

Branko Furst's Radical Alternative

Is the Heart Moved by the Blood, Rather Than Vice Versa?

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"Most heart failure trials yield results that are disappointing or difficult to interpret," Milton Packer, MD, wrote in the April 2016 issue of *Circulation: Heart Failure*.¹ Dr. Packer, Distinguished Scholar in Cardiovascular Science at Baylor University Medical Center in Dallas, has experienced this frustration firsthand as lead investigator of more than 15 large international multicenter heart failure trials. He pointed out that in the late-breaking clinical trials session at the 2015 annual meeting of the American Heart Association, every randomized trial in heart failure "yielded distressing results." Two medications failed to meet primary end-points (the guanylate cyclase stimulator vericiguat and the beta₃ adrenergic receptor agonist mirabegron [Myrbetriq, Astellas]); another (oral nitrates) had adverse effects on daily activity; and yet another (the GLP-1 agonist liraglutide) showed no diminution of clinical symptoms but was linked with possible renal-function harm and increased risk of death or heart failure hospitalization.

Such disappointing findings hardly stand alone among research results in heart failure and cardiac support, recent or otherwise. Attempts to replace failing hearts permanently with fully mechanical ones, after years of experimental and clinical trials, have largely been abandoned because of high patient mortality through combinations of thromboembolic, hemorrhagic, and infectious events leading to strokes and multiple organ failure. Despite success at adjusting cardiac outputs, matching hemodynamics to organ requirements with mechanical devices has remained elusive.²

Experience with intra-aortic balloon pumps (IABPs) serves as a further example. A 2015 meta-analysis by Su et al. of 17 studies including 3,226 acute myocardial infarction (AMI) patients, with or without cardiogenic shock, examined the effect of circulatory assist with IABPs. Analysis revealed no significant difference between the IABP group and controls on short-term mortality (relative risk [RR], 0.90; 95% confidence interval [CI], 0.77–1.06; $P = 0.214$) and long-term mortality (RR, 0.91; 95% CI, 0.79–1.04; $P = 0.155$). The presence or absence of cardiogenic shock did not affect the results.³ Based on this and other similar accumulating evidence, the triumvirate of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology all recently downgraded their recommendations for the use of IABPs in the setting of AMI associated with cardiogenic shock from class Ib (should be used) to class IIb (may/can be used).

Commentators on another recent IABP meta-analysis⁴ showing no survival advantage posited a range of explanations for the benefit that has never appeared over four decades for this seemingly practical and plausible strategy: IABP effects are too weak to counteract failed cardiac function; IABP complication harms overwhelm benefits; clinical trial methods simply fail to accurately capture IABP benefit; and baseline selection bias toward sicker patients dilutes benefits in active treatment groups.⁵

Given how deeply assumptions about heart failure are entrenched, it is understandable that commentators did not entertain the radical-seeming possibility that the prevailing cardiac function paradigm does not accurately reflect the reality of heart function. The success of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers confirmed that chronic neurohormonal activation of mechanisms of myocardial damage and circulatory dysfunction (including impairment of protective mechanisms) play a role in heart failure. That success also shifted the pathophysiological emphasis away from the traditional hemodynamic model. But the possibility that the dominant paradigm is deeply flawed is what Branko Furst, MD, explores in *The Heart and Circulation: An Integrative Model*² in 2014 and in "The Heart: Pressure-Propulsion Pump or Organ of Impedance" in the *Journal of Cardiothoracic and Vascular Anesthesia* in 2015.⁶ In these, he marshals the evidence against the standard propulsion pump model and presents an alternative that may open new avenues for understanding circulation and, ultimately, pharmacotherapy. As a vascular anesthesiologist in a tertiary care medical center, Dr. Furst holds hemodynamic monitoring and support of circulation at the core of his acute-care concerns.

To challenge the prevailing paradigm in any field is difficult, and in the case of heart function, with its notoriously complex dynamics, myriad of interrelated influencing factors, and vast diagnostic and therapeutic implications, it is a prodigious undertaking. Dr. Furst has provided more than 800 supporting references in his book and the journal article. It is far beyond the scope of this article to fairly represent the range of this content. However, we will attempt to review the basic argument and rationale for such a challenge and give the reader a compass for delving more deeply into the underlying research.

In what follows, we examine key evidence against the standard cardiac function model, including failed attempts to address cardiac pathology with pharmacotherapy and devices based on that model. We also describe the alternative model and its supporting research and touch upon its implications for therapy and further exploration.

The History of the Conventional Model

The current heart-as-propulsion-pump model is traditionally traced to William Harvey's 17th century *De Motu Cordis*. It took another 200 years, however, for traces of vitalism to be eradicated from physiological understanding and for Alfred Volkmann to precisely articulate a fully mechanical model as follows: "The heart is a pumping engine and as such has enough power to drive the mass of the blood through the whole vascular system."⁷ Contemporary definitions of heart failure still recognize pump malfunction as a key component, but they also acknowledge the complexity of heart failure diagnosis and treatment. The *European Heart Journal* guidelines in 2001⁸ stated that while no definitions of heart failure

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are entirely satisfactory, a commonly used one is: "Heart failure is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues." The next sentence, however, is: "A simple objective definition of chronic heart failure is currently impossible." The more recent American College of Cardiology Foundation/American Heart Association guidelines (from 2013)⁹ define heart failure as "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood." While pump function is implied, this broader description may suggest an evolutionary direction away from reliance on so simplistic a model as is suggested by Volkmann's strict analogy.

In his book and journal article, Dr. Furst surveys the disappointing findings for pharmacotherapeutic and device strategies developed as specific remedies for the heart when seen as a compromised and incompetent propulsion pump. Potent sympathomimetic amines such as epinephrine, isoproterenol, and dopamine were used widely in the 1960s and 1970s^{10,11} based on the assumption that as inotropes they would strengthen the heartbeat in patients with congestive heart failure, thereby increasing cardiac output and ultimately prolonging survival. Most recently among negative inotrope findings, the ADHERE (Acute Decompensated Heart Failure National Registry) trial,¹² a 2003 registry, showed that of 150,000 patients with acute heart failure, systolic blood pressure was lower than 90 mm Hg in less than 3%, suggesting a harmful effect on heart function. Mortality among those treated with inotropes was 19%, compared with 14% among those not receiving inotropes. American and European medical societies' practice guidelines have since recommended the use of vasodilators and de-emphasized inotrope use in acute heart failure syndrome management.

While inotrope use has been largely abandoned in favor of vasodilators to reduce blood pressure and decrease the resistance that lowers cardiac output, the exception is inotrope administration in a minority of patients with severe systolic dysfunction who cannot tolerate vasodilators due to hypotension.¹³ Of significance is the fact that dobutamine and milrinone are usually selected out of the range of available inotropes because of their substantial vasodilatory effects. Applied to the conventional model, vasodilators "would decrease the pressure head needed by the pump in order to drive the blood around the circuit," Dr. Furst points out.² Also counterintuitive to a propulsion pump model is the proven efficacy and universal recommendation of beta blockers for all patients with stable mild, moderate, and severe heart failure with ischemic or non-ischemic cardiomyopathy and reduced left ventricular ejection fraction.¹⁴ It is suggested that by reducing catecholamines, beta blockers promote ventricular filling and enhanced ejection fraction, but the proven efficacy of treating a failing "heart pump" by weakening the force of ventricular contractions and slowing heart rate remains puzzling.

Failing Heart, Rising Output?

Among the observations most confounding to a heart-as-propulsion-pump model, the instances where cardiac output rises in the presence of a compromised or disabled pump stand out. Partially isolating the heart from the circulation through

aortic cross-clamping, as is typically done during aortic surgery and in experimental settings, should lead to disastrous reductions in cardiac output. But increases in cardiac output of up to 25% in some cross-clamped aortic surgery patients and in an animal model beg explanation.^{15,16} Another paradox presents itself when children with congenital univentricular hearts are helped by the staged Fontan repair that, in the absence of the right ventricle, delivers venous blood directly to the pulmonary arteries. Asking the single, often weakened left ventricle to do double duty—pumping blood for the body and for the lungs—seems extreme, yet it manages quite successfully, sending more than normal volumes of blood to the lungs.

Paradoxical increases in cardiac output are also seen in patients with septic shock, where cardiac output can be doubled or tripled at the same time that cardiac function is declining. Yet another observed example is the lack of significant change in blood pressure when aerobic exercise increases cardiac output several-fold beyond the theoretical limits of the heart's pumping capacity and peripheral resistance drops by two-thirds. Up to 60% of increased contractility may be explained by beta-adrenergic stimulation and improved diastolic compliance (the Frank-Starling mechanism). But greatly increased heart rates shorten diastolic filling time, and the maximally performing exercising heart can account for only about half of the volume throughput measured in high-performance athletes (more than 30 L per minute).² The source of "extra" blood volume remains a long-standing dispute among exercise physiologists, and the concept of a "muscle pump"—a mechanism by which the blood is returned to the heart by the contracting muscles—has long been entertained. Evidence against the existence of such a muscle pump is accumulating, however.^{17,18}

Dr. Furst describes various animal and human studies measuring or modeling heart function and compares them with mechanical propulsion pumps engineered to maintain either constant pressure or flow under varying loading conditions. Dr. Furst's conclusion emerging from studies of isolated heart preparations is that if the heart is in fact a pressure-propulsion pump, it is a "rather poorly designed" one, with its thin apex and relatively low ejection fractions of 50% to 60% (why not 100%).

Dr. Furst, in the introduction to *The Heart and Circulation*, states that, in 1920, Rudolf Steiner suggested that the heart, rather than propelling blood flow, restrains and regulates it.² The venous return model articulated by Arthur Guyton has been the prevailing view since the 1970s and stands in opposition to the pure left ventricular model.² In it, the peripheral circulation controls cardiac output, with elastic recoil energy from the vessel walls "squeezing" blood back toward the heart. Guyton and collaborators also reported that cardiac output is largely unaffected by the heart's activity¹⁹ even with pacing rates up to four times normal. The Guyton model ascribes a dual role to the right atrial pressure. Considered from the perspective of the heart, the right atrial pressure determines the degree of filling of the right ventricle and therefore regulates cardiac output. From the perspective of the peripheral circulation, a positive right atrial pressure exerts a backpressure and therefore *impedes* venous return. This ambiguous depiction of the right atrium's role, according to the model's critics, is mechanistically inconsistent and is a weakness of the model. By assuming an impedance function for the right atrium and

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emphasizing the role of the peripheral circulation, however, Guyton's model nevertheless more closely matches the actual observed phenomena. The fact that the Guyton venous return model still holds the heart as the ultimate source of blood propulsion leaves many unresolved issues, which Dr. Furst reviews in detail in his book and journal article.

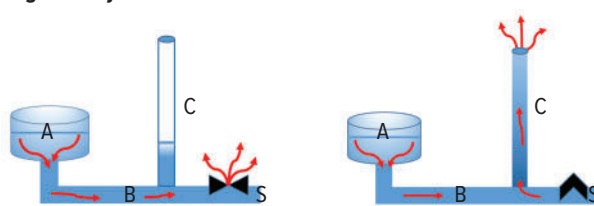
In addition, Dr. Furst questions the validity of identifying similarities between heart and propulsion-pump function based on observing animal preparations with arrested hearts and abolished vasomotor reflexes. The intent of reducing the number of variables to facilitate measurements and isolate factors for study is sound, but the applicability of comparisons based on "the circulatory systems of nearly deceased experimental animals" is open to question. Also, Dr. Furst says, identifying the causal relationships among the set of physical parameters of pressure, flow, and resistance as one would in a closed hydraulic system of known dimensions with rigid tubes and a homogenous fluid may not be reliably analogous to a "highly dynamic circulatory system." The model insufficiently addresses many key variables, including the dimensions and nonconstant elasticity of the vessels, the non-Newtonian fluid moving within them (blood lacks a constant coefficient of viscosity), and the blood's pulsatile flow with reflected waves, pulse-wave velocity, inertial factors, and mechanical, chemical, and thermal energy conversions.

An Alternative Model

The first instance in scientific literature refuting the heart-as-pump model appeared in Germany in the 1930s at about the same time as early discussions of the physics of open systems.² Hans Havlicek pointed to an analogy, both mechanical and morphological, between the heart and a hydraulic ram (Figure 1 and Figure 2).²⁰ The key difference between a hydraulic ram and a propulsion pump is that a hydraulic ram is inserted into the path of an already moving fluid and uses the force of the stream to do its work. Hydraulic rams are used most commonly in construction applications to raise the level of an already moving water supply without any external power source.²¹ A propulsion pump, by definition, is the provider of force to a fluid stream. Dr. Furst quotes the cardiac surgeon Leon Manteuffel-Szoege, who in the 1970s and 1980s published observational studies of chick embryonic circulation and of circulation in patients in deep hypothermic arrest. Dr. Manteuffel-Szoege wrote: "A pump sucks in fluid from a reservoir. ... In the circulation, on the other hand, not only is the blood ejected from the heart, but it flows into the heart. The heart is a mechanism inserted in the blood circuit, and so it is a very peculiar kind of pump."²²

Dr. Manteuffel-Szoege repeated the experiments of S. A. Thompson, who had shown that in asphyxiated dogs, residual circulation continued for up to

Figure 1 Hydraulic Ram



At left, water from the reservoir (A) accelerates with gravity along the drive pipe (B) and escapes from the open spill valve (S) (red arrows).

At right, drag of the accelerating water closes the spill valve (S), creating a back surge (water-hammer effect) and an increase in pressure, forcing water to flow from the delivery pipe (C). A drop in pressure in the delivery pipe (B) opens the spill valve (S) and the cycle repeats.

two hours after cardiac arrest.^{23,24} Other research has shown 20% to 40% increases in canine cardiac output after occlusion of the thoracic aorta.¹⁵

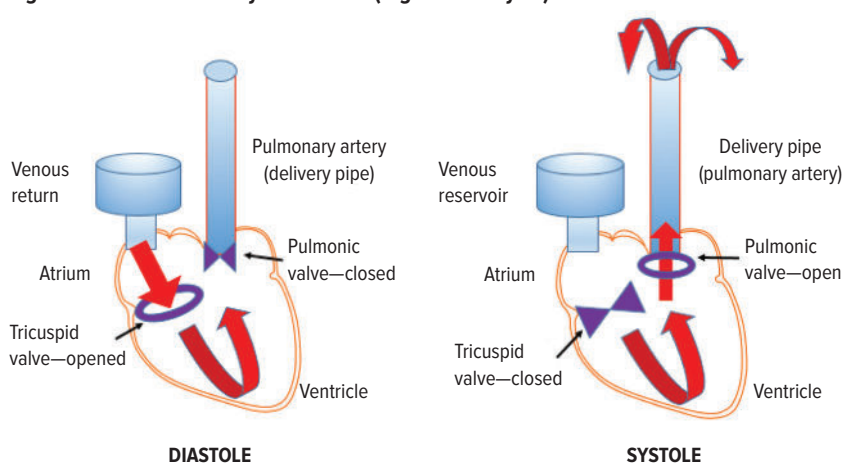
Two Inevitable Questions

What then is impelling the blood if not the ventricular contractions? And what are the ventricles doing if not providing the motive force for the circulation? Dr. Manteuffel-Szoege's conclusion about the first question was that blood has its own kinetic energy derived from thermal conditions of the tissues.²² Before endeavoring to answer the second question, Dr. Furst explores the evidence from embryonic hemodynamics suggesting that blood does not rely on the ventricles for its propulsion.

Embryonic Circulation

The assumption has been, Dr. Furst says, that the *valveless* two-chambered embryonic heart functions like a peristaltic pump, moving blood along its lumen the way the esophagus

Figure 2 The Heart as a Hydraulic Ram (Right Heart Cycle)



Arrows represent direction of blood flow. In diastole, blood flows from the atrium (reservoir) and fills the ventricle (drive pipe). In systole, flow reversal and build-up of pressure in the ventricle close the tricuspid valve (spill valve) and eject the blood into the pulmonary artery (delivery pipe).

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pushes ingested food as a bolus to the stomach. The observation that the velocity of the blood in the embryonic heart lumen exceeds the speed of the peristaltic wave moving through the lumen contradicts that interpretation and supports the notion that the blood is already in motion before a functionally competent heart has developed.²⁵ In primitive vertebrates, like the lancetfish, circulation occurs without a central propulsive organ (Figure 3). The embryonic heart, rather than moving the blood, rhythmically interrupts its flow, Dr. Furst states.

How would demand for oxygen-rich blood in the tissues lead to and regulate blood circulation without reliance on propulsive force from the ventricles? How does blood move itself if it is not being driven mechanically?

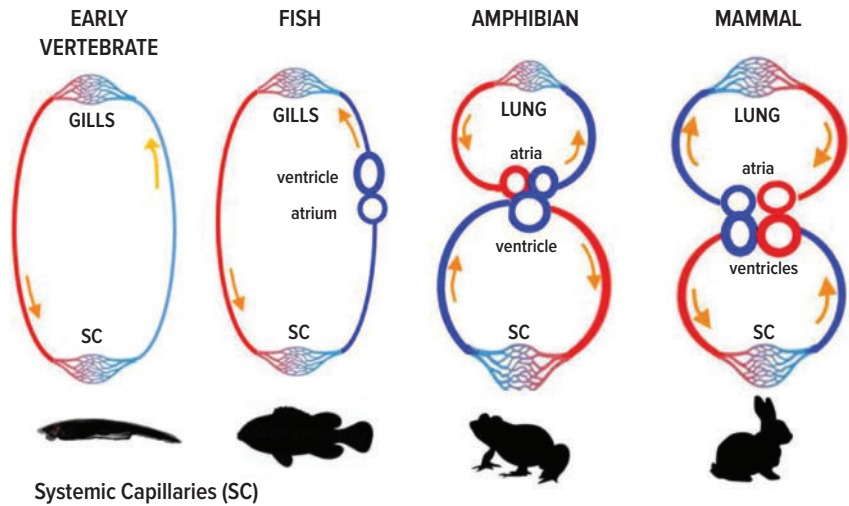
Of course, if it were mechanically driving itself, that would be *perpetual motion* in defiance of the second law of thermodynamics. But by being in a responsive relationship with its environment at the level of the microcirculation at the vascular beds, such behavior of blood may be quite in accord with what is predicted when an organism is considered as a far-from-equilibrium living system, as it is in Dr. Furst's proposed model.

Self-regulation of vessel walls in response to shear stress through release of nitric oxide, a potent vasodilator, has long been recognized.²⁶ Beyond shear stress, vascular tone is affected by intraluminal pressure and local metabolite concentrations.²⁷ The newer insight, however, is that red blood cells may play a more direct role than has been suspected in relation to local biochemical and mechanical factors affecting tissue metabolism.

Ellsworth et al. and others have shown that erythrocytes are not mere suppliers of oxygen; they are also sensors and regulators of tissue oxygen saturation.²⁸ Ellsworth and colleagues also demonstrated that when erythrocytes perfuse a poorly oxygen-saturated (SpO_2) region of tissue, they release adenosine triphosphate (ATP), which in turn stimulates production of nitric oxide. In that manner, low SpO_2 opens the vessel in a retrograde direction, inducing greater flow of oxygen-rich blood to where it is needed (Figure 4).²⁹

Importantly, the pulmonary vessels react in a polar-opposite fashion, complementing the pivotal role that erythrocytes play in supplying oxygen to the metabolically active systemic vascular beds. The systemic vascular smooth muscle reacts to hypoxemia with vasodilation and increased blood flow, but when levels of inspired oxygen in the lung are low, pulmonary vessels constrict, diverting blood away from hypoxic lung

Figure 3 Evolutionary Stages of Circulation²



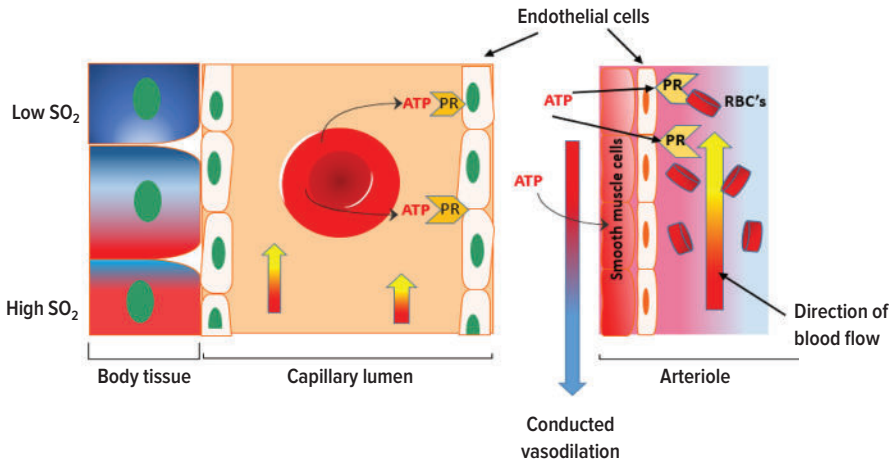
Circulatory systems in early vertebrates, fish, amphibians, and mammals: The lancetfish, a primitive vertebrate, has no heart as a central organ of circulation. The blood moves autonomously within the vessels without endothelial lining. The fish have a single-loop, predominantly venous circulation with a two-chamber heart, a single atrium and a single ventricle, placed *in series* with the gill and systemic circulations. Transition from water to land calls for development of a new organ, the lung, and for metamorphosis of the heart into a three-chamber organ consisting of two atria and a single ventricle. In amphibians, arterial blood from the lung and venous blood from the body mix in the ventricle, which subserves low-pressure pulmonary and systemic circulations now placed *in parallel*. The circulatory system undergoes further development in warm-blooded mammals with high metabolic rates and greater demands for oxygen. This is achieved by a complete separation of the pulmonary and systemic circulations. In addition to the existing ventricle serving the pulmonary circulation, a new chamber, the left ventricle, develops to serve high-pressure systemic (arterial) circulation. The two circulations are placed *in series*.

Adapted from *The Heart and Circulation* (Springer 2014).

regions toward those with higher oxygen levels. Although nitric oxide is produced continuously by the pulmonary vascular epithelium and the respiratory epithelium—inhibiting pulmonary hypoxic vasoconstriction—irreversible binding of nitric oxide to hemoglobin in red blood cells counteracts its vasodilatory effects.³⁰ Gladwin et al. estimated that 25% to 30% of basal human blood flow can be attributed to red blood cell-induced production of nitric oxide by vascular endothelium.³¹ That may be a substantial underestimate, Dr. Furst suggests. Others have proposed that the common denominator in various forms of distributive and cardiogenic shock is this red blood cell-induced release of nitric oxide.³² This feature of the microcirculation has led to its being called the “motor of sepsis” because it is there that a short-circuiting (shunting) of the capillaries takes place—with blood moving from arterioles to venules without supplying oxygen to the tissues and causing increased cardiac output as a downstream result.³³

In mature circulation, Dr. Furst suggests, rhythmic interruption of blood flow by the ventricles pressurizes a pulsatile flow. But this pressure is not the primary engine of systemic circulation. Instead, it is the force behind the rhythmic operation of the heart valves. The pressure sustained by the heart in its joining of the pulmonary and systemic circulations is essential

Figure 4 Erythrocytes as Oxygen Sensors and Modulators of Vascular Tone



Physical deformation of erythrocytes and their entry into tissues with low oxygen saturation stimulate release of ATP from the erythrocytes. The released ATP reacts with endothelial purinergic receptors that stimulate release of vasodilators, including nitric oxide and products of arachidonic acid metabolism. ATP also elicits vascular smooth muscle-dependent vasodilation conducted *opposite* to the direction of blood flow.

ATP = adenosine triphosphate; PR = purinergic receptor; RBCs = red blood cells; SO_2 = oxygen saturation.

has also uncovered *hemodynamic incoherence* after usual treatment strategies are carried out in these conditions. Hemodynamic *coherence* is consistency between the monitored parameters of the systemic macrocirculation and the microcirculation. Resuscitation measures, for example, can succeed in normalizing systemic hemodynamic variables such as blood pressure, cardiac output, stroke volume, and mixed venous oxygen hemoglobin saturation (SvO_2) without leading to a parallel normalization of capillary perfusion and tissue oxygenation,³⁴ according to Ince et al. They point out that morbidity and mortality were increased in several studies in patients in whom videomicroscopy identified a lack of hemodynamic coherence in sublingual microcirculation. They observed, “States of shock, reperfusion, inflammation, and infections can damage the cellular sensing mechanisms needed to regulate blood flow,” and

Dr. Furst described animal models in which endotoxin administration produced endothelial injury, capillary leakage, and interstitial edema with progressing reductions in functional capillary density.

Reduced capillary function implies lowered perfusion with shunting: Blood flow increases from the left to the right side of the circulatory loop, but bypasses the tissues in need of oxygenation. When this blood with higher-than-normal SvO_2 returns to the lungs, it triggers accelerated flow through the mechanism stated earlier. In this proposed manner, microcirculatory dysfunction may underlie the perplexing hyperdynamic circulation (high cardiac output with low systemic vascular resistance) observed in conditions associated with impaired myocardial function.

Dr. Furst notes that microcirculatory dysfunction, as is now widely recognized, is one of the most sensitive predictors of outcome in critical illness,³⁵ and restoration of microcirculatory function has become the principal focus of goal-directed therapy. Indeed, the assumed link between microcirculatory function and global hemodynamics has come into question, and a relative independence for the former has been proposed.³⁶ The recent therapeutic trend, according to Dr. Furst, is to “recruit” the microvascular beds by using vasodilators such as nitroglycerin to open the underperfused capillaries rather than “forcing” them open with increased use of vasopressors, the current standard of care. In spite of improvement in macrocirculatory parameters, such as blood pressure, cardiac index, and left ventricular ejection fraction, vasopressors have limited effect at the level of the microcirculation, and they may cause adverse patient outcomes.³⁷ Ince et al. offered examples of hemodynamic incoherence, where therapeutic strategies based on the conventional assumption

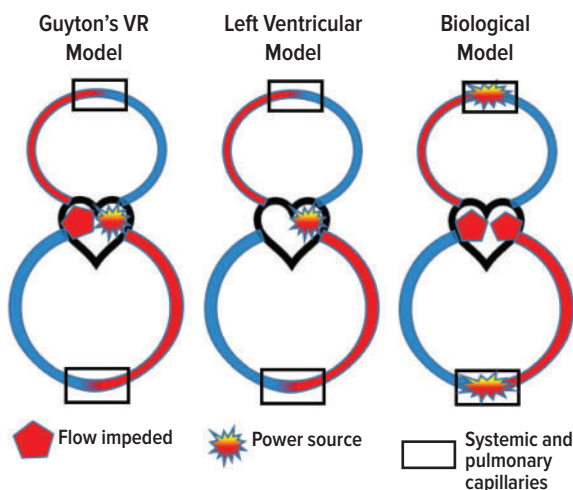
for maintenance of normal physiology, but it is not the primary cause of the moving circulation. Locally, the immediate metabolic demands at the level of the tissues and microcirculation self-regulate blood flow, and, globally, a polarity persists in a dynamic tension between the lung’s supplying of oxygen and the peripheral tissues’ consumption of it. The heart, in this model, is a feedback organ of impedance that maintains a 1:1 balance in flow between the pulmonary and systemic circulations. Its function is ram-like, converting kinetic energy into pressure and maintaining it in the systemic and pulmonary arterial compartments.

An important difference between the pump model of left ventricular propulsion and Dr. Furst’s proposed model is that the former treats the blood as an inert fluid transported by mechanical force, while the latter sees it as a dynamic fluid organ that gains movement through its essential mediating of metabolic processes via reciprocal relationships with the physiological life of the tissues it supplies with oxygen and nutrients (Figure 5).

Implications for Therapy

The recently discovered autoregulatory ATP response of red blood cells to the metabolic needs of the tissues, according to Dr. Furst, has been insufficiently appreciated because of the entrenched pressure-propulsion cardiac model. Recognition of its potentially pivotal role in critical illness, however, has grown with the development of techniques for intravital microscopy. The capacity to image the activity of microvascular beds with orthogonal polarization spectral imaging and sidestream dark-field imaging in animal models and in patients has revealed not only that microvascular hemodynamics are altered in patients with sepsis, hemorrhage, cardiogenic shock, and multiple trauma and during cardiopulmonary bypass, but

Figure 5 A Comparison of Circulation Models⁶



A defining feature of both the classical pressure-propulsion and Guyton models is that the pressure gradient created by the heart is the source of blood propulsion. In Guyton's venous return (VR) model, cardiac output (CO) is predominantly regulated by the circuit parameters, that is, elastic and resistive properties of the blood vessels and blood volume. The right atrial pressure (Pra) plays a dual role; viewed from the heart, increased Pra promotes ventricular filling, thereby increasing CO. Viewed from the circulation, increased Pra exerts "back pressure," impedes venous return, and reduces CO.

The left ventricular model assumes that the flow (CO) is limited by the pump's output and is proportional to the gradient between the mean aortic and right atrial pressures, and inversely proportional to peripheral resistance. The blood is considered an inert, incompressible fluid, and the amount pumped into the arterial side of the circuit is equal to the amount of blood returning at the venous side.

The biological model assumes the existence of "dynamic tension" between the source of oxygen in the lung and its "sink" in the metabolically active tissues. The blood, a liquid self-moving organ, bridges this "tension" and plays a dual role by delivering oxygen and nutrients to the peripheral tissues, and also to itself. The forces for blood propulsion originate at the level of the microcirculation. The heart plays a secondary role and exerts a negative feedback to the metabolic demands of the tissues by rhythmic interruption of the blood flow. Its ram-like function maintains pressure in the systemic and pulmonary arterial compartment and carries the "rhythm of life."

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the problem, Dr. Furst said in a personal conversation in September 2016, "is that there is as yet no consensus on treatment of these complex hemodynamic states. But what Ince et al.^{33,34} have offered, based on numerous published phenomenological observations and quantifications of capillary function, is the first rational treatment strategy for these conditions."

Schematic Versions

Given the limited scope of this article, we have necessarily presented schematic versions of Dr. Furst's hypotheses. Dr. Furst traces the parallel-running evolutionary and embryonic courses of cardiac development, where in the embryo and in fish it is clearly evident that venous-type low-pressure blood flow predominates. In gradually emerging fish-amphibian-mammalian/two-to-four chamber stages, progress leads to arterialization and separation of pulmonary and systemic circuits. Only later in warm-blooded mammalian species is a thick left ventricle required to maintain the same basic function of rhythmic flow interruption at significantly higher pressures (to work the valves and eject blood into the respective compartments). The movement of the circulation is created and regulated locally at the level of the tissues through metabolic demand and globally through a dynamic tension between the lung's supplying of oxygen and its consumption in the tissues.

The idea of autonomous movement of blood is seemingly radical, but Dr. Furst points out, "Conceptually, autonomous movement of the blood is no different than autonomous contraction of the heart, the enterohepatic circulation of bile salts, or the circulation of cerebrospinal fluid."²

If this model of autonomous blood flow is confirmed by continuing research, it may drive the understanding of circulatory and cardiac function further along in a direction it has been taking gradually for some time, at least in the field of pharmacotherapy of heart failure. By superseding the propulsion-pump model, it may steer researchers away from pharmacological and device blind alleys and lead them instead to wide avenues of discovery and progress in therapy.

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