Continuing the Debate:  
**Branko Furst’s Alternative Model And the Role of the Heart**

To the Editor:  
As a progress practicing anesthesiologist—and only a bystander in the progress related to the subject of cardiac output regulation, circulatory equilibrium, heart–lung–vasculature interactions, and clinical hemodynamics—I believe I have some arguments that may enrich the interesting debate started by “Branko Furst’s Radical Alternative—Is the Heart Moved by the Blood, Rather Than Vice Versa?” which appeared in the January issue of P&T, and then continued with Dr. George L. Brengelmann’s “Debating the Role of the Heart” letter to the editor in May.

**Guyton’s Model: The Source of Blood Propulsion and the Role of the Heart**

The problem and controversy surrounding Guyton’s model of systemic circulation have been especially active since the beginning of the 21st century. As anyone interested in the topic must know, this model is centered on the concept of systemic “venous return” and a group of hemodynamic parameters that govern this phenomenon, such as mean systemic filling pressure, right atrial pressure, venous resistance, stressed and unstressed blood volume, and vascular compliance. Furthermore, the model deals directly with the subject brought up by Walter Alexander in his January P&T article, and, of course, by Dr. Furst in his own work: the energy source for blood propulsion or the question of “what makes the blood go around.” While my objective here is not to thoroughly review this controversy and the arguments put forward by the opposing views, I do nevertheless consider this letter an opportunity to point to a rather subtle misconception about an apparent “priority” of Guyton’s model suggested by Furst’s biological model and in Alexander’s review.

Cognizant of the ambiguity and inconsistency of Guyton’s theory, Alexander nevertheless seems to favor the latter on the basis that it “more closely matches the observed phenomena,” referring to the role of right atrial pressure as a “back-pressure” to venous return (reminiscent of the heart as an “organ of impedance”), and probably also to the idea of “autonomous venous return” developed by physiologists Solbert Permutt and Paolo Caldini in the 1980s. On the other hand, Alexander recognizes that Guyton’s model “sees the left ventricle as central,” and Dr. Furst puts forth that “the ultimate source for blood propulsion can be traced to the hydrodynamic equivalent of Ohm’s Law,” so both Guyton’s model and its polar opponent (the so-called “left ventricular model” of the circulation) would “differ only on the surface but not in essence.”

It is important to clarify that Guyton’s model does not conceive of the heart as having a central role, but a secondary (“permissive”) role (as Dr. Furst also acknowledges), which is lowering right atrial pressure, allowing steady venous return to drain from a lumped vascular compartment at mean systemic pressure; in other words, in Guyton’s model, the heart is part of the scheme, but the “propulsion center” in the circuit (functioning as a pressure head) consists of an abstract and algebraically artifactual pressure–energy source located in the systemic peripheral venous segment, which can be represented by “hydrostatic analogs.” So, Guyton’s model, indeed, is a version of an Ohmic/Poiseuillian circuit (the “pressure gradient for venous return”) and a “pressure–propulsion” model, though physically and physiologically inconsistent with the dynamics of the circulation and the conservation of energy. So, it is safe to say that is fallacious. Guyton’s model by no means represents a step toward the overcoming of the pure and classical left ventricular model, but...

**What Is Meant by the Left Ventricular Model?**

The idea that the pressure gradient from the aorta to the right atrium determines the flow, that the heart is both responsible for this gradient and the only one regulator of cardiac output, and that practically no important role is played by the peripheral vasculature has been labeled as the left ventricular view or model (also known as “cardiocentrism”). In addition, defenders of Matthew N. Levy’s interpretation (and Fred S. Grodins’ before that) of the essential dynamics of the circulatory system and the interaction between heart and vasculature have been considered adherents to this left ventricular model. It has been articulated in the prior paragraph that the left ventricular model and Guyton’s model boil down to a pressure gradient responsible for blood flow to occur. Dr. Brengelmann has stressed the nature of this profound misconception in hydrodynamics—the rather informal notion that pressure gradients are somehow primary to fluid flow—at many opportunities; one serious implication being the misinterpretation that the role of the heart is to “raise the arterial pressure which then drives the flow through the system”—an assertion that has erroneously been attributed to Guyton’s model critics (especially to Dr. Brengelmann) ever since the beginning of the debate.

This mistaken and biased attribution has distorted and obscured the important contributions achieved by contemporary Guyton’s model critics, which aimed for a better and more direct understanding of the human circulatory system: the unbreakable interaction between cardiac output, blood volume distribution, and vascular transmural pressures, along with the clarification of Guyton’s experimental procedures and findings, and the true nature and significance of heart–vasculature interaction and Guyton’s model itself; the focus on the pressure–volume relation at the level of the peripheral vasculatures and its fundamental role in determining the preload of the heart through the “veno-ventricular coupling”; the “venous excess” approach and the strong emphasis on the problem behind the conception of venous return as an “Ohmic” flow; the formal demonstration of the algebraic manipulation in Guyton’s venous return equation, and the design of a simplified but coherent model of the cardiovascular system.

This, of course, is a reductionist and incomplete summary of Guyton’s model critics’ work, but the message I’d like to get across is that their focus has been nothing at all similar to a “cardiocentric” view of human circulation. Instead, the emphasis on the peripheral circulation by these authors is crucial and realistic. The left ventricular paradigm ruled for the most part of the modern discoveries in hemodynamics, with a radical turn by the second half of the 19th century after
the contributions of Weber and then Starling; but the left ventricular model and Guyton’s model are “two sides of the same coin,” so it is suggested that Guyton’s model critics would no longer consider adherents to this view.

Classical Models and the Problem of Translation to Clinical Hemodynamics

The current understanding and approach to human circulation in certain medical specialities, along with the assessment of hemodynamic parameters to guide hemodynamic management, moves among three classical standpoints, all of which are model-based and sometimes in deep conflict with each other. These groups are: 1) Poiseuille: in which the main focus is made on the measurement of cardiac output (flow), vascular pressures, and resistance—as the approach to a system driven by a pressure gradient; 2) Guyton: estimation of the “mean systemic filling pressure” by various methods, vascular compliance, and the “stressed blood volume,” as well as the “pressure gradient for venous return” (although, the latter is distinctly “Poiseuillian”); and 3) Starling: assessment of the “stroke volume variation” through a group of surrogates known as “dynamic parameters” that indicate the preload dependence of the ventricles—also referred to as “the position in Starling’s cardiac function curve”—which informs about the “fluid responsiveness.”

It is paradoxical and contradictory that, being one of the main and central goals to determine the “volume status” and to guide fluid therapy, none of these approaches contemplates blood volume as an effective hemodynamic variable. Instead, they fundamentally dismiss the possibility for considering blood volume a “target” variable, and so to assess it directly. Thus, it is my personal conviction that the framework opened by the authors mentioned above as “Guyton’s model critics” altogether would set the basis and rationale for a novel and realistic approach to clinical hemodynamics, based on blood volume as an effective fundamental hemodynamic variable, the reinterpretation of the meaning of classical hemodynamic parameters, and for the definitive overcoming of the Poiseuillian view of human circulation, which seems to be, by far, the prevailing picture in clinical practice and teaching.

Finally, I applaud the passionate struggle and intellectual efforts devoted by all debaters who strive relentlessly for making sense of a complex system and physiology, helping and guiding medical research scientists and practitioners, and extend special thanks to Dr. George Brengelmann.

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Authors’ Response

We would like to thank Dr. Dalmau for clear summaries of the defining characteristics of Guyton’s venous return model and the left ventricular model, but also for a more nuanced picture of the role of the heart in Guyton’s model. Also appreciated is the tireless effort on the part of Dr. Brengelmann to redeem Guyton’s model by pointing out its methodological and conceptual inconsistencies, which, if accounted for, would reconcile the proponents of the two opposing views. After all, as shown and reiterated by Dr. Dalmau, both models are but “two sides of the same coin” in the sense that they are based on principles of hydrodynamic equivalence of Ohm’s law.

However, what is a given in Guyton’s model and the left ventricular model, namely, that blood is an inert fluid pushed by the heart, is contested by the proposed biological circulation model. The physics of a closed hydraulic system proposed by Dr. Dalmau and others undoubtedly holds for the Ohmic/ Poiseuillian paradigm, but we maintain that such a model is not supported by the observed phenomena.

Why then did we give preference to Guyton over the left ventricular model? First of all, experimental observations by
Guyton and others indeed show that the venous and arterial limbs of the circuit are relatively independent of each other.\textsuperscript{3} Secondly, Guyton’s concept that the difference between right atrial pressure and mean systemic pressure (MSFP) provides the “driving force for venous return”\textsuperscript{4} does point to the periphery, to the stored elastic energy in the vasculature as the source of blood propulsion. Finally, an increase in right atrial pressure over the value for MSFP would restrict venous return and make the heart, at least temporarily, into an organ of restraint. It should be emphasized that these phenomena (whether correctly interpreted by Guyton or not) support the proposed biological model of circulation.\textsuperscript{5}

Developmental biology of the cardiovascular system shows that the heart, the vessels, and their contents (the blood) are a unified organ joined by the blood’s autonomous movement. The very notion that blood is an inert fluid is contrary to its nature; it will clot when its movement is sluggish or ceases altogether. The “driving force” for the circulating blood originates at the “periphery,” namely, in the contact between the endothelium and the red blood cells, the purveyors of oxygen and sensors of the metabolic demands in the tissues.

The fact that biological fluids such as lymph and blood move on account of temperature and chemical gradients should not come as a surprise. For example, self-driven flows (i.e., without pressure gradient) of water in hydrophilic tubes\textsuperscript{6,7} have been well described. Importantly, the emergent behavior of self-propelling “active fluids” is a hot topic of research in physics.\textsuperscript{8} One mixture of such fluids consists of synthetic clusters of kinesin molecular motors and ATP, both found ubiquitously in eukaryotic cells. Specific concentrations of ingredients in such systems result in ATP depletion and creation of large-scale vortices which, confined into cylindrical channels, organize into directional flow.\textsuperscript{9} Significantly, active fluids can propel themselves in the range of up to 1 m at velocities of 10 microns per second,\textsuperscript{9} well within the range of red blood cells’ movement inside the capillaries. Given the fact that ATP is actively released during passage of red blood cells through the capillaries, and the sheer numbers of capillaries (e.g., 2.77 × 10\textsuperscript{11} in the lung\textsuperscript{10}), it is conceivable that such nonpressure-driven, autonomous flows do, in fact, exist not only in the microcirculation, but also at the level of macrocirculation.

Finally, the suggestion of Dr. Dalmau that estimation of blood volume could become an effective “target value” in fluid therapy and thus supersede the Poiseuillian view in clinical hemodynamics certainly makes sense within the classic paradigm summarized at the end of his letter. However, there is a problem. As discussed,\textsuperscript{11} experimental and clinical studies show a significant disparity between the macrocirculation and microcirculation in various forms of distributive shock states. For example, Pranskunas et al. showed that patients with organ hypoperfusion signs, such as tachycardia, hypotension, low stroke volume index, oliguria, and increased levels of lactate, benefited by administration of fluids (crystalloids or colloids), but only in the presence of reduced microcirculatory flow (as defined by microvascular flow index). On the contrary, fluid administration in patients with clinical surrogates of hypovolemia and normal or increased capillary flow resulted in neither normalization of clinical signs of organ malperfusion nor further increase in microcirculatory flow.\textsuperscript{12} It is evident that fluid administered in the presence of abnormal macrocirculatory parameters would leak out of the vascular space and add to already increased tissue edema, further compromising perfusion and oxygenation. Given the highly variable distribution and construction of the capillaries (continuous, fenestrated, sinusoidal) and the fact that even in normal physiological states, fluid exchange across the capillary walls amounts to some 80,000 L per 24 hours,\textsuperscript{13} the notion of a “closed” circulatory space or a “steady state volume” should be replaced with the concept of circulation as a highly dynamic, open-system time structure.

In conclusion, the method of direct, noninvasive visualization and quantification of microcirculatory flow, which we see as the great new frontier in experimental and clinical hemodynamics, calls for a new approach to fluid therapy and for radical reevaluation in the way we think about circulatory phenomena. Rather than trying to make them conform to classic physical models, we are challenged to explain them with concepts arising from the observed emerging properties of active fluids.\textsuperscript{14} We believe that the biological circulation model will help direct these efforts.

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