal function curve (y(x)) that are true simply based on how terms in the laws are defined. The "laws" establish nothing about mechanistic (cause and effect) relationships between arterial pressure and sodium output and nothing about the mechanistic determinants of long-term arterial pressure regulation. The "laws" are simply descriptors of mathematical relationships but not necessarily mechanistic relationships.

This analysis of the "laws of long-term arterial pressure regulation" accords with Beard's analysis demonstrating that the Guyton-Coleman laws amount to a series of tautologies.[1] As noted by Beard, the "laws" are "a series of statements that are true merely by virtue of saying the same thing twice."[1] This analysis differs from Beard's

analysis in one respect. Beard did not make the assumption that the chronic renal function curve is a monotonic function.[1] Based on the generally accepted definition of a monotonic function as a function that is either entirely non-increasing or non-decreasing, and given the appearance of the curve plotted by Guyton and others,[2,5-9] we assumed the chronic renal function curve to be a monotonic function. Given how the "laws" were originally stated by Guyton and Coleman,[2] Guyton and Coleman also appear to have considered the curve to be a monotonic function. Thus, in the current analysis, we could substitute algebraic symbols for terms in the laws without changing how the laws were originally stated by Guyton and Coleman.[2] Because Beard did not assume the renal function curve to be a monotonic function, Beard's analysis involved a modification of how the laws were originally stated.[1] However, the difference between the current analysis and the original analysis by Beard does not affect the conclusion that each law is a tautology.

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