The Heart and Circulation

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An Integrative Model

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Dedicated to
Leon Manteuffel-Szoege (1904–1973)
Friedrich Husemann (1887–1959)
Otto Wolff (1921–2003)
For their pioneering work on the
hemocentric model of circulation.

Foreword I

Traditional models of the human circulation based on the generation of pulsatile flow into a coupled viscoelastic arterial system have evolved since man first had the opportunity to observe the movement of blood in mammals. These models are capable of explaining and modeling most of what we observe as clinicians much as Newtonian physics explains what we observe in the physical world around us. It is only when someone, as Branko Furst, MD, has done in this tome, delves deeper into circulatory phenomena that are not so readily observed that we have cause to question the adequacy of the pressure-propulsion model of circulation. I liken the effort made by Dr. Furst here to the use of quantum and string theory to explain phenomena not readily explainable by classic Newtonian physics. There is much about the human circulation that remains mysterious, and in this brilliant work the author has opened our eyes to the necessity of developing a unifying model of the human circulation that can explain all observed phenomena. This book is a must read for anyone interested in the intricacies of the human circulation beyond what can be causally observed.

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Foreword II

The cardiovascular system is complicated. However, frequently it is presented as a pump (the heart) that delivers fluid into a series of pipes (blood vessels) of varying resistance. The relationship between the output of the pump and the resistance in the pipes then determines the driving pressure (mean arterial pressure) which distributes the fluid (blood) around the system. This simple fluid engineering model is then supplemented or expanded by ideas about how various elements of this system are controlled. All of this thinking leads perhaps to what might be described as a cardiocentric view of the cardiovascular system. This cardiocentric view is reinforced by the dramatic events like death that occur when the pump stops for any one of a number of reasons.

In this monograph Branko Furst raises a number of interesting points about the oversimplified view outlined above.

First, how many pumps are there in the cardiovascular system? One could argue that there is the heart itself, the skeletal muscle pump which returns blood from the periphery to the central circulation and can translocate a large volume of blood in a matter of seconds. Perhaps there is a third pump embedded in the large elastic arteries that stores energy after cardiac systole and uses elastic recoil to propel the blood forward? If there is more than one pump, how do they operate together to deliver and return blood flow to the peripheral organs?

Second, the heart is seen largely as a pump, but both old and new ideas suggest that the twisting motions associated with cardiac ejection lead to a sucking action during cardiac relaxation. How much does this sucking action contribute to the filling of the heart and the subsequent delivery of blood to the periphery?

Third, the heart, blood vessels, and peripheral tissues all contain sensory nerve endings that influence cardiovascular function. Just like there is a so-called enteric nervous system, is there a cardiovascular nervous system?

Fourth, in addition to these pumps and the neural network that governs the cardiovascular system, there are a host of local control mechanisms that are too numerous to catalog in this introduction. For example, metabolites released by contracting skeletal muscle can evoke local vasodilation on a scale (50- to 100-fold) that is difficult to imagine. What factors contribute to this and how does the rest of the "system" respond to it?

Fifth and finally, there is the problem of "cardiovascular disease." The traditional view of cardiovascular disease is that it is mostly a pump problem or blood vessel problem. However, diseases like heart failure and hypertension are in fact systemic, and a variety of feedback control mechanisms alluded to above become hijacked over time to reinforce the pathophysiology as opposed to correcting it.

These and other topics, including where the ideas behind various pieces of current dogma came from, are discussed in this book. So, we learn the history of the dogma, the limitations of the dogma, and a variety of altered perspectives that will help students, physiologists, and physicians to think about the cardiovascular system in a more nuanced and functional way. Like all good scientific and medical thinking, asking the right question is ultimately more important than simply mastery of current ideas, and this book is full of the right questions or ideas that will lead the reader to their own right questions.

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Foreword III

Despite remarkable progress in medical treatment within the last 10 years, morbidity and mortality of heart failure are still high: 70–80 % of patients suffering from heart failure will die within the next 8 years. Paradoxically, the prevalence of heart failure remains high as more patients survive myocardial infarctions and fewer are dying from lethal arrhythmias. The traditional biological models used for understanding the cardiovascular function in failing hearts have been inconsistent and impeded the development of newer and more effective therapies. Some of these limitations may result from inaccuracies in modeling the structure and physiology of the cardiovascular system. In particular, the architecture and the working of cardiac chambers, which maintain the highly efficient global function of the normal heart, remain controversial and incompletely characterized.

In this regard, readers will find the current monograph *The Heart and Circulation: An Integrative Model* particularly intriguing. The chapters are well written and comprise vital material that has appeared in print previously in fragments yet never before compiled together and presented in such a concise and masterly way. Following careful considerations of different viewpoints, the author presents a unifying theory of form and function of the embryonic and adult hearts. The contents provide a convincing argument for suggesting that the cardiac chambers generate pressure, yet the pressure does not necessarily work as a driving force. Rather, the evidence suggests that the heart functions as an organ of impedance (as supported by the vortical flow phenomena), a notion that has been around for over a century, yet very few have dared touching it.

The author and publishers should be congratulated for making available this very timely and welcome addition that challenges the traditional tenets of cardiovascular physiology until its universal predictive validity is established.

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Preface

The content of this book, long in coming, was originally intended as a journal article. It became apparent, in due course, that the large amount of accumulated evidence gathered in support of the thesis could only be condensed at the cost of its weakening; hence, the material was arranged into the form currently presented in the book.

Even though I have been loosely aware of the notion that the heart does not function as a propulsion pump for many years, the idea that the heart might be an organ controlling the flow of blood by rhythmic restraint was so "far out on a limb" that I gave it no more than an occasional "spare time musing." The concept seemed, moreover, virtually incompatible with the broad principles of clinical practice, not to mention the core curriculum of resident education, in which I have been involved for well over two decades. It did, however, serve to enhance my interest in basic concepts of cardiovascular physiology and, in particular, in the *source* of the ideas that contributed to their development. Close monitoring of vital functions during anesthesia – the very core of our practice – on patients with a wide range of clinical conditions, as can only be encountered in a large tertiary medical center, provided ample opportunity for direct observation of related phenomena. It wasn't until several years later, after some elementary experimentation on chick embryos and much schooling in perception, that I began to comprehend the link between the respiratory and cardiovascular phenomena in the light of the "integrative" model elaborated herein.

My interest in the subject was heightened after having discovered, while searching the literature, that the question of blood propulsion was far from settled, even among clinicians and specialists in various fields of cardiovascular physiology. Several key areas in basic and clinical sciences were then identified that are at variance with the prevailing pressure-propulsion model. Combined, they strengthened the conviction that the primal phenomenon of circulation needs to be reexamined in the light of a hemocentric view.

For the sake of terseness, I have purposefully deferred from venturing into the broader historical origin of ideas at the core of cardiovascular physiology and have, perhaps at the risk of sacrificing clarity, limited my comments to brief introductory

remarks. More importantly, a thoroughly researched volume on the origins of the cardiocentric model of circulation by Thomas Fuchs is available and can be considered a valuable introduction to the subject [1].

This book is therefore written for all those clinicians, researchers, educators, and students who, having been confronted with the paradox of the circulation, are looking for a broader interpretation of the circulatory phenomena. Should their objective be met even in a modest way, then "this heart's tough muscle, weak still in gratitude" [2] will be content.

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2. Snodgrass WD. Lasting. From collection of poems *Not for Specialists*. 2006.

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Contents

Abbreviations

AGM	Aorta–gonad–mesonephros
ANP	Atrial natriuretic peptide
AO	Aortic occlusion
ASD	Atrial septal defect
ATP	Adenosine triphosphate
bpm	Beats per minute
CFD	Computational fluid dynamics
CHF	Congestive heart failure
CI	Cardiac index
CL	Cardiac cycle length
CO	Cardiac output
COI	Cardiac output index
CPR	Cardiopulmonary resuscitation
CVP	Central venous pressure
$D(a\text{-}v)O_2$	Arteriovenous oxygen difference
dpf	Days postfertilization
DTMRI	Diffusion tensor magnetic resonance imaging
E	Embryonic day
EDMCL	End-diastolic myocardial cord length
EDP	End-diastolic pressure
EDV	End-diastolic volume
E_{max}	Ventricular elastance
ES	Eisenmenger syndrome
ESP	End-systolic pressure
ESPVR	End-systolic pressure–volume relationship
ESRD	End-stage renal disease
EW	External work
FCD	Functional capillary density
FEV	Forced expiratory volume
FFR	Force–frequency relation
HH	Hamburger–Hamilton
HLHS	Hypoplastic left heart syndrome
hpf	Hours postfertilization

HPV	Hypoxic pulmonary vasoconstriction
HR	Heart rate
IABP	Intra-aortic balloon pump
ICD	Implantable cardiac defibrillator
IVC	Inferior vena cava
LA	Left atrium
LAP	Left atrial pressure
LV	Left ventricle
LVAD	Left ventricular assist device
LVEDP	Left ventricular end-diastolic pressure
LVEDV	Left ventricular end-diastolic volume
LVP	Left ventricular systolic pressure
MAP	Mean arterial pressure
MCFP	Mean circulatory filling pressure
MCL	Myocardial cord length
MCP	Mean circulatory pressure
MSP	Mean systemic pressure
NO	Nitric oxide
OPS	Orthogonal polarization spectral imaging
P	Pressure
PA	Pulmonary artery
PAH	Pulmonary artery hypertension
PAm	Mean pulmonary artery pressure
PaO_2	Oxygen tension in arterial blood
PAWP	Pulmonary artery wedge pressure
PCWP	Pulmonary capillary wedge pressure
PDA	Patent ductus arteriosus
PE	Potential energy
PHT	Pulmonary hypertension
Pra	Right atrial pressure
PRU	Peripheral resistance units
P–V	Pressure–volume (loop)
PVA	Pressure–volume area
PVP	Peak ventricular systolic pressure
PVR	Pulmonary vascular resistance
PVWP	Pulmonary venous wedge pressure
Qp–Qs	Pulmonary to systemic flow ratios
RA	Right atrium
RAP	Right arterial pressure
RBCs	Red blood cells
RHB	Right heart bypass
Rp	Peripheral resistance
Rv	Resistance to venous return
RV	Right ventricle
SpO_2	Hemoglobin oxygen saturation percent

S	Somite
SDF	Sidestream dark field imaging
SROC	Spontaneous return of circulation
SS	Somite stage
SV	Stroke volume
SVC	Superior vena cava
SVI	Stroke volume index
SvO_2	Mixed venous oxygen saturation
TAH	Total artificial heart
TBV	Total blood volume
TCA	Total cardiac output
UBM	Ultrasound biomicroscopy
VAD	Ventricular assist device
VMB	Ventricular myocardial band
VO_2	Ventricular oxygen consumption
VO_2 - PVA	Ventricular oxygen consumption per beat
VR	Venous return
VSD	Ventricular septal defect

Introduction

As late as the mid-nineteenth century, a vigorous debate still took place between the "Cartesians" who considered the heart to be the sole source of blood propulsion and the so-called "Vitalists" who maintained that peripheral factors play an equal, if not superior, role in the control of cardiac output.

The introduction of extracorporeal circulation into clinical practice in the 1950s, when the heart could be replaced, at least temporarily, by a mechanical pump, became a practical validation, and for many, the final victory of the pressure-propulsion model over the vitalistic theories of the past. The expression "the heart is a pump" has became a part of the "collective unconscious," so deeply ingrained, that generations of physicians remain unaware of the fact that the question of the energy sources for blood movement is far from being settled.

On occasion the problem reemerges in its elementary form, such as during a recent debate in the physiological literature, where the question "What drives the circulation?" became a subject of vigorous exchange between those who support the primary pressure-propulsion role of the heart (i.e., the "left ventricular" view) and those who, in addition, invoke the peripheral factors (the "venous return" view) as the key determinants in the control of cardiac output. It turns out (as discussed in this book) that the battle of ideas over the primacy of factors that control cardiac output is fought on a spurious plane field without the prospect of it being resolved.

For the most part "the problem" has sunk into subspecialties, such as embryonic cardiovascular physiology, exercise physiology, and pediatric cardiology, to name a few, where the understanding of the pathophysiology of congenital heart defects and associated pulmonary hypertension presents an ongoing challenge. Accordingly, many have called for more encompassing models of circulation.

In the early part of the twentieth century the Austrian philosopher Rudolf Steiner suggested that the heart, rather than being a pump, is actually a flow-restraining organ which regulates, but does not propel, the flow of blood. He further proposed that the best evidence for this can be found in the early embryonic circulation where the valveless tube heart would be unable to act as a propulsion pump, and yet a vigorous circulation is present. In spite of dedicated efforts on the part of

researchers familiar with the idea of autonomous blood movement, most notably, those of cardiac surgeon Leon Manteuffel-Szoege, the firm experimental evidence to support it seemed to be lacking.

It is the premise of this book to trace the development of the basic concepts in cardiovascular physiology in the light of the accumulated experimental and clinical evidence and, instead of making the findings fit the standard pressure-propulsion mold, let the phenomena "speak for themselves."

In the first part of the book attention is turned to the embryonic circulation where peristaltic contractions of the early embryo heart have traditionally been assumed to be the source of blood propulsion. Recent hemodynamic and in vivo imaging data have shown, on the contrary, that the blood passes through the heart at a faster rate than the myocardial peristaltic waves, leaving the question of the mode of action of the heart, and hence of blood propulsion, wide open. Several morphological features such as the lack of valves, the presence of a thick layer of endocardial jelly, and the complex process of looping present a hemodynamic disadvantage to flow generation and suggest that rhythmic contractions of the heart interrupt the flow of blood, rather than function as a source of its propulsion. The transition from tubular to chamber myocardium, with an extensive system of ventricular trabeculations, increases the contact between the endocardium and the blood and further hinders the flow through the heart. The development of endocardial cushions and valves marks a transition from primary to secondary circulations, in which the high-pressure arterial limb of the circuit is functionally separated from the low-pressure venous limb. The heart thus separates the two circulations and generates pressure, but not flow.

Together with the emerging respiratory function, the heart can be seen as a mediator between peripheral and central circulations and serves as a "negative feedback loop" to metabolic requirements of the tissues, which are the primary cause for blood's circulation. This implies that the movement of the blood is autonomous and constitutes an integral part of the autoregulatory, metabolic control of the tissues. Mechanical interference with the blood flow results in acute compensatory changes by the peripheral circulation and adversely affects the development of the heart, affirming its primary epigenetic role in cardiac morphogenesis.

The validity of this model is then confirmed by comparing the key developmental stages of the cardiovascular system with examples from the invertebrate, mammalian, and avian species. Comparative cardiovascular physiology suggests that autonomous movement of the blood/hemolymph is ubiquitous. Microscopic and morphologic features of the "open" lower vertebrate and invertebrate circulations reveal that they are primarily designed to support flow but only limited pressures. The heart, where present, serves the same function as in the vertebrates, namely, as a damming-up, regulatory organ. Heart, vessels, and red blood cells share a common mesodermal origin and can functionally be viewed as a single organ which mediates between the form-giving nerve (ectodermal) pole and the metabolic (endodermal) pole of the organism. The evolutionary (biological) model of circulation attests to a remarkable adaptability of species in transition from water to land and air and can be viewed as a common fulcrum for environmental adaptation.

In the second part of the book the salient morphological and histological features of the myocardium are reviewed with particular reference to its characteristic form – the vortex. The presence of blood vortices in the chambers – known as energy-dissipating fluid structures –suggests, moreover, that the heart impedes, rather than propels the flow of blood. Spiral flows and architectural patterns occur throughout the arterial tree, in particular at vascular bifurcations, and confirm the intimate connection between form and function. Historical emphasis of the myocardial systolic properties is then explored and contrasted with the relative disregard for its diastolic function. Mounting evidence suggests that the presence of stable intracardiac diastolic blood flow patterns and ventricular twist mechanics play an essential role in normal heart function and, when disturbed, lead to pathological states.

Attention is then turned to the regulation of cardiac output and to the arguments advanced by the proponents of the "left ventricular" and the "venous return" models of circulation. Since the common denominator of both models can be traced to the hydrodynamic equivalent of Ohm's law – where the power source is clearly traced to a pump (i.e., the heart) – those seemingly opposing views differ only in semantics, but not in substance. The phenomenon of vestigial circulation is explored as an example of residual blood movement, detectable up to several hours after the cessation of the heart's action. The evolution of the mean circulatory pressure concept is discussed as the centerpiece of Guyton's widely accepted venous return model. Finally, methodological and conceptual deficiencies of Guyton's circulation model are critiqued.

It is further shown that the introduction of artificial respiration had severed the once unified concept of circulatory and respiratory functions of the blood into two separate functions: the respiratory, driven by the thoracic, and the circulatory, driven by the cardiac pumps. The technique of artificial respiration has moreover obscured the key phenomenon of acceleration of blood on its passage through the lung, an event that is concurrent with oxygenation.

In the following section a brief history of isolated heart preparation is reviewed and its potential to disguise the heart's flow-restraining function is discussed, when it is assumed a priori that the heart is a pressure-propulsion pump. The isolated heart preparations demonstrate moreover that even during baseline conditions the heart, paradoxically, operates either at *maximum* power and/or efficiency, a finding that is at odds with sound bioenergetic principles. It is proposed that the apparent energetic and mechanically inconsistent behavior of the heart can be resolved when it is assumed that *mechanically* the heart functions like a hydraulic ram. Limitations of the pressure-propulsion model are further exposed by the experimental and clinical use of ventricular assist devices, where discrepancies are routinely observed between the levels of flow, determined by mathematical models and the actual cardiac output distribution that matches the metabolic demands of the tissues. The abandonment of the "permanent" total artificial heart concept is a testimony to the failure of the prevailing pressure-propulsion model.

The "heart as a pump" model additionally fails to adequately reconcile a large amount of conflicting data from exercise physiology where the concept of "muscle pump" has been evoked in order to account for greatly increased blood flows that

significantly exceed the theoretical pumping capacity of the heart. Review of the literature shows that the data in support of the muscle pump theory is tenuous and upholds the premise that increased "cardiac outputs" can be ascribed neither to the action of the heart nor to contracting muscles, but rather to enhanced movement of the blood in response to greatly increased muscle oxygen and nutrient consumption. Increased diastolic compliance, enhanced systolic torsion, and increased myocardial mass and chamber volume in response to aerobic conditioning indicate that the heart serves as an organ of impedance, setting itself *against* the large increase in "cardiac output" during aerobic exercise.

One of the most convincing interventions that speaks against the pressure propulsion paradigm is the mechanical occlusion of the aorta, a method routinely applied experimentally on animal models and on patients during aortic surgery. The paradoxical increase in cardiac output and a decrease in global tissue oxygen consumption below, as well as above, the level of aortic occlusion and a number of associated phenomena, yet to be explained by the conventional model, become intelligible if the blood is considered to be an organ with autonomous movement and, as such, subject to lawfulness that differs substantially from that of inert fluids.

Further evidence for the flow-restraining function of the heart is a group of conditions associated with hyperdynamic circulation caused by a "short circuit" between the systemic and pulmonary circulations. Congenital heart defects with large, nonrestrictive communication between the systemic and pulmonary circulations at the level of the heart or the great vessels all share a number of similarities. Left uncorrected, they invariably lead to increased pulmonary artery resistance, culminating in pulmonary hypertension and bidirectional shunt, a condition known as Eisenmenger syndrome. It is proposed that the key for the confounding nature of this phenomenon can be found by comparing the hemodynamics of these conditions to the fetal circulation, where, as a matter of course, a "parallel" arrangement with extensive communications between pulmonary and systemic circulations exists. The predominantly "venous" character of the immature fetal circulation bears resemblance to the low-pressure amphibian circulation, in which the three-chambered heart still allows for the mixing of pulmonary and systemic circulations. With transition to air respiration at birth the heart undergoes a radical remodeling; the communications between atria and great vessels (ductus Botalli) functionally close, resulting in a complete separation between the low-pressure pulmonary and high-pressure systemic circulations. Should the connection between the two circuits persist, the short-circuited pulmonary circulation becomes subject to accelerated flows that far exceed the flows through the systemic circulation. Since the normal "flow-restraining" function of the heart is no longer possible, an attempt to balance the two circulations arises in the form of increased pulmonary vascular resistance with concomitant increase in pulmonary artery pressures, which rival systemic pressures, during the final stage of the illness.

Hyperdynamic circulation with disturbed balance between the pulmonary and systemic circulations is moreover observed in a variety of arteriovenous fistulas, confirming the fundamental phenomenon, namely, that a "short circuit" between

arterial and venous compartments leads to self-feeding, accelerating flows with far-reaching effects. While smaller fistulas present with a range of peculiar phenomena such as flow reversal in the feeding arteries and "arterializations" of proximal fistula veins, large-volume fistula flows, on the other hand, result in high-output heart failure or lead to increase in pulmonary vascular resistance and pulmonary hypertension. The above phenomena collectively demonstrate the need for "a restraint" on the path of the circulating blood as is normally provided by the capillaries peripherally and by the heart, centrally. By setting itself up against the flow of blood and providing a "negative feedback loop," the heart thus maintains its role as the central organ of the circulation.

We are met with an almost diametrically opposite hemodynamic situation in the case of hypoplastic left heart syndrome, a group of rare congenital heart anomalies, which, left untreated, would invariably lead to infants' demise, on account of the closure of the ductus arteriosus, the main remaining pathway for the blood to reach the lung. The intriguing evolution of medical and surgical management of these "duct-dependent" conditions is reviewed with particular emphasis on the palliative Fontan repair, which has proven to be an excellent long-term treatment, for the majority of patients with single-ventricle hearts. In the Fontan circulation we are faced with a paradox, where the single, often weakened and underfilled ventricle supposedly provides the "driving force" for the pulmonary as well as the systemic circulations. It is proposed that the intricate nature of the Fontan paradox can be resolved, when its complex hemodynamics are viewed in the light of the biological model of circulation presented in this monograph.

Finally, the salient developmental milestones of the cardiovascular system explored in the first part of the book are summarized and brought into the context of the mature circulation. The differential sensitivity of systemic and pulmonary circulations to hypoxia can be seen as a great polarity in which the blood plays the central role. The red blood cells, together with the vascular endothelium, function as "mobile sensors" and are a key factor in matching ventilation with perfusion in the lung but also regulate the distribution of oxygen to the tissues in accordance with their metabolic demands. In addition to supplying the tissues with oxygen and metabolic substrate, the blood possesses its *own* metabolic requirements. By meeting the metabolic demands of the tissues, as well as satisfying its own need for oxygen, blood as a "liquid organ" thus fulfills a dual role.