The Guytonian Equation: Established Physiological Law?

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Abstract The present collection of papers is meant to focus on old and new concepts about venous return. This essay argues that one widely held old concept is wrong. The misconception would be perpetuated by those who speak of "repurposing the systemic venous return model". The model in question describes systemic venous return as driven through a "resistance to venous return" in proportion to the difference between mean systemic pressure and right atrial pressure.

It arose from experiments in which right atrial pressure (Pra) was recorded while flow was forced through the peripheral vasculature by a pump, with data points taken after pressures equilibrated to each new level of flow. The steady-state flow (F) set by the pump could be taken interchangeably as cardiac output (CO) or venous return (VR). Pra at the zero-flow level settled at what is defined as "mean systemic pressure" (Pms), understood as the pressure at which all the elastic segments of the peripheral vasculature equilibrate in the absence of pressure differences associated with flow. Total circulating volume was kept constant, independent of flow level. The data were approximated by the equation $Pra = Pms - F^*RVR$, alternatively written as F = (Pms - Pra)/RVR. From the point of view of the first formulation, we see Pra falling in proportion to F, starting from Pms at zero flow, a

Introduction

In this present focus on old and new concepts about venous return, why perpetuate an old misconception? For example, Normahani, et al.¹, would address problems of chronic venous insufficiency through repurposing the "systemic venous return model". They take the idea that mean systemic pressure (Pms) "drives" venous return as established Physiological law, formulated in the

concise statement of the actual experimental procedure and findings. The second formulation has been seen from a different perspective; that F is proportional to the net driving pressure, i.e., (Pms – Pra), in which Pra is seen as a back pressure opposing venous return. From this point of view, adopted by a leading researcher of his time, A.C. Guyton, comes the idea that, to increase VR, the heart must somehow reduce Pra.

Re-examining the model that Guyton and his coworkers developed reveals that the appearance of Pms in their equation does not identify this variable as a pressure that exists physically at the upstream end of the pathway for venous return. At best, the model offers a way of looking at the factors that determine the equilibrium between the Pra that results in the peripheral vasculature at a particular steady-state level of flow that is consistent with the influence of Pra on the output of the heart. It has nothing to offer for the advancement of understanding of the pathophysiology of real, dynamic flow within vascular segments.

Keywords venous return, cardiac output, mean circulatory filling pressure, mean systemic pressure, peripheral vasculature, venous system

"Guytonian" equation (where VR is venous return, Pra is right atrial pressure, and RVR is the resistance to venous return":

$$VR = \frac{Pms - Pra}{RVR}; \quad (1)$$





Figure 1 - Physical arrangement corresponding to Equation 1. Adapted from Figure 1 in Brengelmann GL, 2019 (see references).

A physical representation of this equation appears in Figure 1. Two elastic chambers are connected through a resistance. The one on the left represents the venous compartment at pressure Pms. The heart-shaped one is meant to corrspond to the elastic right atrium. In this physical arrangement, the imbalance of forces represented by the higher pressure Pms at the upstream end of the connection and the lower "back pressure" at the downstream end will result in flow, quantitatively in accordance with Equation (1). If, somehow, Pra is reduced, then greater VR will result. This is the fundamental idea behind statements like "to increase VR, the heart must reduce the back pressure at the right atrium."

But for how long will flow occur in the arrangement of Figure 1? If the flow were, say, 1 ml/min, the venous compartment would shrink at that rate and the right atrium would experience the corresponding increase in volume. The conventional idea is that the venous return arriving through the resistance is pumped out by the heart at precisely the right rate to balance the inflow. But what about the venous compartment? To be kept at Pms, it must be refilled at a rate that matches its outflow. What is missing in the picture in Figure 1 is the steady removal of VR by the heart and the steady re-supply of the compartment at Pms.

Once we recognize the missing feature of steady resupply of the venous compartment, we must also recognize that it is not the elastic recoil of the compartment that drives VR, but the pump that resupplies it. For a venous compartment at Pms to squeeze out volume at a rate greater than its inflow rate, it must shrink in volume. Since the pressure within an elastic container depends upon its volume, the decline in volume is accompanied by a decline in pressure, inconsistent with the notion that Pms holds steady. Of course, linked volume and pressure changes happen all the time in the dynamics of intravenous volume, a focal topic in this collection of papers. The dynamics of right heart filling involve energy released from the elastic recoil of venous system compartments. But the description embodied in Equation 1 is not about the dynamics of beatby-beat pulsatile flow and volume. It was developed for the steady state situation in which compartment inflows and outflows are matched and VR is exactly equal to cardiac output (CO)

Equation 1 descends from experiments in which flow through the vasculature was set by a pump. Though the flow level was called venous return and was given the term VR, there was no difference between cardiac output, i.e., pump output, and venous return. Pra data points were collected after pressures stabilized after a new level of flow was set. Plotted against VR, they show progressive decline in Pra in inverse proportion to flow, the pattern known as "venous return curves". Guyton and his coworkers reproduced this relationship with their equation². It was developed from a model of the peripheral vasculature as three elastic compartments with specified compliances (ratio of volume increase to increase in distending pressure) connected by vessels with specified resistances (ratio of pressure difference to flow).

The model behind the equation

The conceptual basis for the equation is illustrated in Figure 2. The peripheral vasculature as represented as comprising three elastic compartments, one for the arterial system and two for the venous system, subdivided into peripheral and central compartments. The resistance of the peripheral vasculature was divided into three segments, one between the arterial and peripheral venous compartments, the next between the peripheral and central compartments, and a third that connected the central compartment to the right atrium.

Schematically, these were arranged as the circuit shown in the inset in which a current source (pump), passes current (analogous to flow, i.e., VR) through the resistors to return to the source. Taking pressure as analogous to electrical voltage, the difference between the pressures at the inflow and outflow ends of a resistive element equals the product of its resistance and the current (analogous to flow) passing through it, so, for example, the difference (P3 – P2) equals R3 multiplied by VR. For each elastic element, the volume (analogous to electrical charge) it contains is the product of its capacitance and its distending pressure. The one corresponding to the arterial compartment, for example, contains volume equal to P3 multiplied by C3.





Figure 2 - Above, the physical model from which Guyton, et al., derived the relationship VR = (Pms - Pra)/RVR. Three compartments, respectively at pressures P3, P2, and P1 correspond to the elastic compartments that comprise the peripheral vasculature: respectively arterial, peripheral venous, and central venous. The inset shows the components of the model arranged as an electrical circuit. Steady flow, VR, from a constant-current generator passes through the resistive segments. Pra is voltage (pressure) at right atrium. R1, R2, and R3 are resistances, P1, P2, and P3 are voltages (analogous to pressures in, respectively, central venous, peripheral venous, and arterial compartments). C1, C2, and C3 are capacitances, analogous to compliances of their respective compartments. Sum of charges in capacitances remains constant, independent of VR, analogous to preservation of fixed total circulating volume analogous to the sum P3C3 + P2C2 + P1C1. Because of this stipulation, the term RVR is found to be the sum R1C1 + R2(C1 + C2) + R3(C1 + C2 + C3) all divided by the sum (C1 + C2 + C3).

A key feature of their experiments was that the total volume within the vasculature was kept constant, so Guyton et al., stipulated that the sum $P3\timesC3 + P2\timesC2 + P1\timesC1$ remain constant, independent of VR. With this stipulation plus the relationship between the pressures, Guyton's equation (Equation 1 above) follows. Those who have an appetite for the algebraic details can consult the original paper², or the appendix in reference 3; the general behavior of the model can be appreciated without resort to algebra.

First imagine the arrangement of compartments and resistors of Figure 2 in the condition of zero flow with the elastic compartments empty, like deflated balloons. Now imagine infusing volume from a syringe. As the volume distributes among the compartments, they expand, and the elastic materials of the compartment walls stretch. The mechanical work of forcing volume out of the syringe is being transferred, in part, to mechanical energy stored in the stretched fibers; the remainder expended in overcoming frictional resistance. The tension that develops in the fibers acts as a compressive force, opposing the force applied to



the plunger of the syringe and manifested as pressure, the so-called distending pressure^[i].

After completion of injection of a certain amount of fluid, any temporary pressure differences across the resistive connections associated with movement of volume between compartments settle to zero, making pressure uniform throughout the compartments. Each takes on a volume in proportion to this pressure and its compliance. For a proper treatment, we should consider that hollow elastic structures can take on volume up to a point without developing a distending pressure; this is the subject of stressed vs unstressed volume, treated in reference 3. Guyton, et al., did not bother with it, nor need we at this point. They simply used the proportionality $P = C \times V$ for the relationship between compartmental pressures and volumes².

What is important to recognize that, once sufficient volume has been infused, a uniform pressure will be felt

in all three compartments. Upon adding more fluid, this uniform pressure will increase; by the terms of the model, it will equal the total volume divided by the sum of the compliances. This is the explicit analogy to what is defined as Pms: the uniform pressure throughout the vasculature that is found after equilibration to the condition of zero flow.

Returning to the three-compartment image in Figure 2, we ask what happens if the flow source is turned on and set to some steady level. Pressure differences develop across the resistive elements. Compartment distending pressures are no longer all the same. Reading from right to left, they ascend stepwise from right atrial pressure, P1, to arterial pressure, P3, each step height proportional to the resistance of the intervening element. Compartment volumes must redistribute accordingly. The compartment(s) now at pressures greater than Pms take on volume at the expense of the compartment(s) now at lower pressures.

Table I Computations based on the model from which Equation 1 was derived				
	Flow: 4.5 liters/min		Flow: 5.0 liters/min	
Compartment	pressure (cm H ₂ O)	Volume (ml)	pressure (cm H ₂ O)	Volume (ml)
C3 (arterial)	124	216	136	237
C2 (peripheral venous)	32.3	4039	34.1	4275
C1 (central venous)	4.1	849	2.9	591
RA	3.1		1.8	

Table 1 lists compartment pressures and volumes calculated according to the model shown in Figure 2 for two different levels of flow. Parameters for compartment resistances and compliances were taken from the set used in reference 3. Total volume was assumed to be 5100 ml. Note that the increase in flow from 4.5 to 5.0 liters/min is associated with a decline in right atrial pressure from 3.1 to 1.8 cm H₂O, (the familiar pattern of inverse dependence of Pra on flow) and a similar decline in central venous pressure from 4.1 to 2.9 cm H₂O. The reduced pressure in the central venous compartment results in a 258 ml reduction of its contained volume, matched by the combined increases in volume of the other two compartments, mostly that of the highly compliant peripheral venous compartment. The

redistribution of volume is illustrated by the comparison of solid and dotted outlines In Figure 3.

The mean systemic pressure computed from these assumed parameters is $15.3 \text{ cm H}_2\text{O}$. Note that no compartment takes on this pressure except when flow is zero.

In short, a given level of steady state flow establishes a particular pressure profile, seen interchangeably as increments relative to Pra or decrements relative to arterial pressure. Changing flow alters the profile and obligates a new distribution of volume. The absolute level of the profile is determined by the total contained volume and the compliances of the individual compartments. For details of how these can be worked out quantitatively, see reference 3.





Figure 3 - Pressures from Figure 2 here labeled as arterial (Pa, corresponding to P3), peripheral venous (Ppv, corresponding to P2), and central venous (Pv, corresponding to P1). Dashed outlines suggest volumes after increase in flow as in Table 1. The lower pressure in the central compartment obligated by the greater pressure differences across resistances results in reduction of volume reflected in increases in the other compartments.

Equation 1 does not support the statement that mean systemic pressure drives venous return

Reflecting on the preparation used by Guyton, et al.², in the light of understanding of how volume redistributes in accordance with new pressure profiles, we see that the decline in pressure at the right atrium in proportion to increased flow was the result of redistribution of volume from the central veins to compartments upstream. Nothing in the physical model dictates that one compartment remain at Pms and fixed volume as VR changes.

In the analysis of Guyton, et al., it was never asserted that one compartment remained steady at Pms, independent of VR. It was only through misinterpretation of the formal appearance of Equation 1 that VR could be understood as the discharge from a compartment at steady pressure, Pms, as represented in Figure 1. The term RVR in Equation 1 was not associated with a specific resistive pathway such as those shown in Figure 1.

Emphatically, RVR was not associated with a physical pathway from a compartment at Pms. It was a complicated parameter expressed in terms of combinations of the resistors and capacitors of the circuit, the consequence of the stipulation that total volume remained constant^[ii].

Utility of the concept of mean systemic pressure

One reason for the persistence of the idea that Pms drives venous return is the need for a rationale to guide clinical fluid management. Because, in principle, Pms varies in proportion to intravascular volume, the thought is that a practical measure of Pms would aid in assessing volume status in the operating room or bedside, preferably without the inconvenience of stopping the heart to obtain zero flow. Various attempts to validate procedures for estimating Pms have been made⁴⁻⁶. But the relationship between pressure at zero flow to blood volume is complicated by the possibility of major changes in compartmental elastic properties. Does discovery of a low value for Pms mean that intravascular volume is low or that widespread relaxation of vascular smooth muscle has been induced?

Perhaps the common acceptance of the idea that Pms drives venous return is a consequence of thinking about hemodynamics in the context of the experiments from which Poiseuille's Law arose. Flow through tubes connecting the bottoms of containers of fluid was related to the pressure difference between the inflow and outflow ends. With one container filled to a depth of 10 cm and the other to 4 cm, for example, the pressure difference could be held at 6 cm H₂O and the effect on flow of altering properties of the connecting tube could be recorded. Despite the fact that what is really driving flow is the force due to gravity, the physical arrangement fosters a bias toward thinking that pressure is somehow primary in the pressure



vs flow relationship. With this bias, one is inclined to look for the pressure at the upstream end of the pathway for venous return as driving VR, opposed by the back pressure at the right atrium.

If an uncomplicated path for VR that drains a physically identifiable compartment existed, we would expect, as a first approximation, that the pressure difference between the inflow and outflow ends of the path would vary in proportion to flow, and indeed that somehow reducing the "back pressure" at the right atrium would result in at least a momentary increase in VR. But, in steady states, what is driving the flow is the continual forcing of volume into the vasculature by the left ventricle. In the conceptual view implicit in the Guyton equation, none of the mechanical energy expended in forcing blood through the vasculature comes from the elastic energy stored in the stretched walls of its segments; the sole source of energy is the squeezing action of the left ventricle.

Pms and the Guyton equation in the context of understanding venous system pathophysiology

Why would you think in terms of mean systemic pressure and Equation 1 when confronted with the problems of interest to the Vasculab group? Pms is not lurking somewhere nearby to take a hand in processes like diversion of flow from superficial to deep veins. The model behind Equation 1 is a highly simplified view of how pressures and volumes interrelate in the peripheral vasculature. At best, it is informative about the relationship between Pra and steady state flow in situations uncomplicated by pumping action of active skeletal and respiratory muscle and the forces due to gravity and, therefore, useful for illustrating how the Pra vs flow behavior and the flow vs Pra behavior of the heart

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The problems of interest to the Vasculab group are in a vastly different realm, one not navigable via an elementary description of overall systemic venous return. Real veins are subjected to forces other than the propulsion from the left ventricle. Their pressure:volume relationships are not simple linear proportions. Pressures due to gravity must be considered. Flow through a vascular segment or compartment may more closely relate to the difference between upstream pressure and surrounding tissue pressures⁷ rather than obey a simple proportionality to the difference between upstream and downstream pressures.

In short, adopting a misconception from the literature of systemic venous return is not likely to lead to useful insights about pathophysiology localized within the peripheral venous system.

Endnotes

[i] This term refers to the difference between the intraluminal pressure and the pressure outside the compartment, here assumed to be zero.

[ii] Guyton, et al., waved away this complication about the form of the RVR term, referring to the parameter as an "impedance". Impedances are circuit elements across which the relationship of voltage difference to current is frequency dependent. Distinguishing between simple resistances and impedances is necessary when analyzing dynamic circuit responses. The derivation of Equation 1 was for steady states, not in any way related to dynamic responses of the circuit. RVR is not frequency dependent. The presence of terms that combined resistances and capacitances was the consequence of the stipulation that total volume was constant.

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