Branko Furst

The Heart and Circulation

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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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.

Part I
Embryonic Circulation

Chapter 1
Early Embryo Circulation

1.1 Introduction

Over the past several decades the search for the unifying paradigm between the form and function of the early vertebrate embryo heart has focused on genetic patterns [1–3] as the blueprints for early heart formation, enhanced by phylogenetic and morphological observations [4–7]. More recently, however, there has been a resurgence of interest in epigenetic factors such as intracardiac flow patterns and fluid forces as significant factors in early embryo cardiogenesis [8, 9] and vascular formation [10–12]. The availability of new techniques such as confocal microscopy, phase contrast magnetic resonant imaging, digital particle velocimetry, and high-frequency ultrasonographic imaging, used for in vivo observation of embryonic flow dynamics, has yielded new insights into the early embryo hemodynamics [13].

While it has been commonly assumed that the early vertebrate embryo heart works as a peristaltic pump, this view has been contested on the grounds of newly acquired imaging and hemodynamic data. The existing evidence no longer supports the accepted mode of the heart's peristaltic blood propulsion and has called for radical reevaluation of the traditionally accepted model of early circulation [14–18]. In the light of new findings Forouhar et al. proposed that the early embryo heart works as a dynamic suction pump (vide infra) [14]. The existing evidence presented in this paper together with the evidence reviewed by Männer [15] suggests that the heart works neither as a peristaltic nor as a dynamic suction pump, which leaves the question of early embryonic blood propulsion essentially unanswered.

Nearly a 100 years ago Austrian philosopher and educator R. Steiner maintained that the blood in the organism possesses its own motive force and that the heart, rather than being the organ of propulsion, dams up the flow of the blood in order to create pressure. Steiner further suggested that observation of the early embryonic circulation offers the best proof of this phenomenon [19, 20]. Despite the fact that over the years several publications have appeared in support of this theory, only a few deal specifically with early embryo circulation [21–25].

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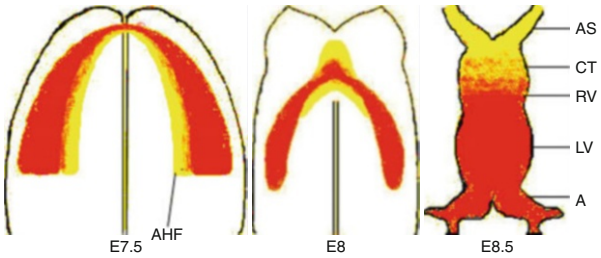

Fig. 1.1 Cardiogenesis in mouse at embryonic day (E) 7.5, 8, and 8.5: The primary heart-forming field is shown in *red* and the secondary in *yellow*. Heart shading corresponds to approximate heart-field contributions to future heart regions. *AS* atria and sinus venosus, *CT* conotruncus, *RV* right ventricle, *LV* left ventricle, *AHF* anterior (secondary) heart field (Adapted from Ref. [28], used with permission of Wolters Kluwer Health)

1.2 Morphological Features

The heart and the system of vessels are the first functional organs to develop in the vertebrate embryos. Although species specific at the subcellular level, the early functional and morphological features are nearly identical among all vertebrates [1, 3, 6]. The early embryo circulatory system is a functional unit, consisting of the extraembryonic yolk sac circulation and of the circulation belonging to embryo proper.

The yolk sac (vitelline) vascular formation is the first to form in the mammalian embryo and consists of mesodermally derived endothelial and erythroid (red blood cell) precursors. They share a common progenitor, the hemangioblast, which differentiates already at the pre-gastrulating stage and migrates into the region of the yolk sac. The erythroid cells amass in a narrow circumferential band at the proximal end of the yolk sac. At this stage the so-called blood island contains only a few endothelial precursors. The majority of the endothelial cell elements, however, are assembled into a loose vascular network, the primary capillary plexus, just distally to the blood island. During subsequent development the endothelial cells partition the erythroid precursors into smaller channels. Finally, the cell-filled vascular bed is formed and is joined with the primary capillary plexus just prior to the onset of circulation. The vitelline circulation supports the nutritive and respiratory functions of the embryo [26, 27].

The first inception of vertebrate heart (mammalian and avian) arises from the presomitic cranial mesoderm (cardiogenic plate) during early gastrulation. The progenitors of bilateral cardiac fields merge at the anterior margin to form the "cardiac crescent." These fields contain precursors for myocardial and endocardial (endothelial) cells (Fig. 1.1). Specification into the cardiomyocytes and endocardial cells occurs just before the formation of the cardiac crescent. The endocardial cells assemble into loose vascular plexus adjacent to developing cardiomyocytes and coalesce into a single, capillary-size endocardial tube which is the first vascular structure of the vertebrate embryo. The resulting tubular heart consists of an

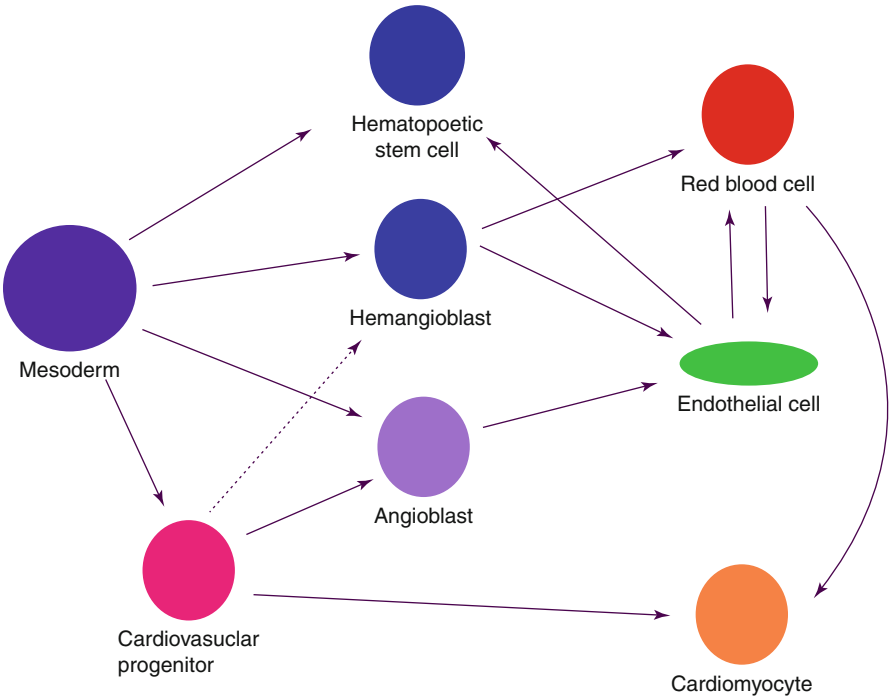

Fig. 1.2 The origin of cardiovascular lineage. Mesoderm-derived cardiovascular progenitor cells serve as precursor of the red blood cell, heart, and endothelial and vascular smooth muscle cell lineages (Adapted from Ref. [29], used with permission of Wolters Kluwer Health)

external myocardial and of an inner endocardial layer [1, 27, 28]. There is evidence that a common cardiovascular progenitor exists, with a potential to become a cardiomyocyte, endothelial and vascular smooth muscle cell, which suggests that the heart, the vessels, and their content, the blood, share the same origin [29–32] (Fig. 1.2).

The tubular heart is formed by progressive fusion of the paired primordia in the caudal direction. At its upper pole the tube consists of the inception of the bulbar sac and of the apical portions of the ventricles. Caudally, it divides into the paired venous limbs, the future sinus venosus, riding over the anterior intestinal portal [33] (Fig. 1.3). The myocardium first invests the endocardial primordia at the bulbar end and then progressively in caudal direction, as the fusion of the endocardial primordia progresses [34].

Further development of the tubular heart is a sequential process of lengthening and bending, as it frees itself from its attachment to the dorsal mesocardium, forming a dorsally oriented C-loop. The subsequent *looping* of the heart tube is marked by pole reversal and torsion, in which the venous pole of the heart tube shifts upward and the arterial pole moves downward, forming a doubly bent, S-shaped organ. The loop heart consists of four distinct parts which follow each other serially in the direction of the flowing blood (caudo-cranially):

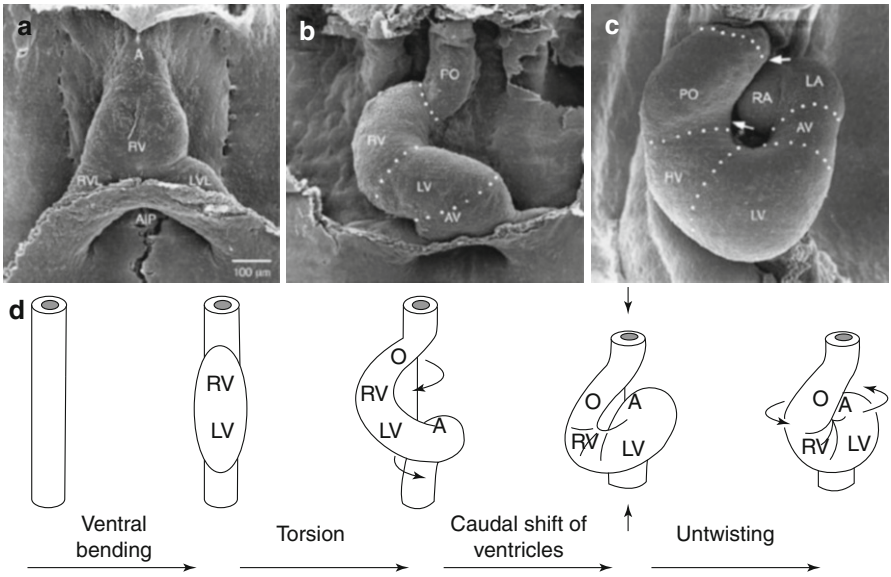

Fig. 1.3 Linear heart tube of HH stage 9 chick embryo (**a**). The vertical portion of the heart consists of tissue mass belonging to the future right ventricle, *RV*; of the aortic sac, *A*; and of paired venous limbs, *RVL* and *LVL*, riding on anterior intestinal portal, *AIP* (**b**). Early torsion and looping of the heart in HH stage 12 chick embryo and (**c**) completed right-handed loop in HH stage 17/18 embryo. *PO* proximal outflow tract, *RV* right ventricle, *LV* left ventricle, *AV* atrioventricular canal, *LA* left atrium, *RA* right atrium. (**d**) Schematic representation of looping. Note torsion and pole reversal in which the caudal, venous end of the heart (RV) shifts upwards and the arterial pole (LV) moves downward, an early morphological gesture indicating that the heart is primarily an organ of impedance rather than propulsion. *RV* right ventricle, *LV* left ventricle, *A* atrium, *O* outflow tract (Reproduced from Ref. [33], used with permission of John Wiley and Sons)

1. The sinus venosus, located at the junction of vitelline veins, receives the blood returning from the yolk sac and the venous blood from the embryo.
2. The early atrium as the first dilation of the heart tube.
3. The ventricle, formed by the bent midportion of the original cardiac tube.
4. The aortic bulb which connects the ventricle with the ventral aortic roots.

At the level of the ventricle, the cross section of the heart tube resembles a blood vessel consisting of the inner endocardial layer, of the cell-free matrix called the cardiac jelly, and of the multilayered outer myocardium. It is noteworthy that the elongation or "growth" of the heart occurs in direction opposite to the flow of blood and that the sinus venosus, as the site of the definitive pacemaker tissue, is the last to develop in the course of heart tube formation.

Transformation of the heart tube into the chambered heart requires emergence of localized dilations, which expand into cardiac chambers in the process of *ballooning*. All embryonic vertebrate hearts have two chambers: the smooth, thin-walled atrium and the thicker-walled, trabeculated ventricle [6, 35] (Fig. 1.4). In the course of further development, the atrium and the ventricle will become the low- and the

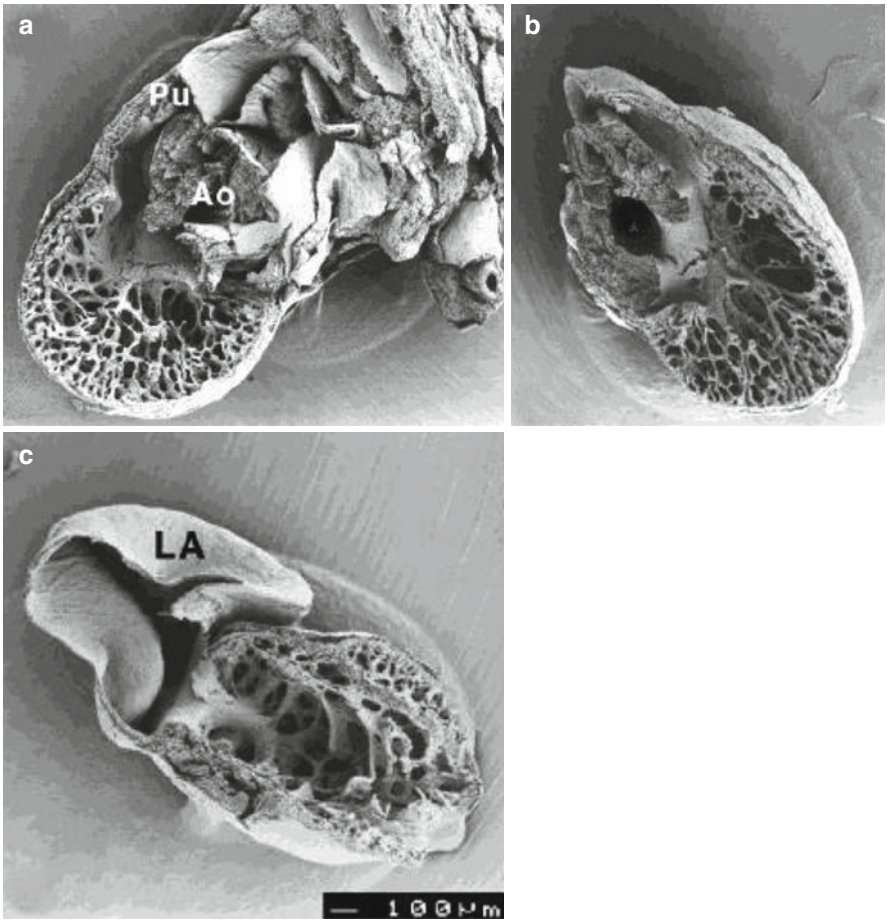

Fig. 1.4 Sagittal section of HH stage 29 (day 6) chick heart. (**a**) and (**b**) show the right and (**c**) the left ventricle. Note extensive spongy trabeculations of the ventricular myocardium and smooth inner wall of atria. *Pu* pulmonary artery, *Ao* aorta, *LA* left atrium (Adapted from Ref. [6], used with permission of John Wiley and Sons)

high-pressure chambers, respectively. Before the formation of the endocardial cushions and, subsequently, of the valves, cardiac jelly plays a vital role in preventing the retrograde flow of blood during the heart's contractions [15, 36, 37].

Until the stage of looping, all vertebrate hearts are morphologically indistinguishable [1]. During the process of looping the primary flexure at the bulboventricular junction moves caudally. In higher vertebrates the primary flexure will become the future left ventricular apex of the four-chambered heart. The secondary flexure, between the sinus venosus and atrium, shifts to the back and upward with respect of the original tubular organ to form the future (venous) inflow into the heart [21, 38]. In higher animals the primitive two-chambered heart develops further through the process of *septation* to become the three- (e.g., amphibian) and four-chambered mammalian hearts.

The presence of the intact endocardium and the fluid forces generated by the flow of blood are essential for the development of chambers and of ventricular trabeculation. It has recently been demonstrated that in zebrafish trabeculation fails to develop in the absence of intact endocardium and of the shear forces generated by the circulating blood [39, 40]. Ventricular trabeculations markedly increase the endocardial surface area and thus the contact between the blood and the (endocardial) endothelial cells. Mounting evidence suggests that the changing flow and shear stress patterns during cardiac looping and chamber formation present important signals for endothelial cells, which serve as mechanosensory transducers for cardiac function and development [10, 11, 41]. Their possible role as the feedback loop between the heart and the peripheral embryonic circulation will be further explored in this monograph.

The nutrient-rich blood of the yolk sac drains into the terminal sinus of the vitelline membrane and, via a network of vitelline veins, back to the embryo. Inside the embryo it is joined by the blood returning from the embryo via the common cardinal veins which drain into the sinus venosus. After traversing the heart, the blood is ejected in the cephalad direction into the paired ventral aortae. The flow of the blood is then directed caudally and exits the embryo via a pair of vitelline arteries (see Fig. 2.1). The vitelline veins, the aortae, and the vitelline arteries are a direct continuation of the endocardial primordia of the heart and are technically considered a part of extraembryonic circulation [38]. During the early stages of development about 80 % of blood circulates through the vitelline membranes, and the nutrients reach the embryo largely by diffusion [42]. With the growth of the embryo, the proportion of distribution of blood between the embryo and the extraembryonic membranes gradually shifts towards the embryo [43]. The embryonic heart thus forms a dynamic bridge between embryonic and extraembryonic circulations. Morphologically this is reflected by the fact that the heart is initially located near the future head of the embryo, and only during the course of development descends and moves dorsally to become the central organ of circulation [21].

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Chapter 2
The Onset of Circulation

It is generally assumed that the blood begins to move as soon as the heart begins its contractile activity. Evidence suggests that there is a marked variability between the onset of the heartbeat and movement of the blood. It further points to a complex relation which exists between the first movement of plasma and the red blood cells. In order to further elucidate this intricate phenomenon, we will take a closer look at the beginning of the circulation in chick, mouse, and zebrafish embryos.

2.1 Chick Embryo

Localized spontaneous action potentials have been detected in chick embryo hearts as early as HH (Hamburger–Hamilton) somite stage 6 [1]; however, the first excitation–contractile activity develops only after the fusion of the paired cardiac primordia into the tubular heart during HH stage 9 or 10 [2, 3]. Contractions are first observed at the right upper margin of the primitive ventricle and spread over the rest of the heart with increasing velocity during subsequent growth. This feeble contractile activity in the ventricle is superseded by the emergence of atrial pacemaker cells at 12-somite stage of development. The fully coordinated peristaltic contractions originating in the sinus node are established by 14-somite stage [4]. Recently developed video-imaging methods of the initial beating patterns in the chick embryo heart are broadly consistent with the pioneering work of Patten who reported ventricular contractions preceding atrial activity already in the 1930s of the last century [5, 6].

The onset of blood circulation in the chick embryo has been variably reported to be between HH stages 10 [7], 12 [8], 15 [9], and 16–17 [5] (Fig. 2.1). Most reports, however, do not distinguish between the primary and the secondary circulations. The first blood movement in the chick embryo, the *primary circulation*, occurs in the centrifugal direction and courses in an arch close to the embryo, initially bypassing the more distal capillary network. As it reaches the furthest point from the embryo, the marginal sinus, it returns via the anterior vitelline vein back to the

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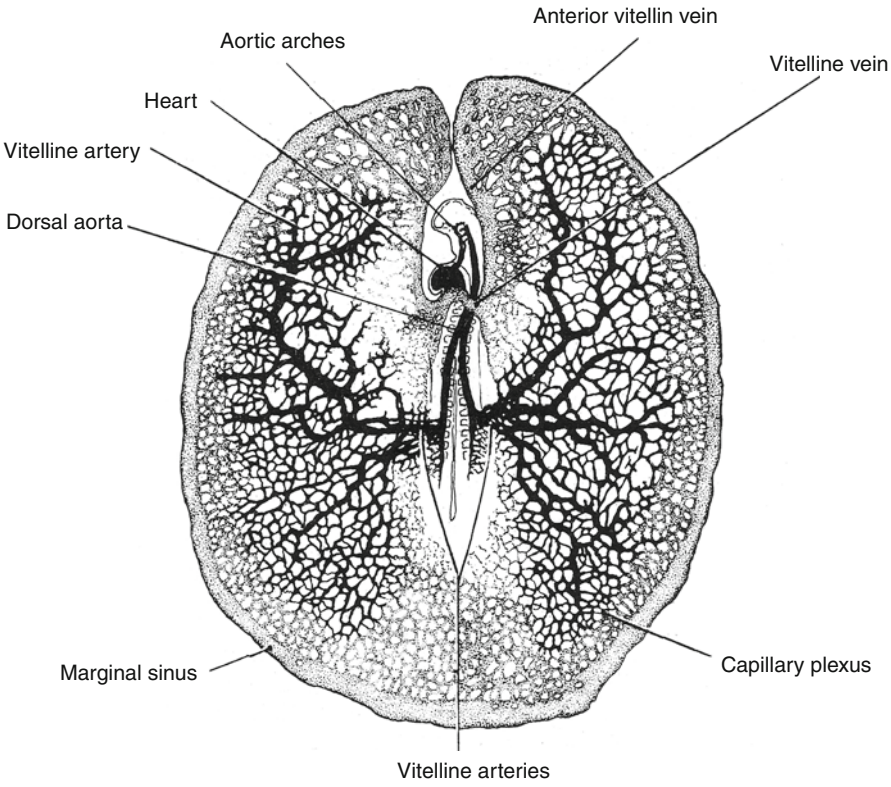

Fig. 2.1 Vitelline circulation of a chick at about 44 h of incubation, HH stage 14. The arteries are dark and veins stippled (Reproduced from Ref. [11], used with permission of The McGraw-Hill Companies)

embryo. The afferent and efferent channels of the primary circulation lie on a single plane. After a period of some 24 h there is a progressive fusion of the capillary segments into larger conduits in which the single-layered plexus becomes remodeled into a two-layered structure, the *secondary circulation* (Fig. 2.2). The venous network is now lying on the top of the arterial. With rapid growth of the vitelline membrane and the differentiation of veins, the return path of the blood to the heart becomes more direct, bypassing the primary channels and increasing in flow velocity. As the blood gains in momentum there is a gradual increase in pressure. It is noteworthy that for the greater part of the developmental period, the low-pressure primary and the higher-pressure secondary circulations coexist: one gaining in importance, the other fading away [10].

It is of interest that like the peripheral circulation, the morphogenetic development of the embryo's heart has likewise been divided into the *primary* or *embryonic* and *chamber* or *working* myocardium. The former is the early heart tube, characterized by slow contractile activity which follows the direction of blood flow and the ability to depolarize spontaneously. Recording of the electrical signal shows a

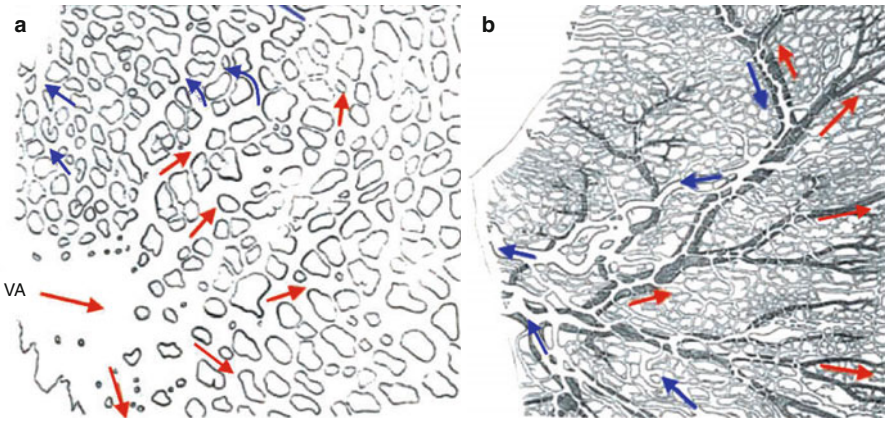

Fig. 2.2 Beginning of circulation in the chick embryo. (**a**) At the onset of circulation the blood flows directly from arteries to veins without passing through a true capillary network. The arteries carry blood away from the heart (*red arrows*), and veins (*blue arrows*) back to the heart. The vascular network is arranged in a single plane with cis–cis configuration. Early stage of vitelline artery (*VA*) formation at approximately HH stage 12. (**b**) Formation of vitelline veins comes about through vascular remodeling of arterial conduits. During the period of the next 24 h after (**a**), at about HH stage 19, the two-dimensional plexus becomes a three-dimensional structure with a network of interconnecting veins lying on top (dorsal) and parallel to the arteries. *Red arrows* mark blood flow in the arteries (*dark*), *blue arrows* in the veins (*light*) (Reproduced from Ref. [9], used with permission of the Company of Biologists)

simple sinusoidal curve [12]. The main features of the working or chamber myocardium are accelerated growth and looping, ventricular trabeculation, and the appearance of a specialized conduction tissue. The impulse generated by the sinus node no longer follows the course of blood but undergoes a *reversal*, generating the familiar mature type EKG [13–15].

The importance of blood flow in the process of vitelline vascular differentiation has been appreciated ever since Chapman showed in the beginning of the last century that in chick embryos, in which the heart has been removed, the vitelline arteries fail to develop, while the capillary plexus (area vasculosa) continues to grow for several days [16]. However, only more recently has the process of vascular transformation, as it occurs under the influence of hemodynamic forces, been actually demonstrated [9, 17]. With the aid of time-lapse video microscopy and in situ hybridization of the specific arterial markers, namely, ephrin-B2 and neuropilin 1, le Noble et al. showed that in addition to vessel positioning and identity, vascular morphogenesis and branching are determined not only by genetic factors but also by flow. With the onset of blood flow, the capillary segments of the vitelline capillary plexus first form branches of the vitelline arteries. In the process, some of the smaller-sized vessels are disconnected from the main vitelline artery and form congested spots or buds in which the blood continues to pulsate. The persistence of pulsatile push in these segments leads to discharge or "flushing out" of the blood into the newly built venous conduits. Thus, the development of the functional

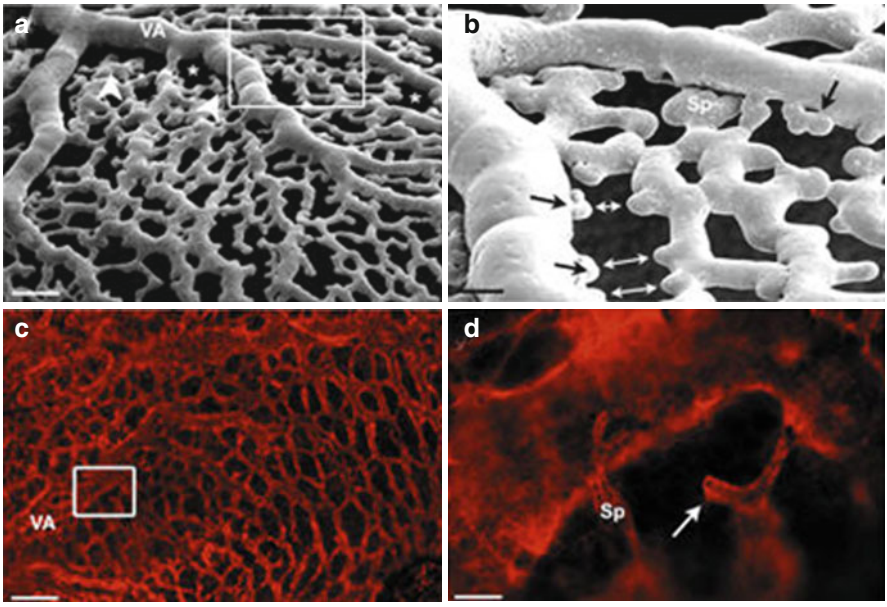

Fig. 2.3 Formation of secondary circulation in the yolk sac of HH stage 35 chick embryo. Vitelline veins are formed by the fusion of the capillary segments of the vitelline artery that have been disconnected from the mother branch. The arterial blood "trapped" within these segments continues to pulsate and forms blood-filled "spots," which form into sprouts perpendicular to the main vessel. (**a**, **b**) Scanning electron micrographs of Mercox-filled vitelline artery and endothelial surface staining (**c**, **d**). *Asterisks* show capillary-free zones. *Arrowheads* show disconnected arterial capillaries which correspond to blood-filled "spots" that are perfused from distal parts. (**b**) Higher magnification of *boxed area* in (**a**). Note blind-ending sacks (*black arrows*) on two branches of the vitelline artery with corresponding buds on the capillary segments (white, *two-headed arrows*). *VA* vitelline artery, *Sp* capillary sprout (Reproduced from Ref. [9], used with permission of the Company of Biologists)

venous system is achieved by disconnecting of the existing efferent (arterial) vessels, which by endothelial cell sprouting, fuse into new afferent (venous) channels (Fig. 2.3). The authors further demonstrated the remarkable flow-driven plasticity of the vitelline circulation by occlusion of the vitelline artery. This intervention resulted in a radical redistribution of flow in which the blood was "attracted" from the terminal sinus at the edge of the yolk sac and perfused the bloodless segment in a *retrograde* manner. In the process, the venous segments conducting blood in the direction towards the embryo became arterialized, while the arterial segments turned into veins. The fact that remodeling was not only functional but also histological was confirmed by rapid up-/downregulation of venous/arterial markers in the endothelial cells of transformed vascular segments. Flow pattern recordings in proximal vitelline arteries display a distinct forward (systolic) and retrograde (diastolic) component, with flow arrest at the end of diastole in the distal parts of the arterial tree. The authors proposed that flow shuttling occurs due to lack of heart

valves [9]. This, however, is in conflict with the pressure propulsion model, where one would expect that the pressure-generating ventricle should maintain enough pressure to sustain a continuous flow at least in the arterial limb of the circuit.

There is considerable evidence that significant blood flow exists in the early embryo well in advance of the need for convective oxygen and nutritive transport by the blood. As mentioned, during this period the demands of the tissues are largely met by direct diffusion through the vitelline vessels, so the functional division of blood into arterial and venous is not possible. On the basis of pooled experimental data, Burggren has questioned the need of embryonic heartbeat and of strong convective blood flows during early embryo development [18, 19]. For example, in chick embryos there is no hemoglobin-mediated oxygen transport up to HH stage 18 (day 3), and it only becomes fully efficient by stages 28–30 (day 6) when the yolk sac vasculature begins to function as a respiratory organ. By this time the four-chambered heart is almost completely developed [20].

2.2 Mouse Embryo

The early mammalian circulation consists of the embryonic, the vitelline, and the allantoic loops to which the placental limb is added. Because of a very short gestational period of 18–21 days, the murine embryo is widely used as a mammalian model of early cardiovascular development. Due to extreme pace of organ development it is difficult to characterize the exact developmental stage on the basis of the time of conception alone. For example, during the period of early heart tube formation, a pair of somites (S) is added every 1.8 h. Variability in the rate of organ development commonly occurs in embryos of the same litter [21]. The onset of heart contraction is reported to occur between S4 and 6, which coincides with embryonic day (E) 7.5–8.5, and the functional circulation is established between S8 and 10 (E 8.5) [22, 23].

To separate out the role of plasma flow from the rheological impact of circulating cells on the vascular development in early mouse embryo, Lucitti et al. conducted a study in which they measured the flow of plasma and separately tracked the movement of erythroblasts. The movement of plasma was observed by injecting fluorescent dextran into the hearts of S2 (somite) to S6 embryos. The presence of fluorescence in the yolk sac was recorded after a 10-min period. While in five of the six S2 embryos the fluorescent dextran was confined to the tube heart, in one of the embryos it had spread through the primitive vasculature of the yolk sac, confirming the patent vascular connections between the embryo and the yolk sac and, moreover, that plasma flow, albeit slow, occurs even before the onset of the heartbeat. The heart starts contracting at S3 which corresponded with gradual increase in plasma flow by up to 20 times as compared to the flow at S2. It is significant that during the first hour after the commencement of the heartbeat, no circulating erythroblasts were observed in the moving plasma. They were still confined to the blood

islands or scattered outside the vasculature as single, stationary cells. Gradually, the intermittent motion of erythroblasts was noted by stages S6–7, with some erythroblasts remaining stationary or forming clumps for up to 3 h before rejoining the circulation. By S8 the circulation was established which was followed by the usual vascular growth and remodeling of the yolk sac vasculature. To further differentiate whether the presence of erythroblasts is necessary for normal vascular remodeling, vascular islands of the early embryos were treated with acrylamide, which prevents erythroblast mobilization from their site of formation in the yolk sac. The treated embryos were then compared with normal controls. Despite normal plasma flow rates, the vascular remodeling failed to occur in treated embryos, confirming that circulation of plasma alone is insufficient to bring about vascular remodeling. On the basis of existing data and their findings, Lucitti et al. proposed that rheological forces, imparted to the flow of plasma by circulating erythroblasts, are needed to initiate a host of force-related signaling pathways, including the activation of endothelial nitric oxide synthase 3 (Nos3), all of which play a key role in bringing about a normal vascular development [24].

McGrath et al. likewise observed a slow initial movement of yolk sac-derived erythroblasts into the embryo proper lasting some 36 h during stages S4–7, indicating "some type of flow" from the yolk sac in the direction of the embryo. This coincided with the fusion of myocardial primordia and the initiation of the heart's contractions. As the heart began to loop at S8, "dramatic change" in the distribution of erythroblasts took place, in which the cells migrated from the yolk sac and were found in increasing numbers in the embryo proper. By S24 there was an equal number of red blood cells in the embryo as there was in the yolk sac, and finally, by S35–40 the ratio was reversed with ten times more red blood cells in the embryo proper than in the yolk sac. By S35 the circulating erythroblasts were dispersed through the entire vascular system. On the basis of their own observations and existing data, McGrath et al. concluded that the functional circulation in the mouse embryo is established only after the maturation of vascular networks, complete with endothelial lining, redistribution of erythroid cells from the yolk sac into the embryo, and remodeling of the cardiac tube into the chambers [23].

The beginning of the circulation in the mouse embryo resembles that of the chick, namely, that despite the presence of significant plasma flow and the beating of the heart, the circulation is not fully established until a sufficient number of erythroblasts enter the vessels. To verify the exact timing of the heartbeat and its relation to the onset of the circulating blood in the mouse embryo, Ji et al. employed ultrasound biomicroscopy (UBM), a recently developed noninvasive method for the assessment of cardiovascular function of the embryonic mouse in utero [25]. It should be noted that the UBM is unable to detect the movement of plasma since the Doppler signal depends on moving blood corpuscles or tissues, i.e., the contracting heart. During stages S2–4, before the initiation of the heartbeat, no intraembryonic erythroblasts were detected. The first rhythmic contractions of the heart in the range of 100–130 bpm were recorded in S5–6 embryos, still without any detectable flow of blood. By S7 aortic Doppler flow signals were first detected and were fully established by S8. Concomitantly, a rudimentary movement of cells was observed in the vasculature of the yolk sac [26].

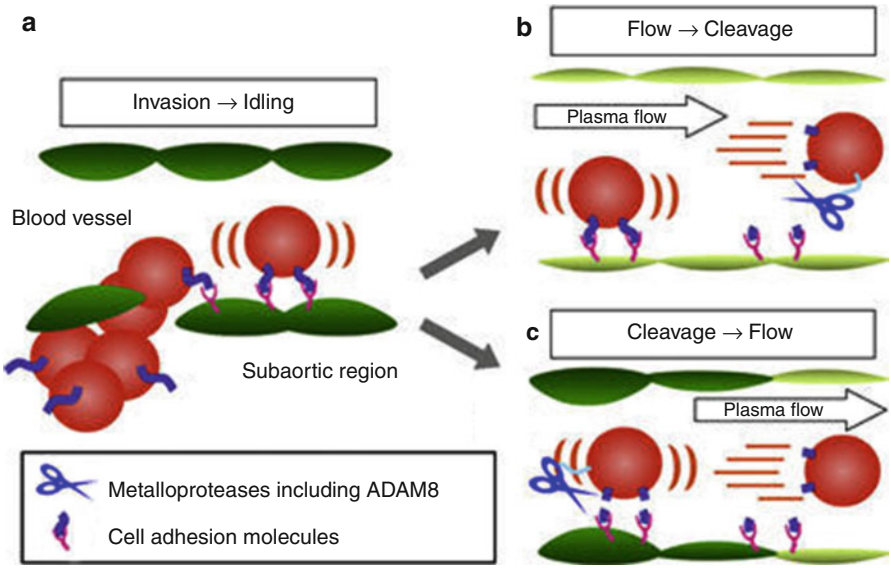

Fig. 2.4 Proposed models for the onset of circulation in zebrafish. During the first stage, "idling," the blood cells migrate through the vascular endothelium and adhere to the lumen (**a**). The circulation begins either by simultaneous release of red blood cells from the endothelium through the activation of ADAM8 (a metalloprotease-containing lytic enzyme) at critical plasma flow velocity (**b**) or by direct ADAM8-dependent release of erythroid precursors from the endothelial adhesion sites (**c**) (Adapted from Ref. [27], used with permission of Elsevier)

2.3 Zebrafish Embryo

Recent work on zebrafish confirms the existence of plasma flow between the embryo and vitelline membrane and demonstrates that just before the onset of blood circulation a series of key steps occur in the zebrafish embryo [27]. At the time of formation of the yolk sac capillary plexus, erythroblasts from the AGM (aorta–gonad–mesonephros) region inside the embryo begin to migrate into the lumen of the aorta, where they remain attached to endothelial cells. In this way they resemble the migrating leukocytes of the mammalian blood line. What follows is the "idling" phase during which the primitive red blood cells remain stagnant in vascular lumens, despite the fact that there is an active heartbeat and a detectable flow of plasma. The beginning of blood circulation is marked by a virtually simultaneous release of erythroid cells into the lumen of the dorsal aorta and into the posterior cardinal vein. This is a complex process in which the adhesion of erythroid cells is suddenly freed through a metalloprotease-mediated release process [27] (Fig. 2.4). In addition, nitric oxide (NO) produced by the endothelial cells has been found to play a key role in the process of endothelial cell migration, angiogenesis, and regulation of vascular tone at the onset of the zebrafish circulation [28].

The reviewed evidence suggests the existence of plasma flow either before or at the onset of the first contractions of the tubular heart. This primary flow or "progenitor circulation" is essentially of low-pressure type and can be compared with lymphatic flow in higher vertebrates. Its possible function is transport and distribution of erythroid progenitors produced in the yolk sac into the embryo [22, 28, 29]. The timing of this event does not appear to be linked with the onset of cardiac contractions. The combination of valveless heart and immature vessels with incomplete endothelial lining is unfavorable to efficient pressure propulsion. The primary streaming should be differentiated form the secondary or oxygen-carrying circulation which fully assumes its role of delivering oxygen to tissues only after a considerable delay.

In contrast to more recent "high-tech" studies, it is revealing how close to observing the primary phenomenon of the blood's movement some investigators of the past century have stood while simply observing the embryonic circulation at low magnification. Here is a description of the onset of blood movement from a study by Goss:

> Circulation of the blood began with embryos with 8 somites. Prior to this there has been backward and forward motion of blood cells in the yolk sac vessels or of the occasional free cells seen in the aorta and heart. As the time for circulation approached, the cells in the vitelline veins moved a little further toward the heart then they did back again. Finally a complete circuit was established in the endothelial tubes and blood cells progressed haltingly into the heart. At first there were only a few cells in the circulating fluid, but the number increased rapidly as more were washed out of the yolk sac capillaries. The atrium had acquired distinct morphological outlines at this time but its physiological significance was confined to its power as a pacemaker, since it appeared to contribute nothing to the mechanical pumping. The period of time between initiation of contraction and the beginning of the circulation is from 12 to 15 hours. [30], used by permission of the American Physiological Society

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Chapter 3
Hemodynamics of the Early Embryo Circulation

Development of the embryonic heart and the peripheral circulation is a dynamic process of rapid growth and continuous remodeling, closely bound to hemodynamics. Paralleling the increasing metabolic needs are changes in heart rate, cardiac output, blood pressure, and decreasing peripheral resistance. A number of studies report comparable values of hemodynamic parameters in avian, zebrafish, and amphibian embryos [1]. Recent advances in invasive intravital Doppler flow imaging have added new insights into the developmental hemodynamics of mammalian embryos [2–4]. We will now examine some of the basic hemodynamic parameters in chick, zebrafish, and mammalian embryos. See Table 3.1 for the developmental milestones of heart development in chick, zebrafish, mouse, and human embryos.

3.1 Chick Embryo

At the onset of circulation, the chick embryo heart tube consists of three to five layers of myocardial mantle, enveloping a thick, cell-free layer of cardiac jelly and a single cell layer of endocardium [8]. Within the individual myocytes, the contractile elements are in spatial disarray and only parts of them are functional [9, 10]. The early embryo heart and vasculature are devoid of nerve elements. The parasympathetic limb of the autonomic nervous system is the first to develop and is functional by HH stage 39 (development day 12) and the sympathetic by stage 42 (day 17) [11].

The initial period of heart formation is accompanied by rapid expansion of the extraembryonic bed. Hu and Clark measured the rate of growth of chick's embryo ventricle from stages 12 to 29 and compared it to the combined weight of the embryo and its membranes. They noted a marked disproportion in growth rates between the heart and the rest of the embryo. At stage 12 the ventricle represents 4.5 % of the total embryo mass, and by stage 29, the ratio drops to 1.2 %. During the same period the weight of the ventricle increased by a factor of 30, while the mass of the embryo increased 120-fold [8]. While the relative weight of the ventricle decreases during

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Table 3.1 Comparative cardiovascular developmental stages in different species

	Chick	Zebrafish	Mouse	Human
Developmental landmarks	HH	hpf	E	Days
Formation of single heart tube	7–9	19	8	22
First myocardial contractions	7–10	22	8.5	23
Heart looping	11–13	33	8.5	24
First blood flow through heart	10	26–28	9.5	24
Endocardial cushion formation	13–22	48	9–11	28
Atrial septum, begins	15–23	n/a	10–12	29
Ventricular septum, completion	26–31	n/a	13–15	35+

Chick embryo stages according to Hamburger–Hamilton (HH), zebrafish stages marked as hours postfertilization (hpf), mouse stages as postconception days (E), and human stages as developmental days. Observations collated from Refs. [4–7]

this period, its work, paradoxically, increases [12]. The relative size of the embryo compared to the vitelline vascular bed is reflected in the distribution of cardiac output. At stage 18, some 80 % of cardiac output is delivered to the extraembryonic vascular bed, and by stage 24, with increasing growth and metabolic requirements of the embryo, the ratio drops to 65 % [13].

Concomitant with growth there is a linear increase in heart rate of the developing embryo between successive stages [14]. During stages 12–29 stroke volume increases from 0.01 to 0.69 mm^3 [8]. Burggren et al. found a relatively modest increase in heart rate of 100–130 bpm in stages 16–24 (day 3–4) but a fivefold attendant increase in stroke volume. Moreover, there was a "dramatic" 10- to 15-fold increase in cardiac output over the same developmental period. They suggest that the wide inconsistency in measured parameters clearly points to unidentified factors in our understanding of early embryonic cardiovascular dynamics [15]. In contrast to mature animals, where there is a reciprocal relationship between the size of the heart, the weight, and the size of the animal, a paradoxical relationship exists in the embryo, where an increase in weight is accompanied by increase in heart rate. In spite of the fact that the increase in heart rate markedly shortens the time of ventricular filling, there is a steady increase in stroke volume and aortic blood flow (cardiac output) [12].

Vitelline artery pressures in stage 12 chick embryos are in the range of 0.32 mmHg for systolic and 0.23 mmHg for diastolic and increase linearly to 2.00/1.22 mmHg by stage 29. The pressure wave forms are similar to those in mature animals (Fig. 3.1). Ventricular systolic and end-diastolic pressures rise geometrically from 0.95 to 3.45 mmHg and 0.24 to 0.82 mmHg, respectively, during the same developmental period [8, 16]. Existing data suggest that the thin-walled early embryo tube with single atria and ventricle successfully interrupts the flow of blood but still lacks capacity to generate significant pressures. We will see (Chap. 11) that this is consistent with low circulatory pressures found in fishes and amphibians whose circulation bears the character of a venous type, even in adult species. Only after the formation of valves, septa, and chambers does the heart become more effective in the generation of pressure, i.e., at stage 29 and higher in the case of chick embryo [5].

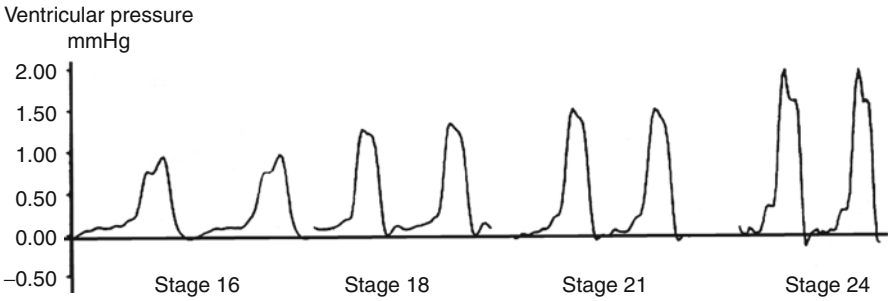

Fig. 3.1 Representative ventricular pressure curves from HH stages 16 to 24 chick embryos (Adapted from Ref. [26], used with permission of John Wiley and Sons)

Several studies comment on the invariant relation between the rate of embryo growth and cardiac output. During each developmental stage there is approximately a doubling of aortic blood flow and stroke volume which, when normalized to embryo weight (without the embryonic membranes), remains *constant*. That is to say that across a 120-fold increase in embryo weight, from stages 12 to 29, the blood flow per milligram of embryo weight remains remarkably constant [8, 12, 14]. The wave propagation velocity, arterial pressures, and circulating blood volume are likewise tightly regulated and optimized within a narrow range across developmental stages [18]. Since the heart and embryonic circulation lack innervation and hormonal control, the obvious question arises: how does the heart "sense" and meet the changes in its own development and match them with the specific metabolic demands of rapidly developing tissues, with such consistency? It has been proposed that the metabolic demands of the tissues directly regulate cardiac output [16]. Moreover, recent evidence suggests a tight link between the metabolism, angiogenesis, and endothelial factors controlling vascular growth [19], implying that, with respect to peripheral tissues, the heart plays only a secondary role in the overall embryonic hemodynamics. This remarkable as yet unexplained matching between metabolic demands and blood flow clearly points to the periphery as the primary determinant of flow.

By applying the hydraulic reservoir model, i.e., the three-element windkessel, it is possible to estimate the arterial impedance (opposition) of vasculature to steady and oscillatory flow (see Fig. 16.6). The model is based on electrical analogue and assumes that pressure and flow are linearly related in the frequency domain. It allows for the calculation of total, steady-state, and oscillatory power generated by the ventricle, by simultaneous measurement of ventricular flow and pressure. According to this paradigm, the steady-state or mean power is the energy required by the heart to drive and maintain the flow and pressure. The oscillatory component of the total power, on the other hand, is expended on rhythmic expansion of vessels and is considered as "wasted" power spent on arterial pulsations [20, 21]. (The merit of this and other models of circulation will be discussed in Part II.) Clark and Hu reported a dramatic increase in steady-state cardiac power of 350-fold between

stages 18 and 29. During the same developmental period the peripheral vascular resistance, calculated from the ratio of stroke volume and vitelline artery pressure, drops by a factor of 5 to 24 [8, 12]. Lucitti et al. reported a more moderate increase in steady-state power by a factor of 8 between stages 21 and 27 [22], while Zahka et al. found a 27-fold increase between stages 18 and 29 [23].

Would the immature embryonic heart be able to sustain such extremes in workload within such a short time span? And if so, what are its limits and regulatory mechanisms?

3.2 Zebrafish Embryo

In zebrafish embryo the individual myocytes begin to contract irregularly at 20 h postfertilization (*hpf*) (22 somite stage, SS) at the rate of about 25 beats/min. By 22 *hpf* (26SS) when the first movement of blood is observed, the heart beats rhythmically at about 90 bpm with a corresponding shift of the pacemaker to the venous (caudal) end of the heart tube. As the heart begins to loop at 33 *hpf*, the frequency of contractions gradually increases from 140 to 180 bpm at completion of looping [6, 24].

By 48 *hpf* the heart consists of a smooth-walled tube, partitioned into four identifiable parts, namely, the sinus venosus, the atrium, the ventricle, and the bulbus arteriosus. The heart tube is lined with endocardium and consists of a single layer of myocardium, except in the ventricle, where it is two or three cell layers thick. The endocardial jelly is gradually resorbed from the ventricle but can still be seen in the atrium and the bulbus [17]. The heart is covered with epicardium and lies in the pericardial cavity. There are no valves separating the atrium, the ventricle, and the aortic bulb at this stage. The valves appear only 3 days later, by day 5. The functional significance of the jelly now becomes more apparent, since, despite the presence of endocardial cushions, the unidirectional flow of the liner heart gives way to significant backflow between the atrium and the ventricle (72–96 *hpf*) [25]. Comparable to the ventricular growth pattern in the chick embryo, the zebrafish ventricle of a 48 *hpf* embryo represents 10.5 % of its total weight and decreases to 1.8 % in a fully grown animal [17].

Hu et al. have pointed out to the unique role of the aortic bulb (conus arteriosus) in zebrafish which, like in higher vertebrates, has initially a myocardial character but becomes replaced by smooth muscle in the course of 4 weeks postfertilization, when the animal matures. They suggest that the bulbus functions as a “capacitor,” maintaining a continuous rather than pulsatile flow of blood in the gill arches [17]. A similar mode of action has been described in chick embryos [26] and larval bullfrog embryos, where during early stages the aortic bulb generates pressures in *excess* of ventricular systole [27]. We shall see (Chap. 11) that a functional analogue of this organ can be found in a number of invertebrates and lower vertebrates, e.g. the lancetfish, where berrylike dilations in the blood vessels, the so-called peripheral hearts, serve to temporarily dam up the flow of blood and eject it into the downstream vessel at a higher pressure.

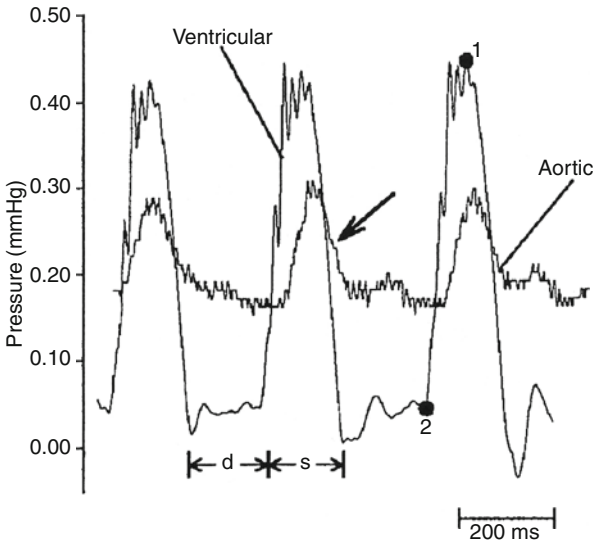

Fig. 3.2 Example of ventricular and dorsal aortic pressure waveform in 5-day postfertilization zebrafish. *d* diastolic component, *s* systolic component, *1* ventricular peak systolic pressure, *2* ventricular end-diastolic pressure. (*arrow*) indicates dicrotic notch. Note similarity with adult pressure recordings (Reproduced from Ref. [17], used with permission of Wolters Kluwer Health)

Only limited hemodynamic data are available for the early zebrafish heart, which is hardly surprising, since its size is only the width of human hair. Hove et al. measured blood flow velocity in the 37*hpf* fish embryo and found it to be in the range of 0.5 cm s^{-1} [28]. Interestingly, similar flows were recorded during ventricular filling *and* ejection, suggesting that the heart barely interrupts the flow of blood. When adjusted for size, these flows exert a surprisingly large shear wall stress of about 75 dym/cm^2, which is about half of that in the adult human aorta [29]. By 5 days postfertilization Hu et al. reported peak aortic systolic and diastolic pressures in the range of 0.5–0.08 mmHg, respectively. Negative early diastolic pressures were recorded from 48*hpf* to 3 months postfertilization. Thus, the early zebrafish heart fills under extremely low pressure, which, the authors suggest, may be facilitated by negative pressure [17] (Fig. 3.2).

3.3 Mammalian Embryo

In mammals, the placental loop becomes fully functional only after depletion of yolk sac nutrients, which for obvious reasons are significantly more limited than in the case of the avian embryo (Fig. 3.3). The dynamic nature of the shift from the yolk sac to placental circulations can be appreciated from the study of Mäkikaillo et al., who with the use of Doppler ultrasound detected an increasing rate of arterial flow, with distinct systolic and diastolic forward-flow components in the yolk sac between the 5th and 7th week of gestation in human embryos. By about 10 weeks the yolk sac flow ceased. The chorionic and umbilical artery (placental) flow was first detected at 5 weeks and then steadily increased by 8–10 weeks, indicating that

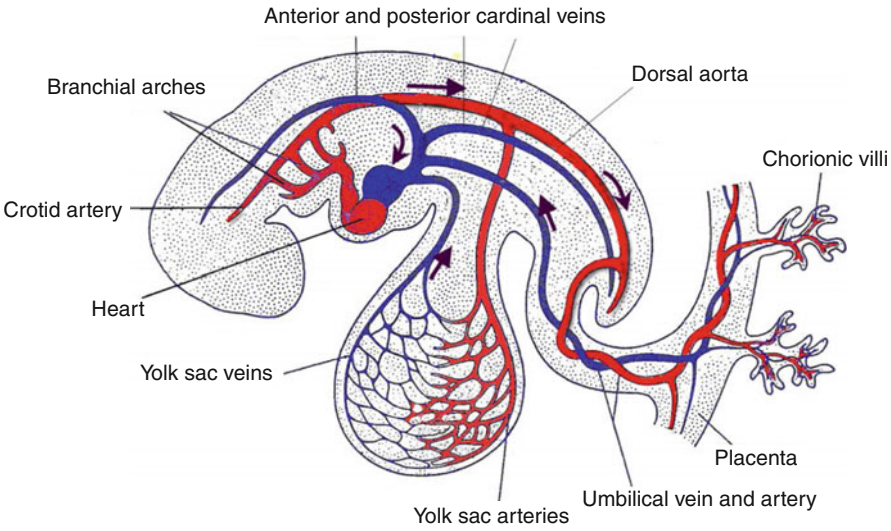

Fig. 3.3 Schematic diagram of mammalian embryo circulation. The circulatory system consists of embryonic yolk sac and placental vascular loops. Umbilical cord contains two arteries (not shown) and one vein. Umbilical vein brings oxygen and nutrients to the embryo. *Arrows* show the direction of blood flow (Adapted from Ref. [34], used with permission of Wolters Kluwer Health)

the placenta becomes the major source of blood supply to the embryo. It is significant that no end-diastolic flow was detected in the umbilical artery [30]. Absence of end-diastolic forward flow in the umbilical artery was also reported in mice up to embryonic day (E) 16.5 and has been attributed to high placental impedance [31–33]. Of note is the fact that the gestational period in mice lasts only 18–21 days, suggesting that, at least in mice, the absence of umbilical artery diastolic flow persists during the greater part of pregnancy. These findings conflict with the chick embryo studies cited above, which clearly show a decrease in peripheral resistance, concomitant with growth of the developmental membranes and the opening of new vascular loops (Fig. 3.4). The situation is further confounded by data from Phoon et al., who showed that cardiac contractility, estimated from the acceleration time period of arterial waveforms, did not change in mice embryos between E9.5 and 12.5. In fact, the concomitant increase in heart rate during this period suggests that cardiac contractility may even *decrease* during the course of gestation. The authors suggest that the geometric increase of cardiac output during the observed period occurs on account of increasing blood volume and decreasing afterload or "downstream" impedance [32].

The absence of forward diastolic flow is also known to exist in the mouse embryo dorsal aorta [32, 33] (Fig. 3.4a). The curious phenomenon of absence of diastolic flow points to the fact that during this stage of development, the heart, in addition to generating only minimal pressures, contributes little to forward flow of the blood. On the other hand, the biphasic flow profile with late diastolic reversal is found in the inferior vena cava (Fig. 3.4d). Enhanced caval diastolic flow reversal has been

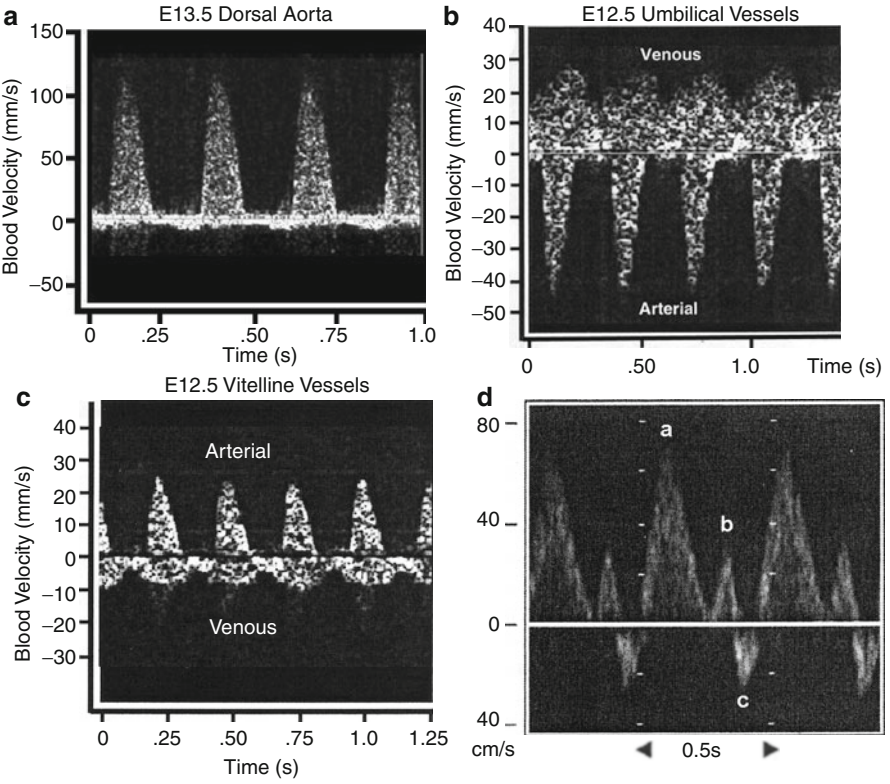

Fig. 3.4 (**a**) Dorsal aortic flow Doppler waveform recordings in mouse embryo at E13.5 (embryonic day). Observe the absence of diastolic flow. (**b**) Umbilical and (**c**) vitelline vessel flow velocity profiles. Note continuous flow in vitelline and umbilical veins and the absence of diastolic flow in the respective arteries (Reproduced from Ref. [32], used with permission of the American Physiological Society). (**d**) Proximal inferior vena cava waveform. There are two phases of forward flow during systole, *a*; and early diastole, *b*. Copious flow results in flow reversal in late diastole, *c* (Adapted from Ref. [35], used with permission of Elsevier)

recorded in fetal dysrhythmias and various forms of heart failure [35] and points to the flow-impeding function of the heart.

One of the most bewildering aspects of perinatal cardiovascular physiology is the so-called TRAP (twin reversed arterial perfusion), found in rare cases of acardiac, acephalic monozygotic twins. The embryo with the functioning heart, the "pump or the donor twin," is said to provide circulation to the affected twin. The blood reaches the acardiac fetus *retrogradely*, usually through a single umbilical artery, via arterio–arterial placental anastomoses. In spite of a supposedly enormous strain, the donor twin heart does not usually show signs of hypertrophy or failure, unless associated with other cardiovascular abnormalities [36]. The acardiac twin can reach a considerable size of up to 1,900 g and can be diagnosed as deceased, due to the absence of heart beat, until noted to be growing, on repeated ultrasonic exam. Various medical and surgical interventions have been tried in order to prevent the

donor twin from developing heart failure due to hyperdynamic circulation, often with detrimental outcome [37].

Over half a century ago De Langen questioned whether the immature fetal heart can muster the force that would be required to perfuse itself, the placenta, and the acardiac twin. He observed that the umbilical vein nearest to the placenta is the first to stop pulsating after the delivery and in the process transfers 100–150 ml of blood to the newborn. An extensive valvular system in the placental vein allows for blood flow towards the fetus but prevents its retrograde movement. This, together with the rhythmic movement of the placental villi, creates the pressure gradient for the flow of blood into the veins and thus to the fetus. De Langen further suggested that "the capillary is like a tiny, incomplete heart, which exerts pressure on the blood passing through it, hereby propelling it and furthering and regulating the filtration," and that the sum total of the placental capillaries act as a "peripheral heart" which drives the circulation [38].

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Chapter 4
Flow Patterns in the Early Embryo Circulation

The fact that the forces for propulsion of the circulating blood do in fact originate in the periphery, specifically in the microcirculation, is further substantiated by specific flow patterns, originating in the peripheral circulation, which continue relatively undisturbed as they course through the heart. Invariant flow patterns present strong evidence against the heart as a suction or pressure propulsion pump.

The ease of reproducibility and transparency of the zebrafish and chick embryos offer a unique model for the study of such patterns. A number of studies exist, which were performed with the aim of elucidating the effect of blood flow on early embryo's heart development [1–3]. The most illustrative work is perhaps that of Hogers et al., who reproduced detailed circulation maps for chick embryo HH stages 12–17 (Figs. 4.1 and 4.2). Their flow diagrams reveal vitelline and intracardiac flow patterns which are consistent with developmental changes of the yolk sac circulation. The first heart beat in the chick embryo occurs at around stage 9; however, before stage 12 the blood flow is still reported to be irregular with occasional backflow. From stage 12 onwards, a steady laminar flow can be observed by means of injected intravital dye, such as India ink, into the vitelline veins. Soon after the onset of the circulation, the blood courses along the marginal sinus of the vitelline membrane and flows towards the heart via the left and right anterior vitelline veins, symmetrically from each half of the embryonic disc, with respect to the embryo's longitudinal axis. Despite of heart pulsations, the blood can be observed to course in parallel streams through the heart to supply specific regions in the embryo proper. From stage 12 on, with the accelerated growth of the embryo in craniocaudal direction and increased vascularization of the vitelline membrane, the original left–right symmetry of blood flow shifts to anterior–posterior, giving way to six "watershed" regions of the vitelline membrane which supply the embryo [2]. Oxygen tensions in the specific parts of the intra- and extraembryonic circulations have been reported, and it is possible that different embryonic organs are supplied with blood containing specific respiratory gas and nutrient compositions [4].

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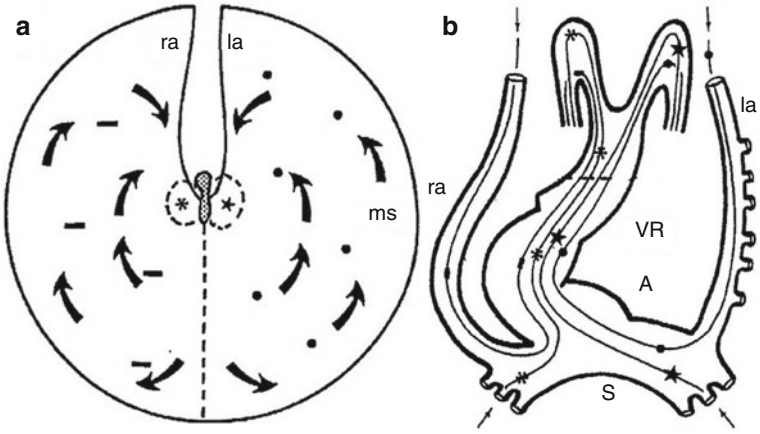

Fig. 4.1 Schematic representation of yolk sac circulation and intracardiac flow patterns in early chick embryo, HH stage 12/13. (**a**) Blood from each half of the yolk sac courses in loops parallel to the marginal sinus (ms) and reaches the heart through right (ra) and left (la) anterior vitelline veins. Areas lateral to the embryo (✶ and *) drain directly to sinus venosus. (**b**) Ventral view of the heart. Blood from different regions of the yolk sac (−*•✶) courses in parallel currents through the tube heart. The currents maintain their identity in spite of the heart's contractions. *S* sinus venosus, *VR* ventricular region, *A* atrial region (Adapted from Ref. [2], used with permission of Wolters Kluwer Health)

4.1 Heart Vortex Formation

Transformation from the tube to a chamber heart brings about several important hemodynamic consequences. While systolic contraction resulted in *complete* emptying of the tubular heart, this is no longer the case with the onset of chamber formation. From now on, there is an *incomplete* systolic emptying of the ventricle, the ejection fraction being about 60 %, a number very close to values in the adult mammalian heart [5]. Moreover, the flow through the looping heart does not maintain its laminar nature, but assumes another form. With the aid of digital particle velocimetry Hove et al. demonstrated the presence of paired vortices in the ventricle during the filling phase (Fig. 4.3). A vortex pair is likewise observed in the aortic bulb during the course of ejection [5]. Close examination of their video also reveals vortical flow in the atrium fed by the paired vitelline veins. While vortex formation during the diastolic ventricular filling in the adult heart has long been recognized, Hove et al. were the first to demonstrate its formation in the early embryo heart. In the mature heart the negative pressure gradient in early diastole is known to occur during rapid ventricular filling on account of vortical flow pattern. Negative pressures recorded in the early diastole in embryo hearts may be a

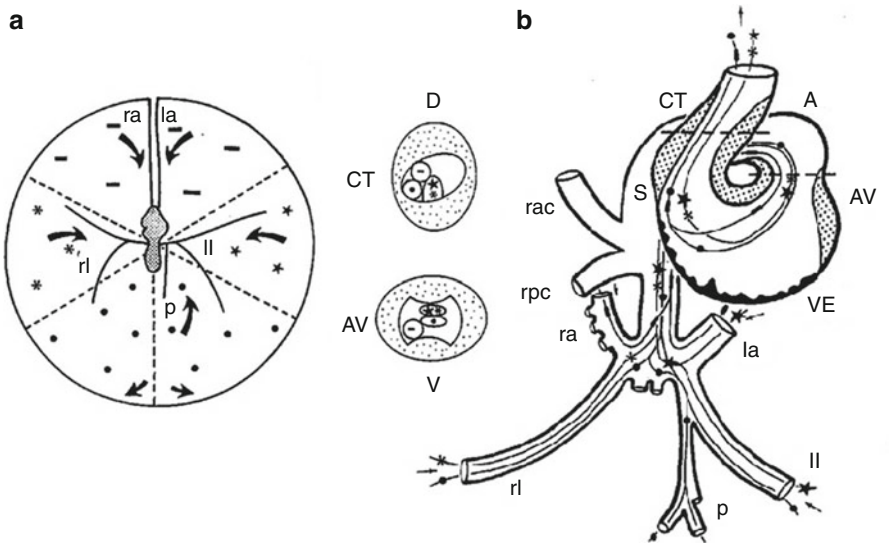

Fig. 4.2 (**a**) Yolk sac circulation pattern in HH stage 16 chick embryo. Note that the lateral regions have extended radially to the marginal sinus. The blood flows in six "watershed" regions towards the embryo with the exception of flow near the marginal sinus. *ra* right anterior vitelline vein, *la* left anterior vitelline vein, *rl* right lateral vitelline vein, *ll* left lateral vitelline vein, *p* posterior vitelline vein. (**b**) Ventral view of the heart with individual streamlines (–*•✶) corresponding to watershed regions on the yolk sac as they continue through the heart. Blood streamlines maintain their identity as shown in cross sections at the level of cono-truncus (CT), and atrioventricular canal (AV). Markings as above and the following: *rac and rpc* right anterior and posterior cardinal veins, *S* sinus venosus, *A* atrium, *AV* atrioventricular canal, *CT* conotruncus, *VE* ventricle, *D* dorsal, *V* ventral (Adapted from Ref. [2], used with permission of Wolters Kluwer Health)

related phenomenon [6–10]. The presence of ventricular diastolic suction has been invoked as an important element of the pressure/suction paradigm of blood propulsion [11, 12].

According to Pasipoularides' recently published comprehensive review on intracardiac blood flow dynamics, an increasing number of studies on structure/function relationships pose a rising challenge for clinical, investigative cardiology, as well as for basic research:

> In view of the difficulty of effectively unlinking embryonic cardiac function from blood flow, sophisticated and carefully designed studies are called for to elucidated interacting contribution of myocardial function and endothelial shear stress on cardiac morphogenesis. In this context, it is inspiring to note that the striking spiral histoarchitectonic arrangement of the myocardial fibers in the heart walls bring to mind images of the archetypal spiral flow patterns that are exemplified in the diastolic filling vortices and in secondary flows. [14], used with permission of the People's Medical Publishing House

The functional significance of intracardiac flow pattern generation will be further discussed in Chap. 13.

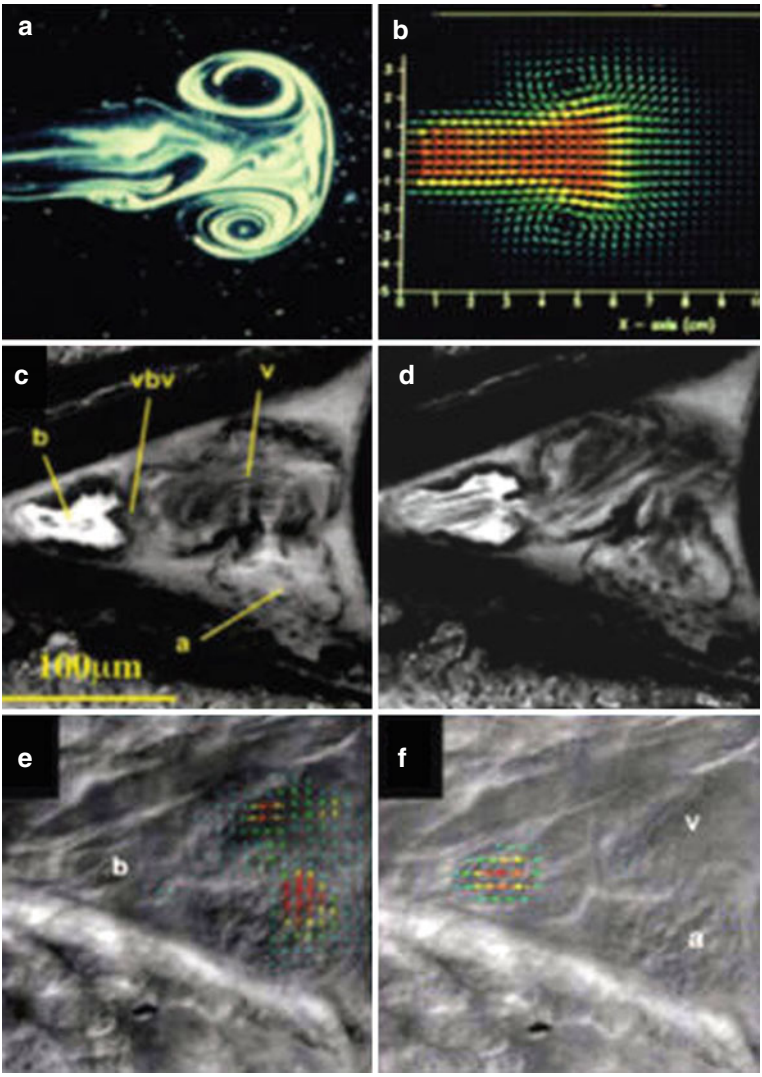

Fig. 4.3 Visualizing blood flow through zebrafish heart. (**a**) Digital particle image velocimetry (DPIV) of a fluid jet rolling up into a torus seeded with reflective particles and illuminated by a pulsed Doppler laser. (**b**) Velocity vector field representing cross section from **a**, with yellow–red spectrum indicating higher-velocity and blue–green indicating low-velocity vectors. (**c**, **d**) High-velocity blood flow in a 4.5 dpf (days postfertilization) zebrafish embryo obtained by confocal imaging of ceramide-stained embryos. (**c**) Atrial systole and ventricular filling. (**d**) Ventricular systole and atrial refilling. (**e**, **f**) Real-time overlay of DIPV velocity fields with confocal images showing vortex flow pattern in the filling ventricle (e) and aortic bulb (**f**). *a* atrium, *b* aortic bulb, *v* ventricle, *vbv* ventriculo–bulbal valve (Reproduced from Ref. [13], used with permission of the Nature Publishing Group)

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Chapter 5
Is There a Circulation Without a Heart?

We see, then, that there may be a circulation without a heart, or contractile propulsive power; and as to the next stage, a circulation with the aid of the heart, which however, evidently could not by itself maintain the circulation.

I. Thudichum, 1855

5.1 Heart Ablation Studies

The premise that lower vertebrate embryos not only survive but continue to develop after the removal of their heart goes against the grain of the widely accepted physiological concept that the heart is the essential "motor" of circulating blood. Buried within the literature are reports which, despite the fact that they were primarily designed to demonstrate a host of related cardiovascular phenomena, clearly point to the primary role of the peripheral circulation.

Well over a century ago Loeb demonstrated that fish embryos continue to develop after their hearts have been arrested with KCl [1] and frog embryos continue to live up to 2 weeks after the removal of their heart primordia [2]. Stöhr carried out a series of experiments in bullfrog larvae to determine the relative morphogenic potential inherent in the early embryo's heart as compared to the effect of flow-induced forces of the circulating blood [3]. An attempt was made to separate out the hemodynamic variables in two ways: either by isolating the heart from the stream of blood or by altering inflow/outflow conditions of the existing heart. In the first experiment the heart primordium of another embryo at the stage of the tube heart was implanted into the abdomen of the host embryo and turned 180^0 in respect of longitudinal embryonic axis. Stöhr noted that the transplanted heart cells not only developed into a normally oriented heart, integrated into the existing circulatory stream, but grew in size beyond normal and even assumed the dominant role. The original heart, on the other hand, continued to beat, but, deprived of blood, soon became pale and failed to develop further.

To determine the effect of blood flow on the heart's morphology, Stöhr explanted the tube heart of an early bullfrog larvae and reimplanted it in the same embryo in its normal place but turning it 180°, *against* the stream of the inflowing blood. To Stöhr's surprise, the blood continued to flow in the normal direction, despite the fact that the heart now contracted in the opposite direction, i.e., from the arterial towards the venous pole. A significant hemodynamic disturbance was created, resulting in gradual yolk sac edema and the embryo's death over the next couple of days. Stöhr

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commented that while it is possible to rotate the heart, it is evidently not possible to reverse the direction of the circulating blood. We will see that yolk sac or whole embryo edema is a characteristic feature, not only of the failing heart but also in conditions where the heart fails to beat, or is absent altogether. It points to the fact that the blood possesses its own movement, since it continues to move for a considerable amount of time, even in the absence of the heart.

In the 1950s Kemp showed that frog embryos continue to develop for 4–5 days after the heart had been surgically removed. In spite of significant blood loss sustained during surgical intervention, Kemp was still able to observe that "some ebb and flow of blood occurred in the vessels near the heart." During the first day after excision of the heart, the larvae were as active as controls but became less vigorous thereafter. Gradually, generalized swelling of the head and of the peritoneal cavity of the larvae occurred, leading to their demise [4]. In a different paper Kemp reported the survival of salamander larvae for up to 15 days, after the removal of the pre-cardiac mesoderm [5].

5.2 Cardiac Mutants

In 1965, a mutant *gene c* ("cardiac lethal") was discovered as a natural variant in Mexican salamander (*Ambystoma mexicanum*), in which the heart seemingly develops in normal fashion but fails to beat. The affected larvae show normal swimming and righting movement and survive up to 2 weeks, until the exhaustion of the yolk nutrients. The larvae homozygous for *gene c* are easily recognizable by their grossly edematous, pear-shaped forms, resulting from accumulation of hemolymph in the heart, the pericardium, and the cephalic portion of the trunk. Microscopically, the thin-walled, distended heart exhibits sparse, disorganized myofibrils [6]. The extended survival of heartless larvae and embryos has been a source of conjecture and surprise among physiologists, since the lack of circulation, the primary means of oxygen and nutrient transport, is by all accounts not compatible with survival. In order to determine just how important the delivery of oxygen is for survival and development, Mellish et al. measured oxygen consumption and circulatory transport in the (1) normal salamander larvae (*Ambystoma mexicanum*) and compared them to embryos at the same developmental stage, (2) whose hearts' primordia were explanted, and (3) to naturally heartless embryos that were homozygous for *gene c*. The operated larvae were given 8–9 days to recover from the procedure. To their surprise the results showed that oxygen uptake and transport were the same for all three groups. They concluded that the circulatory system is not required for oxygen transport during early embryonic period and that the embryo's needs are met solely by diffusion. They moreover suggested that the heartless embryo succumbed due to extensive edema, which might have hindered diffusion of oxygen [7].

Because of the similarity of the early vertebrate heart development in lower and higher vertebrates, the zebrafish mutants have been used extensively as a model for abnormal human heart development. In the course of normal development the

paired zebrafish heart primordia fuse into a single tube by 19 h postfertilization (*hpf*), the heart starts beating at 22 *hpf* and undergoes the process of looping by 33 *hpf*. At about 36 *hpf* a vigorous circulation is established [8]. A number of zebrafish heart mutants have been identified, collectively named the *silent heart*, in which the morphology of the early heart seems normal but fails to contract. In spite of this gross aberration, some of the embryos show normal motility and response to touch, but in the course of 3 days the heart gradually disintegrates and the embryos die [9].

In addition to morphological aberrations, several zebrafish mutants have been described, which mimic a group of phenotypic conditions, resembling cardiomyopathies of the higher vertebrates. The embryos with hypertrophic or obstructive type have hearts with increased thickness of cardiac jelly, which severely restricts endocardial lumen. The resulting defect hinders the blood's return to the heart, causing regurgitant flow in the region of sinus venosus and atrium. In the course of several days, the cardiac function in these embryos invariably deteriorates, resulting in whole body edema. Gross edema is likewise a common terminal feature of various hypokinetic and dilated zebrafish heart mutants [9, 10].

A variety of avian and mammalian heart mutants exist which show, depending on severity, a similar overall pattern of circulatory phenomena. For example, a genetic strain of mice has been developed in which a targeted inactivation of Na/Ca exchange gene ($Ncxl^{-/-}$) results in a defective cardiac contraction-coupling mechanism and an abnormal myofibrillar organization [11]. The homozygous mice fail to initiate the heart beat on embryonic day E8.25, as is the case in normal embryos, but nevertheless continue to develop through E10 when heart looping takes place. Beyond E11 the embryos become severely retarded in growth and die by E11.5. In addition to proving that survival is possible without a beating heart, this model has been used to demonstrate the migration of hematopoietic progenitor cells from the yolk sac to the embryo, indicating that at least a rudimentary circulation exists between the two.

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Chapter 6
The Embryo Heart Is Not a Peristaltic Pump

Rhythmic contractions of the embryonic heart have traditionally been assumed to be the mechanical cause for impelling the blood around the circuit. The proposed nature of these contractions is a peristaltic wave which originates in the sinus venosus and follows the direction of blood towards the outlet of the tubular heart. The time-sequenced nature of the propulsive myocardial peristalsis in the chick embryo has been the subject of investigation ever since the myogenic contraction of the heart was first described in the nineteenth century (for review see Refs. [1, 2]).

In fact, the term "peristaltoid" rather than peristaltic was specifically chosen by Patten and Kramer because of the absence of definite longitudinal and circular muscles characteristic of hollow organs such as the gut or the ureters which have a differential dilating effect on the wall [3, 4]. With the help of lumen silhouette tracings from motion pictures of the early chick heart, Patten and Kramer documented passive dilation of the lumen and "heaping up" of plasma *ahead* of contraction waves. They further commented that "Although there is unmistakably fluid in the heart for a considerable time previous to the beginning of circulation we were not able to satisfy ourselves that this passive dilation was appreciable until just about the time that the blood began to be propelled through the heart. Its significance, of course, lies in the well-known heightened responsiveness of stretched muscle" [3].

No doubt Patten and Kramer here described the movement of plasma from the yolk sac to the heart *before* the function of the sinus-node pacemaker. It is possible that during this stage the heart does contract in response to being stretched just like other hollow organs. To that extent the term "peristaltic" is certainly justified. Despite the fact that the peristaltic nature of the valveless tube heart clearly differs from its mature counterpart, the actions of the two were considered to be analogous in the sense that they both effect fluid propulsion.

Depending on the range of pressure within which they operate, the biological peristaltic pumps, such as hollow organs and even hearts, are considered positive displacement, low or high impedance pumps [5]. They function by enclosing fluid in a chamber (organ lumen) and expelling it by reducing the chamber volume in the process of muscular contraction. The mechanical equivalent of such a pump is a roller

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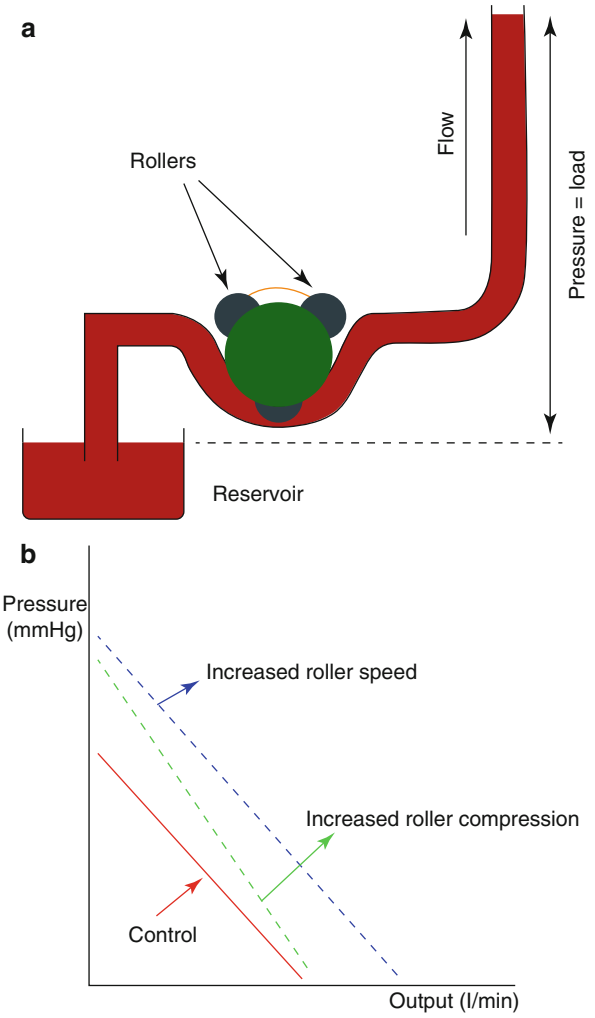

Fig. 6.1 Schematic diagram of a roller pump (**a**) and pump function diagram (**b**). At constant roller speed the pump operates at a given (control) pressure and output (*red*). At increased roller speed the pump operates at higher working pressure and gives higher output (*blue*). When the pump works at increased pressure (load) at control speed, the output remains at control levels (*green*) (Adapted from Ref. [6], used with permission of Springer)

pump of the type used during cardiopulmonary bypass or in hemodialysis machines. It is a characteristic of these pumps that the fluid bolus displaced is equal to the amount of wall deformation produced by external compression (roller) on the tubing. The volume flow is a function of the pressure head generated by the pump and is proportional to the frequency of compressions (Fig. 6.1).

On the basis of high-resolution imaging data analysis of the early zebrafish heart, Forouhar et al. showed in a landmark study that the valveless zebrafish tube heart does not function like a peristaltic pump for the following reasons [7]:

(1) The maximal RBC velocity recorded in the lumen of the early tube heart *exceeds* the contraction wave velocity along the heart tube wall; in other words, the blood travels faster through the heart than the contractile wave which is supposed to propel it. This contradicts the peristaltic model where as mentioned, the peak

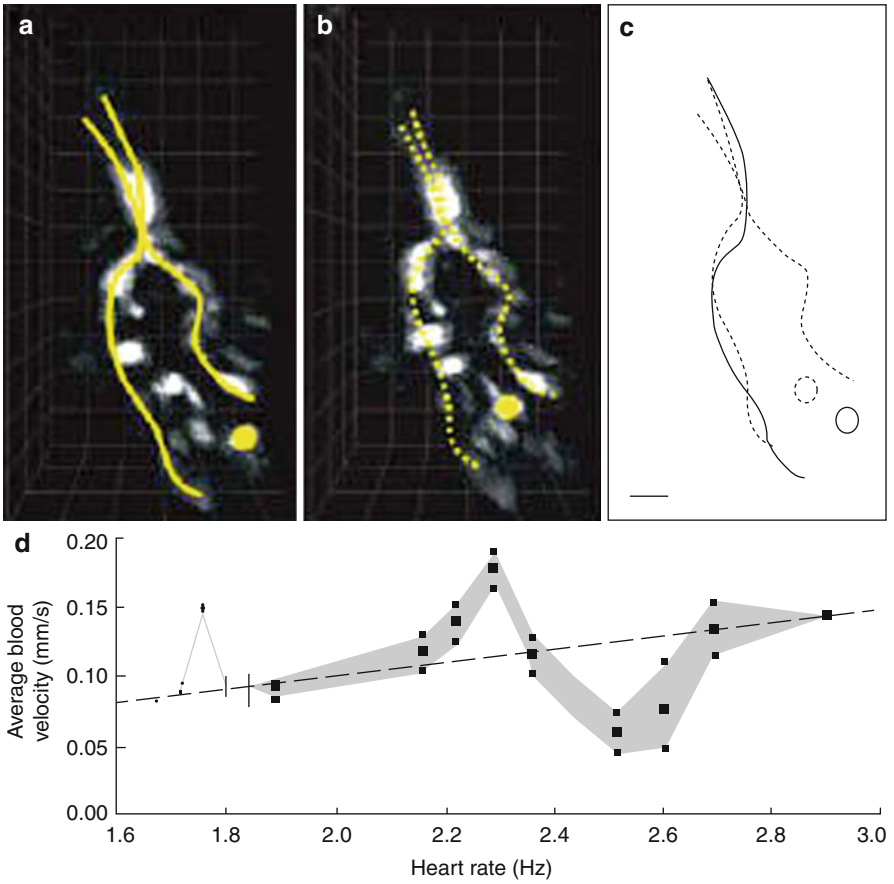

Fig. 6.2 Blood cell motions demonstrate non-peristaltic mechanism of the embryonic heart tube of 26 *hpf* (hours postfertilization) zebrafish. The endocardial layer and a red blood cell have been marked in *yellow* in each image (**a**) and (**b**). (**c**) Superposition of images (**a**) and (**b**) shows that blood cell displacement is much greater than travelling wave crest displacement, indicating that blood cells do not passively follow the travelling wave, but *exceed* its velocity. (**d**) The nonlinear frequency-flow relationship in 26 *hpf* zebrafish heart. Resonance peaks at 1.75 and 2.3 Hz exceed the estimate for peristaltic pumping (*dashed line*) (Reproduced from Ref. [7], used with permission of AAAS)

blood velocity matches the travelling wave velocity. (2) An increase in the embryo's heart rate (caused by an increase of temperature of the embryo mount) did not increase the velocity of blood flow. This violates the above criteria for the peristaltic pump where a linear relationship exists between the flow volume and frequency of compression. (3) A synchronous expansion of cardiac jelly was noted at the side of atrial contraction, which rather than propelling, would *inhibit* the flow of blood during the systole (contraction) and finally, (4) in addition to the contraction wave travelling in the direction of the moving blood, they also recorded a phase-shift wave, reflected from the opposite direction, creating a possible suction effect (Fig. 6.2).

In place of a simple peristaltic pump model, Forouhar et al. suggested that the embryo heart functions as dynamic suction pump. This is a technical term for a valveless, tubular pump of the type first described in the 1950s by the German cardiologist Liebau, who performed his own observations on early embryo hearts in order to explain their unique action. In the process he devised various mechanical models and fortuitously discovered a valveless pumping principle, which he proposed to be the mechanism of the embryo's heart action. Briefly, the Liebau pump consists of a flexible, open-ended tube placed in a bath. The bulk flow in the tube is created by rhythmic compression (i.e., hand squeezing) of the end of the tube. The complex wave dynamics and flow generated in such a system have only recently been elucidated. (See [1] for a complete set of references on Liebau's valveless pump principle.) The application of the dynamic suction pump model to the early embryo heart has been critically reviewed by Männer who agrees with the powerful evidence *against* the peristaltic pump propulsion theory of the early embryo heart. In addition, Männer points to several problems with the proposed Liebau pump theory, such as the fact that the flow in the Liebau pump is prone to flow reversal at certain compression frequencies. More importantly, the lumen of the Liebau pump becomes occluded only at sites of active compressions, whereas the travelling waves in the embryo tube heart cause complete occlusion along the *entire* length of the lumen, giving the tube heart the ability to "expel" all of its contents during each contractile sequence. This well-described phenomenon occurs due to the presence of cardiac jelly and persists until the onset of ventricular chamber formation [1, 2, 8] (Fig. 6.3).

The importance of cardiac jelly for the global function of the chick tube heart was recently confirmed by McQuinn et al., who observed a wave of apposition travelling from the atrioventricular canal to the aortic sac which sequentially obliterates ventricular lumen on high-frequency ultrasonic imaging. No residual volume was detected (i.e., the ejection fraction of 100 %) until the ventricular jelly regressed and the ventricle started to balloon at HH stages 16–17. The authors question the validity of the "piston-pump" propulsion model prior to stage 16 and call for a revised model of ventricular function [9]. This poses the question whether the embryo heart is a "more efficient pump" than the mature heart which, even in the presence of valves, achieves ejection fractions of 65 % at best.

In their own work Männer and colleagues observed a peculiar baso–apical systolic stretching, seen on the cross section of the ventricular segment in a stage 16 chick embryo heart [2]. They contrasted this with the distension of cardiac lumen occurring during diastolic filling. The fact that stretching occurs when the myocardial cells undergo maximal shortening was "puzzling" to the authors, since one would expect that the cross-sectional area of the ventricle would diminish during the systole. When the authors observed the heart contractions in the embryo emptied of blood, the endocardial lumen was occluded during systole *and* diastole, suggesting that the energy developed during contractions could not be used to propel the intraluminal fluid. In other words, contraction affects the deformation of endocardial jelly, rather than causing propulsion of the blood. On the basis of their observations and existing literature, Männer et al. suggest that the cardiac jelly is an

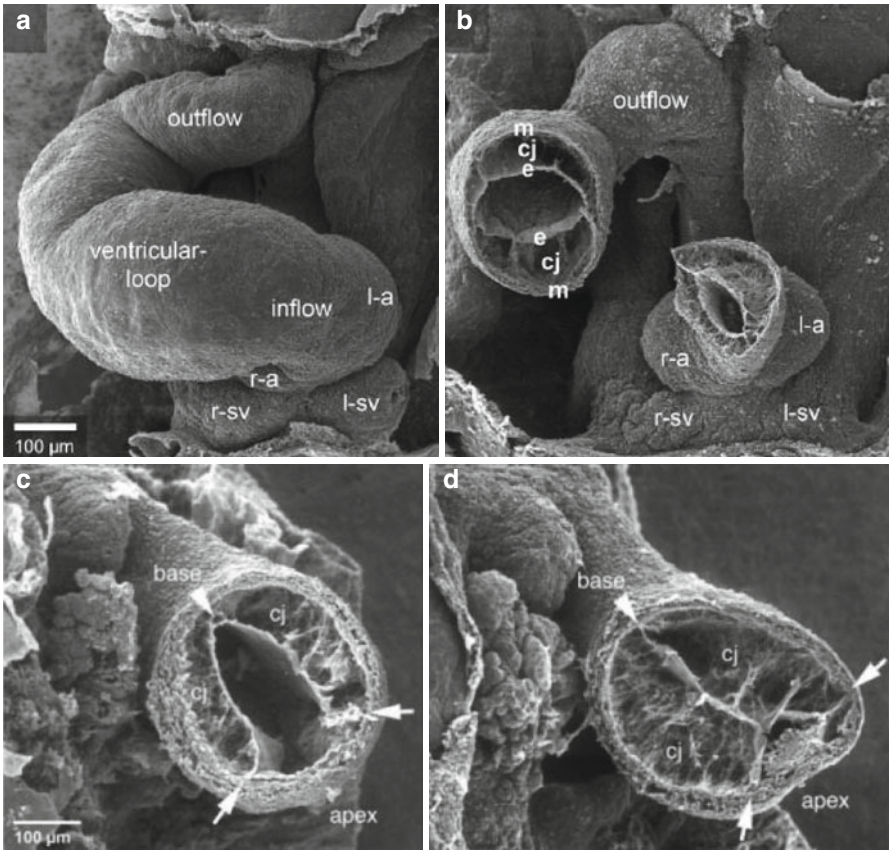

Fig. 6.3 (**a**) Scanning electron micrograph of a tubular heart of a 3-day-old chick embryo (HH stage 14) and (**b**) a cross section with ventricular loop removed to show wall components, consisting of an outer myocardial layer (*m*), of thick middle layer of cardiac jelly (*cj*), and of the single cell layer of endocardium (*e*). Other abbreviations: *l-a* future left atrium, *r-a* future right atrium, *r-sv* right venous sinus, *l-sv* left venous sinus (Reproduced from Ref. [1], used with permission of John Wiley and Sons). (**c**) Ventricular cross section of HH stage 16 chick embryo heart when filled (diastole) and (**d**) when emptied (systole). Note complete occlusion of the lumen in systole and a baso–apical *expansion* of the jelly during systole. *cj* cardiac jelly, *base* inner (basal) curvature of the ventricular bend; apex, (outer) curvature of ventricular loop; *white arrows* and *arrowhead* show bell-shaped distribution of cardiac jelly (Adapted from Ref. [2], used with permission of John Wiley and Sons)

elastic component of the heart wall, which stores a part of contractile energy and releases it during diastole, thus creating a suction effect that draws the blood into the ventricle [2].

It is proposed that a more plausible explanation of this arguable phenomenon can be given. Since we already know that a thin layer of immature myocardial cells would, as yet, be unable to generate enough power to occlude the flow of streaming blood, a "temporizing measure" exists in the form of an elastic endocardial jelly,

which during expansion interrupts the flow of blood. It moreover provides protection against the backflow of blood before the formation of valves. The cardiac jelly thus works as an effective pinchcock valve which, due to its incompressible nature, causes systolic stretching of the myocardium [2]. It is noteworthy that in their study Hove et al. also reported a complete collapse of the endocardial lumen in 37 *hpf* fish embryo heart during systole and found it "intriguing" how the heart can act both as a valve and as a pump [7].

The existing peristaltic/suction theories of the embryo tubular heart and the newly proposed hydro-impedance theory of Forouhar et al. differ only in the degree of generated pressure/suction, but essentially all consider the heart as the sole source of blood's propulsion. After decades of intense research into the action of the embryonic heart, the observed phenomena clearly do not correspond with the existing models and call for reevaluation of the nature of the movement of blood and the role of the heart in the overall dynamics of embryonic circulation. What then is the function of the early embryo heart?

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Chapter 7
Flow Perturbation Experiments

On account of relative ease of accessibility, the early embryo circulation is an eminently suitable model, which can help unravel the age-old question of the relative importance of the peripheral circulation, versus that of the heart. Its "simplified" morphological plan, i.e., the absence of valves and lack of innervation, serves as additional advantages over its mature counterpart. Finally, the embryonic and extra-embryonic circulations occur on a single plane, rendering the force of gravity almost negligible, in comparison to a horizontally placed animal or vertically oriented human circulatory system. We will now examine several studies where the fundamental question of heart versus circulation has been addressed by the investigators.

To assess the influence of blood flow on early (37 *hpf*, hours postfertilization) and fully formed (4.5 *dpf*, days postfertilization) zebrafish heart development, Hove et al. [1] inserted a single 50 μm glass bead into the sinus venosus of the transgenic zebrafish embryo hearts, in order to either (a) partially or (b) completely obstruct the *inflow* of blood into the heart. In a separate experiment (c) a bead was implanted into the ventricle to obstruct the *outflow* from the heart (Fig. 7.1). A group of sham-operated embryos, in which the bead had been placed and removed within 1 h, was run as a control. The embryos were checked after 20 h of bead implantation. The sham-operated embryos showed normal blood flows and patterns of heart development. In the group of partially obstructed embryos, there was a reduced blood flow through the heart but no morphological changes. A very different set of events occurred in the case of completely obstructed embryo hearts. At both levels of occlusion, i.e., at the inflow into the heart and at the outflow, severe regurgitation and accumulation of blood corpuscles were noted at the *inflow* to the heart. In addition, the ventricular outflow obstruction resulted in atrial and ventricular distension. Significantly, in all cases of complete obstruction, a marked yolk sac edema was noted, indicating that the blood continued to move *towards* the heart, in spite of its alleged propulsive action being blocked. The primary importance of flow was further demonstrated by significant morphologic abnormalities, such as failure to develop the outflow tract, the defect of looping, and finally by the collapse and fusion of the heart walls. The authors concluded that the lack of shear forces of the

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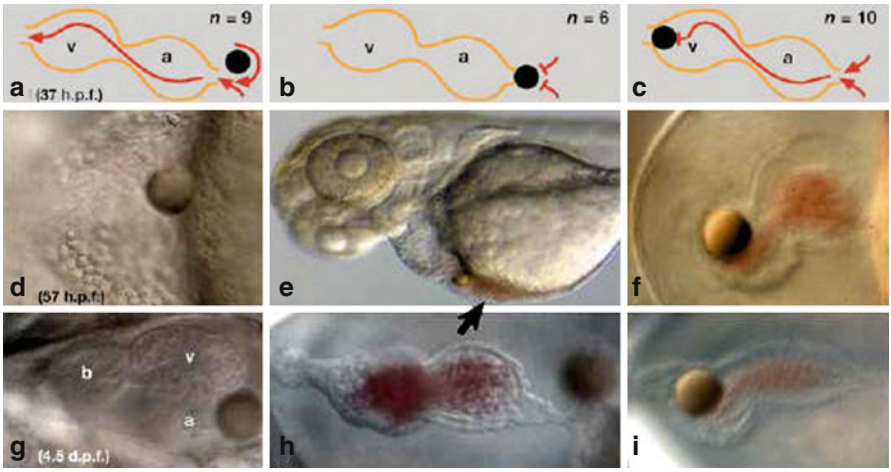

Fig. 7.1 Effect of impaired blood flow though early (37 *hpf*) zebrafish heart. Glass beads (50 **µ**) were inserted into the venous sinus *without* obstructing the inflow into the heart (control) (**a**). In front of venous sinus, to block the entrance into the heart (**b**) or to block the outflow from the heart (**c**). Successful blockage was checked after 20 h. Note extensive accumulated blood on the yolk sac in front of the bead (**d**–**f**), while the atrium contains no erythrocytes (**e**, *arrowhead*). Chamber development was checked after 4.5 dpf and appears normal in nonocclusive bead implant (**g**) and severely disrupted independent of blockage location. Aortic bulb formation is reduced, looping does not occur, and the walls of venous sinus and outflow tract collapse (**h**, **i**) (Reproduced from Ref. [2], used with permission of the Nature Publishing Group)

flowing blood, rather than the lack of transmural pressure, was responsible for the severe cardiac morphologic defects.

Another important observation made by the authors was that both, inflow- and outflow-blocked 4.5 *dpf* hearts, failed to develop valves. Does this suggest that the primary role of the heart is indeed to set itself *against* the flow of blood, working as an organ of impedance? Furthermore, does the presence of glass beads remove the mechanical stimulus needed for normal formation of the valves supplied by the sheer stress of the flowing blood? This view is further corroborated by the fact that the absence of blood flow through the heart results in complete obstruction of the lumen by proliferation of cardiac jelly [3]. A similar, possibly related phenomenon was also observed in the abovementioned obstructive zebrafish heart mutants [4, 5] (Chap. 5).

It should be noted, parenthetically, that during the preliminary flow observations in the 37 *hpf* embryo heart, the authors found it "intriguing" that despite the lack of valves, "the early embryonic heart can act as both a valve and a pump" with ejection fraction of up to 60 %, a value comparable to adult mammalian hearts [1].

The primacy of the peripheral circulation in the overall embryonic hemodynamics is further demonstrated by experiments where selective clipping of major venous conduits causes perturbance in flow. It has been shown that chronic unilateral vitelline vein ligation results in diversion of vitelline blood flow and alters intracardiac flow patterns, adversely affecting normal cardiac morphogenesis [6, 7]. Stekelenburg-de Vos et al. found an acute decrease in heart rate, stroke volume,

peak systolic velocity, and mean blood flow by clipping the right lateral vitelline vein of HH stage 17 chick embryo. As expected, there was a damming up of blood in the vitelline vascular bed with concomitant decrease in venous return. During the course of several hours the blood, normally drained by the right vitelline vein, was redirected to the posterior vitelline vein via a small capillary vessel, which had, in due course, expanded into a conduit large enough to accommodate the excess flow. Within the study period (5 h), the heart rate and mean blood flow had returned to control values [8]. A similar study performed on stage 17 chick embryos showed a decreased rate of passive ventricular filling as a function of decreased venous return. When observed a day later, at HH stage 24, the stroke volumes and dorsal aortic flows were within the range of unclipped controls [9].

Wagman et al. measured the effect of acute increase of the circulating blood volume in stage 18, 24, and 29 chick embryos, by injecting isotonic Ringer's solution in aliquots ranging from 0.9 to 14.9 % of circulating blood volume. (The circulating blood volume ranges around 80 μl in stage 18 embryo.) The acute decrease of intravascular volume was affected by the withdrawal of 10 μl of blood from the circulation at the rate of 0.5 μl/s and reinjected 15 s later. Heart rate, dorsal aortic blood flow, and arterial and ventricular pressures were measured, and stroke volume index (SVI, SV per cardiac cycle) and peripheral vascular resistance (PVR) were derived. While there was no increase in heart rate, compared to controls, the dorsal aortic flow, stroke volume, SVI, and arterial blood pressure increased linearly in response to volume of infusion. There was a concomitant decrease in calculated PVR. The opposite changes were observed during blood withdrawal. After a short time all changes equilibrated towards baseline values, pointing to an efficient hemodynamic control of hemodynamic parameters [10].

Given the fact that the heart undergoes such significant morphologic changes during this developmental period, i.e., from being a simple tube to a four-chambered heart, the authors were at a loss to explain such a large and linear response in SVI across stages when injected volumes were normalized for average weight of the embryo at each stage. Moreover, the lack of innervation, together with immaturity of the myocytes and their myofibrillar disarray, points to the fact that the heart does not in fact exert the primary control over hemodynamics at this stage.

Atrial natriuretic peptide (ANP) is widely distributed in embryonic myocardium [11, 12]. It exerts a profound effect on embryonic hemodynamics by causing venous dilation, possibly affecting vascular permeability across the capillary beds. Nakazawa et al. demonstrated a dose-dependent fall in arterial pressure and dorsal aortic blood flow, when stage 21 chick embryos were infused with an increasing dose of ANP. Despite of some 50 % drop in aortic flow and arterial pressure and a decrease in vitelline venous pressure to one-third of control, the heart rate remained the same as in control animals [13]. Hu et al. quantified the effect of ANP on the heart in stage 21 chick embryo and showed that the drop in above parameters occurs due to decrease in passive diastolic filling. In addition, the atrial component of ventricular filling, known as active ventricular filling, was likewise shortened [14]. Hu et al. concluded that the lack of heart rate and adaptive contractility response point to the importance of ventricular preload (venous return) in embryonic hemodynamics.

Unchanged heart rate and shortened phase of passive ventricular filling, in response to vitelline vein clipping, were also reported by Ursem et al. [9].

The importance of the peripheral circulation was further demonstrated by Bowers et al., who tested the effect of NO on embryonic vascular tone and ventricular function, by using nitroprusside as a source of exogenous nitric oxide in stage 21 chick embryo and compared it to hemodynamic response in embryos of the same developmental stage, in which venous hemorrhage was induced by severing a fourth-order vitelline vein. They found that, like the venous hemorrhage, nitroprusside linearly reduces end-diastolic volume (preload), stroke volume, and cardiac output. There was no change in heart rate except for a 7 % drop at the highest rate of nitroprusside infusion and no effect on the arterial circulation as defined by arterial elastance. They concluded that the embryonic cardiovascular system is dynamically regulated at the tissue level, possibly through vascular tone, as is the case in fetal and adult circulations [15].

The above studies demonstrate that should the blood be impelled by the heart, the heart rate and the peak systolic velocity would increase to compensate for such a large acute drop in venous return. In spite of relatively rapid compensation, this however, does not occur. It has been proposed [6] that cardiovascular equilibrium in the embryo, at least until stage 24, is maintained by vascular and endocardial endothelium, which responds directly to local pressure. Thus, altered shear stress caused by change in blood flow can release a variety of endothelins, which modify contractile characteristics of the adjacent vessels and the myocardium [16–18].

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Chapter 8
Heart Rate Perturbations

To further substantiate the importance of metabolism as the primary factor, affecting the movement of blood, let us look at several experiments where the metabolic rate has been changed by subjecting the embryo to environmental hypo- or hyperthermia. Since the chick embryo is poikilothermic, its hemodynamic functions are exquisitely sensitive to change in temperature. When the temperature was raised from 37 to 40 °C in HH stages 18, 21, and 24 chick embryos, there was a linear increase in heart rate and aortic flow, while the stroke volume remained unchanged [1]. Similarly, a global decrease in temperature to 31.1 °C in the chick embryos at the same developmental stages resulted in a proportional decrease in heart rate, vitelline artery pressure, and aortic flow but no change in stroke volume [2].

In his pioneering efforts to demonstrate autonomous movement of the blood, Manteuffel-Szoege subjected stage 24 chick embryos to progressive cooling and observed the movement of blood in the vitelline vessels. Blood in the venous limb of the circuit was the first to slow down and the flow ceased at 20–25 °C; however, the blood in the arteries continued to oscillate with each heartbeat, without any net macroscopic movement. By 30–90 min after cessation of the circulation, congestion was noted in the arterial limb of the vitelline circulation, confirming continuous movement of blood at the level of microcirculation. In the second experiment, the embryo's heart was excised, and the movement of the blood was observed under normothermic conditions. In spite of hemorrhage, the movement of the blood continued in the vitelline veins for 10–15 min, but interestingly, rather than flowing backward, the blood in the arteries continued to move in the centrifugal (peripheral) direction. On the basis of this (and other experiments to be reviewed in Part II), Manteuffel-Szoege concluded that the blood possesses its own motive energy, which is "inseparably connected with the thermal conditions" of the embryo [3].

In addition to the altering of the embryo's thermal environment, the embryonic heart rate can be selectively manipulated by transient thermal probe application. The method allows the study of rapid alterations in heart rate, without associated metabolic effects. Since such an experiment is notoriously difficult to perform in an animal with intact cardiovascular reflexes and hormonal feedback loops, the early embryo circulation is, once more, an ideal model.

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Cuneo et al. subjected stages 17–27 chick embryos to selective increase/decrease of heart rate by applying a heated/cooled metal probe to the area of the chick's sinus venosus and measured changes in aortic flow and stoke volume during each developmental stage. For each developmental stage there was a decrease in aortic flow, with either an increase or a decrease of heart rate beyond the embryo's own *intrinsic* rate. Moreover, there was a reciprocal relation between the *intrinsic* heart rate and stroke volume, i.e., it increased during slower rates and diminished when the heart was stimulated above its intrinsic rate [4]. Applying a similar method, the heart-rated dependence of ventricular filling was also confirmed by Phelan et al. [5].

The unique nature of the coupling between blood flow and intrinsic heart rate has been further demonstrated by direct cardiac pacing. When the site of presumed sinus venosus in stage 24 embryos was artificially paced at rates that were 150 % above the *intrinsic* heart rate, the stroke volume (SV) decreased from 0.36 ± 0.02 to 0.12 ± 0.02 mm^3/beat. Only a slight increase in SV was noted when pacing rate was set at 50 or 75 % of the intrinsic heart rate. The disproportionately low stroke volumes were ascribed to lack of synchrony between active (atrial) and passive (ventricular) filling. While pacing near the intrinsic rates resulted in aortic flows that were comparable to normal, there was a significant decrease of aortic flow at the extreme pacing rates, either above or below the intrinsic. This was in marked contrast to heart rate perturbation with a heated probe, where the synchrony between the active and passive ventricular filling was maintained even at decreased heart rates [6].

The critical importance of passive ventricular filling in maintaining of aortic flow is further demonstrated when pacing is applied directly to the embryonic ventricle. Dunnigan et al. compared cardiac inflow and outflow velocities during sinus venosus and ventricular pacing in stage 24 chick embryos and compared them to normal controls. They noted that during sinus pacing at intrinsic rates, ventricular filling pattern remained similar to controls; however, at faster rates, the passive filling rate decreased, due to shortening of diastolic time. When the pacing electrode was placed *directly* on the ventricle, there was a precipitous drop in aortic blood flow to near-zero value, prompting the investigators to question "why is the embryonic heart so critically dependent on passive filling?" [7] (Fig. 8.1). Similar drops in stroke volume and mean umbilical artery flow velocity were reported by MacLennan during bipolar artrial and ventricular pacing in early mouse embryo. Significantly, a complete cessation of flow occurred during ventricular pacing. MacLennan's group proposed the existence of an "intrinsic heart rate" which, like in the case of chick embryo, assures effective, rate-dependent matching between the placenta and the embryonic circulation [8] (Fig. 8.2).

To address this question and the intriguing observation that cardiac output is maximal near intrinsic heart rate (HR), Casillas et al. investigated acute alterations in the cardiac cycle (CL) on ventricular function and cardiac output [9]. A randomly preheated or cooled probe was applied to sinus venosus in stage 21 chick embryos

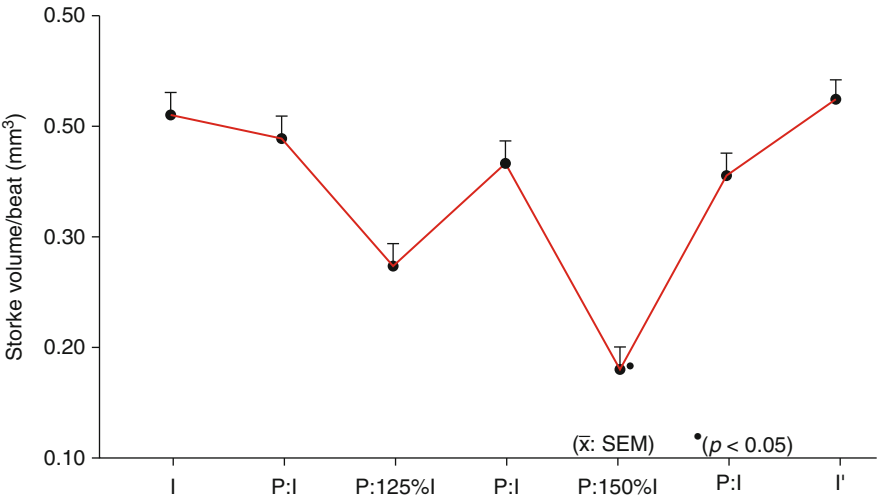

Fig. 8.1 Stroke volumes per beat during sinus pacing in HH stage 24 chick embryo. Stroke volumes were similar at intrinsic (*I*), paced intrinsic (*P:I*), and post-pacing intrinsic rates (*I'*). However, stroke volume decreased significantly with pacing at 125 % of intrinsic rate (P:125%I) and at 150 % of intrinsic heart rate (P:150%I) (Adapted from Ref. [7], used with permission of Macmillan Publishers Ltd)

to transiently alter the heart rate from 73 to 191 % of baseline control. Systolic and diastolic time intervals were determined from pressure–volume loops (P–V loops) by a method of direct ventricular pressure recording and video planimetry. Stroke volume (SV) and cardiac output were subsequently calculated from the P–V loops. The results showed that SV is inversely related to HR. Moreover, the increase in CL was linearly related to increase in SV and end-diastolic volume (EDV) and decrease of end-systolic pressure (ESP). However, the change in CL bore no statistically significant relationship to the cardiac output. The study confirmed the above findings by Cuneo et al. [4] that the heart rate is controlled so that it is matched to maximal cardiac output. It moreover shows that the embryonic cardiovascular system acutely regulates preload as well as afterload in order to optimize ventricular–vascular coupling. The authors further comment on the unexpected finding of the study, namely, that an acute increase in SV can occur without a simultaneous increase in ventricular pressure. They suggest that this may be related to acute decrease in peripheral resistance which allows for more complete emptying of the ventricle.

In conclusion, the above studies suggest that, in spite of significant interference with the cardiac function, the cardiac output remains remarkably stable. Gross interference with myocardial function, such as ventricular pacing at rates outside the limits of intrinsic heart rate, compromises the blood flow and can lead to its complete cessation. Collectively, these observations point to metabolic, "auto-regulatory" factors as the primary controllers of cardiac output.

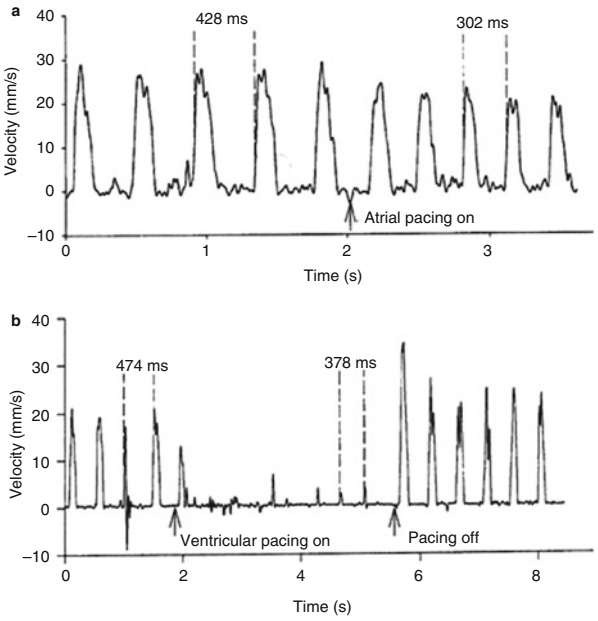

Fig. 8.2 Umbilical artery velocity profile in embryonic day E13.5 mouse embryo at baseline heart rate and (**a**) following atrial pacing and (**b**) during ventricular pacing. Note a slight decrease in umbilical artery flow during atrial pacing. During ventricular pacing, forward flow ceases (Reproduced from Ref. [8], used with permission of Elsevier)

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Chapter 9
The Heart as Generator of Pressure

We have seen that, while traversing the heart loop, the blood stream undergoes not only a complete reversal in direction of flow but encounters significant resistance, as it passes through the spongy endomyocardial trabeculations (Chap. 2). Additionally, the blood flow is subject to rhythmic interruption by the contracting heart, giving rise to upsurge and dissipation of pressure. Taken together, the morphological and hemodynamic phenomena suggest that the heart, rather than being the source of flow, is an organ whose function is the rhythmic generation of pressure. Of the total power produced by the ventricle, about 75 % is expended on maintaining of pressure, and the balance is used for pulsatile distension of the arterial bed. This ratio appears to be tightly controlled and is preserved during perturbations of flow and volume [1]. In addition to promoting the endothelial cell division, the pulsatile flow at an increased mean pressure in the arterial loop of the circuit is the essential factor in normal development of organs and vascular beds. We have further seen that, at the early stage, the simple tube heart can do little more than interrupt the flow of blood, creating only minimal pressures. Essential components for the generation of pressure appear to be the "priming" and the "pressure" chambers, i.e., the atrium and the ventricle of the *primary* myocardium, which convert the kinetic energy of the moving blood into hydraulic energy or pressure. The combination of flow-generated shear forces and genetic factors gives rise to the *secondary* myocardium, which, with its valves and septa, is better "equipped" to perform the pressure-generating function. Several studies have shown that any interference on the part of this essential task is met with an acute hemodynamic compensatory response and is followed, in due course, by structural remodeling.

Clark and colleagues studied the effect of increased functional load in HH stage 21 chick embryo hearts by constricting the conotruncus with a nylon loop. The embryos were incubated and evaluated at stages 24, 27, and 29 of successive development. Compared to normal controls the artificially imposed obstruction to ventricular ejection caused increased peak ventricular systolic pressures by an average of 68 % at stage 24. There was no change in cardiac output. The authors further noted a time-related increase in ventricular weight due to hyperplasia of the myocytes, however, without an increase in the *total* weight of the embryo [2].

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Lucitti et al. measured hemodynamic response in stages 21, 24, and 29 chick embryos by left atrial ligation (LAL). Simultaneous dorsal aortic blood flow and pressure measurements were performed at 1 h, at 14 h (stage 25), and at 30 h (stage 29) after ligation and compared to sham-operated controls. In addition, the steady power and the oscillatory hydraulic power were calculated from the hemodynamic data. One hour after ligation, the systolic, mean, and diastolic pressures remained similar to controls and increased appropriately with the developmental stage. Minute aortic flow (CO) and stroke volume (SV) initially dropped to about half but recovered to control values by stage 29. The acute drop in flow-related parameters is brought about by reduction of the effective chamber size to half its normal volume, thus reducing the total cross-sectional area available to flowing blood. By stage 29 significant remodeling of the existing chamber had occurred, thus allowing for normalization of flow-related parameters [3].

In a separate group of embryos (stage 21) Lucitti and coworkers ligated the left vitelline artery (VAL) and performed hemodynamic measurements, as was done in the left atrial ligation (LAL) group. Of note is the fact that at this stage, roughly 75 % of cardiac output passes through the vitelline arteries and only a quarter (25 %) through the embryo's aortae [4]. Obstruction of the vitelline artery thus represents a significant increase in impedance to the embryo heart. One hour after ligation there was an acute decline in stroke volume and aortic flow to about half of the control values; however, all *pressure* parameters remained similar to control values. By stage 29 stroke volumes and aortic flow remained reduced by an average of 23 and 70 %, respectively. Of further significance is the fact that in both groups (LAL and VAL), the oscillatory and mean power parameters dropped significantly post-ligation but were normalized by stage 29 [3] (Fig. 9.1). The authors concluded that the maintenance of arterial pressure, but not arterial flow, is crucial to embryo survival. Regardless of the acute compensatory changes brought about by atrial or vitelline artery ligation, the investigators maintain, "it is evident that rapid restoration of arterial pressure is a primary directive of the embryonic vascular system." [3]

To assess the changes in ventricular morphology under increased loading conditions, Sedmera et al. subjected stage 21 chick embryos to conotruncal banding and carried out a series of morphometric observations until stage 29. Care was taken, when initially tying the nylon loop, not to obstruct the flow of blood; however, with the growth of the heart, the loop nevertheless imposed an increasing obstruction to the ejected blood. By 12 h (stage 24) the increased pressure caused pronounced changes in myocardial architecture, ranging from the heart dilation and elongation to trabecular coarsening and thickening of the compact myocardial layer. There was a marked dilation of conotruncus downstream after constriction and hypoplasia of conotruncal ridges. Whereas in normal hearts, between stages 21 and 31, the spongy

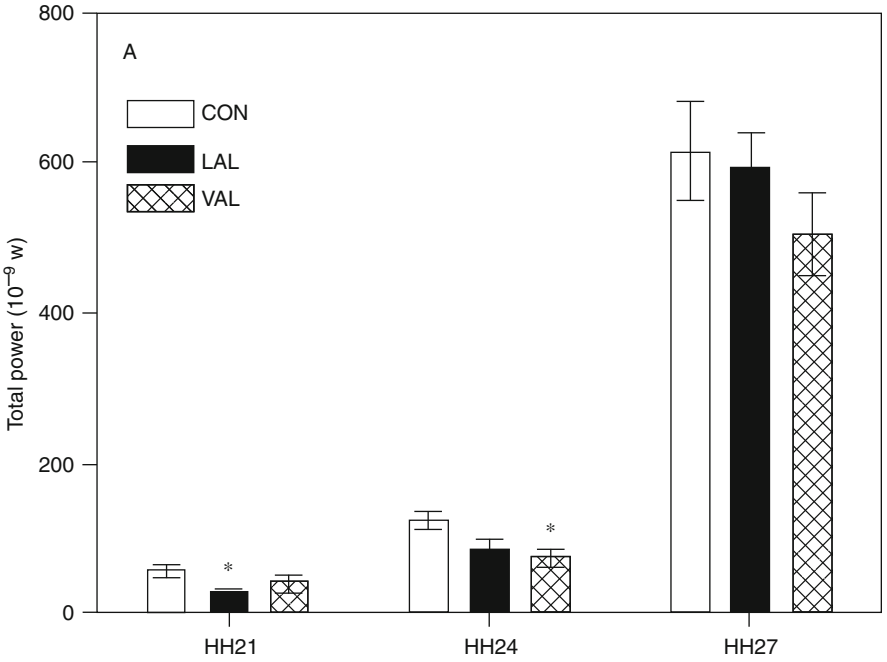

Fig. 9.1 Effect of altered pressure and flow on total power generated by developing chick embryo heart. Arterial flow was reduced by left atrial ligation (*LAL*), and the load on the ventricle was increased by right vitelline artery ligation (*VAL*) in HH stage 21 chick embryos. Embryos were incubated for 1 h (HH21), 14 h (HH24), or 30 h (HH27) and compared with control group (*CON*). Total power generated by the ventricle declined significantly (*) after left atrial ligation (LAL), reflecting a decrease in preload in HH stage 21 and in vitelline artery group (VAL) at HH stage 24. By HH stage 27 the values normalized between the groups. Note a dramatic increase in power generated by the ventricle between stages HH24 and HH27 (Adapted from Ref. [3], used with permission of the Company of Biologists)

trabeculae fill the entire ventricle, a distinct lumen was apparent in banded embryo hearts [5] (Fig. 9.2). Moreover, a leftward spiraling of the trabeculae (viewed from base to apex) was noted, a feature not known to exist in control hearts at this stage. The authors suggest that spiraling is a mechanism by which the pressure-overloaded embryonic heart increases its pumping efficiency [5]. Similarly to the above, this study clearly points to the primary, pressure-generating role of the ventricle, which, when subject to increased arterial load, exhibits signs of accelerated development. The spiral arrangement of the trabeculae points to the already mentioned vortex flow patterns [6].

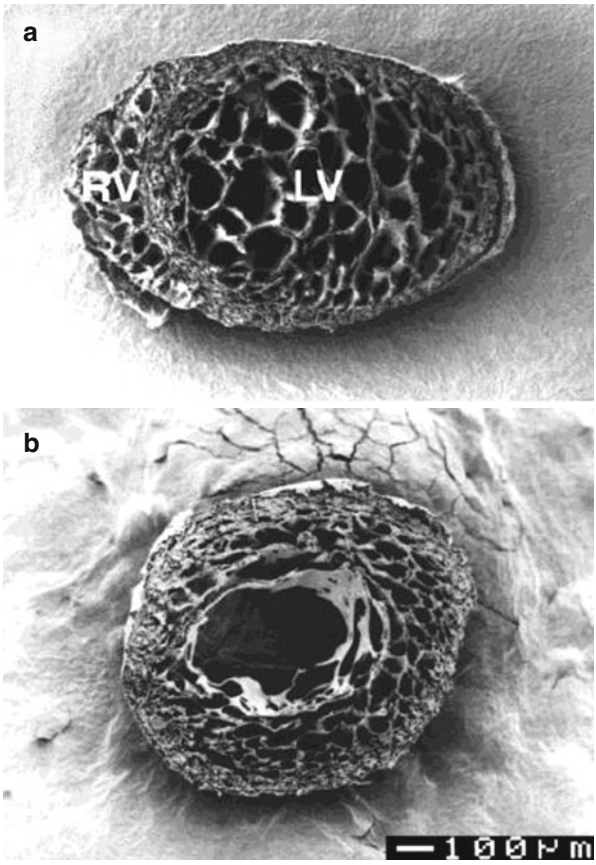

Fig. 9.2 Effect of increased loading conditions on left ventricular development. Short axis cuts through the apex of normal (**a**) and banded (**b**) HH stage 29 chick embryo heart. The conotruncal tie was in place from stage 21, i.e., for 12 h. Note the honeycomb arrangement of the left (LV) and right (RV) ventricular trabeculation in normal heart (**a**). The banded ventricle shows a distinct lumen and spiral arrangement of trabeculae (**b**). Scale bar = 100 **µ** (Reproduced from Ref. [5], used with permission of John Wiley and Sons)

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Chapter 10
Ventriculo-Vascular Interaction

The complex equilibrium existing between the pressure generated by the ventricle and the flow has been extensively investigated in mature circulation. Numerous difficulties in studying the relationship between the ventricle and the arterial compartment arise on account of rapid changes within the ventricle itself, i.e., in its dimension and contractility, as well as due to dynamic changes in the aorta and the associated arterial compartment [1]. A large amount of literature exists on the topic and only the aspect pertaining to embryonic circulation will be briefly discussed. (See Ref. [2] for review.)

A simultaneous recording of ventricular pressure and volume during cardiac cycle generates pressure–volume (P–V) loops which represent a cyclical nature of the pressure–volume relationships in a cardiac cycle. The end-systolic pressure–volume relationship (ESPVR) plot is obtained when aortic pressure is varied over several beats, and a line is fitted through end-systolic points of the recordings. The slope of the line corresponds to maximal ventricular elastance ($E_{max)}$ during contraction. Implicit in this model is the fact that the performance of the ventricle (contractility) can be characterized as time-varying elastance which waxes and wanes during the heart cycle but is independent of instantaneous pressure and volume (Fig. 10.1). During a stable contractile state, the slope of the ESPVR line is a reproducible index of contractility. Since the heart's energy expenditure is related to its mechanical work, a close relationship exists between its energetic demands and mechanical activity. The total work of the heart consists of the external work which the heart performs against the aortic pressure (afterload) and the internal work needed for excitation–contraction coupling. Suga showed that the total mechanical energy expended by the heart corresponds to the area under the ESPVR curve [3, 4]. It has been further demonstrated, purely on phenomenological grounds, that the left ventricular oxygen consumption per beat (VO_2–PVA) corresponds linearly with the systolic pressure–volume area (PVA) [5]. It is of note that at a given contractile state, the VO_2–PVA cost shows a remarkable stability under various pre- and afterload conditions. The VO_2–PVA cost is moreover independent of heart rate; the type of contraction, i.e., whether ejecting or isovolumic; and also of cardiac output, as will be shown in Sect. 16.6.

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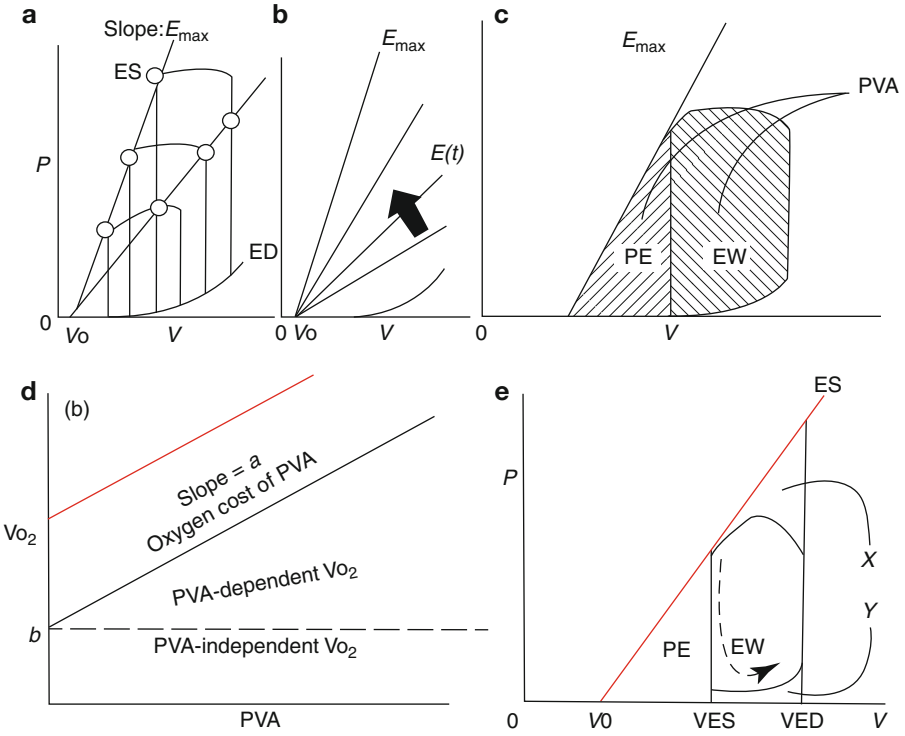

Fig. 10.1 Ventricular pressure–volume relationships. (**a**) When the ventricle contracts against increasing load, a series of pressure–volume (*P–V*) loops are generated whose left upper corner falls on a straight line (*ES*) with a slope of maximal elastance (E_{max}). (**b**) Time-varying elastance model of left ventricular contraction. Ventricular performance of single beat can be characterized in terms of elastance which increases during contraction, decreases with relaxation, and reaches its maximum at end systole (E_{max}). (**c**) The pressure–volume area (*PVA*) of a single beat represents total mechanical energy, which the ventricle expends during ejection (*EW*) and during isovolumic contraction (*PE*). (**d**) Ventricular oxygen consumption (VO_2). Quantitatively, the expended energy of contraction corresponds to the amount of oxygen consumed during each beat (oxygen cost of PVA). In addition to contraction costs, oxygen is needed for basal metabolic rate (PVA independent VO_2). The VO_2 intercept of each VO_2–PVA relationship corresponds to unloaded contraction and is linearly related to contractility (E_{max}). The slope of VO_2–PVA relationship (oxygen cost of PVA) remains relatively constant and is independent of E_{max}. Increased contractility results in increased oxygen cost (*red line*). *P* pressure, *V* volume, V_0 unstressed ventricular volume (**a–d**, Adapted from [6], used with permission of John Wiley and Sons). (**e**) Diastolic work performed on the ventricle during passive filling. Its magnitude can be represented by the sum of areas *X* and *Y* on the PV diagram between end-systolic (V_{ES}) and end-diastolic (V_{ED}) segments of PV loop. This "negative work" performed by the blood has been consistently excluded from PVA calculations. Known myocardial resistance to stretch suggests that it forms a substantial part of PVA energetic balance. *Broken arrow* indicates direction of time. *ES* end-systolic pressure–volume relationship line, *PE* potential energy, *EW* external work (Adapted from [7], used with permission of Elsevier)

In spite of its extensive application in experimental and clinical cardiology, the minute scale of the embryo has precluded the use of P–V concept in the embryonic circulation. However, a method of simultaneous measurement of ventricular

pressure and estimation of ventricular volume by video microscopy has been described and applied in early embryo circulation [8].

In an effort to define ventricular–vascular interaction during altering loading conditions Keller et al. generated ventricular pressure–area loops in HH stages 16, 18, and 21 chick embryos. They found a linear increase in stroke volume and arterial elastance (distensibility) in all stages. When the ventricular preload was increased by infusion of 1–2 μl of physiological buffer into the sinus venosus, the peak systolic ventricular pressures and volumes initially increased and then, soon after, decreased. There was a concomitant increase in arterial elastance. The heart rate remained stable, suggesting the pacemaker function is preserved despite acute changes in load. The authors showed that the ventricle works near the *optimal* working volume and, when filled with additional volume, becomes overdistended and begins to fail. Thus, a close, highly responsive matching exists between the heart and the circulation, which can acutely adapt to perturbations of volume [9].

In order to separate out the contractile function of the ventricle from its tight coupling with the arterial circulation, a further study was performed where stage 21 chick embryos were subjected to acute increase or decrease of circulating blood volume. In addition, the outflow from the ventricle was acutely occluded to force the ventricle to contract against maximal possible (after-) load. The results showed that stroke volume increased/decreased linearly with the preload. Compared to control, there was a significant increase/decrease in end-diastolic volume in response to infusion and hemorrhage, respectively. End-systolic pressures stayed similar to control, except during acute conotruncal occlusion, when the pressure rose by one-third above the control. Surprisingly, the heart rate remained stable even during occlusion. The authors concluded that in contrast to mature circulation, the embryonic circulation rapidly alters systemic resistance in response to altered flow and were thus unable to show that the embryonic ventricle conforms to a time-varying elastance model [10].

As mentioned, numerous studies in cross-circulated animal preparation and in intact animal hearts have consistently shown mostly linear ESPVR [5]. Those experiments have been difficult to replicate in embryo models, which exhibit marked deviation from linear ESPVR due to concurrent changes in vascular tone [9, 10]. However, when assuming for the geometric factor [11], such as wall thickness and wall stress – a unique value for each heart – and by applying a gradual, rather than sudden aortic occlusion, Tobita et al. were able to demonstrate that the early embryonic heart does in fact possess a load-independent maximal systolic elastance (E_{max}) [12]. This is an important finding which (even in the absence of embryonic heart oxygen consumption data) confirms the basic premise that at a given contractile state, the embryo's heart, like its mature counterpart, works not only at its *peak* efficiency, as determined by intrinsic heart rate, but that its contractile efficiency is *independent* of pre- and afterload.

We have seen that during each developmental stage, the embryonic circulatory system functions within a narrow range of heart rate, stroke volume, and pressure. Moreover, the interaction between the low-pressure, energetically limited myocardium and the vasculature is "set," so that the maximal (optimal) aortic flow matches the intrinsic heart rate. It was further shown that the heart rate, although acutely

sensitive to changes in temperature, remains remarkably stable in the face of perturbations in flow and pressure, a phenomenon yet to be explained. It is further unclear how the pre-innervated embryo regulates peripheral vascular tone. Many of these contentious issues can be resolved when the action of the heart is regarded as *secondary* to the movement of the blood and, as such, *directly* linked to the metabolic demands of the tissues.

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Chapter 11
A Brief Comparative Phylogeny

The main function of the circulatory system is to uphold a specific inner environment, which according to the type, is essential for the life and development of the organism. This includes, but is not limited to, distribution of nutrients and removal of metabolic waste, immune defense, thermoregulation, reproduction, and transport of respiratory gases. There are two basic types of circulation. The open circulatory system of invertebrates is characterized by a system of body cavities or coeloms connected with vascular conduits, both of which lack an endothelial cell layer. This simple arrangement allows the circulating fluid, the hemolymph, to bathe the inner organs *directly*, thus fulfilling the *dual* function of tissue fluid and blood. We will see that in this respect, it functionally resembles the early embryonic circulation of vertebrates *before* the formation of continuous vascular endothelium. In contrast, the closed circulatory system of the vertebrates is phylogenetically younger and consists of a network of continuous vessels in which the blood does not come in direct contact with the surrounding tissues. However, a significant overlap exists at the level of local circulations and individual organs within the vertebrate and invertebrate circulations. For example, while most of the capillary beds in the mammalian circulation are of the continuous type with tight endothelial junctions, the vascular sinuses of the bone, liver, and spleen are lined with fenestrated capillaries, readily permeable to plasma and large molecules. Technically, they too belong to the open circulation. Similarly, several classes of invertebrates such as the *Cephalopoda* and the *Oligochaeta* have, in addition to coelomic spaces, continuous vascular loops which resemble the closed circulations of vertebrates.

11.1 Invertebrates

The circulatory systems in invertebrates are as diverse as the large phylum to which they belong, with numerous species having no heart and only a rudimentary circulatory system, in contrast to others, with well-developed hearts and highly responsive peripheral circulation. The circulation in the common earthworm (*Lumbricus*

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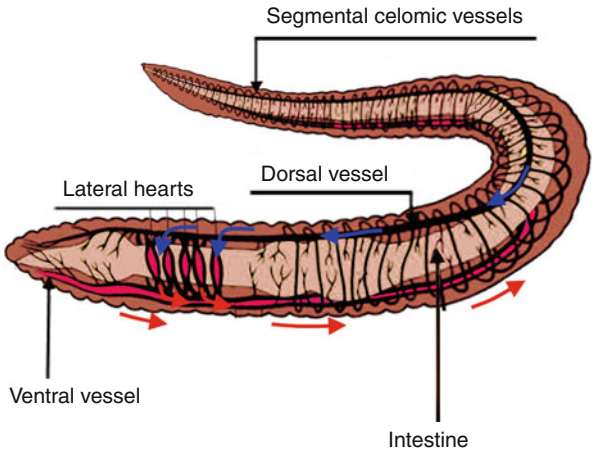


Fig. 11.1 Schematic representation of earthworm's circulatory system (*Lumbricus terrestris*). The blood from segmental vessels is collected in the contractile dorsal vessel and flows towards the head pole of the animal. Five pairs of segmental vessels with thickened muscular walls (lateral hearts) direct the blood into the ventral vessel and back towards the tail (*blue* and *red arrows*). In addition to transporting nutrients, the function of the blood and of the coelomic fluid is to maintain the internal fluid pressure, i.e., the hydraulic skeleton, essential for burrowing and locomotion. The pressure in the active (contractile) loop of the circuit is *lower* than in the noncontractile ventral vessel, suggesting that the source of blood propulsion lies within the capillaries, rather than in the contractile vessels themselves

terrestris/*Oligochaeta*) is typical of a large group of lower invertebrates. The large coelomic cavity is divided into some 150 compartments by externally visible septa. The degree of septal filling with coelomic fluid regulates the form and movement of the animal and serves as "hydraulic skeleton." Although the circulating fluid in earthworms is referred to as blood, this is a misnomer, since the respiratory pigment, a large heme-carrying molecule (erythrocruorin is about 36 times larger than hemoglobin) is not contained within the erythrocytes, but floats freely in plasma. Moreover, the vascular basement membrane is located on the *luminal* side of endothelial cells which contain contractile elements.

It has been suggested that the basement membrane plays a similar role in keeping the heme molecules within the vascular system, as does the erythrocyte membrane in containing the hemoglobin [1]. There are no specialized organs of respiration in the earthworm, the skin being the only organ available for gas exchange.

The blood moves along the contractile dorsal vessel to the front of the animal and returns backward via the ventral vessel (Fig. 11.1). The two are connected via a series of segmental vessels which collect the blood from the vessel sinuses distributed along the intestinal tract, nephridia, and skin. Five pairs of frontal segmental vessels have thickened muscular walls, which exhibit strong contractile activity (lateral "hearts") and are joined via valve-like folds to the dorsal and segmental vessels. Anterior to those hearts, the flow in the ventral vessel occurs in the frontal direction. The dorsal vessel and the lateral contractile vessels are assumed to be the major

propulsive organs for the blood [2]. Additional valves in the lumen of the dorsal vessel and inside the lateral hearts ensure directional flow of blood [3]. The rate of contraction of the dorsal vessel in a resting animal is 10–15/min and varies with environmental temperature and activity of the animal. The paired lateral vessels beat in synchrony at their own pace but can adopt the rhythm of the dorsal vessel [4]. Johansen and Martin measured simultaneous pressures in the dorsal and ventral vessels in a giant earthworm (*Glossoscolex giganteus*) (measuring up to 120 cm and weighing 500–600 g). At rest, the pressures in the dorsal and ventral vessel reached about 15 and 75 cm H_2O, respectively. During activity, which is marked by thinning and elongation of a segment of the animal, the pressure in the ventral vessel increased up to 120 cm H_2O. The experiment confirms that contraction of the body wall exerts a marked effect on the intravascular pressure. Of interest is the fact that, unlike in the vertebrate circulation, the pressure in the active loop (dorsal vessel and lateral hearts) was significantly *lower* than in the noncontractile ventral vessel, suggesting that the source of blood propulsion lies in the periphery, rather than in the contractile vessels [5].

To assess the contribution of the lateral hearts for the maintenance of the circulation, Johnston removed the frontal somites of the worm and observed the survivors during regenerative phase for several weeks. The vessels at the anterior part of the animal were *greatly crowded and distended with blood*, while the posterior parts remained relatively unfilled. Serial sections showed the greatest distension of the dorsal vessel and of the vascular plexuses of the intestinal wall, while the ventral vessel appeared normal in size [2]. Unfortunately Johnston did not comment on the level of activity in the surviving animals, but the experiment nevertheless points to the importance of the lateral hearts in *directing* the flow and in *maintaining* the pressure in the ventral vessel. The congestion of the dorsal vessel and of the capillary beds further suggests that the capillary flow continues in the original direction, in spite of the major disruption of the vascular integrity and a partial loss of the *hydraulic skeleton*.

The importance of intravascular pressure in maintaining mobility among invertebrates can be appreciated in the class of *Cephalopoda*, a group of very active animals, whose level of activity can be compared to that reached by vertebrates. They too have a "closed" circulatory system, with vascular and extracellular compartments, averaging 5.6 and 28 % of total body weight, respectively, a proportion similar to that in the vertebrates. Their level of metabolic activity is higher than that of other molluscs [6].

A schematic diagram of the circulatory system in a cephalopod is shown in Fig. 11.2. The deoxygenated blood returning from the head and body region is collected in the vena cava which symmetrically divides into two branches and enters the kidney sac (nephridia). The blood then continues into the muscular branchial heart, which ejects it into the gill (ctenidium). Like the heart, the ctenidium exhibits rhythmic contractions. The oxygenated blood passes via the efferent branchial vessel into the median ventricle. There are no valves between the heart and the vessels leading to it. The ventricle ejects the blood through the anterior and posterior aorta back to the systemic vessels. Like in the *Oligochaeta* the blood of the cephalopod

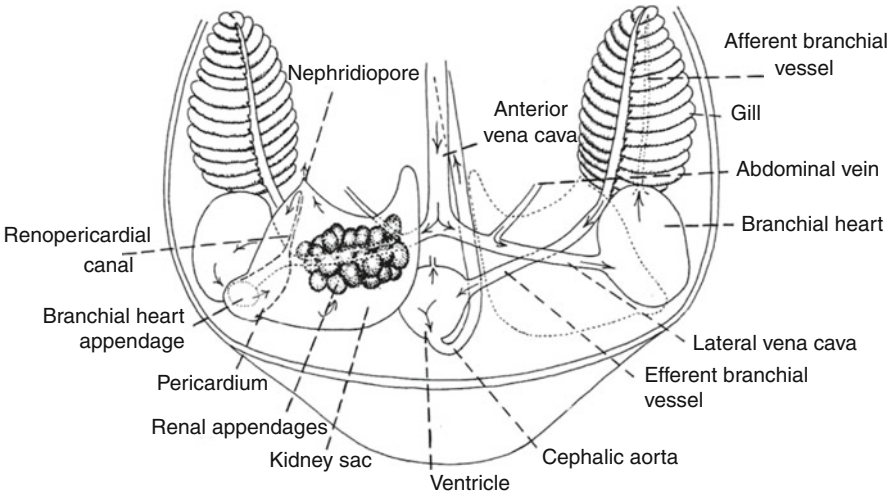


Fig. 11.2 Circulatory system of a cephalopod (*Octopus dofleini*). Deoxygenated blood returns by vena cava and abdominal veins into the paired branchial hearts and is ejected into the gills. The oxygenated blood collects via efferent branchial vessels in the valveless systemic ventricle and is expelled into the paired aortae. Direction of blood flow as indicated by *arrows* (Reproduced from Ref. [8], used with permission of John Wiley and Sons)

contains freely circulating oxygen-binding pigment hemocyanin consisting of 24–48 oxygen-carrying subunits, with molecular weights of 75,000. (These pigments are significantly larger than the mammalian hemoglobin which consists of 4 hemes, each attached to 14,000 molecular weight units [7]).

Johansen and Martin investigated circulatory dynamics during rest and exercise in the large octopus (*Octopus dofleini*) [9]. Simultaneous intravascular pressures in the aorta, branchial vessels, and vena cava were measured in unrestrained animals. Baseline aortic pressures were in the range of 55 cm H_2O for systolic and 40 cm H_2O for diastolic. The caval pressures (pulsatile synchronously with respirations) were between 2 and 15 cm H_2O. The heart rate was in the range of 6–8 beats/min. During slow, short movement (less than a minute), the systolic pressure increased to 73 cm H_2O and diastolic to 60 cm H_2O, with the pulse pressure of 13–14 cm H_2O, without any change in heart rate. During sustained exercise (3 min), the heart rate increased from 6 (at baseline) to 8 beats/min, and peak systolic pressure rose to 75 by the end of the exercise period. In the immediate postexercise period, the diastolic pressures remained markedly elevated for 10–15 min. before dropping back to baseline levels. The authors were at loss to explain the sudden increase of pressures at the onset of exercise, considering that there was little or no change in heart rate. This, together with the lack of valves, would make the central ventricle an inefficient propulsion pump, at best. The authors invoke contraction of the general body musculature as a factor in sustaining the increased diastolic pressure during activity, a view also supported by Chapman [10]. However, this does not explain the curious observation that the systemic ventricle can stop beating for a considerable period (up to 2 h), without

a significant drop in aortic pressure. Despite the fact that during asystolic periods, an increased activity was noted in branchial hearts, this could not account for the sustained aortic pressure, since the hearts are placed in the venous limb, *before* the extensive capillary network of the ctenidia (gills). The authors suggest "a massive peripheral vasoconstriction" as possible cause of sustained aortic pressure during periods of asystole, but do not provide evidence for its existence [9].

11.2 Tracheate Insects

The tracheate insects are highly evolved invertebrates in which the respiratory and circulatory systems developed separately but nevertheless achieved remarkable level of specialization. Together they serve the insect's highly efficient metabolic system that is unparalleled in the animal kingdom. The circulatory system of an insect (fly) is depicted in Fig. 11.3. A pair of thin membranes, the dorsal and the ventral diaphragm, separates the insects' body into three horizontal compartments, the blood sinuses. Along the posterior wall of the abdomen and thorax runs the main structural component of the insect's circulation, the heart or the dorsal vessel, which serves as a conduit for hemolymph. In the abdomen, the vessel is divided segmentally into chambers into which drain a pair of segmental vessels. While some species have a valve-like structure called the ostium, at the confluence of the segmental valve with the dorsal vessel, others have none [11]. A pair of alary muscles is attached laterally to the walls of each chamber. The chamber fills as the alary muscles relax (diastole) and allow the inflow of hemolymph from segmental vessels. Rhythmic contractions of the alary muscles regulate the pulsatile flow through the heart, typically in the range of 30–200 beats/min. While the abdominal part of the dorsal vessel is referred to as "the heart," its continuation in the thorax, which lacks the valves and supporting muscles, is called the aorta.

The insect's hemolymph is a thin plasma-like fluid consisting mainly of water, proteins, amino acids, sugars, and electrolytes. The cellular components known as the hemocytes represent only 10 % of hemolymph's total volume and their function is clotting, cellular defense, and phagocytosis. In comparison, the cellular component in vertebrate plasma is significantly higher, up to 50 %. The hemocytes do not contain hemoglobin or other oxygen-carrying pigments, since a separate tracheal system exists for the delivery of oxygen. The flow of hemolymph in the dorsal vessel is generally in the direction from the abdomen towards the head where, emerging from the aorta, it bathes the organs of the head and flows caudally via the three abdominal sinus cavities until it is collected again in the heart.

In keeping with the time-honored biological notion that a rhythmically contracting heart equals a pump, the insect heart is likewise assumed to function as such. However, much like in the case of the vertebrate embryo, the control of insect circulation has been the subject of renewed interest in recent years and several phenomena, which point to an automatons movement of hemolymph, have been observed but, unfortunately, not recognized.

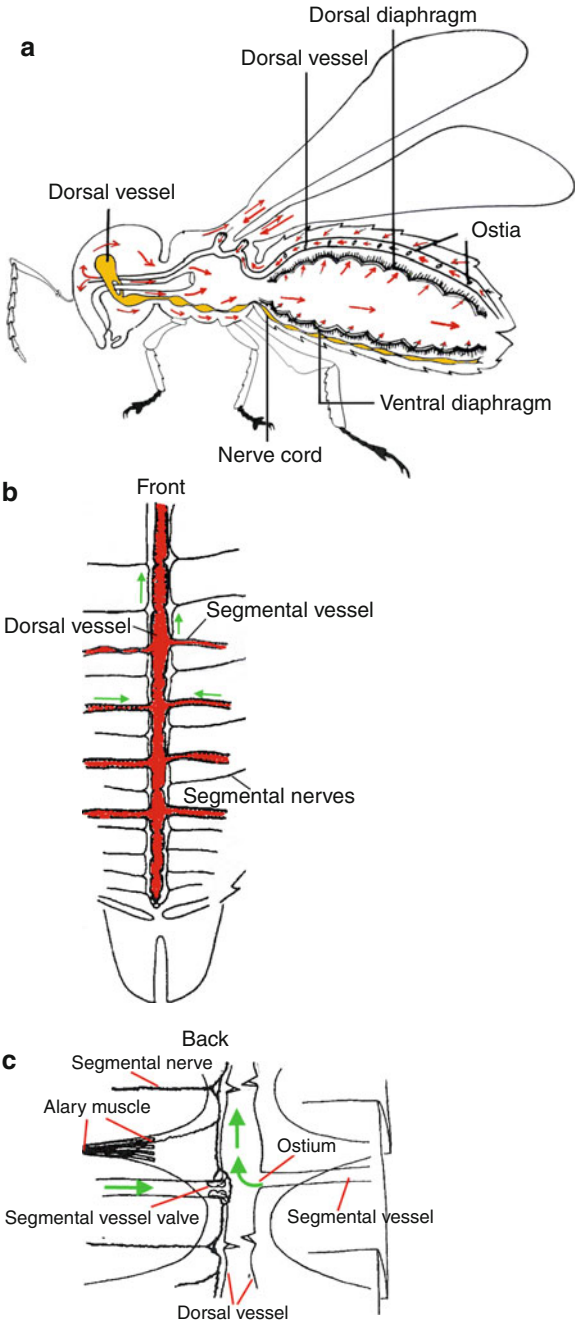
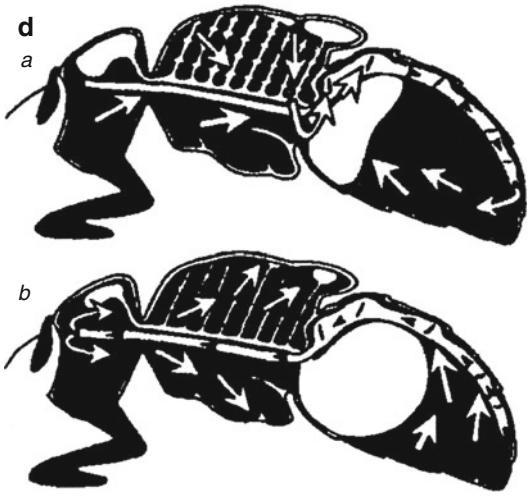


Fig. 11.3 (**a**) Insect circulatory system – schematic. Hemolymph enters the contractile dorsal vessel (aorta) via paired segmental vessels terminating with the ostia. The ostia open during alary muscle relaxation (diastole) to allow the flow of hemolymph into the dorsal vessel. The dorsal vessel flow continues cephalad, bathes the organs of the head, and enters into sinuses along the thorax and returns into the abdomen, before it reemerges in the dorsal vessel. (*Arrows* indicate the flow of hemolymph). (**b**) Diagram of the insect dorsal vessel (*Periplaneta americana L.*). The walls of the heart consist of a single layer of multinucleated striated muscle cells. In spite of rich innervation, cardiac contractions are myogenic. The entire dorsal vessel contracts simultaneously, possibly interrupting the autonomous flow of hemolymph. (**c**) Detail of abdominal heart segment in a cockroach. (*Periplaneta americana L*). *Arrows* indicate flow direction of hemolymph. (**d**) Hemolymph flow reversal in adult blow fly (*C. vicina*). Tidal movement of hemolymph into the thorax (*a*) alternating with movement into the abdomen (*b*). In some insect and larval species, rapidly alternating tidal movements of hemolymph occur, coupled with respiration and abdominal movement. The role of the heart in impelling the flow of hemolymph has been questioned (Figure (b) and (c) adapted, Fig (d) reproduced from Ref. [12], used with permission of Elsevier)

Fig. 11.3 (continued)



Over the past several years, the difficult question of primary neurogenic control of insects' hearts has been resolved. In some species the heart has no innervation and all myogenic cells clearly possess the pacemaker activity. In addition there are numerous species with richly innervated heart tubes. It has been argued that those, too, exhibit autonomous activity when anatomically or chemically denervated [13].

The real difficulty with the purported pressure propulsion arises, when we consider the mechanism of hemolymph propulsion through the insect. In theory, the peristaltic contraction of the alary muscles forces the hemolymph from chamber to chamber, while during relaxation phase (diastole), the ostia open and allow the flow of hemolymph from the segmental vessels to refill the heart. However, the role of the dorsal heart as an effective organ of propulsion has been questioned, since the pressures generated in the abdomen are 100–500 times greater than those generated by the heart [14]. In some insects, such as in the ordinary house fly, the heartbeat varies between 0 and 300, occurring irrespective of the insect's resting state, or of flight. More remarkably, the fly can sustain the metabolic activity at 100-fold its basal level, far surpassing any mammal [15]. In comparison, the exercising dog can increase its metabolism up to 40 times, world-class athletes by about 20 times [16]. This raises the question of the mechanism involved in the almost instantaneous overcoming of the fluid inertia, every time the flow of hemolymph comes to a halt. To make the matter even more complex, there is the peculiar phenomenon of hemolymph flow reversal, (observed already by Malpighi in the seventeenth century), which occurs in several species of flies and in the pupal stages of a number of insects [12, 17] (Fig. 11.3d). Given such complex "to-and-fro" movements of the hemolymph, how can the heart act as a bidirectional pump, and what would be its

possible control mechanism, given the fact that the heart exhibits autonomous (myogenic) contractions in response to stretch and filling volume? Should the heart work as a peristaltic pump, as the theory proposes, how can one account for the pumping mechanism of the cockroach heart, for example, whose dorsal vessel contracts *simultaneously* along its entire length, rather than peristaltically as is the case in other insects (Fig. 11.3b) [12]? The concept of pressure-driven circulation implies that the system of vessels is sufficiently tight to withstand the pressure generated by the circulating pump. Such a system is clearly not possible in the case of an open circulation with its system of coelomic spaces, which would soon become filled with excess amount of circulating fluid. Moreover, vessels devoid of the basement membrane and tight endothelial junctions would not be effective in containing the pressurized hemolymph. Given the fact that the circulation of the insect is closely coupled with its metabolic activity and, to some extent, with the environmental temperature, it becomes clear that the movement of the hemolymph is the expression of the metabolic activity of the insect itself and that the heart is inserted in the circuit in order to check or impede its flow. It is evident that, as in the case of vertebrates, the primary control of the insect circulation is metabolic and that the heart plays a secondary role, rhythmically restraining the flow of hemolymph.

11.3 Early Vertebrates

The open circulatory system persists among many classes of animals which represent the transition between the ancient chordates and the vertebrates. The *tunicates*, also known as sea salps, are ubiquitous marine animals that are sessile and actually lack a backbone but nevertheless belong to chordates on account of their free-swimming tadpole larvae which already have a primitive spine, the notochord. The adult animal has a remarkable vascular system in which the circulating fluid reverses direction, much like in the case of some insects. The heart is a tubular U-shaped organ, formed by folding of the pericardial membrane. The two vessels exiting from the heart continue for a short distance on either side, before they widen into a larger sinus cavity or coelom, filled with sheets of loose connective tissue, the mesenchyme. The sinus cavities lack true walls and are freely permeable to the circulating fluid. The hemolymph consists of plasma and a number of cellular components derived from the mesenchyme resembling lymphocytes and phagocytic amebocytes, none of which contains oxygen-carrying pigments. The circulation is a type of “ebb and flow” where the tubular heart contracts about 20 times/min, impelling rhythm to the flow of hemolymph for a period of 2–3 min, until it reverses, after a short pause, and flows in the opposite direction [7, 18]. The functional significance of flow reversal over one-way circulation has been the subject of lively debates among marine biologists in terms of the “adaptive advantage” of one system over the other. High metabolic rates in some salp species, clogging of vessels with blood cells in the gut region, and periodic exhaustion of pacemakers have been cited as

the cause of flow reversal [19]. The fact that the flow comes to a halt at the end of each heart stroke, without any backflow or noticeable slowing at the end of contraction period [19], clearly points to an autonomous movement of hemolymph (Fig. 11.4).

The lancelet (*Branchiostoma lanceolatum*) already represents the next step in development of the vascular system, in that it resembles a fish with bilateral symmetry, although without a distinct head structure (Fig. 11.5). Its body is segmentally arranged and is supported by a notochord, a flexible organ that defines its axial symmetry. There is no distinct respiratory organ and the respiration occurs entirely through the skin, consisting of simple epithelium. The presence of numerous gill slits around the pharynx is devoted solely to the filtering of water for the purpose of extracting of nutrients. The lancelet possesses a unique circulatory system in which the vessels are formed from the original coelomic cavity and are lined with simple epithelium, lacking the basal lamina. Although the vessels are joined in a complete circuit, the vascular system is technically considered to be *open* [21]. As in higher chordates, the blood in the lancelet moves forward ventrally and backward dorsally. The blood lacks circulating cellular elements and oxygen-carrying pigments resembling the invertebrate hemolymph. There is as yet *no heart*, as the organ of central circulation, and the sinus venosus acts as a collecting organ for the blood returning from the gut and the liver. At the base of the alternate primary gill vessels, a series of contractile elements, the bulibulli, eject the blood dorsally through the gill bars and on to the dorsal aortae. They represent a transition point between the centripetally and centrifugally flowing blood. Like the bulibulli, the aortae and the larger arteries are capable of rhythmic contractions due to myoepithelial cells embedded in the base of the coelomic epithelium [22].

11.4 Vertebrates

Given the above indications about the functional similarity between the early embryonic circulation and the circulatory systems in invertebrates, is it possible that this early, primitive circulation still exists beyond the early embryonic period?

11.4.1 The Origin of Lymphatic Circulation

In vertebrates, vascular and lymphatic circulations play a complementary role, in the sense that the excess plasma, not reabsorbed by Starling forces at venous ends of the capillaries, is returned via lymphatic vessels into the venous system. However, this is only one of several functions performed by the lymphatic system, which unlike the vascular system, does not form a circular loop, but originates in the interstitium and drains the excess tissue fluid centripetally into the venous system. Before entering the venous system, the lymph passes through the lymph nodes,

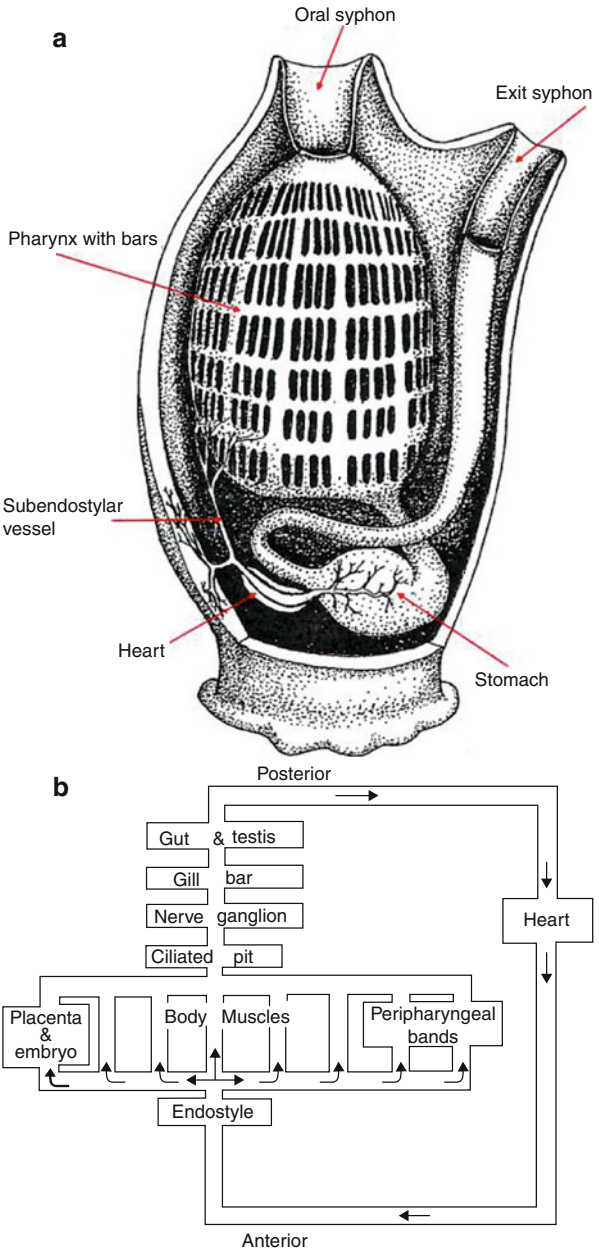


Fig. 11.4 (**a**) Schematic diagram of a sessile adult tunicate, sea salp with an open circulatory system. Part of the mantle removed to show the inner structure. The tubular heart consists of single atrium and ventricle, has no structural valves, and is enveloped by the pericardial fold. Myogenic peristaltic contractions are initiated by pacemaker cells at each end of the heart and occur at the rate of about 20 times/min (Adapted from Ref. [20], used with permission of Springer). (**b**) Linear diagram of the path the blood traverses during the forward flow phase in sea salp (*Thalia democratica*). The blood flows along the vessels which lack endothelium to bathe various organ systems. It reverses after a pause and flows in the opposite direction (Reproduced from Ref. [19], used with permission of Cambridge University Press)

where in collaboration with the antigen presenting cells, T and B cells recognize the "nonself" antigens and mount an immune response, by releasing white blood cells and antibodies into the circulation. In addition to maintaining interstitial homeostasis, lymphatics play a crucial role in lipid intestinal absorption.

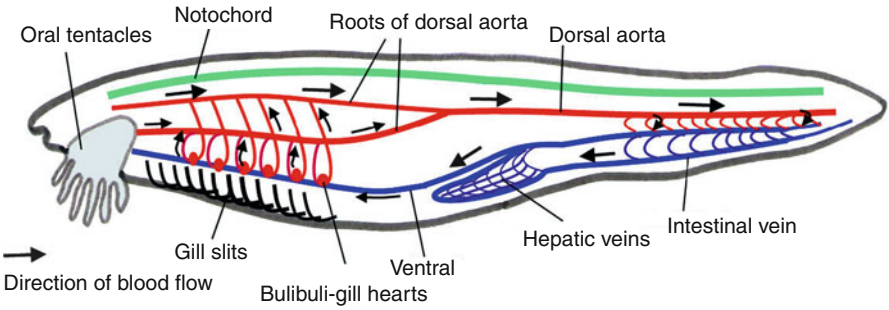


Fig. 11.5 Circulation in lancet fish. The blood moves in complete circuit from back to front ventrally and returns via the dorsal aorta. There is no heart as the organ of central circulation. A series of peripheral hearts, the bulibulli, serve as nozzles, accelerating the blood through the gill arches. *Arrows* show the direction of blood flow

A rapid expansion in the field of developmental immunology, over the past several years, has significantly advanced our understanding of the origins of the lymphatic system. The discovery of specific lymphatic growth factors, receptors, and transcriptional regulators together with a successful isolation and cultivation of vascular and lymphatic endothelial cells has enabled comparative molecular and cellular analyses of these two genetically and developmentally closely related cell lineages [23, 24].

The lymphatic system of capillaries consists of a network of a single layer of endothelial cells surrounded by an incomplete basal lamina. This makes it very porous to plasma and accounts for easy permeability of the cellular components through its walls – both characteristic of the open circulation. This feature points to a remarkable *functional similarity* between early embryonic and lymphatic systems, since the uptake of interstitial fluid seems to be an important function of early embryonic vessels. For example, by day 4, the primary capillary plexus of the chick's chorioallantoic membrane still has the appearance of undifferentiated capillaries without basal lamina, which appears complete only by embryonic day (E) 8 [25]. By morphological criteria, the dedicated lymphatic system begins to develop at E4.5 in the chick and on E10.5 in the mouse embryo [26]. In the mouse the first lymphatic sprouts are a distinct population of endothelial cells, expressing lymphatic-specific transcription factor Prox1 and differentiate from the endothelium at the junction of anterior and posterior cardinal veins [27]. This is in keeping with the traditional "centrifugal" theory, which maintains that the lymph sacs develop from the neighboring veins. However, more recent work involving endothelial cell markers suggests that the early embryonic vessels are in fact lymphatic vessels, by virtue of carrying the lymphendothelial receptor VEGFR-3, which is expressed in all endothelial cells – at least in the mouse and chick during early development – but is later restricted to lymphatic endothelial cells only [26, 28]. Just over a 100 years ago, Huntington intuited on phenomenological grounds that "in spite of structural and functional differences between the venous and lymphatic

organization, the two systems are but parts of an original single and united whole, and hence must be primarily and of equal origin…In spite of predominance of haemal (vascular) over lymphatic structures in higher (animal) forms, the latter should be recognized as the phylogenetically older primary structure" [29].

It has been proposed that the original circulation found in lower vertebrates and insects is a type of primary streaming of plasma-like fluid, consisting of few cellular elements with immunologic/defensive and nutritive functions. The vascular channels are porous and lack endothelial cells and communicate freely with coelomic tissue spaces, both being the hallmarks of the open circulation. With further organ differentiation, together with increased metabolic demands and oxygen requirements, there is a gradual separation of the original *single* circulatory system into the future lymphatic system and the secondary, blood circulation system. In due course, the lymphatic system assumes a more specialized role, such as that of immune defense but even in vertebrates it continues to retain its original, *nutritive role* of lipid absorption from the gastrointestinal tract and transporting them *directly* into the venous circulation close to the heart. The blood circulation system, on the other hand, undergoes further metamorphosis in which the predominantly venous tubular heart, consisting of a single atrium and ventricle, is a characteristic form of all vertebrate embryos.

11.4.2 Fish

In fishes, the system of heart and vessels is lined with endothelial cells and becomes a *closed loop* bridged by the capillary bed (Fig. 11.6). The gill and the systemic circulations are placed *in series*. The S-shaped heart still retains a single, nonseptated tubular character and is inserted into the venous limb of the circuit, before the gills. In comparison with mammals, the low arterial oxygen content, arterial pressure, and flow velocities point to a "venous" character of the fish circulation [30]. The heart does not yet occupy a central position and is located on the ventral side near the abdominal wall. The gas-exchange unit in fishes not only receives entire cardiac output but is perfused at *a higher* pressure head than the systemic vascular bed – the reverse of the mammalian circulation. Ventral (pre gill) and dorsal (post gill) aortic pressures in a generic teleost, e.g., trout are 35 and 25 mmHg, respectively, with CO of 15 $ml^{1} \cdot kg \cdot min$ [31]. However, ventricular systolic pressures as high as 100 mmHg have been recorded in albacore tuna (*Thunnus alalunga*) [32], posing a question as to what kind of physiological mechanism prevents stress failure of the gill capillaries [33]. Although it is agreed that an increase in metabolic demands in fish during exercise is accompanied by an increase in CO, exactly by what mechanism this occurs is contentious, with some arguing that it results from an increase in SV (stroke volume), while others suggest that it primarily comes about through an increase in HR. (Unlike in mammalian hearts, ejection fraction in many teleost species is close to 100 % and cannot be increased during exercise). For example, Sandblom et al. measured hemodynamic

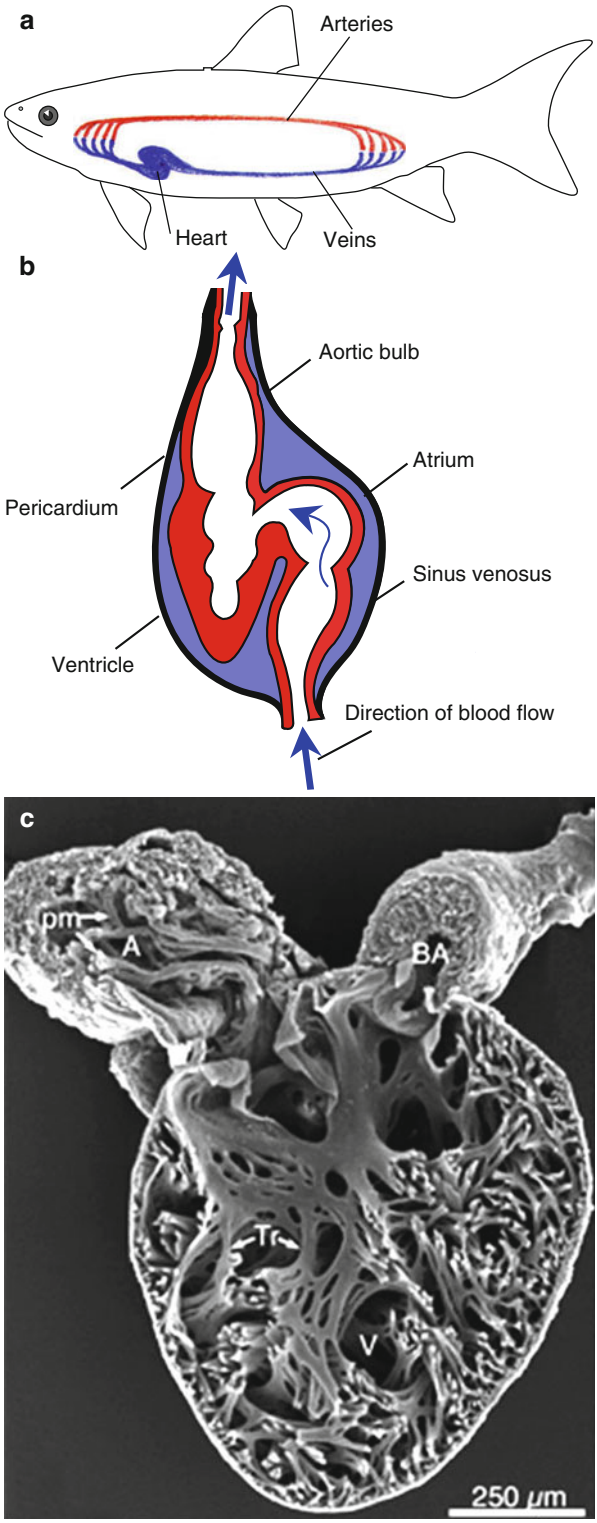


Fig. 11.6 (**a**) Simplified diagram of the circulatory system in fish. The S-shaped cardiac tube is in the venous limb of the circuit *before* the pahryngeal arches. (**b**) Schematic illustration of a fish heart in bony fish (teleosts). Note the nozzle-like constriction at the exit of aortic bulb which serves to maintain presssure in the aorta and smooths out the pulsatile nature of flow. Its functional analogue in cartilagineous fish, e.g., sharks and rays, contains a series of valves. The atrium is thin with smooth walls, the ventricle is filled with muscular trabeculations. (**c**) Cross section through adult zebrafish heart. The ventricle is filled with trabeculae. Note smooth atrial wall and only a thin layer of compact ventricular myocardium. *A* atrium, *PM* pectinate muscles, *BA* aortic bulb, *V* ventricle, *Tr* trabeculae (Reproduced from Ref. [35], used with permission of Oxford University Press)

parameters in sea bass at rest and while swimming. When compared to baseline, significantly increased HRs, ventral aortic, and CVPs (measured in sinus venosus) were obtained. Stroke volume and dorsal aortic pressures, however, remained unchanged. They proposed that an increase in CO results from increased mean circulatory pressure (MCFP) and, in turn, increased gradient for venous return, (the pressure difference between the MCFP and CVP), a parameter commonly employed in mammalian physiology [34]. (See Sect. 14.4 for methodological issues associated with MCFP concept).

A further unique feature of the piscine circulation is a differential *constriction* of the gill (branchial), and *dilation* of the systemic arteries to hypoxia [36], a response which shares similarities with mammalian hypoxic pulmonary vasoconstriction (HPV) and systemic vasodilation [37]. In addition to being an efficient "membrane oxygenator" (depending on temperature, water contains only about 35 ml O_2/l, as opposed to air, which contains 210 ml O_2/l of air at standard temperature and pressure/dry), the gills are increasingly recognized to play an active role in metabolism and in production of numerous vasoactive peptides and biogenic amines [31]. As the contact organ between the internal and external milieu of the fish, the gill may be the primary regulator and, as explored in Chap. 21, the primary source of blood propulsion.

11.4.3 Amphibians

A fundamental step in the development of the circulatory system occurs during transition from water to land, where the water-mediated gill respiration is superseded by the lung respiration (Fig. 11.7a). The branchial (arch) circulation is now functionally remodeled, in that it no longer directs the oxygenated blood directly to the periphery, as was in the case in gill respiration, but returns it back to the heart which undergoes a series of structural changes. In amphibians this takes the form of atrial septation, as a response to the oxygenated blood returning from the newly developed lung. The oxygenated blood from the lung drains via pulmonary veins into the newly acquired left atrium. The primitive skin respiration is retained and provides a limited amount of oxygenated blood which drains into the sinus venosus where it is joined with the venous blood from the body. The two mix in the right atrium and pass into the right part of the ventricle during atrial contraction. Oxygenated blood from the left atrium, on the other hand, flows as a separate stream into the left side of the ventricle. The right and the left parts of the ventricle contract sequentially and direct the two streams of blood into contractile aortic trunk (conus arteriosus). A spirally shaped endothelial valve in the aortic trunk keeps the two streams separated, directing the venous blood via paired aortic arches into the pulmonary arteries and on to the lung. Predominantly oxygenated blood from the lung is ejected into the paired aortae and distributed to the rest of the body (Fig. 11.7b).

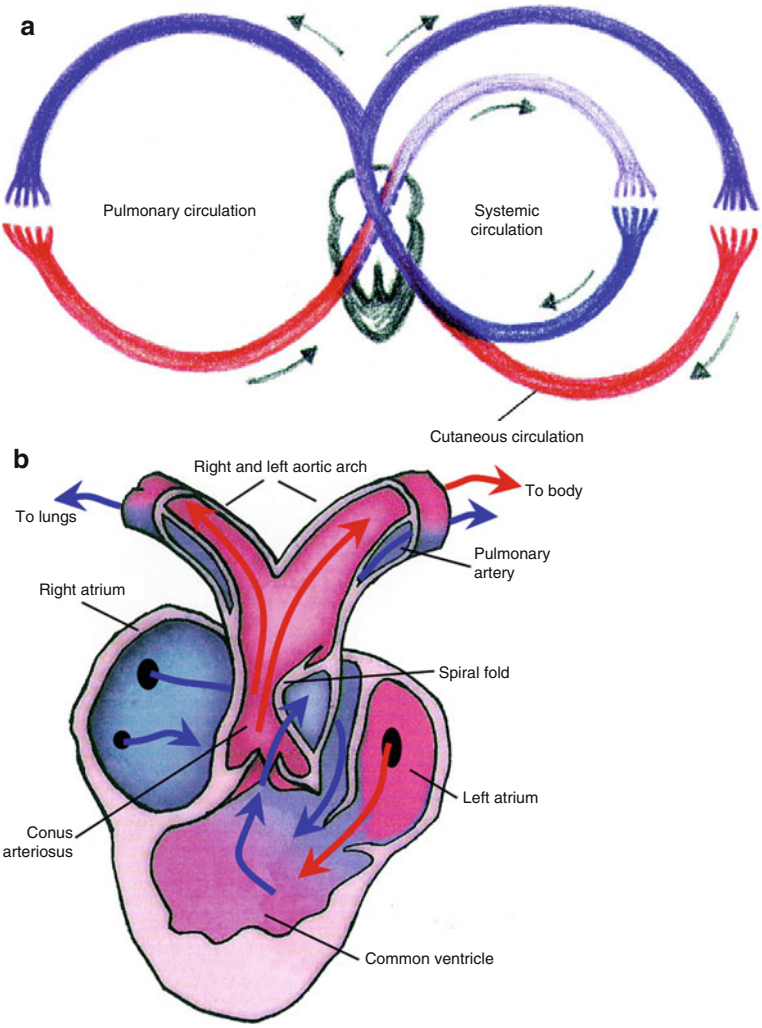


Fig. 11.7 (**a**) Amphibian circulation. In addition to the systemic circuit, amphibians have pulmonary and skin circulations placed in parallel (Adapted from Ref. [38], used by kind permission of Prof. J. W. Rohen). (**b**) The amphibian heart has three chambers. Venous blood from the body and oxygenated blood from the skin flows via sinus venosus into the right atrium. Arterial blood from the lung enters into the newly acquired left atrium. Functional separation of the two types of blood is maintained in spite of a single ventricle. Spiral endothelial fold in the aortic trunk directs venous blood into the paired aortae and on into the pulmonary arteries

Of note is the fact that the amphibian pulmonary and the skin circulations likewise exhibit differential constriction to hypoxia by a mechanism involving *direct* contraction of vascular smooth muscle. In this respect they resemble piscine gill and mammalian pulmonary circulations [37].

The next evolutionary step brings about a series of further transformations in the heart and the great vessels, collectively known as *septation*. This is the process in which the heart gradually becomes the central organ of circulation. It is inserted between the systemic and the newly forming pulmonary circulations. Before this final step is reached, however, two major transitions occur. In amphibians the symmetry of the circulation is still preserved with two aortae arising from the common ventricle which, via a series of pharyngeal arches, supplies systemic and pulmonary circulations with the blood consisting of arterial and venous components. In the land-bound reptiles, e.g., the lizards, the cutaneous circulation is no longer present and the right ventricle directs venous blood via the pulmonary artery into the lung. While two major vascular conduits originate in the right ventricle, namely, the pulmonary artery and the left aorta, the newly differentiated left ventricle is vented into the right aorta. Due to persistence of the two aortae, the anatomical separation of the systemic and pulmonary circulations is not yet possible and the communication must be preserved between the ventricles, i.e., via the foramen of Panizza. Due to increased metabolic demands, the importance of the pulmonary circulation increases. This step occurs in paralleled with gradual rise in systemic arterial pressure and the increasing supply of oxygenated blood to the sense organs and the brain.

11.4.4 Mammals and Birds

Complete separation between the pulmonary and systemic circulations is possible only with the preservation of a single aortic arch together with fully developed atrial and ventricular septa. Of the two possible arrangements, the warm-blooded mammals have retained the left aortic arch. The birds, on the other hand, have kept the right aortic arch and developed the pulmonary circulation, which, in efficiency, far surpasses the mammalian. In contrast to the mammalian respiratory system, where the lung serves a dual function of respiration and alveolar gas exchange, the bird has, in addition to the lung, a system of air sacs, which serve as air reservoirs. In place of dead-end alveoli, the bird lung contains an extensive system of parabronchioles, or air capillaries, where highly efficient gas exchange occurs in unidirectional flow of air supplied by the air sacs [39, 40] (Fig. 11.8). The air capillaries are substantially smaller than the mammalian alveoli and are arranged in a honeycomb pattern between the pulmonary capillaries providing superior mechanical support to high transmural pressures. Paradoxically, in spite of higher pulmonary artery and capillary pressures achieved during flight, the blood–gas barrier of the bird lung is about three times thinner and 15 % larger for body size than the mammalian,

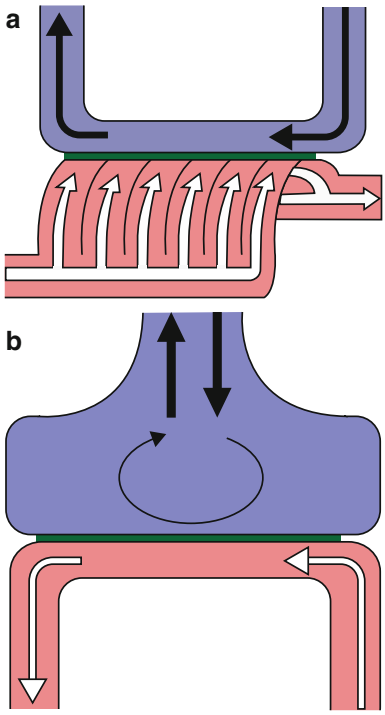


Fig. 11.8 Schematics of bird and mammalian gas exchange. (**a**) In the crosscurrent (countercurrent) avian model the air flows unidirectionally in rigid parabronchioles that are oriented perpendicular to the capillaries and is more efficient than uniform pool (concurrent) model of mammals and other terrestrial vertebrates (**b**). *Black arrows* denote direction of air, white arrows direction of blood flow (Adapted from Ref. [40], used with permission of the Company of Biologists)

allowing for the highest mass-specific, maximal sustained oxygen consumption of all species [33] (Fig. 11.9).

The enhanced gas-exchange efficiency of the lung, together with the hemoglobin species with a higher oxygen affinity, allows for a unique avian ability to fly in hypoxic environments of high altitudes. Quantitative analysis of arterial blood gases indicates that, for a given inspired PO_2, the arterial PaO will be higher in a bird than in a mammal [41]. Well known, for example, is the legendary performance of birds in hypobaric environments which would render an un-acclimatized mammal unconscious [40]. The cardiovascular system of the bird is similarly well adapted to maintain higher metabolic rates, as indicated by resting body temperatures ranging from 40 to 42 °C. The birds have larger hearts and higher MAP, resting SV and CO than mammals with similar body mass [42] (Fig. 11.10). Studies on pigeons flying in wind-tunnel report rates of oxygen consumption from the basal of 17.8 to 310 $ml \cdot kg^{-1} \cdot min^{-1}$, with increase in CO from 330 to 2,244 $ml \cdot kg^{-1} \cdot min^{-1}$ at maximal speeds (Peters et al., 2005). For comparison, peak O_2 consumption in an elite, 75 kg athlete is in the range of 72 $ml \cdot kg^{-1} \cdot min^{-1}$, with cardiac output of 27 l min^{-1}, or 360 $ml \cdot kg^{-1} \cdot min^{-1}$ [43].

This overall remarkable cardiorespiratory adaptation has enabled the birds to "overcome" gravity and become the creatures of air [38, 45]. The question naturally arises what kind of evolutionary or environmental factors would cause such an

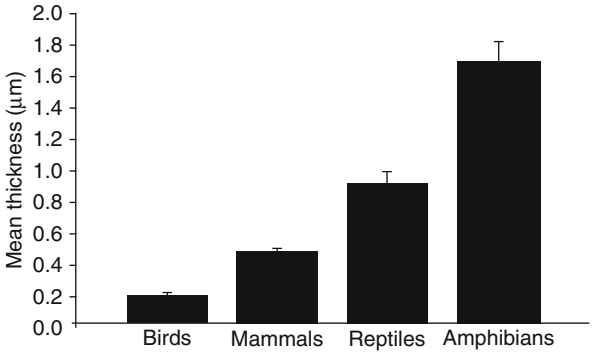


Fig. 11.9 Comparative thickness of blood–gas barrier in birds, mammals, reptiles, and amphibians. There is a relatively small variation in thickness of barrier within each vertebrate class. Note extreme thinness of the respiratory membrane in birds, e.g., down to 0.01 **µ** in a hummingbird. Only homeothermic species (mammals and birds) are capable of high, sustained oxygen consumption (Reproduced from Ref. [33], used with permission of the American Physiological Society)

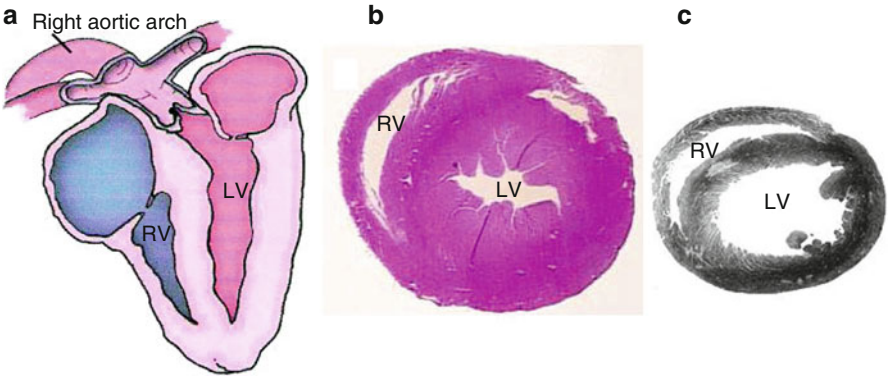


Fig. 11.10 (**a**) Schematic diagram of the four-chambered avian heart. Note the elongated, left ventricle and right aortic arch. (**b**) Cross section of an avian heart (chicken) shows thickened left ventricle; an adaptation to physiologically increased arterial pressure and high cardiac outputs (Reproduced by kind permission of UC Davis School of Veterinary Medicine). (**c**) In comparison, the cross section of a mammalian heart (mouse) shows significantly thinner left ventricular wall and relatively larger chamber. (Compare also with the low-pressure fish heart, with paper-thin ventricular wall; see Fig. 11.6c.) Images not to scale (Reproduced from Ref. [44], with permission by Elsevier). *LV* left ventricle, *RV* right ventricle

outstanding cardiorespiratory adaptation. We will attempt to answer this question in the final section of the book.

In summary, it has been shown that the long evolutionary road which the animals have trod in their transition from water to land and, finally, to air is reflected in morphology and function of the cardiovascular system, and can be viewed as a common fulcrum for further development (Fig. 11.11). The circulatory system is the pivital

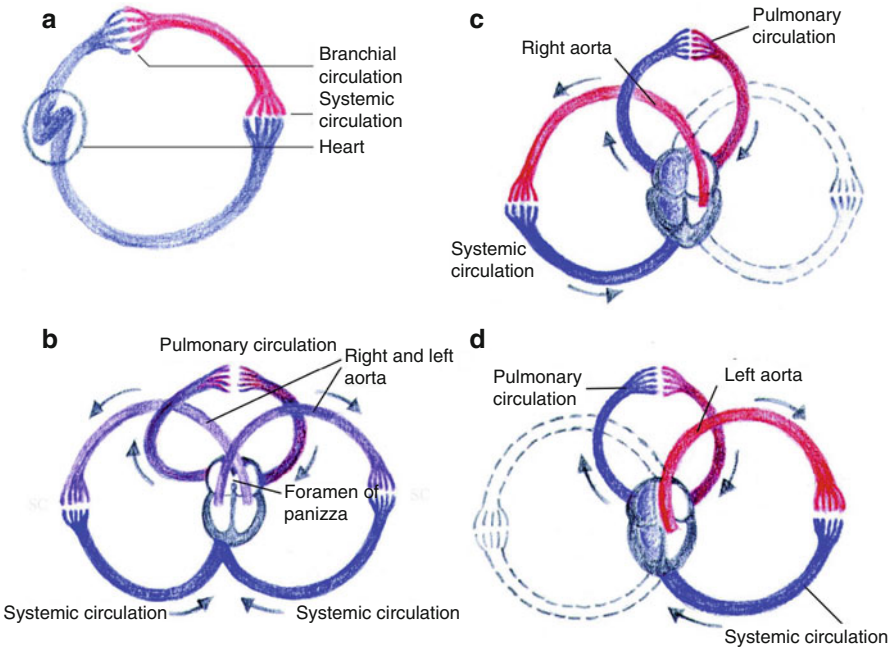


Fig. 11.11 Comparative anatomy of the circulatory systems in fishes, reptiles, birds, and mammals. (**a**) Single circuit, in-series circulation in fish. (**b**) In reptiles the heart has four chambers, but the separation between the pulmonary and systemic circulations does not occur due to the presence of the left aorta which originates in the right ventricle. The blood mixes in the ventricles via foramen of Panizza. (**c**) In birds septation of the heart is complete with total separation of arterial and venous blood. There is a four-chambered heart with right aortic arch. (**d**) In mammals the left aortic arch is preserved (Adapted from Ref. [38], used by kind permission of Prof. J. W. Rohen)

organ in the development of species (phylogeny) as well as of the individual animal form (ontogeny). As already noted by Aristotle, it is the first to form and the last to function.

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Chapter 12
Evolutionary Aspect of the Rhythmic System

Whoever says: that the heart as a pump drives the circulation, does not consider that this so-called pump itself arises out of the blood.

E. Kolisko, 1922

The idea that the development of a single organism indicates the evolutionary changes passed on through the forbears was first proposed by von Baer and J. Mueller on the basis of their studies of invertebrates. Mueller's student, Ernst Haeckel, an avid proponent of Darwin's evolutionary theory, developed the hypothesis further and called it the "biogenetic law." In its simplified version the law states that during its embryonic development, the organism recapitulates the overall evolution of its ancestors. Although the details and the applicability of the law have been subject to considerable debate among the specialists, it is nevertheless true that early developmental stages, e.g., morula and gastrula, are similar in all animals [1, 2]. What is of interest in the present context is that individual animal phyla represent an explicit, as if "frozen in time" developmental stage of a particular organ system. For example, the hypoplastic left heart syndrome, the fourth most common congenital heart abnormality in humans, can be considered a developmental delay at the level of the three-chambered amphibian heart. A much rarer condition of double right ventricular outlet morphologically resembles a reptile heart. A number of other cardiac developmental abnormalities exist for which a corresponding animal model can be found. Large-scale genetic screens have been documented which catalog cardiovascular abnormalities in zebrafish [3]. Besides, zebrafish mutants have been identified with cardiac abnormalities, which resemble those in humans, such as obstructive and dilated cardiomyopathies [4].

The question arises whether a deeper link exists between the patterns of heart development between higher and lower vertebrates and possibly humans. Genetic analysis of cell fate maps is one approach where enormous efforts have been made in the past few decades to unravel some of these complicated relationships. For example, a close connection is known to exist between the cardiac progenitor cells and vascular markers in fruit flies (*Drosophila*) and mammals (mice) [5, 6]. Likewise, embryos deficient for *tinman* gene fail to develop the heart primordium in drosophila [7] and frog (*Xenopus*) [8]. A similar family of transcription factors controls the early heart and skeletal muscle development in mice [9] suggesting that the regulatory mechanisms of heart expression may be conserved even between distant species. However, inhibition of similar transcription factors in mice does not

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inhibit the development of heart progenitor cells, but results in severe malformation, such as failure of looping and of development of the right ventricle, suggesting that organ formation is subject not only to single genetic developmental cues but also to their products, i.e., neighboring tissues [10]. It is apparent that there is a hierarchy of genes and their regulators which trigger development of the entire or parts of the organ systems. Finally, the growth and the function of the heart need to be integrated into the rest of the organism. The current theory draws on the concept of "heart field" which originated in the 1930s [11] and has recently been reviewed in light of current knowledge [12]. According to the theory, three tissues in the cardiogenic plate of the early vertebrate embryo contribute to spatial orientation and patterning of the heart. The first is the so-called organizer, which originates from the dorsal lip of the blastopore just before the onset of gastrulation. This is the heart-forming mesoderm, without which no heart would develop (cf. Chap. 1). It is also responsible for its axial symmetry. The presence of endoderm is needed for proper myofibrillogenesis and contractile function of the developing myocardium. The ectoderm, on the other hand, appears to exhibit *inhibitory* effect on the heart development, possibly controlling its size [12].

A complementary method to genetic analysis between distantly related species was explored by Heidenhain (referenced in [13]) who, in an effort to characterize growth and regeneration of tissues, adopted a functional approach. In his theory of "synthetic morphology," Heidenhain proposed that the organism consists of a hierarchic order of interdependent organ parts which goes beyond the atomistic theory of cells and genes. According to Heidenhain, the organism consists of interpenetrating units or "histomeres" which are *functional*, rather than anatomical entities. The histomeres dominate over the single cells and arrange them into organ systems. More recently, Rohen developed the theory further by combining these units into *functional systems* that are shared equally between simple and complex organisms [13]. For example, in a unicellular organism such as the ameba, the basic functions of digestion, respiration, movement, reproduction, and rudimentary sensation are all contained into a seemingly simple mass of protoplasm, containing several nuclei. While in multicellular organisms some of these functions are integrated into organs which increase in number as we move up the evolutionary tree, the individual cells continue to possess some or most of the basic functions. According to Rohen all of the possible functions that can develop in an organism are encompassed by *three* elementary functions of (1) exchange of substance or metabolism, (2) respiration and transport distribution, and (3) exchange of information.[1]

To each of these functions can be ascribed the corresponding organ systems of (a) digestion, (b) respiration–circulation, and (c) the systems of nerves and senses. More importantly the organic basis of these functions can be traced to the three germ layers which already contain the starting genetic and epigenetic (in the broadest sense) material for all organ systems. The *nerve–sense system* serves the organism to receive and process information. It has its anatomical basis in the sensory

[1] See Ref. [24] for further elaboration of Rohen's concept of "functional threefolding," originally introduced by R. Steiner in 1917.

organs and all levels of nerve organization whose elements are derived from the ectoderm. Its corresponding function on the cellular level is found in DNA/RNA signaling and receptor function. The *rhythmic system*, a derivative of mesoderm, mediates the transport of nutrients and the respiratory exchange. It includes the cardiovascular and respiratory systems. The corresponding equivalent at the cellular level can be found in mitochondrial respiration and intracellular transport of substances. The *metabolic system* stems from the endoderm and supports metabolic functions including the uptake, digestion of and elimination of metabolic substrates, all of which also exist on a sub-cellular level.

It is evident that these three systems play very different roles within the organism, as well as within the cell, in fact it can be argued that the nerve–sense and the metabolic systems represent two *opposite* poles. There is constant turnover of substance and energy in the metabolic system which, on the whole, has a large regenerative potential, e.g., mucous membranes, liver, and bone marrow. The organization of the nervous system on the other hand is highly structured with little regenerative potential; here the energy turnover takes only secondary role to information processing. The middle system is a true mediator between the nerve–sense and the metabolic systems not only in functional but also in topographic sense, in the case of vertebrates, since its organs are found largely in the middle of the body.

We encountered one of the best examples of the functional threefoldness in early embryo where the vitelline membranes (and the placenta, in the case of mammals) assume all of the basic organ functions, such as nutrition, respiration, blood cell production, and immune defense. With the development of specific organ systems within the embryo, the supporting role of the embryonic membranes is no longer needed. They are discarded through birth or hatching. Of interest is the fact that in birds and reptiles (*Sauropsida*), the amnion consists of a mesodermally derived layer of syncytium cells which exhibits autonomous myogenic contractions. In the chick, for example, rhythmic contraction of the amnion can be observed by embryonic day 3–4; by day 12 the frequency of contractions peaks at 10–12/min and then gradually subsides by day 16 [14, 15] (Fig. 12.1). These contractions have been compared to the functional equivalent of the peripheral hearts. In other species, the embryonic development occurs either directly in water or within the embryonic membranes of the womb, which is subject to rhythmic movement of the mother's heart [16].

As already mentioned in Chap. 1, the heart, the vessels, and the corpuscular elements of the blood share common progenitors and together form a highly dynamic organ system which is differentiated within itself. We have further seen that the heart primordium is the size of a capillary, which becomes pulsatile even before it becomes a conduit for the flowing blood. As the heart matures the pacemaker and the conducting tissue cells become anatomically confined; however, all myocytes, depending on location, retain some degree of spontaneous depolarizing activity.

The pacemaker cells have been called "the oldest" cells in the heart which, like the neurons, have lost their regenerative potential [17]. Ontogenetically, the heart as an organ is located at a particular *space* within the organism and can be viewed as

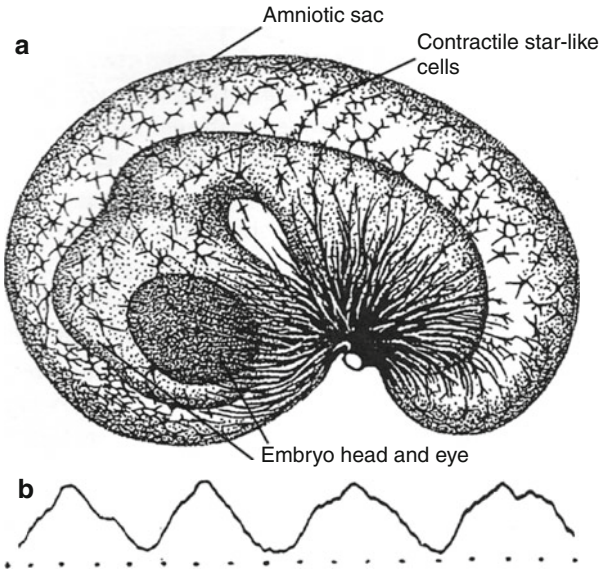

Fig. 12.1 (**a**) Schematic diagram of the chick embryo enveloped in amniotic sac. The membrane is studded with syncytial cells which exhibit autonomous contraction. (**b**) Cathode ray "electroamniogram" on the fifth day of incubation shows rhythmic amniotic sac movements at the rate of 12/min. Line irregularities are registrations of the embryonic heartbeat. Time intervals are marked in seconds (Adapted from Ref. [15], used with permission of Karger)

an enlarged, transformed blood vessel in which the pacemaker tissue assumes the role of the nerve sense or *form* pole. However, the *function* of the pacemaker potential generation unfolds in the dimension of *time*. According to Rohen the heart is the organ in which spatial and temporal elements coexist. In this context the heart can be seen as the form pole which, although rhythmically contracting, remains in place. On the other hand, the circulating blood cells represent the incessantly moving fluid pole. Between the two there is a system of vessels with various degrees of mobility [18]. Unlike the pacemaker cells, the red blood cells have a short life span and are continuously regenerated. Apart from the well-established endothelial and flow-dependent regulation of the microcirculation [19], mounting evidence suggests that the red blood cells are not only passive suppliers of oxygen to the tissues but play an active role in matching oxygen supply with local tissue demand through oxygen-dependent release of ATP, a potent vasodilator [20–23]. The blood thus actively participates in the metabolic function of organs and tissues.

The heart with the system of vessels and the blood can therefore be viewed *functionally* as a threefold organ which rhythmically mediates between the metabolic and nerve–sense functions of the organism (Fig. 12.2). An increased demand for oxygen and metabolic substrate in the tissues is met by a proportional increase in perfusion. Should the two be matched, there has to be an organ within the vascular loop which acts as a moderator, exerting a negative feedback. The perfusion within

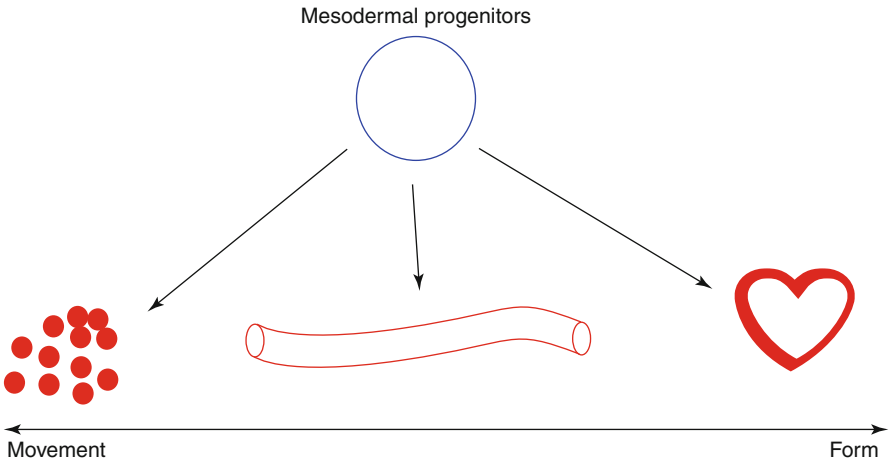

Fig. 12.2 Circulatory system as a functional unit. The circulatory system derives from common progenitors which in due course differentiate into three main components of the cardiovascular system: the blood, the vessels, and the heart. In this paradigm, the heart represents the *form* and the blood the *movement* part of the rhythmic system

the tissues, i.e., within the microcirculation, is said to occur according to organ autoregulation which critically depends on the perfusion-pressure maintained within the macrocirculation by the heart. It is proposed that the definition of tissue (organ) "autoregulation" be expanded to include the autonomous movement of the blood. In this context the heart can be seen as an organ within the vascular loop which not only maintains the perfusion pressure but acts as an organ of restraint, setting itself up *against* the flow of autonomously moving blood (See also Chap. 21).

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Part II
Mature Circulation

Chapter 13
Functional Morphology of the Heart

The test of a scientific theory is not how good or reasonable it sounds, but how well it fits the facts and, in particular, how fruitful it is in generating further penetration into the mysteries of nature.

Keith Francis, 2012

As mentioned in Chap. 1, the embryonic heart is a modified blood vessel which in the process of looping transforms from a straight tube to a complex, four-chambered organ. However, unlike in the lower vertebrates, e.g., fish and amphibians, where the muscular elements within the myocardial walls are ring shaped [1, 2], the three-dimensional structure of mammalian hearts is characterized by spiral arrangement of muscle fibers. Resemblance between helical forms and flows in nature and the myocardial structure was already known to the Renaissance anatomists and has been a subject of fascination to researchers ever since. Leonardo da Vinci believed that the heart is a "vessel made of dense muscle" and proposed that closure of the aortic valves results from vortical flow in the sinuses of Valsalva [3]. Leonardo may have been the first to describe the difference between the rotational and irrotational vortex, a key concept of circulation in hydrodynamics [4].[1] Richard Lower published the first detailed drawings of the separate myocardial muscular layers–overlapping much like rings of an onion – and drew attention to the fact that the endocardium and epicardium meet directly at the apex which is free of muscular elements [5]. In 1728, Senac demonstrated that the myocardial fibers are organized in spiral, three-dimensional arrangement, a finding repeatedly confirmed by investigators over the next 200 years. (For review, see [6–8].)

Among the numerous available studies of anatomical dissections of the heart, morphological descriptions and superb illustrations by Scottish anatomist J. Bell Pettigrew stand out and continue to be quoted as a classic in the field [1]. In his monumental work "Design in Nature" published in 1908, Pettigrew draw attention

[1] Leonardo correctly observed that the velocity of movement in swirling water draining from a tub, or hitting a stationary object, is faster towards the axis of rotation, where the product of tangential velocity and radius is invariant (constant). An object caught in such a "free" or *irrotational* vortex, e.g., a seed of grass, always points in the same direction as it circles around the center. Irrotational vortices occur in the sinuses of Valsalva, as observed by Leonardo, and also in the ventricles [4]. When, on the other hand, the fluid is impelled into movement by spinning its container, a vortex is formed in which the tangential velocity is proportional to its distance from the center of rotation. In addition to rotating around the center of the container, the seed of grass floating on the surface of such a vortex will also spin around its own axis; hence, the vortex is said to be *rotational*.

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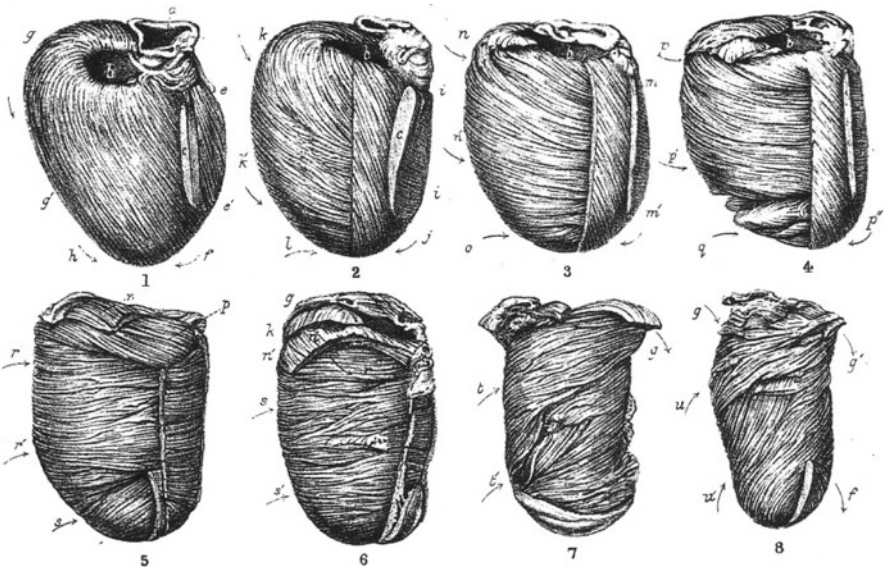

Fig. 13.1 Posterior view of the left ventricle of a sheep's heart with successive layers of the myocardium removed, as dissected and photographed by Pettigrew-Bell in 1864. Note the nearly vertical course of the outer and the innermost layers running in the opposite directions and a horizontal orientation of the mid-wall fibers (Reproduced from Ref. [9])

to ubiquitous presence of spiral forms in all kingdoms of nature and suggested that understanding of the common architectural plan of "perplexing" arrangement of myocardial fibers is a "Gordian knot" of anatomy holding the key to its function [9]. Pettigrew maintained that the heart is a transformed blood vessel where the thin-walled atria represent the continuation of the great veins, while the thick-walled ventricles and aortic and pulmonary outflow tracts mark the beginning of the arteries. He further argued that, unlike voluntary muscles, myocardial fibers have neither origin nor insertion but form continuous spirals (lemniscates) between the apex and the base and, moreover, exhibit spontaneous rhythmic movements of a syncytium.

Using an "innovative" tissue preparation technique (by stuffing sheep hearts with dry oatmeal and boiling them for 4–6 h, a method he called "a truly Scottish procedure") [10] and laborious dissections, Pettigrew demonstrated that the myocardial wall consists seven layers which "overlap externally and internally and equilibrate each other according to mathematical law" [1, 9] (Fig. 13.1). The outermost layer runs from left to right obliquely from the base to the apex, while the second and the third layers assume a more obtuse angle as they sink deeper into the wall. Fibers of the fourth layer define the mid-wall and run like a circular band horizontally around the ventricle. Finally, fibers of the three inner layers spiral in the opposite directions, from apex to base. The point of inflection of the inner and outer helical system occurs at the apex forming a characteristic whorl or "vortex cordis" (Fig. 13.2). Pettigrew's remarkable observations have struck a note with several generations of investigators; here, for example, is a quote by Pasipoularides:

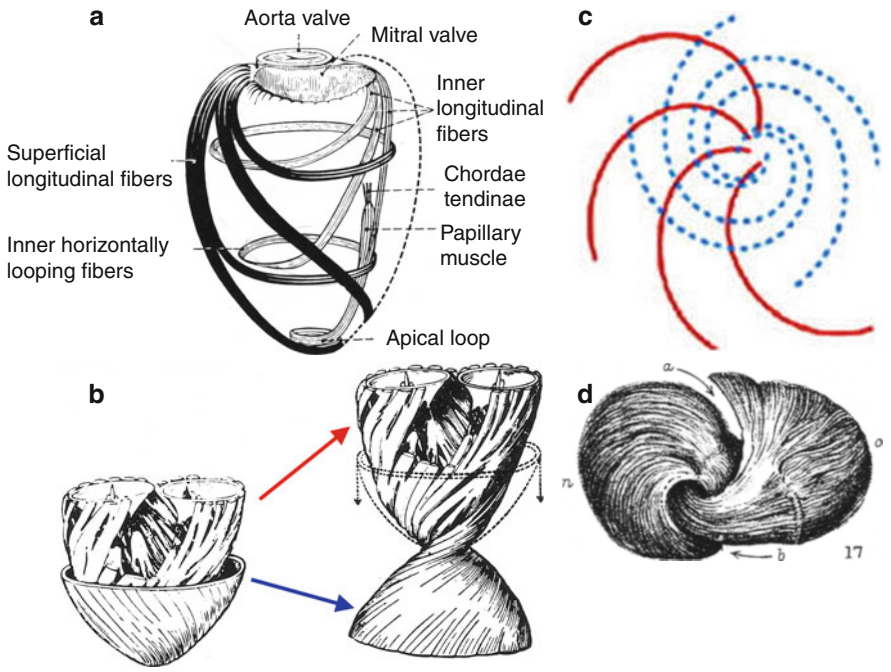

Fig. 13.2 Schematic representation of left ventricular architecture in three dimensions (**a**). Superficial fibers (dark) originate at the base and sweep longitudinally towards the apex where, turning sharply, they continue as the middle (horizontal), or inner, vertical layer forming the papillary muscles (light) or return back to the base (Adapted from Ref. [12], used with permission of Elsevier). (**b**) A stylized drawing of the vortical structure of the heart where the outer layer has been "peeled" and inverted to show the counter-directional course of the inner and outer layers (Adapted from Ref. [13], used with permission of Elsevier). (**c**) Schematic representation and (**d**) interlocking of the apical fibers (Reproduced from Ref. [9])

> The spiraling and looping pattern of myocardial fibers, including the vortex cordis, is a reflection of intracardiac blood movements. In the heart, form and movement unite in a rhythmical process in space and time: the organ, a form in space, is simultaneously a movement in time…the movement of the cardiac walls is a physical replication of the creative fluid flow movements which they enclose. [11] (Used by permission of the People's Medical Publishing House)

Other, perhaps less phenomenologically oriented, researchers have found it difficult to reproduce Pettigrew's ingenious dissections and morphological descriptions of discrete muscular layers within the ventricular walls. Preconceived notion that the heart is the organ of blood propulsion has compelled some to emphasize the elements in myocardial architecture which would primarily make it into an efficient pump (reviewed by Brecher and Galletti [14]). Carl Ludwig introduced the concept of a muscular cylinder as the principal structure of the left ventricle enveloped by endocardial and epicardial layers crossing at the right angles of its longitudinal axis in the form of an X [15]. This model was further refined by Krehl who named the circular fibers the "triebwerkzeug", or "propelling tool", in literal translation from the German [16], technically known as the "actuating fibers" in English. The concept

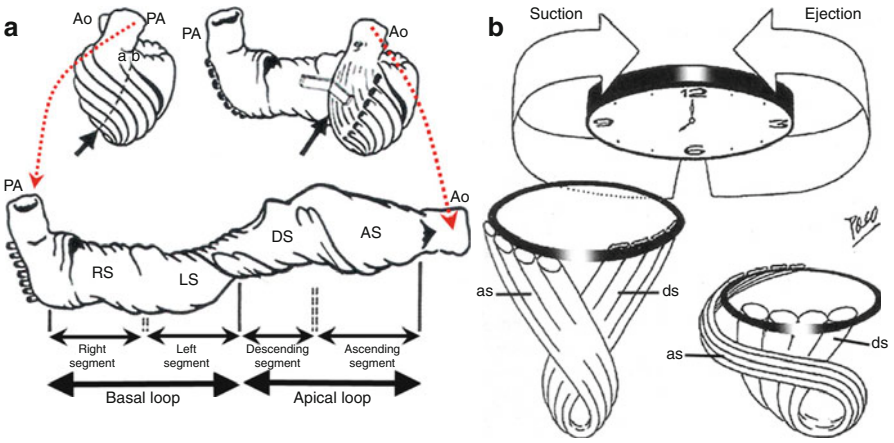

Fig. 13.3 Ventricular myocardial band of Torrent-Guasp (**a**). The right ventricle is cut along the *dotted line* (**a**, **b**) to allow separation of fibers into a single muscular band consisting of two loops (basal and apical) spanning from pulmonary artery to aorta (*dotted arrows*). Each loop can be further divided into two segments. *Ao* aorta, *PA* pulmonary artery, *RS* right segment, *LS* left segment, *DS* descending segment, *AS* ascending segment. (**b**) Operation principle of the two segments of the apical loop in Torrent-Guasp model. Contraction of the descending segment (*ds*) causes counterclockwise rotation, descent of the base and reduction in cavity, i.e., ejection. Contraction of the ascending segment (*as*) causes the ventricle base to ascend, untwist (clockwise rotation), and widen in order to fill in diastole (Adapted from Ref. [6], used with permission of Oxford University Press)

gained further momentum with the work of MacCallum who stressed the crucial role of the cardiac "fibrous skeleton" [17]. According to MacCallum's anatomical model, four interconnected fibrous rings around the orifices of the great vessels and AV orifices serve as attachments of cardiac valves and also as points of insertion for ventricular muscles, of which several groups had been identified by functional anatomists at the time, such as the "bulbospiral" and "sinospiral" tracts described by Mall [18]. It should be noted parenthetically that during the time, a functional similarity between the skeletal muscle and the myocardium was emphatically supported by Frank [19] and Starling [20, 21] and that seminal experiments were performed on the isolated heart preparations culminating in Starling's formulation of the "law of the heart" [22]. (See Sect. 15.1.) Subsequent work demonstrated that in comparison to skeletal muscle, the myocardium is capable of developing only a fraction of active tension (2–5 kg/cm^2, vs. 200 g/cm^2 of cross section of the muscle) [23].

The most notable attempt to portray the heart not only as pressure propulsion but as a "pressure–suction pump" is the concept of ventricular myocardial band (VMB) of Torrent-Guasp [6, 24] (Fig. 13.3). The topology of the model is based on a unique dissection method by which the heart is unfolded into a single muscular band extending between aorta and pulmonary artery. Accordingly, the architectural plan of the ventricles is formed by a pair of counter-directional (apical and basal) loops, each consisting of two segments. Fibers of the basal loop, forming the free wall of the right ventricle and the basal portion of the left ventricle, course predominantly in circumferential fashion. On the contrary, the two segments of the apical loop

(descending and ascending) run mainly in the vertical direction (parallel to long axis of the left ventricle) and cross at about 90° [6]. Functionally, the apical portion of the VMB is the principal force generator acting in the manner of twisting and untwisting of the ventricular cone (e.g., wringing of a wet towel), without any net movement of the apex. Contraction of the descending fibers brings about systolic ejection through simultaneous descent of the ventricular base, counterclockwise rotation and LV cavity reduction. Ventricular filling, on the other hand, is brought about by contraction of the ascending fibers of the ventricular loop, with clockwise rotation, ascent, and cavity augmentation (Fig. 13.3b). Diastolic chamber elongation, affected by muscle *contraction*, is a unique but controversial element of the Torrent-Guasp model [25]. It supposedly augments venous return by generation of (active) ventricular diastolic suction, referred to as *vis a fronte* by the antique physicians (see Sect. 15.2). It is of interest that a "force from the front" pulling the blood towards the heart was still a viable concept in the 1950s, before the almost universal acceptance of Guyton's venous return model [26, 27] (see Sect. 14.3). The existence of VMB has, moreover, been contested on purely anatomical grounds, in the sense that it is not possible to dissect the myocardium according to the Torrent-Guasp method without disrupting the myocardial wall at multiple points and thus forgoing the essential link between "form and function," as proposed by proponents of the model [28] (see also [29, 30] for reviews).

The pendulum of research into myocardial architecture swung in the other direction when it became apparent, in due course, that beyond general orientation of the myocardial fibers, identification of explicit muscular layers is *not* possible by histological techniques [31]. Grant maintained that the syncytial nature of the myocardial fibers, with multiple connections and branching, is beyond the laws of plane geometry applied by Lower and his successors who, by means of anatomical preparations, frequently "created the planes they sought" [32]. Streeter and Bassett were unable to find evidence of specific muscle layers and suggested that the myocardium be described as a "continuum" rather than consisting of discrete muscle bundles and performed the first quantitative measurements of muscle fiber orientation within the heart wall [33]. Researchers from the same group subsequently demonstrated that the overall alignment of myocardial fiber aggregates varies up to 180° (with respect to ventricular equator) within different depths of ventricular wall [34] (Fig. 13.4).

On account of marked uniformity of ventricular wall architecture, Hunter and Smaill introduced the concept of "continuum approach" and proposed that methods of continuum mechanics provide a suitable theoretical framework for analysis of the complex interaction between mechanical, metabolic, and electrical functions of the heart [35]. Greenbaum and coworkers confirmed major variation of myocardial fiber orientation within the myocardial wall and warned against regarding the ventricle as having a simple geometric shape or a uniform structure [8]. It is recognized today that every part of the ventricular wall possesses a unique architecture, and while it is still possible to identify groups of myocytes contained within perimysial compartments (secondary structure), it is no longer feasible to distinguish discrete anatomical layers (tertiary arrangement) [29] (Fig. 13.5).

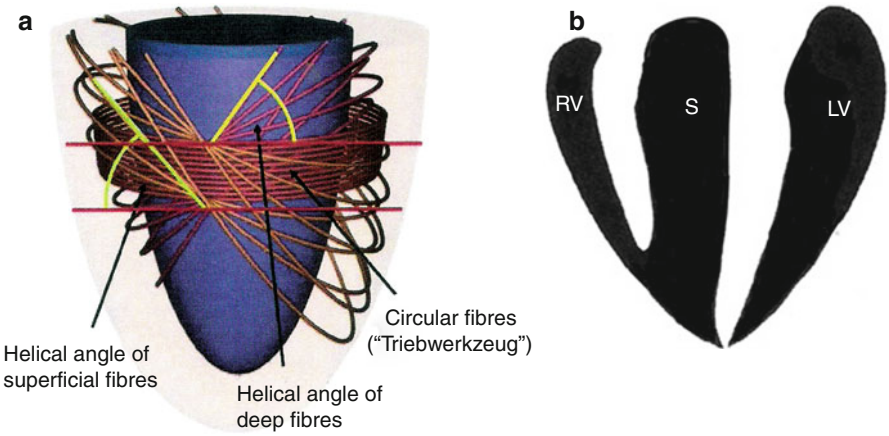

Fig. 13.4 A composite diagram of angles (*yellow lines*) followed by myocardial fibers at different depths relative to the equator of the left ventricle, as demonstrated by Streeter and coworkers. (**a**) The circular or actuating fibers, given prominence by Krehl (1881) were thought to play a pivotal role in the pressure-propulsion model of the heart (Reproduced from Ref. [29], used with permission of Oxford University Press). (**b**) Schematic cross section of the ventricles showing relative thickness of wall components. Thin apical segment denotes a poorly designed pressure-propulsion pump. *RV* right ventricle, *S* septum, *LV* left ventricle

An important contribution to understanding of the myocardial fiber architecture has been the use of diffusion tensor magnetic resonance imaging (DTMRI), a novel technique which enables visual "tracking" of the aggregated myocyte chains within ventricular walls. While DTMRI studies cannot confirm or exclude the presence of discrete myocardial sheets, they have independently verified previous histological findings. Importantly, they have corroborated the remarkable three-dimensional helical fiber patterns which, according to Smerup et al., "are entirely compatible with the illustrations produced by Pettigrew 150 years ago following careful dissection of the ventricular mass" [28] (Fig. 13.6). Directional arrangement of the myofibers within the ventricular wall and their contraction sequence within a single cardiac cycle have been further confirmed by Tissue Doppler Imaging and by sonomicrometry, a method of implanting miniature ultrasound crystals directly on the ventricular wall [36].

Similarly to ventricular fiber architecture, the flow of blood through the heart also appears to follow invariant patterns (Fig. 13.7). It has been demonstrated that streams from superior and inferior vena cava do not collide, but flow past each other to form an atrial vortex [37]. Systolic and mid-diastolic vortical flow pattern also occurs in the left atrium [38] and during diastolic filling in the ventricles [37, 39, 40].[2] Magnetic resonance velocity mapping studies of chamber flows reveal asymmetric vortex flow patterns, which, according to Kilner and coworkers, redirect the momen-

[2] See Markl et al. [40] for time-resolved three-dimensional MRI video of intracardiac flow paths (Ref. [38]).

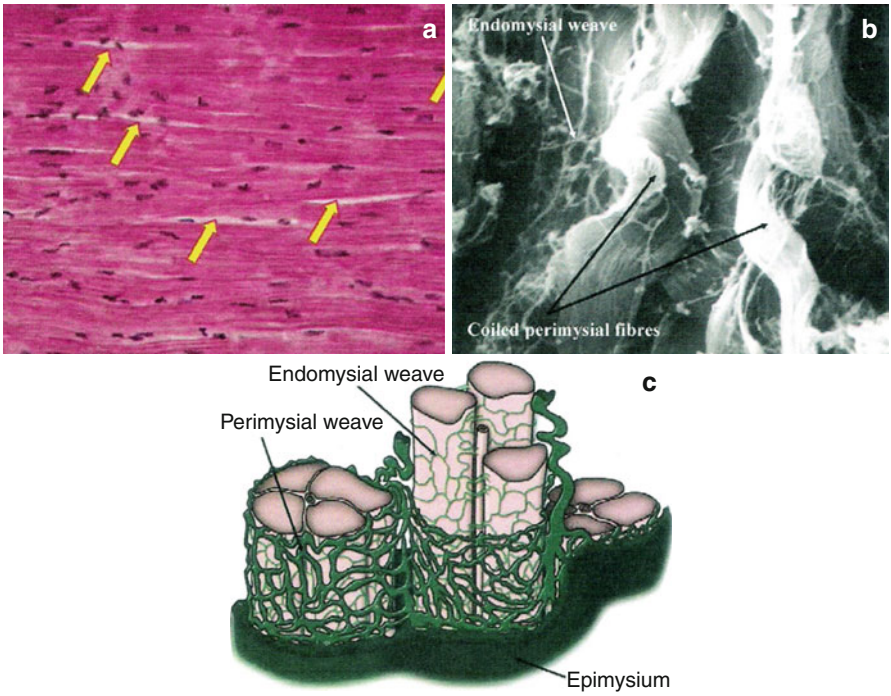

Fig. 13.5 A section of ventricular wall at low magnification showing a uniform orientation of individual myocytes. The spaces between the cells (*yellow arrows*) are filled by the supporting fibrous matrix (**a**). A scanning electron micrograph of endomysial weave, surrounding each individual myocyte, and a pair of coiled perimysial fibers that bind groups of myocytes into so-called myofibers (**b**). Three-dimensional architecture of the supporting myocardial matrix suggests that, in comparison with skeletal muscle, the myocardium is well protected to withstand excessive filling (distension) (**c**) (Adapted from Ref. [29], used with permission of Oxford University Press)

tum of instreaming blood towards the atrioventricular valves and thereby enhance ventriculoatrial coupling [37]. It has been further demonstrated that optimal vortex formation and flow dynamics during left ventricular filling is a sensitive indicator of healthy myocardial performance [41, 42] and plays an essential role in ventricular chamber expansion [43]. By employing the method of digital particle image velocimetry for intracardiac flow visualization in anesthetized pigs, Sengupta and coworkers [44] demonstrated formation of a large anterior, and a smaller posterior vortex flow pattern during early diastolic filling spanning across the anterior and posterior mitral valve leaflets, respectively. The vortex size increased during isovolumic contraction, upon which the initial, base-to-apex flow was suddenly reversed and redirected into the outflow tract, to be expelled during ventricular ejection (it should be noted that the two vortices are, in fact, two-dimensional representation of a single, asymmetrical ring vortex) (Fig. 13.7c). The importance of vortex flows in the overall dynamics of ventricular function was further demonstrated by electrical pacing of the ventricles at the base, resulting in a loss of vortex formation,

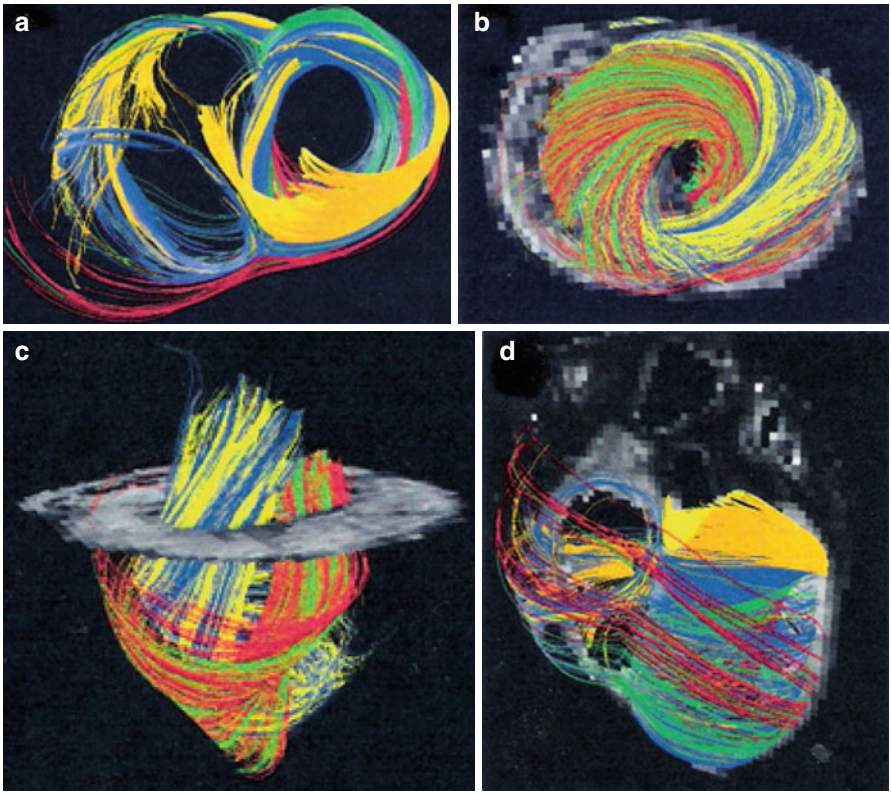

Fig. 13.6 Diffusion tensor magnetic resonance imaging (DTMR) of the three-dimensional track progression of myocardial fibers of the base (**a**), apex (**b**), papillary muscles (**c**), and of the mid-wall section (**d**) of the myocardium. Individual tracks are color coded and extend in a figure-of-eight pattern between the base and the apex of the heart (Adapted from Ref. [28], used with permission of John Wiley and Sons)

turbulent flows, and a reversal of normal apex-to-base flow during pre-ejection period. The authors noted that "These observations argue against the conventional appreciation of the left ventricle as a chamber that contracts and dilates for ejection and filling, with intervening isovolumic phases of hemodynamic stasis. Rather, leading vortices make a dynamic contribution to flow redirection and provide efficiency for momentum transfer" and moreover that "…the direction of electromechanical activation in adult mammalian heart, matches and maintains a synchrony between the timing and direction of activation and blood flow" [44].

In a recently published "opus magnum" on the intracardiac blood flow phenomena, Pasipoularides confirms that in the heart, form and function have, indeed, become one: "In a way, what the blood does as a fluid has fashioned muscular histoarchitectonics of the cardiac ventricles… In spiraling paths, myofibers sway down to the heart's apex and then rise again to its base. They make the same movements and emphasize the same vortical streaming of the filling vortex within the

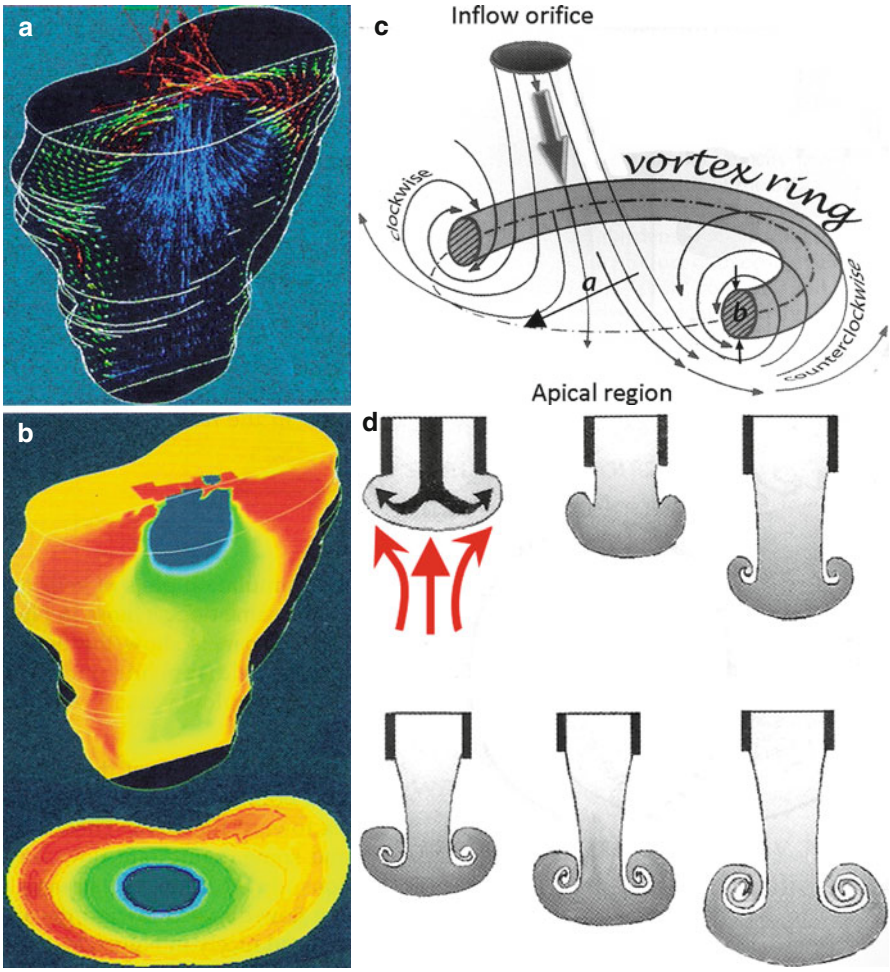

Fig. 13.7 Intracardiac blood flow visualization. Flow velocity fields (**a**) and color maps (**b**) during early diastolic filling of the right ventricle in a dog. The transverse cut (*bottom* of figure **b**) is taken 2.5 cm from the ventricular orifice. *Red* and *yellow* spectrum represents positive velocities, *green* and *blue*, negative (Adapted from Ref. [45], used with permission of the American Physiological Society). (**c**) Three-dimensional representation of the ventricular vortex ring. Note the clockwise and anticlockwise direction of rotation of the facing vortex poles. (**d**) The contact between the rapid diastolic flow and residual blood (*red arrows*) in the ventricle results in a toroidal filling vortex, a major energy dissipating structure (Figure (**c**) reproduced and (**d**) adapted from Ref. [43], used with permission of the People's Medical Publishing House)

ventricles. Therefore, interventricular blood flow and the pattern of the muscular histoarchitectonics of the heart are mutually intertwined" [11] (used with permission of the People's Medical Publishing House).

As mentioned, earlier reports on mechanics of contraction emphasized the presence of vortical flow patterns as important energy-preserving structures to be

released during ejection [37, 38, 41, 46, 47]. More recent studies, however, have entirely contradicted these claims. Maire and coworkers showed no difference in functional status and exercise tolerance between patients with mechanical or tissue mitral valve prosthesis with normal and abnormal ventricular flow patterns [48]. In addition, investigations in dogs and computational fluid dynamics (CFD) simulations by Pasipoularides and coworkers [45, 49] and numerical and experimental ventricle models [39, 50] demonstrated that flow patterns during diastolic filling of the ventricles significantly *reduce* kinetic energy of the moving blood and have an overall effect of *decreasing* the chamber pressure (Fig. 13.7d). According to Pasipoularides ventricular vortices act as sinks or traps of energy which can no longer be recovered:

> The key to the proposed useful physiological role of diastolic filling vortex lies in its *impounding* of a certain amount of energy, and this becomes manifest as a decrease in the pressure energy of the inflowing blood. By *shunting* the inflow work and kinetic energy, which would otherwise contribute an inflow-impending *pressure-rise* between inflow orifice and the endocardial surface of the expanding chamber, *into kinetic energy of the vortical motion* that is destined to be *dissipated as heat*, the diastolic vortex actually *facilitates filling* and the attainment of higher end-diastolic volume. (emphasis by the A. Pasipoularides) [51], used with permission of the People's Medical Publishing House

In the wake of these findings, Pasipoularides has formulated the concept of "convective deceleration" [45, 49, 51] according to which the geometry of the ventricle – together with the residual blood remaining in the ventricle after ejection – significantly reduces diastolic pressure gradient during the period of rapid ventricular filling, thus averting a potential chamber overdistension. A portion of blood's kinetic energy is thus impounded as a fluid vortex and dissipates into heat, as the vortex disintegrates during ventricular ejection into turbulent jets and eddies. Helical flows with recirculation have, moreover, been demonstrated in the aorta (Fig. 13.8) [52, 53], as well as at the bifurcations of major arteries [54], and have been subject to detailed rheological analysis in models of arterial tree [55]. Like vortices in the heart, they too impede forward flow of the blood and contribute to energy dissipation of the flow.

Increasing recognition of the importance of diastolic filling in the overall myocardial function (and dysfunction) over the past few decades among the clinicians and basic scientists has helped to shift, at least in part, the prevailing notion that the heart functions as a pressure-propulsion pump. It is a well known but underappreciated fact that the myocardium possesses a significantly higher resting tension than the skeletal muscle [56]. Its high resistance to stretch has been attributed to several distinctive features. For example, the myocytes are connected by intercalated discs consisting of structural protein titin, which together with the abovementioned supporting network of fibrous elements (endomysial and perimysial fibers), account for a unique myocardial stiffness (Fig. 13.5). In addition, the myocardial resting tension is increased due to spontaneous oscillations of sarcomere lengths by release and uptake of calcium by the sarcoplasmic reticulum [57]. Of note is the fact that contraction *and* relaxation, i.e., systole *and* diastole, are active, energy-consuming processes. The heart is thus uniquely equipped to "resist" the inflow of blood by stretch-dependent generation of passive and active tension [58]. Richly trabeculated inner walls of the heart chambers (trabeculae carneae), together with the steep angle

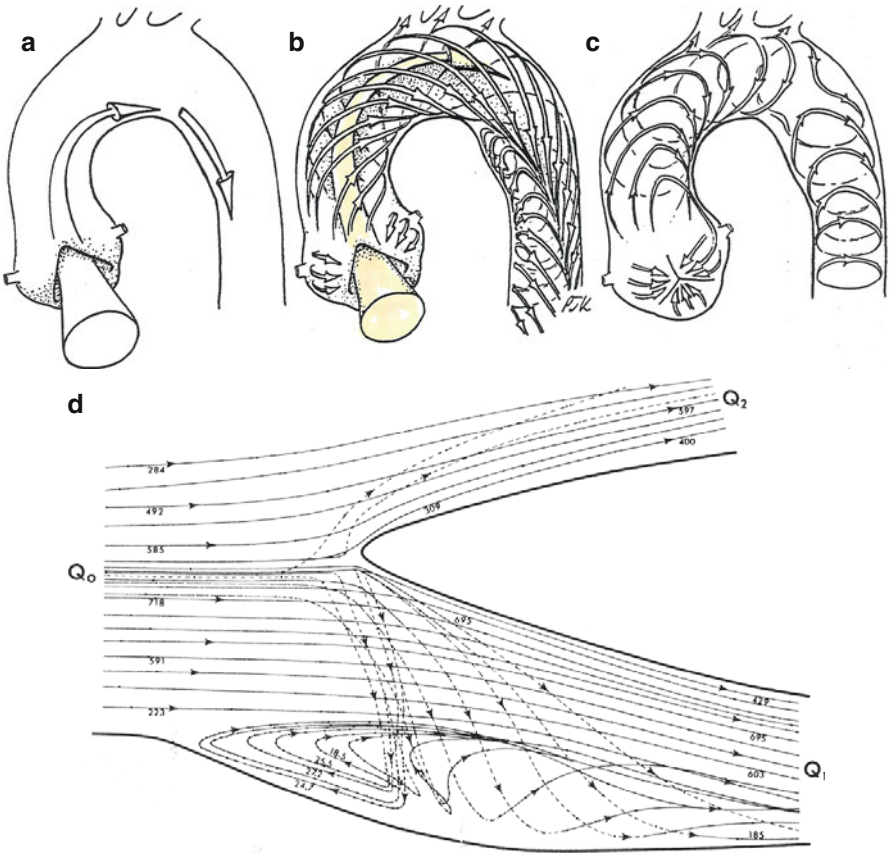

Fig. 13.8 Three-dimensional aortic flow patterns during early systole (**a**) with *arrow* showing the highest axial flow velocities, at mid-to-late systole; secondary helical flows are superimposed on axial flow (**b**) and end systole (**c**), when recirculating secondary flows persist after aortic valve closure (Reproduced from Ref. [52], used with permission of Wolters Kluwer Health). (**d**) Detailed flow patterns of particles during a steady flow through a glass model of human carotid artery bifurcation. *Solid lines* mark particle paths close to medial plane, and *dashed lines*, away from medial plane (Adapted from Ref. [55], used with permission of John Wiley and Sons)

of ventricular outflow tracts, are additional mechanical features which markedly increase frictional resistance to blood flow and support the concept that the heart is primarily an organ of impedance (Fig. 13.9).

In summary, morphological, rheological, and energetic features of the complex, three-dimensional helical structure of the heart, with a thin apex, devoid of muscular support,[3] suggest that the heart is a "poorly designed" pressure-propulsion pump – with low energetic efficiency (10–15 %; see Sect. 16.6) and ejection frac-

[3] In a novel technique of minimally invasive (i.e., without resorting to open-heart surgery and cardiopulmonary bypass) aortic valve replacement know as TAVI (transcatheter aortic valve implantation), the aortic valve is deployed into the aortic root through the heart's apex, without apparent disruption of left ventricular integrity.

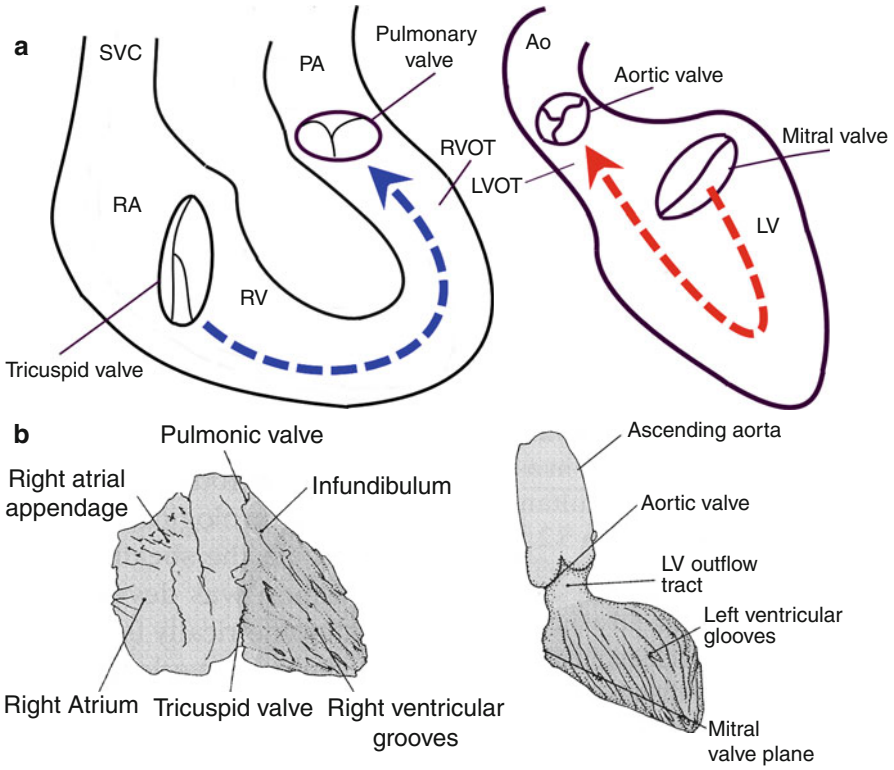

Fig. 13.9 Frontal projections of the inflow and outflow tracts of the right and left ventricles (**a**). The sinuous course of the right ventricular outflow tract is significantly longer than the left and forms an angle of about 90° with the inflow tract. The corresponding angle in the conically shaped left ventricle is more acute (about 30°). *SVC* superior vena cava, *RA* right atrium, *RV* right ventricle, *RVOT* right ventricular outflow tract, *PA* pulmonary artery, *Ao* aorta, *LVOT* left ventricular outflow tract, *LV* left ventricle. (**b**) Plaster casts of a dog's right and left ventricles (anteroposterior and right anterior-oblique views, respectively). Ventricular grooves (trabeculae carneae) increase the contact between the endocardium and the blood and, together with inflow–outflow tract angulation, markedly increase impedance to blood flow (Adapted from Ref. [43], used with permission of the People's Medical Publishing House)

tion (in the range of 50 %) – and indeed argue against the conventional appreciation of the left ventricle as a chamber that contracts and dilates for ejection and filling [44]. While the absence of normal atrial flow patterns, as is the case during atrial fibrillation, is a well-recognized risk factor for thrombus formation, the importance of normal ventricular vortical rotation of the interventricular blood, where formed and unformed elements of the blood are kept in suspension, may play a crucial role [45]. An increasing interest in intracardiac flow patterns and ventricular twist mechanics [47] has uncovered a new, hitherto unrecognized aspect of myocardial function and represents a significant step towards a better understanding of its form.

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Chapter 14
Regulation of Cardiac Output

The subject of cardiac output regulation is so important that all possible analytical ap proaches to its understanding deserve widespread support and exploration.

A. Guyton, 1979

Models are used in order to simplify a group of observable events to readily understandable concepts. Over the years numerous models of circulation have been developed in an effort to elucidate fundamental hemodynamic principles. They attest to ingenuity on the part of investigators but also point to the complexity of the subject at hand. Because the heart is the organ which is thought to provide the total hydraulic energy to the blood, the idea of the heart as a pressure-generating pump is implicit in most commonly used models. Just how much of a role the heart plays in blood propulsion and the relative contribution of the peripheral circulation in the regulation of cardiac output continues, however, to be the subject of ongoing debate [1–5]. Because of the multitude of factors which contribute to regulation of cardiac output, the subject will be approached from the two commonly used perspectives: that of the heart and of the peripheral circulation [6].

14.1 Left Ventricular View of the Circulation

An account of the historical development of ideas, which culminated in the understanding of the heart to be the primary source of blood propulsion, is beyond the scope of this monograph, and for a comprehensive review, the reader is referred to the work by T. Fuchs [7]. William Harvey, the discoverer of the circulation, sought the primary causes for the movement of the blood in the early embryonic circulation. The blood, he maintained, is "the principal portion of the body, prior to its receptacles," while the heart and vessels are "constructed for the sole purpose of its distribution" [8]. Contrary to popular opinion, Harvey did not liken the action of the heart to a pump [9, 10], but considered "vital heat" the cause of its inherent (perpetual) motion and "the prime cause" of the pulse of the heart and of the arteries.

B. Furst, *The Heart and Circulation*,
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In a letter addressed to Jean Riolan, the celebrated Parisian anatomist and adherent of Galen, Harvey suggests:

> I do not believe that the heart is the fashioner of the blood, neither do I imagine that the blood has powers, properties, motion, or heat as the gift of the heart…for I hold that the part of the pulse which is designated the diastole depends on another cause, different from the systole, and must always and everywhere precede any systole. I hold that the innate heat is the first cause of dilatation and that the primary dilatation is in the blood itself …. [11]

It appears that, for Harvey, the cause of motion is different for blood entering or leaving the heart. The atria distend (i.e., atrial diastole) under the impetus of the blood's "innate heat," whereas the ventricles are "impellers" of the blood that is already in motion "…much like a ball player can strike the ball more forcibly and further if he takes on the rebound" [12].

Harvey evidently sought a wider explanation for his newly discovered circulatory phenomena in the Aristotelian vitalistic cosmo-conception, as is apparent from the following passage: "Which motion (of the blood) we may be allowed to call circular, in the same way as Aristotle says the air and the rain emulate the circular motion of the superior bodies (planets)" or from the statement, "The heart, consequently, is the beginning of life; the sun of the microcosm, even as the sun in his turn might well be designated the heart of the world" [13].

It is ironical that Descartes, Harvey's contemporary, was one of the first natural philosophers to embrace Harvey's revolutionary circulation theory and widely promoted it, although in altered form, through his writings [14]. Unlike Harvey, known for his meticulous observations and *inductive* method of investigation, by which sense perceptible phenomena are analyzed in the light of primal (Aristotelian) principles, Descartes employs a method of a priori (*deductive*) reasoning, where scientific truths are derived from what is known "clearly and distinctly" to the intellect. Descartes' physiological and cosmological doctrines are first presented as "hypotheses" which serve as "models" of the universe and of the organism in the modern sense. The blood, for Descartes, is no longer a "vital fluid" but only a mixture of materials and a collection of special food particles which serve as fuel for the fire maintained by the heart. The concept of "vital heat" is reduced to a continuous process of combustion – a mere physical–chemical event. Mechanical analogies, if any, implied by Harvey for the explanation of circulatory phenomena become explicit and central in Descartes' writings [15]. The ultimate aim of Descartes' natural philosophy was to identify material causes and define mechanical laws that are applicable with equal measure to an organism as well as to a mechanism. In this sense, "The mechanical no longer represents an element within vital organization; through the *paradigm of the automaton*, it embraces the organism itself" (emphasis by T. Fuchs) [15].

By all accounts, Harvey "despised" the mechanical philosophy that had facilitated the success of his circulation theory and confronted Descartian and Baconian philosophers head-on by writing his most comprehensive work well over two decades after "De Motu Cordis" (1628). "On Generation of Living Creatures" (1651) contains a summary of Harvey's lifelong research efforts, "a sort of

apotheosis on the blood" [16]. In spite of his enormous efforts, Harvey and his adherents were not a match to the advent of the new mechanical–intellectual tide that swept across Europe after the 1640s, which rejected vitalist and Aristotelian principles and sought to interpret living phenomena through mechanical associations that necessarily follow from the physical laws of nature.[1]

Borelli, recognized as the father of modern biomechanics, emphasized hydraulic properties of the circulation and proposed that the heart acts like a piston ejecting blood into flexible tubes, the arteries. In a treatise "On the Movement of Animals" (1680), Borelli compared the heart's work to the skeletal muscle and calculated that the motive force exerted by the heart is equal to supporting an excess of 3,000 lb [17]. Others applied an array of mechanical contraptions to explain the circulation, for example, Johannes Bohn (1697) who stated: "What a hydraulic pump or piston achieves, the heart brings about in the living machine and the circulatory movement of all liquids. Just like the former does with water, so the latter gives the blood its first impulse by driving it forward. When the heart and pump stop, the fluids of both also stand still" (cited in [18]).

The first direct measurement of arterial pressure and estimation of minute volume by Stephen Hales in a horse and in a variety of animals in 1773 was an early attempt to quantify pressure as the principal source of blood propulsion. By the middle of the nineteenth century, more sophisticated, though still entirely mechanistic, ideas about the circulation abounded. In his treatise on hemodynamics Volkmann (1855) made the following remark:

> If we take the process of the circulation of the blood with the greatest generality, then we are dealing with the movement of the fluid through the tubes, which in a circular way, turn back onto themselves, and with the course of this movement in a certain amount of time. This task is of a purely mechanical nature; nothing prevents the assumption that the heart's pump, as a mechanical middle, is adequate to solve this task. The heart is a pump and possesses as such enough force to drive the mass of blood in a circular movement through the entire vascular system. (Cited in [18])

Understanding of the physical laws governing the flow of fluid through a system of tubes in the eighteenth and nineteenth century has been the starting point for investigation of flow-related phenomena in living systems. Poiseuille's experiments on a steady flow in the capillary tubes, in combination with Hagen's observation that flow is proportional to the fourth power of the radius, were given a theoretical formulation in the form of Hagen–Poiseuille's equation

$$\Delta P = \frac{8\mu LQ}{\pi r^4} \tag{14.1}$$

[1] It is noteworthy that over the last 50 years the traditional (positivistic) interpretation of Harvey's research has been revised by a number of scholars that have adopted more nuanced approach towards Harvey's scientific works. (See Refs. [14–16].) It appears that some of the better known Harvey biographers of the nineteenth and twentieth century regarded Harvey's "forays into cosmic philosophy as the lesser side of his genius" while seeking to present him as a rational man, whose empirical research proceeded in a logical manner towards the "great" truth, i.e., the discovery of the circulation.

where ΔP is the pressure gradient along the tube, L is the length of tube, μ is the dynamic viscosity, Q is the volume flow rate, r is the radius, d is the diameter, and π is the mathematical constant.

Although the physical conditions under which Poiseuille's law is applied are implicit in the method by which it was derived experimentally, it was nevertheless applied widely to circulation phenomena and formed the framework for the pressure-propulsion theory [19].

However, the application of Hagen–Poiseuille's lawfulness to a system of vessels requires – in addition to the knowledge of the physical properties of the (Newtonian) fluid such as viscosity and temperature – values for pressure gradient, volume flow rate, and dimension of the vessels. (Blood is a non-Newtonian fluid with viscosity three to four times that of water.) It may be conceivable to calculate the dimensions of a small capillary bed and to measure pressures at the inflow and outflow in order to experimentally derive the resistance, but such information for individual organs or for the systemic circulation does not exist. Moreover, the capillary beds are highly dynamic units where the Starling's law of the capillaries plays an active part, so only gross approximations of real-time events are available at best. Therefore, a simplified formulation of equation has been adopted from the Ohm's law in electricity:

$$\mathrm{P1} - \mathrm{P2} = Q \times \mathrm{Rp} \tag{14.2}$$

where the pressure gradient (voltage) (P1 – P2) is the difference between pressures of the left ventricle and right atrium, the flow (Q) is cardiac output (CO), and (Rp) is the fluid resistance [19]. Assuming a zero value for right atrial pressure, and if the mean aortic pressure (MAP) is taken as the average pressure generated by the left ventricle (pressure source), the equation can be rewritten as

$$\mathrm{Rp} = \mathrm{P_mAo} - \mathrm{Pra} / \mathrm{CO} \tag{14.3}$$

where Rp is peripheral resistance, $\mathrm{P_mAo}$ is mean aortic pressure, and Pra is right atrial pressure. The result is expressed either in standard physical units (dynes-s/cm^3) or in arbitrary units such as PRU (peripheral resistance units). The problem of applying the concept of resistance to biological systems has been aptly summarized by Fishman:

> The idea of resistance is unambiguous when applied to rigid tubes perfused by homogenous fluid flowing in a laminar stream…complexities are introduced when these concepts are extended to the pulmonary (as well as to systemic) circulation: the vascular bed is a non-linear, visco elastic, frequency-dependent system, perfused by a complicated non-Newtonian fluid; moreover, the flow is pulsatile, so that the inertial factors, reflected waves, pulse wave velocity, and interconversions of energy become relevant considerations…as a result of many active and passive influences which may affect the relationship between the pressure gradient and flow, the term "resistance" is bereft of its original physical meaning: instead of representing a fixed attribute of blood vessel, it has assumed physiological meaning as a product of a set of circumstances. [20] (Used by permission of the American Physiological Society)

Since flow (CO) and pressures are readily obtained by invasive (and noninvasive) methods, this formulation (Ohm's law for fluids) has found a widespread application among investigators and clinicians alike. The presence of such relationship is certainly suggested by experiments where the heart has been replaced by an artificial pump, and an increase in pump flow (output) results in increase in arterial pressure and a simultaneous decrease in central venous pressure [21–23] (See also Sect. 16.7). However, the problem arises when *a causal* relationship existing between the three variables, namely, voltage, current, and resistance, which are independently verifiable, is transposed on to a complex system of conduits comprising the circulation. Such an oversimplification can give an erroneous idea about the state of organ perfusion in various hyperdynamic circulatory states, where low values of resistance are obtained in the face of decreased organ perfusion, leading to multiple organ failure. For example, in a patient with septic shock, a decrease in arterial pressure up to 50 % of control, the vascular resistance may increase in a nonreactive bed, such as the skin, but might decrease in the brain, heart, and skeletal muscle with overall resistance unchanged. Another example is about three times increase in cardiac output during dynamic exercise in highly trained athletes, in the face of decreased peripheral resistance to one-third of its resting value, while maintaining normal or slightly decreased mean arterial pressures [24]. Since the additional energy for blood propulsion during exercise is supposedly provided by contracting muscles (skeletal muscle pump), application of Ohm's law to define global cardiovascular function is arguable [25].

It has become apparent over the years that, in fact, a far more complex relationship exists between the heart-chamber filling pressures, aortic pressure, and cardiac output as purported by LV view of the circulation. Numerous studies have failed to demonstrate significant correlation between CVP, pulmonary capillary wedge pressure (PCWP), and CO and call for a better understanding of clinical hemodynamics [26–30]. It is a little surprising that treatment modalities [30] and classification of heart failure [31] and pulmonary hypertension have undergone through so many revisions [32].

Since its inception in the 1950s, the concept of PCWP has been subject to considerable debate. Among several criteria adopted at the time for deciding whether it is a dependable measure of left atrial pressure, none was found to be consistently reliable [33]. The problems associated with clinical application of PCWP in heart failure are well known (see [31] for review) and have lost significant ground to more dynamic Doppler studies. There is little appreciation among clinicians of the fact that pulmonary venous wedge pressure (PVWP) is, in fact, slightly *higher* than pulmonary artery wedge pressure (PAWP) [34] or that the pressure gradient between the mean PA pressure and LA can be as low as 1–2 mmHg [35], raising the question whether the pressure gradient across the pulmonary circuit is the sole driving force for the blood.

Another commonly used formula by which cardiac output (CO) equals stroke volume (SV) times the heart rate (HR)

$$\mathrm{CO} = \mathrm{SV} \times \mathrm{HR} \tag{14.4}$$

is equally problematic, since it implies that that the heart is a pump coupled to a closed system of rigid tubes. Only in such a pump-limited system would a volume displaced by a pump at its outflow (aorta) be equal to what returns at the inflow into the pump (right atrium). On the surface this appears to be true, since at a steady state, the output and input volumes are closely matched for systemic as well as for pulmonary circulations. However, this equilibrium is easily upset by a variety of physiological perturbations and pathological states, suggesting a far more dynamic interaction between the heart and the peripheral circulation. For example, artificial pacing of the heart in animals [36] and humans [37, 38] at rates up to four times above baseline shows that CO remains the same or even drops. There is no change in CO even if a technique of paired electrical pacing is employed, in which a second depolarizing stimulus is delivered just after the refractory period, which markedly increases the inotropic state of the heart [39].

The trends in pharmacological therapy of acute heart failure syndromes are an eloquent example of a shift from treatment modalities in the 1960s and 1970s, which primarily support the pressure-propulsion concept of heart's action, such as the use of potent sympathomimetic amines (epinephrine, isoproterenol, and dopamine) [40, 41], to a ubiquitous use of vasodilators. In fact, the use of inotropes (dobutamine and milrinone) is currently reserved for the treatment of a minority of patients with severe systolic dysfunction who do not tolerate vasodilators due to hypotension [42]. For example, data from ADHERE registry illustrate that fewer than 3 % of acute heart failure patients (from a group of 150, 000) had a systolic BP of <90 mmHg [43], and of approximately 14 % of those who were treated with inotropes, 19 % had higher mortality compared with non-inotrope-treated patients (14 %) [44]. Accordingly, the clinical practice guidelines of the Heart Failure Society of America (HFSA), the American College of Cardiology Foundation/American Heart Association (ACCF/AHA), as well as the European Society of Cardiology (ESA) recommend the use of vasodilators and de-emphasize the use of inotropes in the management of acute heart failure syndromes [45]. It is of note that, from the range of available inotropes, dobutamine and milrinone are chosen for their significant vasodilatory effect. Of further interest is the fact that, in addition to standard treatment (diuretics, ACE inhibitors), the use of β-blockers is universally recommended in all patients with stable, mild, moderate, and severe heart failure with ischemic or nonischemic cardiomyopathies and reduced LV ejection fraction [46]. Surely, such pharmacotherapy is counterintuitive, if the heart is supposed to be a pressure-propulsion pump! According to this model, the β-blockers would further weaken the failing heart (pump) and the vasodilators decrease the pressure head needed by the pump in order to drive the blood around the circuit.

Ever since the introduction into clinical practice by Kantrowitz and colleagues in 1968, the intra-aortic balloon pumps (IABP) have been widely used in patients with myocardial infarction complicated by cardiogenic shock with the goal of improving coronary perfusion by afterload reduction, with concomitant increase in CO and perfusion to vital organs [47]. The purported hemodynamic effect of IABP's was evidently based on the "heart as a pump model," and over the years the insertion of IABP's has become a standard of care (class I recommendation), in spite of several outcomes studies showing their limited effectiveness [48]. It is hardly surprising

that recently published results of IABP-SHOCK II trial found no difference in 30-day mortality or hemodynamic improvement in patients in cardiogenic shock and early revascularization procedure, with or without the IABP [49]. In the editorial accompanying this landmark study, O'Connor and Rogers question continued use of the IAPB and call for "development of novel and innovative strategies to treat this condition." They further note that "The results of IABP-SHOCK II trial parallel those from many recent outcome trials that have challenged our understanding of the management of acute and chronic heart failure, including those regarding the use of pulmonary artery catheters and the role of revascularization in ischemic cardiomyopathy" [48].

14.2 Regulation of Cardiac Output by the Periphery

Since venous return model is based on the concept of mean circulatory pressure (MCP), it would serve us well to take a short detour and examine its development. As is often the case, the original idea was not conceived out of research on the circulation but from a related field. In the early part of the nineteenth century, brothers Ernst Heinrich Weber, a physiologist, and Wilhelm Eduard Weber, a noted physicist, investigated the rate of wave propagation in distensible tubes [50]. In order to better represent the behavior of blood vessels, E. H. Weber constructed a model in which two segments of ileum, with an intact ileocecal valve, were sown together on one end to serve as unidirectional valves of the heart. The opposite ends of the gut were joined over a glass tube (which prevented propagation of fluid waves from arterial to venous compartments) occluded with a sponge that was used to simulate a bank of capillaries [51] (Fig. 14.1). The system was filled with water and when rhythmically squeezed at the level of the "heart," a pulsatile flow was observed in the limb of the circuit before the glass segment. When the rate of pumping increased, the water moved progressively into the "arterial" compartment, but the flow was limited by collapse of the gut on the "venous" side. Weber carefully measured luminal pressures at different segments of the circuit during no-flow state, when the pressures equilibrated and called it the "mean hydrostatic pressure". The pressures during pumping were designated as "hydrokinetic". To his surprise, the mean pressure during intermittent contractions was the *same* as during no-flow state. The only way to increase the hydrostatic and hydrokinetic pressures was to add more fluid to the system. The mean pressure, concluded Weber, does not depend on the action of the heart, but on the amount of fluid in the model.

Several decades later Bayliss and Starling were investigating the role of microcirculation in the genesis of peripheral edema in heart failure at the time when, in their view, undue importance was given to the heart and to the arterial pressure in the overall control of cardiac output [53]. To support their hypothesis, they experimented on a series of dogs in which the autonomic reflexes were abolished by high spinal cord transaction and the action of the heart was excluded by opening of the chest, leading to asphyxia and cardiac arrest. The effect of various circulatory interventions was then tested, such as intravenous infusion of saline or blood and

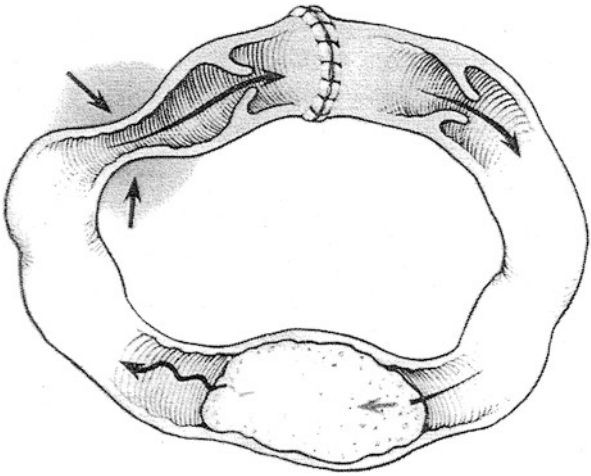


Fig. 14.1 Weber's circulation model. Two ends of the gut with intact valves are sewn together to simulate heart valves. The sponge represents the microcirculation. Compression of the gut (*arrows*) causes water to flow in one direction. Pressures at different points of the circuit are measured at rest (hydrostatic mean pressure) and during pumping (hydrokinetic mean pressure) (Reproduced from Ref. [52], used with permission of Springer)

occlusion of the aorta, inferior vena cava, or of the portal vein. They introduced a novel technique of *simultaneous* measurements of pressure in the limb artery and at different points in the venous system [54]. Judging by the opening paragraph of their paper, Bayliss and Starling left no doubt that a significant insight into the riddle of the circulation had been had:

> The experimental results which we wish to bring forward are largely such as might be predicted by anyone with a knowledge of elementary principles of circulation. Our justification in bringing them forward however is that they have not been so predicted, and it was only after obtaining the results that we asked ourselves why they had not occurred to us before. In fact they seem to form part of a forgotten or disregarded chapter in the physiology of the circulation, although they are of great importance for the question of pressure in the capillaries of the abdominal organs and therefore of the physiological processes of secretion and transudation which take place in these organs. [54]

In the Theoretical Considerations of their paper, Bayliss and Starling stated that the "forgotten chapter" in physiology is, in fact, Weber's work "whose experimentation is confirmed by the whole of our observations." They reproduced the diagram of Weber's model and quoted his conclusions as the summary of their own work, namely:

> We see on the simplified model of the circulation that the pump (the heart) cannot increase the mean pressure exerted on the walls of the system of the tubes by the fluid contained within them. It can in fact only give rise to unequal distribution of the pressure, by diminishing the pressure in the veins by pumping fluid out of them and increasing the pressure in the arteries to a corresponding extent by pumping the fluid into them. The mean pressure of the fluid in this model can only be increased by distending the tubes to a larger extent by the injection of more fluid into them. [54]

Starling went on to refine the concept of the mean systemic pressure by further experimentation and delivered a series of lectures on heart failure in 1897, where he proposed that "Somewhere in the circulation there must be a point where the pressure is neither raised nor lowered and where, therefore, the pressure is independent of cardiac activity" [53]. The location of this point would be of great significance in

the genesis of heart failure; should it be located in arterioles (upstream of the capillaries), the capillary pressure would *rise* and the filtration of fluid into interstitium would increase. If, on the other hand, the point was in the veins (downstream of the capillaries), the pressure would *fall*, as the (left) heart failed. This occurs, reasoned Starling, due to resistance in the vessels which incurs a loss of energy of the flowing blood, as dictated by the law of conservation of energy. In the capillaries with a large total cross section, the flow is very slow, but the pressure is relatively large. In the veins, on the other hand, the flow velocity is greater but occurs at a lower pressure. "It thus follows," concluded Starling, " that the neutral point in the vascular system, where the mean systemic pressure is neither raised nor lowered by the inauguration of the circulation, lies considerably on the venous side of the capillaries – at any rate, in most parts of the body" [53]. Starling stressed the importance of mean systemic pressure (MSP) and, in turn, of venous circulation on CO by experimenting on a mammalian heart–lung preparation. Together with the "law of the heart," the concept of MSP became an essential component of the pressure-propulsion model of circulation [55].

The significance of mean circulatory pressure was reexamined by Starr and Rawson who constructed a mechanical model of circulation in order to simulate various forms of heart failure. The model predicted that an increase in MSP (termed "static pressure" in their study) was brought on as a compensatory mechanism in congestive heart failure, and not as a result of it [56]. To verify the theory, Starr performed direct measurements of "dead pressure" on "recently deceased patients" suffering with congestive heart failure (CHF) and concluded that "systemic venous congestion of the congestive heart failure is not fully explained as the direct mechanical consequence of weakness of either right or the whole heart." Clearly, other factors such as the hypothetical "static pressure" play an important role [57].

14.3 Guyton's Venous Return Model

The model conceived by Weber and Starling was fully developed by Guyton and his coworkers, who systematically investigated the importance of peripheral circulation in the control of cardiac output. The sheer volume of their work, spanning over several decades, has shaped the basic understanding of cardiovascular physiology for generations of students as well as clinicians.

The starting point for Guyton's work was the familiar cardiac function curves, first generated by Frank on isolated frog heart in 1895 and later by Patterson and Starling on the mammalian heart–lung preparation [58] (Fig. 14.2). While cardiac function curves represented the ability of the heart to eject the blood at various values of right atrial pressure, they only poorly reflected the function of the peripheral circulation. To complete the picture, a method was sought by Guyton and his collaborators which would characterize the *systemic* circulation in terms blood returning to the heart. In order to achieve such measurements under controlled conditions, it was necessary to "break" the continuity of the vascular loop and use a mechanical pump in place of the heart. The first venous return curves were obtained on "recently

dead" dogs [59] in which the vasomotor reflexes were abolished by total spinal anesthesia and the arterial pressure was supported by infusion of epinephrine [60]. A number of experiments were run to study the response of venous circulation at different levels of right atrial pressure (RAP) which was controlled by varying the height of collapsible tubing (Starling resistor) inserted between the right atrium and the bypass pump, replacing the right ventricle [59–61]. Guyton plotted the results in the form of the well-known "venous return curves" which show the dependence of venous return (pump flow) on right atrial pressure (Fig. 14.3). It is evident from Guyton's graphic analyses that as the RAP decreases, venous return increases. Further decrease in atrial pressure (brought about by an increase in pump-flow rate) would result in leveling off the flow at a certain maximal rate due to *collapse* of the great veins. Elevation of the RAP, on the other hand, results in a rapid decrease in venous return, approaching zero value when the pressure reaches about 7 mmHg. The zero-flow pressure is equivalent to MCP. It should be noted parenthetically that elevation of right atrial pressure to levels by which venous return fall to near zero

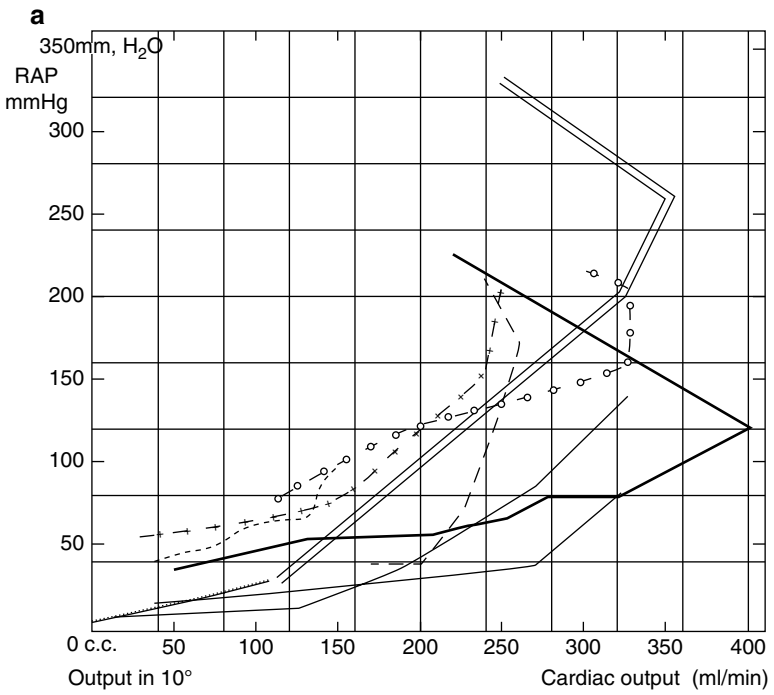
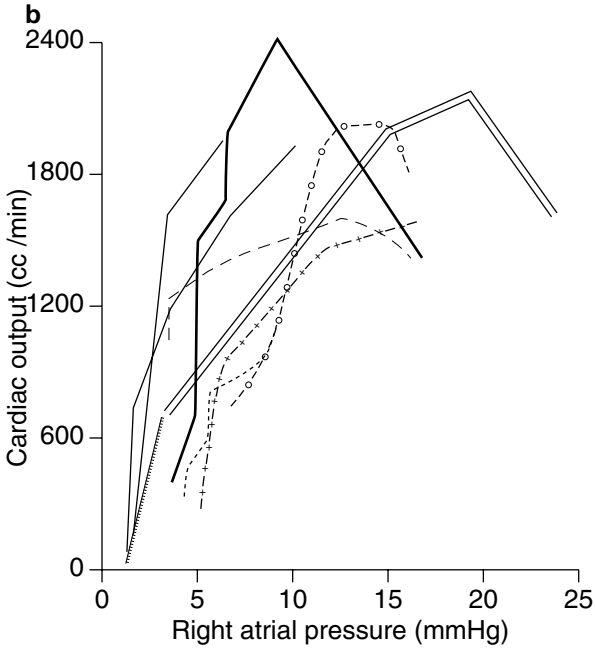


Fig. 14.2 Patterson and Starling's original experiment on the isolated dog heart–lung preparation. (**a**) A group of cardiac output curves was obtained in nine experiments by changing the height of venous reservoir, i.e., pressure, above the level of the heart. An increase in inflow into the heart (recorded as cardiac output on *X*-axis) results in rise in right atrial pressure (*RAP*) (Reproduced from Ref. [58]). (**b**) Cardiac function plotted as a function of right atrial pressure. Note that the original axes of Patterson and Starling's illustration have been reversed in this reconstruction by Guyton and coworkers to show cardiac output as a *function* of right atrial pressure (Reproduced from Ref. [62], used with permission of Elsevier)

Fig. 14.2 (continued)



(intersect on the abscissa) for more than a few seconds proved "extremely traumatic to the preparation," evidently due to overstretching of the right ventricle beyond its optimal working point, resulting in its failure [60]. It was demonstrated in these experiments that the right atrial pressure essentially presents an *impedance* to blood returning from the systemic circulation, i.e., to venous return.

The concepts of right atrial pressure and of the MSP are at the core of Guyton's "venous return" model of circulation [6]. In place of MSP used by previous investigators, Guyton introduced the term mean circulatory filling pressure (MCFP) and defined it as the equilibrated pressure generated by elastic recoil in the *entire* circulation, i.e., of the systemic and pulmonary circuits, during no-flow state. In his work, Guyton carefully distinguished between the mean pulmonary, systemic, and circulatory (systemic and pulmonary combined) filling pressures, noting that the latter two are virtually identical (around 7 mmHg), with the mean pulmonary pressure being slightly lower (about 5 mmHg).

A dog model was devised in which – unlike in previous models, where due to irreversible trauma, the animal expired after a single measurement – repeated measurements on anesthetized animals could be performed. The difficulties in obtaining reproducible results of these measurements are well documented [63]. Accurate measurement of MCFP is compounded by the fact that after 7 s of cardiac arrest (either by electrical fibrillation or vagal stimulation), an intense vasoconstriction ensues in an animal (dog) with intact autonomic reflexes, which results in progressive rise in MCFP, only to level out in the course of 15 min. Consequently, the measurement has to be executed within the first few seconds of cardiac arrest (between 2 and 7 s) (Fig. 14.4) upon which the heart can be defibrillated and the

measurement repeated. To facilitate rapid equilibration between the arterial and venous limbs of the circuit, blood is transferred by means of a mechanical pump from a large artery into a central vein after the onset of cardiac fibrillation. In addition to animals with intact autonomic reflexes, numerous experiments were carried out on dogs subjected to total spinal anesthesia, in which arterial pressure was maintained with controlled infusion of epinephrine. By combining venous return and cardiac function curves on a single graph, the "equilibrium point" between the functions of the heart and the systemic circulation can be represented for each value of RAP, making it possible to visualize the cumulative changes in both, with a caveat, however, that one of the functions is plotted *backward* [23, 64] (Fig. 14.5).

As mentioned, the formula for cardiac output (Eq. 14.3) offers little insight into overall control of the circulatory function, because a change in one factor brings about changes in the other two. The situation is compounded when, in addition to systemic, the pulmonary circulation is considered. A formulation was therefore

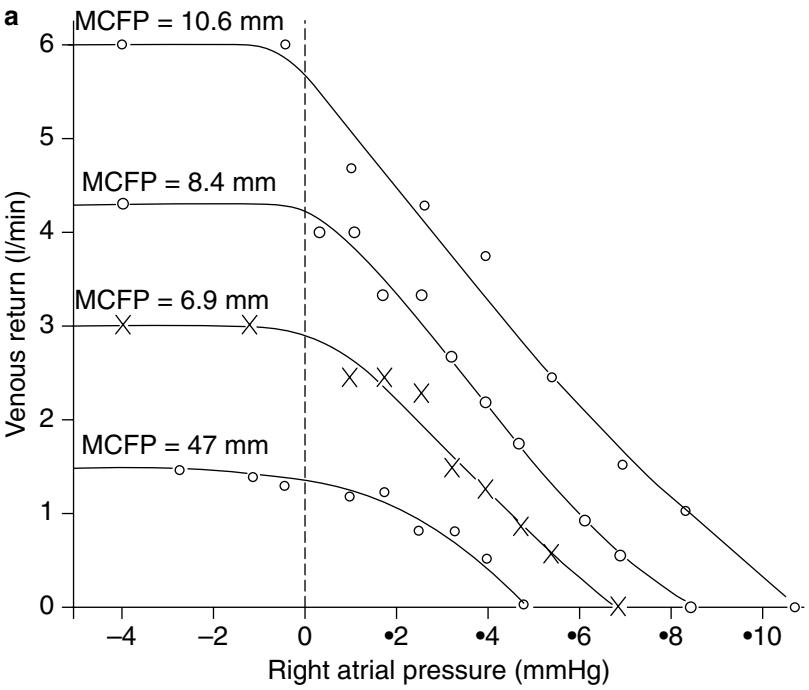
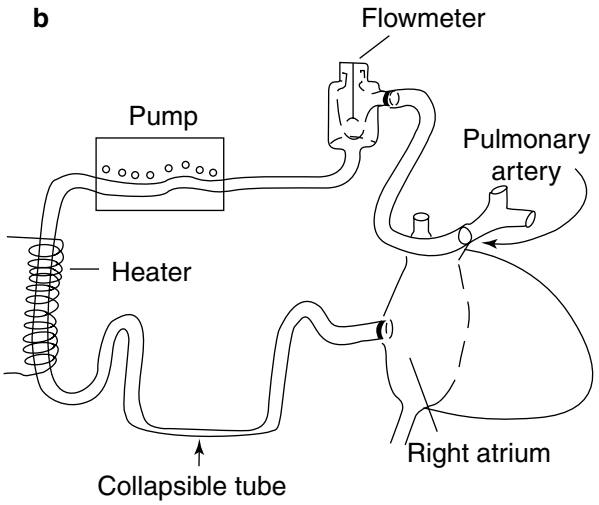


Fig. 14.3 (**a**) Venous return curves obtained in "recently dead dogs" with circulation supported by a perfusion pump. Each curve represents venous return as a function of mean circulatory filling pressure (MCFP). Note that venous return drops to zero when right atrial pressure equals the MCFP (Reproduced from Ref. [59], used with permission of the American Physiological Society). (**b**) Schematic diagram of right heart bypass circuit of the type used by Guyton and coworkers for measurement of venous return/cardiac output on dogs. Blood returning from systemic circulation passes through collapsible tube (Starling resistor). The height of the tube determines the back pressure, i.e., right atrial pressure, controlling venous return (Reproduced from Ref. [62], used with permission of Elsevier)

Fig. 14.3 (continued)



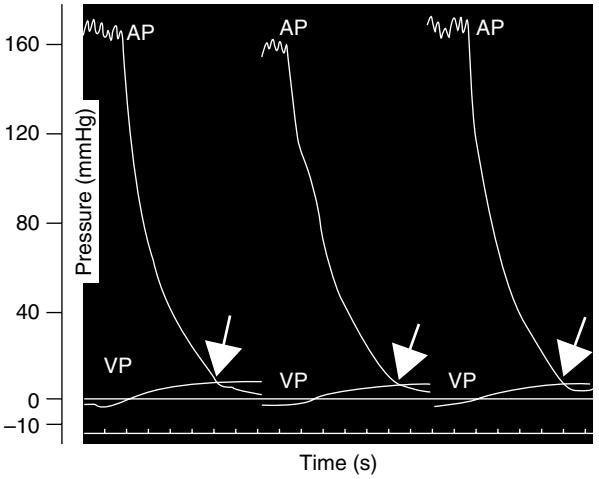


Fig. 14.4 Repeated measurements of mean circulatory filling pressure in a dog. See text for explanation (Reproduced from Ref. [62], used with permission of Elsevier)

sought by Guyton and his coworkers that would explain the regulation of cardiac output in term of parameters "which are entirely independent of each other" [6].

In his mathematical model, Guyton took the difference between MSFP and right atrial pressure (RAP) to be the driving force for venous return (VR)

$$\text{MSFP} - \text{RAP} = \text{VR} \times \text{Rv} \tag{14.5}$$

where Rv is resistance to venous return. Cardiac output at steady state can now be expressed as a relationship between the gradient for venous return and the resistance to venous return [6]:

$$\text{CO} = \text{MSFP} - \text{RAP} / \text{Rv} \tag{14.6}$$

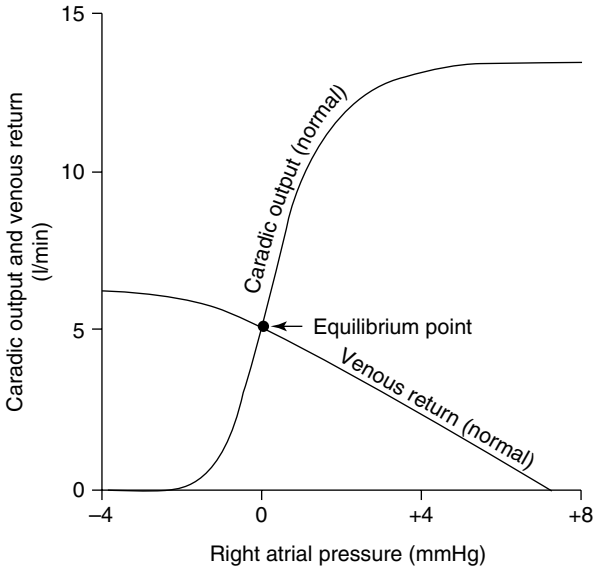


Fig. 14.5 Combined plot of cardiac output and venous return as a function of right atrial pressure (RAP). The curves intersect at the "equilibrium point." Such representation implies that one of the functions is necessarily plotted backward. See text for explanation (Reproduced from Ref. [62], used with permission of Elsevier)

Thus, in agreement with the graphic analysis, any increase in RAP would proportionally impede venous return and bring it to a halt when equal to MCFP (Fig. 14.3).

If the "venous return theory" was to stand on its own, it needed to be tested also in respect to left ventricular function. Guyton assessed this by arterial injection of glass beads of 250 μm in diameter which would progressively occlude arterioles in the same diameter range [59]. In spite of marked increase in peripheral resistance (in the range of 2.6 times the baseline), venous return decreased only by 10 %. This was the range which was predicted from mathematical and computer models [6, 59, 61]. Thus, Guyton was satisfied that his venous return/right atrial pressure formulation of control of cardiac output was, within limits, also independent of arterial pressure.

During early days of his research, Guyton maintained that the multiplicity of factors which control MCFP are beyond our understanding [6]. However, in his later years he believed that metabolic demands of the tissues are the ultimate regulator of blood flow and tissue perfusion which, in turn, regulate the level of MCFP [65].

The venous return model was elaborated further by Permutt and Caldini who recognized the pivotal role played by the right atrial pressure (RAP) in control of cardiac output; however, in their analysis, the model does not adequately address the range of cardiac outputs which can occur at the same RAP [66] (reviewed by Sylvester et al. [67] and Jacobsohn et al. [52]). They proposed a circulation model based on a well-recognized flow–volume relationship in pulmonary physiology, where the maximum flow of mid-expiration is effort independent but highly dependent on lung volume. The analogy is drawn here between the driving pressure for expired air, determined by the elastic recoil of the lung and the elastic energy stored in the vasculature, as represented by the MCFP. The general shape of the venous

return curves do in fact resemble forced expiratory (FEV) volume curves at different lung volumes. In their mathematical analysis Permutt and Caldini further invoke the familiar fluid-mechanical principle employed by Starling, namely, that "There is a locus in systemic circulation where the pressure is equal to the static pressure and that the resistance between this locus and the heart depends only on the properties of the blood vessels and not on the flow are points of great importance in the regulation of cardiac output. The significance is this: for a given volume and set of resistive and elastic properties of the systemic circulation, the only way the heart can increase the systemic blood flow is by lowering the right atrial pressure…which has the same effect as lowering of tracheal pressure has on expiratory flow from the lungs" [68].

According to this view, the heart plays a *dual* role in the sense that on the arterial side, it pumps the blood into elastic container to keep its volume constant, even though it is continuously draining. However, "the heart cannot cause the container to drain more quickly that it would spontaneously." While for the inflow (venous) side, say Permutt and Caldini, "it is ironic that at constant systemic volume, other than transferring the venous drainage back to the systemic circulation, the heart can do nothing more than impede venous return in proportion to how high a filling pressure the right heart requires to transfer blood" [68]. (Used by permission of The MIT Press)

Permutt and Caldini relate convincing account of the phenomenon of "autonomous" venous return from their laboratory work on pulmonary diffusing capacity in a dog model [68]. In order to regulate the amount of flow through the lung, the right heart was bypassed by connecting the right atrium to the inflow of the roller pump and the pulmonary artery to the outflow, with the flowmeter interposed (c.f. Fig 14.3b). Initially, the pump speed was set to match venous runoff into the atrium. In order to increase the flow, the speed of the pump was increased; however, the right atrium began to collapse, thus failing to increase the venous flow. To circumvent "the problem" a wire frame was then inserted into the RA to prevent its collapse. This intervention resulted in a further collapse of the great veins in the thorax. Finally, they inserted two large metal tubes into the venae cavae and attached them directly to the pump, but, to their surprise, they were still unable to obtain an increase in flows. Even simultaneous bypassing of the *left* heart could not increase existing flow above the baseline [68].

It is indisputable that the negative pressure of the intact thoracic cavity significantly improves venous drainage (and cardiac output) through venous distention; however, it would be erroneous to think that more blood could return to the heart by applying additional suction. The constraints of replacing the heart by a mechanical pump are readily apparent during any routine cardiac bypass surgical procedure, where any increase in pump flow is limited by the rate of venous return. If, on the other hand, an additional volume of blood is pumped into the aorta from the primed reservoir, one soon ends up with an over-pressurized arterial compartment, with little or no increase in CO.

Over the past couple of decades, several reports of measurement of MCFP on intact circulation in experimental animals and patients appeared in critical care

literature. Maas and colleagues employed the technique of inspiratory-hold maneuvers in ventilated patients by which the central venous pressure is temporarily increased. Assuming that cardiac output equals venous return, values for MCFP were extrapolated by linear regression from the slope of venous return (cardiac output)/CVP plots. It is of interest that the linearity of their curves did confirm Guyton's graphic analysis obtained in animal experiments where MCFP equals CO of zero (cf. Fig. 14.2a); however, their estimated values of MCFP were in the range of 18 mmHg which are considerably higher than previous estimates of around 7 mmHg [69]. The inspiratory pause method of estimation of MCFP has also been used in dogs [70] and pigs [71, 72] confirming the linearity of Guyton's venous return curves under various circulatory perturbations. Schipke and coworkers measured systemic filling pressures on patients undergoing ICD (implantable cardiac defibrillator) placement in which artificially induced ventricular fibrillation episodes were induced lasting up to 20 s. Despite a precipitous drop in mean arterial pressures from 77.5 (±33.4) to 24 (±5.3) mmHg and a gradual rise in mean central venous pressure from 7.5 (±5.2) to 11 (±5.4) mmHg, the pressures failed to equilibrate. Estimation of time constants (2.9 and 3.6 s for arterial and venous pressures, respectively) from pressure decay curves indicated that their observation window was sufficiently long to accommodate for further significant changes (longer than five time constants). The persistent pressure difference was ascribed to vascular waterfalls (Starling resistors) within the microcirculation [73].

14.4 Critique of the Venous Return Model

In spite of the widespread acceptance of Guyton's circulation model, several criticisms have appeared in the literature over the years. (For review, see [74].) Levy repeated Guyton's right heart bypass experiment [60] but excluded collapsible tubing between the right heart and the right atrium [23]. The pump rate (flow output) was altered (manually) and therefore represented the dependent variable in the system. Unlike in Guyton's experiments, a reverse relationship was found between right atrial pressure and pump flow. Levy pointed out to liberal use of dependent (venous return, cardiac output) and independent variables (right atrial pressure) in Guyton's graphic analysis of circulation. Namely, when representing the effects of cardiac and vascular functions in a single graph, one of the functions is necessarily plotted *backward*, thus blurring the relationship between the cause and effect (Fig. 14.5). Such switching, according to Levy, amounts to "circular reasoning," in which cause and effect are reversed, which is to say that the periphery, rather than the heart, is the source of blood propulsion, thus making the model into a "mathematical abstraction." Levy further proposed that the "venous return" concept be dropped in favor of "vascular function" [23]. In the comments section of Levy's paper, of which Guyton was the reviewer, Guyton explained that he was aware of

the inconsistencies and proposed that "in the actual circulation, neither of the two theoretical assumptions for independence holds true. Indeed, both the cardiac output and the systemic venous pressure are dependent variables" [75].

Careful examination of Guyton's method indeed reveals that venous return was set by a pump at different levels of *steady* flow at which the right atrial pressures were measured [60]. The graphs were then drawn with venous return as dependent variable (abscissa) and the right atrial pressure as independent variable, conveying the impression that the right atrial pressure determined venous return, rather than the flow of the bypass pump [64, 76] (Fig. 14.5). Similarly, Brengelmann has argued that the right atrial pressure, as the determinant of venous return (MSP-Pra/Rv concept) in the single-circuit circulation model of Guyton, gives the erroneous impression that the stored elastic energy of the vasculature (MCFP) propels the blood, rather than the pump, i.e., the heart [3, 77]. Upon stopping the heart (the power source) the blood volume can only passively distribute itself through various (elastic) segments of the vascular compartment and the pressure gradient (MSP-Pra) has a real meaning only at zero flow [78].

Of note is the fact that the value of CO at any instant is a dynamic equilibrium between the action of the heart and of the peripheral circulation which occurs *in time*. By taking into account the steady-state flows and pressures as is implicit in Guyton's analysis, the time-dependent factors are negated and the model collapses into its generic form, i.e., of the electrical analogue of Ohm's law, where the steady-state rate of energy output comes from the power source (the heart).

Reddi and Carpenter raised further objections that, unlike in the arterial circulation, where a well-defined error signal exists in the form of arterial pressure and its regulation, Guyton's model of venous return lacks this essential requirement, making it "imprecise and intangible, a frequent cause of confusion that may lead to errors of clinical practice." In its place they propose a new variable of "venous excess" which represents the accumulation of any mismatch between the blood entering the great veins and their rate of emptying, i.e., the cardiac output. The former is apparent clinically by the adequacy of perfusion or measured as CO, while the latter is directly observable on the patient's jugular veins or measured as CVP [76]. And finally, Beard and Feigl maintain that, in addition to the abovementioned omissions, a key variable is missing from Guyton's analysis of circulation, namely, that with increase in flow in the systemic circulation, the right atrial pressure falls because of the shift in blood from the venous to arterial capacitance vessels [79]. By all accounts, we have gone "full circle" and arrived back to Weber, Bayliss, and Starling, the originators of the theory.

In summary, it is possible to conclude that the LV and VR views differ more in semantics than in content, since both trace the source of blood propulsion back to the heart. Their conceptual and mathematical proof draws on the hydrodynamic equivalent of Ohm's law where the power source is clearly determined. Mathematical equations used in support of the model are purely relational, where no causality is implied and as such (probably) do not reflect the reality. The LV view purports that the pressure gradient between the mean aortic pressure and the right atrium, is

the source of blood propulsion and thus the major determinant of cardiac output. The model further assumes that the volume of the systemic circulation remains constant and the MCFP is a transient (hypothetical) pressure which will change with the change in cardiac output [79]. The venous return view, on the other hand, claims that the gradient between MCFP and the right atrium is the main determinant of flow and, therefore, of cardiac output. In spite of methodological [64] and "mechanistic" inconsistencies [79] leveled at VR model, the significance of Guyton's work for advancement of cardiovascular physiology cannot be overestimated. It promoted the importance of the peripheral circulation between the 1950s and 1980s when it was obscured by the brilliant advances in the field of extracorporeal circulation and open-heart surgery, during the era when, in the words of Gerhard Brecher, "the knowledge of the pumping action of the heart has made it possible to bypass the 'heart as a pump' with a 'pump as a heart".[2]

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[2] Personal note to C. Wiggers, book inscription, photocopy with the author.

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Chapter 15
Circulatory and Respiratory Functions of the Blood

The actual life is in the blood vessels, towards the periphery. They are the system of conduits and the heart is the point that determines the direction.

W. Goethe

The mean circulatory pressure (MCP) is a dynamic measurement which can be extrapolated from the rate of rise in venous pressure when the activity of the heart is suddenly stopped and the pressure is equilibrated from the aorta to the right atrium. As mentioned, an accurate measurement of MCP is difficult to obtain in laboratory animals because of numerous compensatory mechanisms that are elicited at the time of induced cardiac arrest. (For review, see [1].) The question naturally arises: to what extent is such a radical intervention representative of the actual events at the level of the microcirculation, accounting for the fact that the distribution of flow is tightly bound to metabolic demands of the tissues and/or individual organs? The only substitute for such "flow averaging" is to examine the actual phenomenon itself, i.e., the capillary flow at this critical juncture in the life of the experimental animal or the human subject. (As discussed in Chap. 21, the methods for direct observation of the microvascular beds during normal conditions as well as in critical illness exist and have provided valuable new insights into microvascular dynamics.) However, such information will not able to give us an answer about the actual conditions, unless we are acquainted with the true nature of underlying phenomenon. We will now examine two separate groups of "near-death" circulatory phenomena: the first pertaining to venous and the latter to arterial circulations. Please note that in this context the term "venous circulation" encompasses the entire compartment occupied by the venous blood including the pulmonary vasculature. By analogy, the "arterial" compartment occupies the rest of the circuit containing the arterial blood.

15.1 Phenomenon of Vestigial Circulation

As mentioned, early attempts to acquire measurements of "static pressure" were carried out on "recently dead dogs" [2–4] and "recently deceased" patients, by a method of transthoracic cardiac puncture, as described by Starr [5]. Nevertheless, it is evident from Starr's paper, that more was afoot than expected, when he comments that:

B. Furst, *The Heart and Circulation*,
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"Occasionally small rhythmic fluctuations in the static blood pressure made one wonder if all vital activity had ceased. Similar fluctuations were seen in the animal experiments. In a number of instances I attempted to demonstrate a persistence of vascular activity in the patients by injecting histamine and adrenalin into the skin. There was no visible response in any case" [5]. Similarly, Guyton in one of his early papers submits that: "The mean circulatory filling pressure as it exists in the body at any given instant cannot possibly be measured because life is dependent on dynamic circulatory conditions" [2]. Despite of the obvious ingenuity of the Guyton's technique for repeated measurements of MCP in dogs by which a rapid equilibration of volumes (and pressures) is possible, there is a problem. The experiment was evidently designed to support the concept of MCP in the venous return model and, as such, did not take into account the more subtle phenomenology that accompanied it.[1]

In the 1940s Thompson investigated the possible beneficial effect of negative pressure during the expiratory phase of mechanical ventilation in a dog model. Anesthetized, intubated, and heparinized dogs were asphyxiated by clamping of the endotracheal tube, resulting in demise by asphyxia in 8–10 min. Thirty minutes after the cardiac arrest, mechanical ventilation and oxygenation was resumed and continued for 1 h. To assess the residual movement of the blood, if any, tracer substances (radioactive sodium and fluorescein) were injected and sampled at predetermined intervals, and hemoglobin oxygen saturation was measured. The results showed a gradual rise in arterial oxygen saturation up to normal levels, signifying a continuous movement of blood though the pulmonary and systemic circulations. Concentrations of dye and radioactivity were measured in various organs and reported – confirming their distribution according to perfusion – but no quantitative data on blood flow was given. Non-heparinized, non-ventilated controls were also run, in which no significant movement of substances was detected, possibly due to blood clotting. Thompson concluded that mechanical ventilation as such (without the action of the heart) is the cause of significant residual circulation, which is enhanced by introducing of a negative expiratory phase during mechanical ventilation [6].

These experiments were repeated in the 1960s by Manteuffel-Szoege and coworkers on three groups of dogs. Oxygen saturation in arterial and venous bloods was measured as an indicator of blood's movement. In the first group, where mechanical ventilation was resumed 30 min after hypoxic cardiac arrest, the arterial O_2 saturation levels reached 100 %. An estimation of blood circulation time gave the values in the range of 5–8 min (dye dilution technique), which is some 20–30 times longer than in normal controls. The estimated circulating blood volume in 6 of 13 dogs showed values of 105–962 ml. In the second group, oxygen was insufflated (*without* mechanical ventilation) via the endotracheal tube 10–15 min. after cessation of the heartbeat. The arterial oxygen saturations increased from a baseline of 20–30 to 85 %. In the third group, neither ventilation nor insufflation of oxygen was given. In these dogs the dye injected intravenously was not recovered in the

[1] Distension of the right heart can be readily observed in patients after failed cardiopulmonary resuscitation with the aid of transesophageal echo probe, suggesting that the blood continues to move against the pressure gradient for a considerable time after cardiac arrest.

arteries; however, observation of the omental vessels confirmed blood movement lasting up to 2 h [7, 8].

Manteuffel-Szoege performed further experiments on anesthetized and curarized dogs with an open chest in which aorta and both venae cavae and aorta were cross-clamped simultaneously for over 2 h. A "*pressure reversal*" was observed in which the brachial artery pressure dropped to zero and the caval pressure rose to 13 mmHg. While the blood continued to flow in the normal direction, it flowed *against* the pressure gradient. The peculiar phenomenon of "*pressure reversal*" was also observed by Manteuffel-Szoege on patients during open-heart surgery in moderate and deep hypothermia and also in dogs [9, 10]. A number of further experiments were performed on dogs in deep hypothermic circulatory arrest (core temperature 10 °C). After the extracorporeal circulation was stopped and both venae cavae and the aorta were occluded, the blood continued to flow in the small arteries and capillaries of the omentum for 15–30 min, whereas flow in the veins soon came to a halt. No vasomotor activity was observed due to deep hypothermia. The phenomenon of "pressure reversal" has also been demonstrated, but not recognized as such in the pulmonary circulation [11].

Manteuffel-Szoege maintained that the phenomena of pressure reversal (in larger vessels) and continuation of flow in the normal direction (but *against* the pressure gradient) at the level of the microcirculation suggest that the blood has its "*own motor energy*," which persists for some time in spite of increased viscosity and "sludging" of blood at low temperatures. He proposed that this motive energy is "inseparably connected with thermal conditions of the animal" [12, 13]. The phenomenon of vestigial circulation was further demonstrated by excising a portion of the omentum of a dog in which "intensive blood movement could be observed for 2–3 minutes and slower movement up to 10 min. after the excision." Rapid removal of parenchymal organs such as hearts and kidneys from dogs demonstrated bleeding (up to several minutes) from the veins and *gaping empty arteries*. In an excised liver, the blood flowed from hepatic veins while the portal vein was empty [7]. On the basis of those and additional experiments on the chick embryo (mentioned in Chap. 8), Manteuffel-Szoege suggested that the movement of blood against the pressure gradient lends further support to the fact that the blood possesses its "own kinetic energy." The vestigial movement is further demonstrated by congestion of the great veins and distension of the heart after circulatory arrest as seen in an asphyxiated, open-chest dog and clinically as distension of neck veins in patients dying of cardiac arrest [9].

Additional evidence for vestigial movement of blood after clinical death comes from forensic pathology where uneven distribution of blood within individual organs has been documented. For instance, the distribution of blood in the kidneys of victims dying suddenly from electric shock shows a tendency for the blood to collect in the venous system. Similarly, in the victims of acute hemorrhage, the renal arteries and capillaries are empty, while renal cortical veins and venae rectae (of the medulla) are filled with blood [14].

The fact that arteries are free of blood after death, unlike veins, was already known by the ancient Greeks. In an 1850s review on the causes of emptiness of the arteries

after death, London pathologist Thudichum noted that "I, for my own part, never met with any blood in any artery in several hundred dissections, in the five years during which my attention has been directed to the subject" [15]. Even though the importance of this seemingly trivial observation seems to have fallen by the wayside in more recent times, it continues to make its appearance under different guises and has been difficult to ignore. For example, it is generally known by the forensic toxicologists that significant distribution of substances (drugs) occurs postmortem. Ample evidence exists that concentration of drugs in the central circulation can be several times greater than in the peripheral circulation [16]. Animal models show that significant distribution of drugs occurs up to 24 h postmortem [17]. Although the uneven distribution is ascribed to diffusion, this would clearly have to occur *against* the concentration gradients. Thus, the unrecognized existence of vestigial circulation presents an ongoing dilemma in human toxicology, expressed by one of the authors as: "We conclude that this poorly studied phenomenon creates major difficulties in interpretation and undermines the reference values in the data bases where the site of origin of post-mortem blood samples is unknown" (Pounder and Jones [18]).

The phenomenon of spontaneous return of circulation (SROC) after failed resuscitation is a medical curiosity that has likewise eluded a rational physiological explanation. It was first described in the literature in 1982 and is popularly known as the "Lazarus syndrome," or autoresuscitation. To qualify, the patients must have experienced a monitored asystole or pulseless electrical activity, from which they could not be resuscitated, followed by an unexpected, spontaneous return of circulation. In a recent review of 38 cases, collected mainly from the anesthesia and intensive care journals, 14 patients had complete neurological recovery, in 5 patients it was considered "good," and the rest died of complications [19]. Various explanations for the phenomenon have been proposed such as, among others, artificial ventilation, auto-PEEP, due dynamic hyperinflation of the lung during CPR, and delayed drug action, none of which are generally accepted [20]. The authors stress that death is not an event but a process during which various organs supporting the continuation of life fail. They further maintain that the absence of pulse and respiration alone is not a sign of definitive death [19]. There continues to be a lack of consensus on the time interval between the termination of CPR and diagnosis of death [21].

We have seen that the attempts to measure MCFP under "steady conditions" by stopping the heart and rapid equilibration of blood among the vessels obscure the phenomenon of vestigial circulation which can persist for several hours after the cessation of the heartbeat. The concept of MCFP is therefore more than just a hypothesis which, according to proponents of left-ventricular-centered view of the circulation, is *inconsistent* with their model of circulation but plays a dynamic role in the intact circulation, as argued by proponents of the venous return (VR) model of circulation. As proposed by Manteuffel-Szoege, the phenomenon is a residuum of blood's own kinetic energy and confirms its autonomous movement. It is moreover apparent that existing models of circulation fail to give a consistent answer to questions about the relative role of the heart and of the peripheral circulation in regulation of cardiac output.

15.2 Significance of Artificial Respiration

The method of artificial respiration remains one of the most important procedures ever introduced into the practice of medicine. Accordingly, it has played an unparalleled role in shaping the way we think about the pulmonary physiology and, in particular, about the pulmonary circulation. It is widely appreciated that, in addition to providing a beneficial exchange of respiratory gases at minimal metabolic cost to the patient during general anesthesia and during states of critical illness, this remarkably well-tolerated procedure introduces a host of "unphysiological" pulmonary, as well as circulatory, changes. The mechanism of these changes has been, and continues to be, the subject of numerous studies. It is proposed, however, that a key aspect of the artificial respiration tends to be overlooked, and yet it plays a pivotal role in the maintaining of the arterial circulation. As seen, the experiments by Thompson and Manteuffel-Szoege on asphyxiated dogs demonstrate the curious phenomenon of sustained blood movement that continues well beyond the time of cessation of heart's action. In order to appreciate the nature of this phenomenon, it will be necessary to take a brief detour into the history of artificial respiration and, by way of illustration, examine accounts of those who were the first to witness and attempted to fathom this novel experiment.

The intricate link between respiratory and circulatory functions of the blood was fully recognized by antique physicians. According to Galen's respiratory doctrine, rhythmic expansion of the thorax during respiration caused the right auricle to expand with blood, acting as a reservoir or as a buffer, preventing its tear and overdistension. (In the ox heart used for dissection by Galen, the indistinct atrium is a continuation of the vena cava, whereas the auricle is a sizeable chamber, a situation unlike in the human heart, where the auricle is relatively small.) Auricular contraction, in turn, expels the blood into the right ventricle from where a part flows into the pulmonary artery and the remainder "percolates" through the pores in the interventricular septum to reach the left heart. The flow of blood through the pulmonary vessels thus depends more on the respiratory movement of the thorax than on the action of the heart [22, 23].

Rather than causing the propulsion of blood, the principal action of the ventricle in Galen's physiology was to "attract"[2] the blood during diastole, as is evident from the following passage: "The [ventricle of the] heart attracts, the cavities of the auricles push, and the great veins conduct the blood [into the heart]" [24].

We have already mentioned that Harvey likewise did not compare the action of the heart to the pump but, like Galen before him, used the simile of water bellows to describe the role of the lungs and of the diaphragm. Contraction of the ventricles, considered only of secondary importance, contributed to the forward flow of blood, but did not change, in principle, the blood's propulsion through the lung on account of the respiratory pump [22]. The function of the heart, fitted with semilunar valves,

[2] The power of attraction exerted by the heart, known as "vis a fronte," or the "force from the front," and is often equated with suction [23].

called "clacks," was rather to assure one way flow of blood through "the water bellows" consisting jointly of the heart and the lungs. In an early Lumleian lecture on circulation, Harvey refers to this physiological principle in the following passage: "It is plain from the structure of the heart that the blood is passed continuously through the lungs to the aorta as by two clacks of a water bellows to raise water" [22]. Harvey only makes a brief reference to artificial respiration in the best known of his books *De motu cordis* (1628) and also in *De motu locali animalium* (1627) but did not consider that it contributes significantly to the understanding of blood's circulation [25].

The idea of artificial respiration coincided with the age of great experimentation during the renaissance and was regularly employed as the method for in situ demonstrations of the action of thoracic organs from the fifteenth century onwards. The technique was of great interest during and after Harvey's time and is known to have been actively explored by several members of the Royal Society. Robert Hooke, one of its prominent members, filed the following description of reviving an open-chest dog:

> In prosecution of some enquiries into the nature of respiration in several animals, a dog was dissected, and by means of a pair of bellows, and a certain pipe thrust into wind-pipe of the dog, the heart continued beating for a very long while after all the thorax and belly has been opened; nay after the diaphragm had been in great part cut away, and the pericardium removed from the heart. And from several trials made, it seemed very probable, that this motion might have been continued for as long, almost, as there was any blood left within the vessels of the dog: for the motion of the heart seemed very little changed, after about an hour's time, from the first displaying the thorax; though we found that upon removing the bellows the lungs would presently grow flaccid, and the heart begin to have convulsive motions: but upon renewing the motion of the bellows, the heart recovered its former motion, and the convulsions ceased. (1664) (cited in [25])

Hooke diligently observed that little change occurred in the action of the heart as long as there was a sufficient amount of blood in the vessels but would "grow flaccid and begin to have convulsive motions" as soon as the action of bellows would cease. The most important part of the discovery, however, is related by Hooke at the conclusion of the experiment:

> Towards the later end of this Experiment a piece of the Lungs was cut quite off; where 'twas observable that the blood did freely circulate, and pass through the lungs, not only when the lungs were kept thus constantly extended, but also when they were suffer'd to subside and lye still. Which seem to be Arguments, that as the *bare* Motion of the *Lungs without fresh Air*, contributes nothing to the life of the animal, he being found to survive as well, when they were not mov'd, as when they were; so it was not the subsiding or movements of the Lungs, that was the immediate cause of Death, or the stopping of the Circulation of the Blood through the Lung, but the *want of sufficient supply of fresh Air*. (Emphasis by R. Hooke, cited in [25])

This and a host of similar experiments demonstrated that an asphyxiating animal could effectively be brought back to life simply by *passive insufflations* of air into the trachea, *without* any respiratory movements. The technique of artificial respiration, and in particular of insufflation, thus radically changed the way in which the function of respiration was perceived. The link between the respiratory and circulatory functions, the core tenet of Galen's and Harvey's conception of circulation, had effectively been *severed* [25].

Of further interest is the fact that Hooke went so far as to examine the possibility whether the animal would survive by exposing its blood to fresh air alone, *without* passing it through the lung, a radical thought, considering that it took another 300 years, before the membrane oxygenator was invented. Only 2 years after Harvey's death, Richard Lower, Hooke's associate, demonstrated, by using Hooke's new respiration pump, that the blood became *lighter* in color as it passed through the lung on its way from the right to the left heart. The idea that a component of air rather than air itself was the basis for external and internal respiration still had to wait for another century before Priestley discovered oxygen and Lavoisier linked respiration to "internal combustion," i.e., the tissue metabolism [26].

A detailed discussion on the evolution of mechanistic concept of blood propulsion is beyond the scope of this chapter, and the reader is referred elsewhere (see [27]). However, even a cursory look at the medical literature dating as late as the 1850s shows that a spirited debate divided the proponents of the "heart-centered" model of circulation and those who supported the importance of "peripheral forces" as "the motor" of blood propulsion. In place of the pumping action of heart, the latter invoked "the capillary power," also referred to as *vis a tergo*, the principal agent for the movement of the blood. The comment of Thudichum, concerning the force required to overcome the capillary resistance, at a lecture delivered at the Physiological Section of Medical Society in London, certainly captures the mood of the time: "if there were no other force promoting circulation than the heart, the heart of a whale would be required in the human chest, to affect even a very slow and languid circulation" [15].

In the same report, Thudichum related the following observation on an open-chest dog preparation in support of the "capillary force" acting in pulmonary circulation. He carefully distinguished it from the "capillary force" of the systemic circulation which, in spite of asphyxia, continued to propel the blood towards the heart, to the point of causing its distension. The collapse of arterial pressure, on the other hand, is attributed to "lack of interchange of air and blood," that is to say, due to deficiency of "the force from behind," generated on contact of blood with the air in the *pulmonary* capillaries.

> I opened the chest of a dog to witness the action of the heart during suffocation, which I induced by admitting the air into the pleural cavities. I was astonished to see the frantic efforts of the right ventricle which resembled so many shocks of electricity rather than so common quiet contraction of the heart. The right auricle was distended to its utmost size. The left side of the heart never showed any diastole, and the pressure of the blood in the aorta sank nine-tenths of its strength immediately. Notwithstanding this interruption of vis a tergo, the venous blood kept on accumulating, and its pressure attained a height which confirmed in the impression, that death in asphyxia is caused by apoplexy, sooner and more often than by the insufficiency or absence of the arterial supply. There was no vis a tergo in the arteries; but there was vis a tergo exerted towards the lungs, and still capillaries of those organs effectually obstructed the circulation. One principal factor in the sum of forces —the interchange of air and blood — was suspended by the destruction of the mechanism of the respiration. [15]

It should be mentioned parenthetically that *vis a tergo*, mentioned by Thudichum in the above passage, was used in the context of the forces acting "at the periphery" in the capillaries of animals, as well as plants: "The lactiferous circulation of the plants we know to be entirely capillary. The single vegetable errant cell, and the

largest Indian fig-tree, grow and live alike, with only capillary circulation. The sap traverses the distance of several hundred feet in length, with no propulsive power but the capillary" [15].

Discussion on the effects of respiratory movements and of the "capillary force" (*vis a tergo*) on venous return continued unabated [28], and it took well over a century before the "vitalistic theories" became devoid of meaning and vanished from the physiological literature [29, 30]. In the meantime, they had taken on another identity in the form of the concept of mean circulatory pressure and/or the elastic recoil of the arteries. The "force from the front" (*vis a fronte*), on the other hand, had metamorphosed into ventricular diastolic suction [31].

Pettigrew's idea that, morphologically, the thin-walled left atrium can be considered a *continuation* of the pulmonary veins and the thick-walled ventricle with its outflow tract, the *beginning* of the aorta, suggests that an alternative, possibly more realistic, view of the circulation, and in particular of the heart's function, can be had [32] (cf. Chap. 13). Considering that the blood receives the impetus or renewed momentum for its movement during oxygenation, i.e., on its passage through the pulmonary capillaries, the *separation* of *flow* and *pressure* now becomes possible. Accordingly, mechanical function of the ventricle – positioned at the *beginning* of the arterial limb of the circuit – is to generate and maintain (with the help of aortic valve) the pressure in the systemic arterial compartment. By analogy, the right ventricle can be functionally seen to be placed at the *end* of the venous limb of the circuit. It's function is the generation of pulmonary artery pressures, if only at nominal values. As will be shown, the experimental work on animal models in the 1950s – later applied successfully to patients with single ventricle hearts – has confirmed that not only survival but also a reasonable quality of life is possible without the right heart complex, a curious phenomenon that will be examined in Chap. 20.

In the light of the forgoing, it is possible to conclude that for all its benefits, the introduction of artificial respiration has confounded conceptual understanding of the pulmonary circulation and introduced a number of unintended consequences. Most importantly, the separation of respiratory and circulatory functions of the blood has obfuscated the key contribution of pulmonary circulation to blood's propulsion, thus shifting the "burden" to the heart. Gradually, the "hemocentric" doctrine of circulation upheld by physicians of antiquity has been replaced by the cardiocentric view where the heart becomes the principal "motor" of blood's propulsion. The consequences of this inadvertent substitution will be explored in the remaining sections of the book.

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Chapter 16
Models of the Heart

The complex nature of interaction between the heart and the circulation was well recognized among the early nineteenth-century physiologists, and in spite of numerous technical challenges associated with "opening of the circuit," attempts were made to investigate the mechanical behavior of the heart itself. The ideas that led to development and application of this radical experiment have played a key role in the evolution of the current understanding of the mechanical and energetic action of the heart, which, as will be shown, is far from complete. Several reviews on the history of the isolated heart preparations exist [1–3], and only a few highlights, relevant to our discussion, will be mentioned.

16.1 Early Isolated Heart Preparations and the "Law of the Heart"

The first isolated heart preparation was developed by Cyon in 1866 at the renowned Physiological Institute in Leipzig. This was a recirculation model of a frog's heart which aptly demonstrated the pumping action of the heart but was not amenable to hemodynamic recordings [1] (Fig. 16.1). Czermak is credited to have developed the first *non*-recirculating preparation in which direct measurements of chamber pressures were possible [3]. The importance of this preparation lies in the fact that it was further modified by Otto Frank, the youngest of the generation of investigators working under Carl Ludwig at the Leipzig Physiological Institute. Frank constructed a small, elegant preparation of the (single ventricle) frog heart, perfused with ox blood, in which preload and afterload could be altered independently (Fig. 16.2). The improved model allowed for a continuous recording of pressures and volume output. Frank measured maximal pressures generated by the ventricle when the aortic outflow was closed and observed that the heart muscle behaves similarly to the skeletal muscle, in which the force of contraction depends on the initial fiber length (preload) [2]. Frank also noted that the maximal tension (isometric maxima) developed by the ventricle depends on diastolic filling (preload) and was one of

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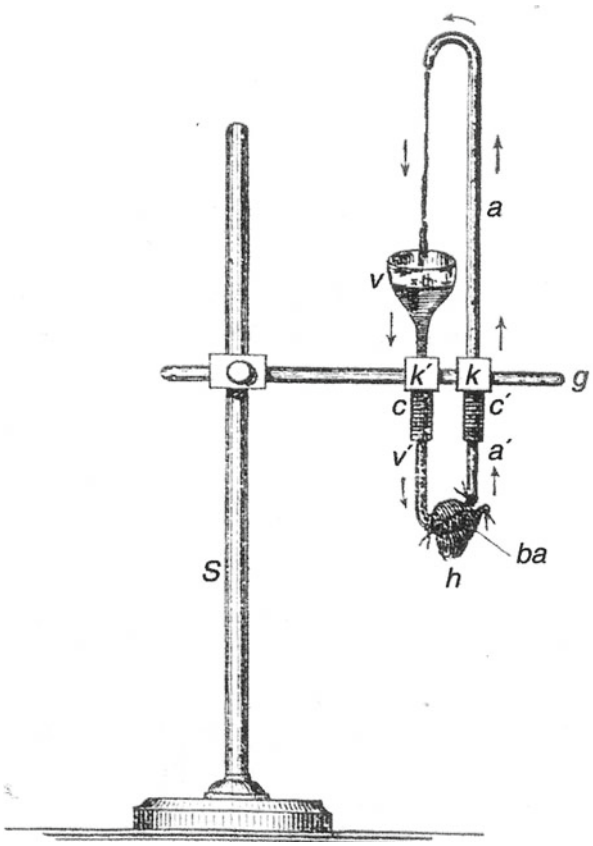

Fig. 16.1 Recirculating isolated frog heart preparation of the type used by Czermak for public demonstrations. The heart was filled with serum or 0.5 % saline from a reservoir (*v*) via a cannula inserted into the inferior vena cava (*v′*), from where it was ejected rhythmically by the heart (*h*) into the aorta (*a′*). The preparation functioned for several hours until the serum seeping through the heart walls had to be replaced (Reproduced from Ref. [3])

several investigators who contributed towards discovery of the "the law of the heart" [4, 5]. Finally, Frank was the first to observe that the end-systolic loci of both isovolumic and ejecting contractions fall on the (same) straight line and are independent of the end-diastolic volume. However, he found it difficult to obtain consistent results when altering aortic pressure against which the heart was ejecting (afterload) and thereby recognized the complexity of ventricular–aortic interaction [6, 7].

Newel Martin of Johns Hopkins was the first to construct the mammalian heart–lung preparation in 1881. The whole animal (cat or dog) was placed into a large warm tank. The blood filled the right atrium via superior vena cava by way of a constant pressure reservoir. The left ventricle ejected the oxygenated blood into the aorta fitted with a stopcock, by which ejection pressures could be manually adjusted. Newel Martin observed that rising of venous pressure resulted in increased output by the heart [9].

Ernest Starling resumed investigations on the circulation in 1910 when he turned his attention on the heart in an effort to quantify its mechanical function under varying conditions, since previous work on the whole animals by others has given such widely differing results [9]. During the course of former studies on anesthetized, open-chest dogs, Starling noticed a marked weakening of the heart's action and

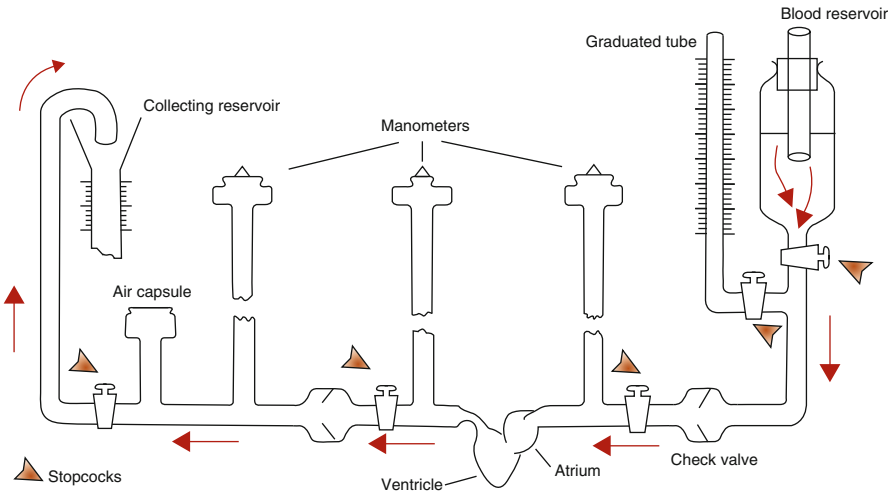

Fig. 16.2 Frank's improved isolated frog heart preparation. Blood flowed by gravity via a series of stopcocks and a check valve into the heart and ejected through aortic cannula into the collecting reservoir. The model was fitted with three manometers and a pressure capsule (Windkessel). By closing of stopcocks on either side of the heart, Frank was able to record atrial and ventricular pressures during isovolumic contractions. *Red arrows* represent the direction of flow (Reproduced from Ref.[8]). Note conceptual resemblance to the hydraulic ram model (cf. Fig. 16.6; see text for explanation)

resolved to construct a model where heart rate, venous inflow, and arterial resistance could be varied independently [10, 11]. Over subsequent years, Starling and his coworkers performed a number of improvements of their original cat heart–lung preparation and finally settled on a dog model, in which lower circuit resistance would better represent the heart's mechanical performance [9] (Fig. 16.3). Several studies followed, in which the effect of changes in heart rate and of the atrial and aortic pressures was assessed in terms of heart's size (volume) and its output. It was shown, for example, that for a given venous inflow, cardiac output remains fairly constant over a broad range of arterial pressures and temperatures. When the inflow was increased (by rising of venous reservoir beyond a certain point), the heart began to distend, exhibited diminished output, and failed. Starling came to the conclusion that"…the rise of venous pressure must be regarded as one of the mechanical means which are operative in enabling the heart to maintain an output corresponding to the blood it receives from the venous system" [12]. In subsequent experiments, Patterson and Starling showed that the only factor which consistently varies during altering of venous inflow and aortic pressure is the size (volume) of the heart, i.e., the length of muscle fibers. Thus, in the heart–lung preparation, the right atrial pressure controls the degree of ventricular distension (preload) and is the major determinant of cardiac output. This relationship is curvilinear and shows that the contractility of the heart (Starling's curve) increases to an optimal point at peak output, beyond which the heart distends and fails [10] (see Fig. 14.2).

It is of interest that Starling did not express the "law of the heart" in terms of stroke volume or minute output. He was, of course, well aware of the fact that, "The heart-lung

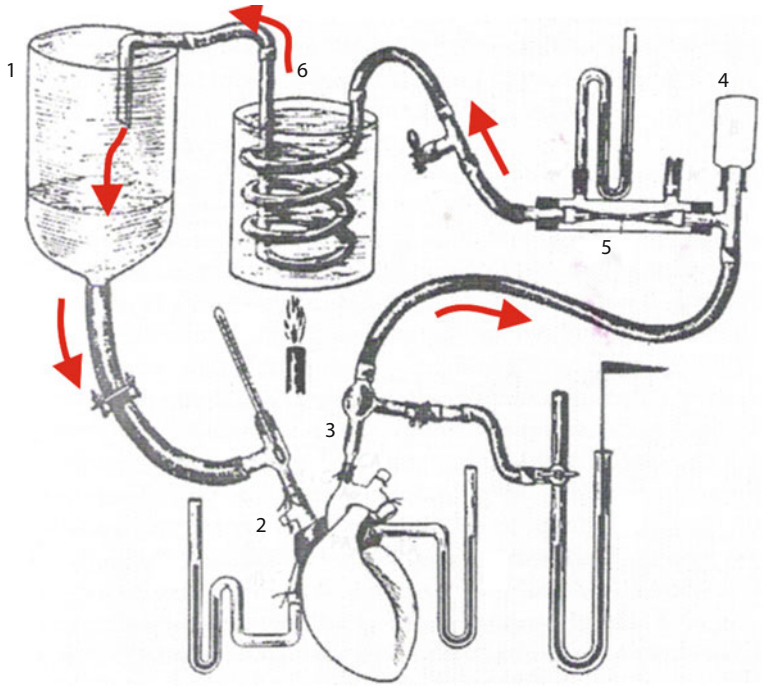

Fig. 16.3 Improved isolated heart preparation of Paterson and Starling. The blood flows from the reservoir (*1*) via tubing into superior vena cava (*2*) and is ejected into aortic cannula (*3*), which is fitted with an air capsule (*4*), passes through "Starling resistor" (*5*) to water bath heater (*6*), and returns back to the reservoir (Adapted from Ref. [10])

preparation will obviously give us no information as to the amount of blood which can be regarded as normal for that animal at rest," let alone during exercise, since the heart was essentially "separated" from the animal [10].

The ultimate aim of Starling and his coworkers was to find the "underlying principle, on which the heart's power of self regulation may depend," and which would ultimately determine the force of its contractions. The analogy was therefore sought between the skeletal muscle - where, according to contemporary research, the power of contraction is determined solely by the extending (linear) force- and the ventricle, where the volumetric expansion (preload) was considered to play a similar role [13]. Starling later summarized this "regulating principle" in his Linacre lecture: "The law of the heart is thus the same as the law of the muscular tissue generally, that the energy of contraction, however measured, is a function of the length of the muscle fibre" [14].

It is clear that Starling and his collaborators could not quantitate the mechanical function of the heart. In spite of the ingenuity of the model, they were not able to control the multiplicity variables which they encountered. It was later shown by several investigators that a stepwise increase in ventricular filling pressure at

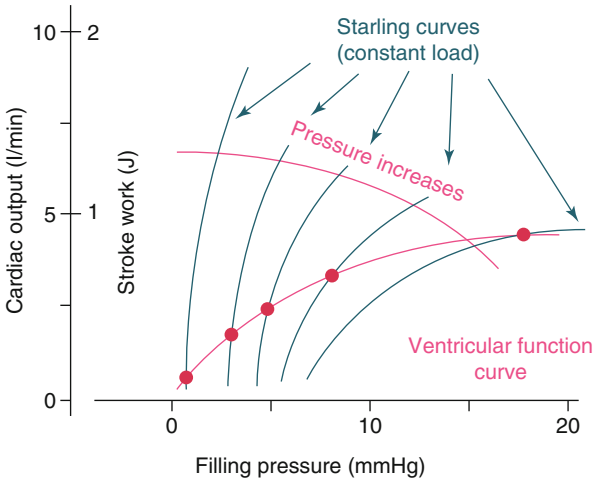

Fig. 16.4 Ventricular function curve (*bottom*) depends on aortic pressure and is therefore load dependent. When the ventricle contracts at increasing filling pressures against the same systolic pressure (constant load), a family of Starling curves is obtained (Reproduced from Ref. [16], used with permission of Springer)

constant aortic pressure (afterload) results not in a single but in a family of Starling curves (Fig. 16.4). However, this did not deter Starling, a skilled communicator, from applying his experimental findings to a broad range of clinical scenarios [4]. Starling's interpretation that the heart responds to increased workload with an increase in size (dilation) polarized physiologists and evoked misgivings on the part of clinicians of the early twentieth century, who considered an increased heart size as a sign of failure [4]. It was later shown by Hamilton and others that in acute settings, the heart becomes smaller during acceleration but increases in size when it slows down, on account of increased filling time. Thus, changes in rate preclude the application of Starling's work in the intact animal [15].

As pointed out by Elzinga [17] well over 20 years ago, Frank–Starling's law has, notwithstanding its original form, undergone "a historical misinterpretation," such as in this definition by Guyton: "Stating once again, this very important principle, known as the Starling's 'law of the heart': within physiological limits the heart pumps all the blood that comes to it without allowing an excessive rise in peripheral venous pressure" [18]. Evidently, Guyton here adapted "the law" in support of his venous return model of circulation. In fact, most physiology texts to this day depict at least one form of "Starling's curves," where cardiac output, stroke volume, or stroke work is represented as a function of right atrial or ventricular filling pressure (see Fig. 14.2).

16.2 An Obscure Model (Hydraulic Ram)

> It is evident that the heart could not continue to throw out more blood than it received…
> Patterson and Starling, 1914

While Otto Frank performed his classical experiments on the isolated frog heart model, an article appeared in the *Viennese Medical Weekly* by K. Schmid entitled

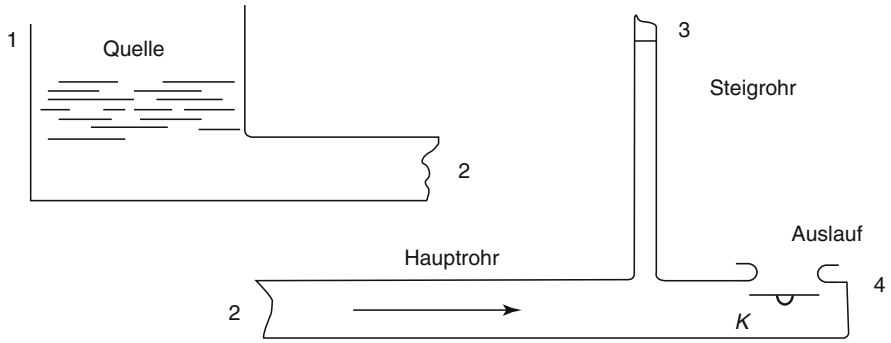

Fig. 16.5 Schematic drawing of a hydraulic ram by Schmid, consisting of reservoir (*1*), drive pipe (*2*), delivery pipe (*3*), and outflow with spill valve (*4*) (Reproduced from Ref. [19])

"On the apex beat of the heart and the pulse waves" [19]. At the time, several theories about the origin of the apex impulse were discussed in the literature. Schmid proposed that the apex beat comes about when the contracted wall of the left ventricle strikes against the chest wall, due to a sudden deceleration of the moving blood against the closed mitral valve. This phenomenon, argued Schmid, is equivalent to a pressure surge created in the hydraulic ram, when the flow of water is suddenly stopped by closure of the spill valve (Fig. 16.5). It is of note that in the late 1800s and the beginning of the 1900s, before the widespread use of electrically powered pumps, water rams were in common use. At the beginning of the twentieth century, R. Steiner made several references to Schmid's article, the significance of which goes well beyond the generation of the apex impulse. As already mentioned in Part I, Steiner maintained that the blood moves autonomously and that the heart functions as a damming-up organ whose mechanical function can be compared to a hydraulic ram which is flow-activated [20]. Needless to say, this theory was far ahead of its time and was largely unnoticed. Over the years, sporadic studies appeared, such as a paper by Havlicek, who drew a mechanical and morphological analogy between the heart and the hydraulic ram and even constructed a physiological model of the hydraulic ram [21]. The most consistent efforts "to put the heart in its place" came from Manteuffel-Szoege and his collaborators, who systematically pursued the issue of autonomous blood movement from embryological and hemodynamic perspectives. In a review paper on the subject, Manteuffel-Szoege made the following observation: "Is it really true that the heart works like a pump? A pump sucks in fluid from a reservoir, which is a hydrostatic system and not a hydrodynamic one. In the circulation, on the other hand, not only is blood ejected from the heart, but it flows into the heart. The heart is a mechanism inserted into the blood circuit, and so it is a very peculiar kind of pump" [22]. The monograph summarizing his life's work was published posthumously in 1977 [23]. What then is the function of a hydraulic ram?

The hydraulic ram is a cyclical water pump in which the kinetic energy of water is converted into pressure. The unique feature of the hydro-ram is that the

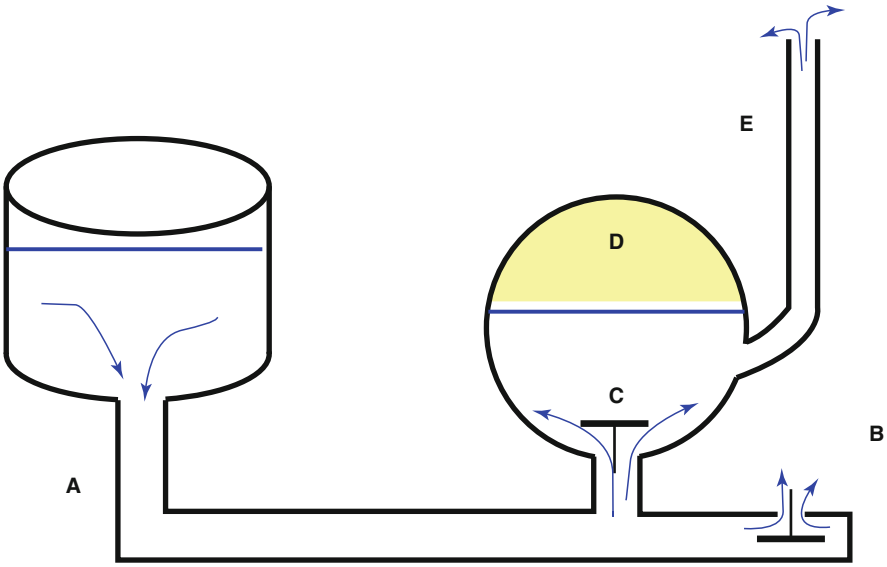

Fig. 16.6 Components and working cycle of a hydraulic ram. Water from the reservoir accelerates with the force of gravity along the drive pipe (*A*) and escapes via the loaded spill valve (*B*). The increasing drag on the water causes the spill valve to close, creating a back surge (water hammer) which opens the delivery valve (*C*) and forces the water into the pressure vessel (Windkessel) (*D*) and up the delivery pipe (*E*). The increase in pressure above the water level in the pressure vessel (D) closes the delivery valve (C) and causes water to flow via the opened waste valve (B), completing the cycle

hydraulic power of water does not power the machine parts, such as turbine blades, but works on itself and therefore does not require an external source of power for its operation. The ram is thus an impedance pump which generates pressure, but not flow.

The hydro-ram's components and work cycle are depicted in (Fig. 16.6). Please note that the pressure vessel (D) is not essential for operation of the ram, but increases its efficiency and converts pulsatile flow from the delivery pipe into a steady flow. Automatic operation of the ram requires careful "tuning" of the pipe diameters and adjustment of the valves. The efficiency (the ratio of delivered vs. wasted water) of the ram varies between 20 and 60 % and depends on construction design, on the amount of available water and on the desirable working pressure. Like other industrial pumps, each hydro-ram operates at its own working point and can be adjusted to deliver larger flows at smaller pressures, or smaller flows at larger pressures [24].

Basfeld demonstrated on a model ram that increasing compliance of the working chamber, i.e., by gradual increasing the ratio of air to water in working chamber (decreased stiffness), the water pumped by the ram quickly reaches a peak and remains at optimal level. In terms of efficiency, the ram delivers greater volumes when it operates at lower frequencies and lower working pressures (delivery height).

However, when ejecting at higher pressures, the delivered volume is optimal at higher frequencies of operation [25].

Of note is the fact that functionally, the hydraulic ram bears more than a casual resemblance to the isolated heart preparation, where (see Fig. 16.6) the reservoir and the delivery pipe (A) correspond to atrium, spill valve (B) to AV valve, pressure vessel (D) to the ventricle, and check valve (C) and delivery pipe (E) to aortic valve and aorta, respectively. Thus, the great veins and the atrium represent the reservoir from which the blood empties at great speed (rapid ventricular filling) into the ventricle. Abrupt closure of the mitral (spill) valve causes a steep rise in pressure and opens the aortic (delivery) valve. The air cushion of the ram can be compared to the contractile elements of the heart, i.e., the myocardium. Unlike in the heart where the pressure oscillates between systolic and end diastolic, the hydraulic pressure in the ram's pressure vessel (Windkessel) is high throughout the work cycle. One could object that there is no "spill valve" in the isolated heart preparation; however, the form of the ventricle, which promotes vortical flows, and the autonomous activity (or electrical stimulation) of the heart are such that one need not resort to excess flows, in order to convert kinetic energy of flow into pressure, a critical element of the ram's function. Morphological features of the right ventricle with a thin, highly compliant wall and a long, gently curving outflow tract suggest that its ram-like function is adapted for high flows at *low* pressures. The opposite is the case with the left ventricle, where a short, acutely angled outflow tract and a thick, poorly compliant wall are "designed" to generate *high* pressures (cf. Fig. 13.9). Last but not least, taking into account the low (energetic) efficiency of the heart (13–20 %) and of the ram, a mechanical comparison between the two is not too far off the mark.

Manteuffel-Szoege was, unfortunately, not familiar with the work done on the isolated heart preparation and did not compare the two; however, he sought out correspondences between the function of the ram and the heart and constructed his own prototype of a model ram [22, 23]. Like the heart, the ram ejects only a part of delivered volume from the working chamber (ejection fraction), and in both, the amount of volume delivered (cardiac output) depends on the height of the reservoir (filling pressure) and loading conditions (aortic pressure).

Cyclical performance of the ram can, moreover, be compared with a time-varying elastance model of the ventricle proposed by Suga [26] (see Sect. 16.4). It is significant that, within given design constraints and experimental settings, the ram works at optimal power and efficiency which depend on hydraulic energy of the driving flow. This is not unlike the heart which works at (hitherto unexplained) *optimal power* and *efficiency*. The fundamental discrepancy, known to exist between the cardiac oxygen consumption and cardiac output, can be compared to the operation of the ram in which only a part of the total water energy "driving" the ram is converted into useful work and the rest is "lost" through the spill valve. Thus, the comparison, evoked by Steiner, between the hydraulic ram and the heart as a damming-up organ is teleologically sound and clarifies a number of unsolved problems encountered in existing models of the heart.

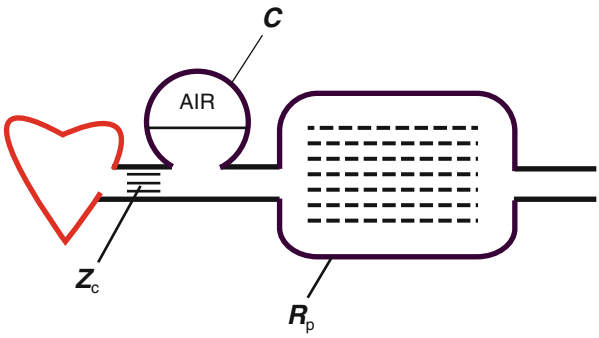

Fig. 16.7 The three-element Windkessel model is a lumped parameter model of arterial circulation consisting of characteristic impedance (Z_c), compliance, and peripheral resistance (R_p)

16.3 Quantification of Ventricular Pump

Between the 1950s and 1970s, numerous indices appeared in the literature which purported to embody various aspects of the mechanical heart's performance, such as the ejection fraction, peak systolic pressure, stroke work, maximal velocity of shortening, and peak isovolumic pressure at a given volume (dP/dt_{max}), to name a few, but, as noted by Elzinga and Westerhof, "… there is no theoretical reason to think that these indices are in any way quantitatively related to the amount of blood the heart can pump against various pressures" [27]. In order to do that, the heart performance would have to be tested against a system in which the mechanical parameters of the arterial circulation could be controlled. Thus, a model arterial tree was constructed, a three-element Windkessel, consisting of mechanical modules which would simulate compliance (air chamber, i.e., Windkessel) (Fig. 16.7), resistance, and characteristic impedance. It was shown that the impedance values for systemic and pulmonary circulations obtained with this model under experimental conditions were similar to in vivo results in man, cat, and dog [28].

Variations of the three-element Windkessel model have been used extensively as arterial loads for testing of isolated hearts and for modeling of ventriculo–arterial interaction and derivation of CO. (For review, see [29].) A sophisticated isolated heart preparation was then developed by Elzinga and coworkers to test performance of the left ventricle against the arterial model on a beat-to-beat basis. Carefully executed experiments on the isolated cat heart during conditions of constant diastolic filling, contractility, and fixed heart rate, against different values of aortic impedance, showed that the left ventricle is neither a source of pressure nor flow but a pump with a final "source resistance" related to its load [30]. The model was based on the electrical (Ohmic) analogue where the driving pressure produced by the pump corresponds to "hydromotive pressure," i.e., voltage, the flow is equivalent to current, and resistance corresponds to "apparent source resistance" defined as the ratio of mean aortic pressure and mean outflow. The resistance of the arterial system (peripheral resistance), on the other hand, is represented as the ratio of mean aortic pressure and mean flow [31–33].

According to this model, interaction of the ventricle and the arterial tree is expressed in terms of *mean* ventricular pressure and flow (cardiac output) and is

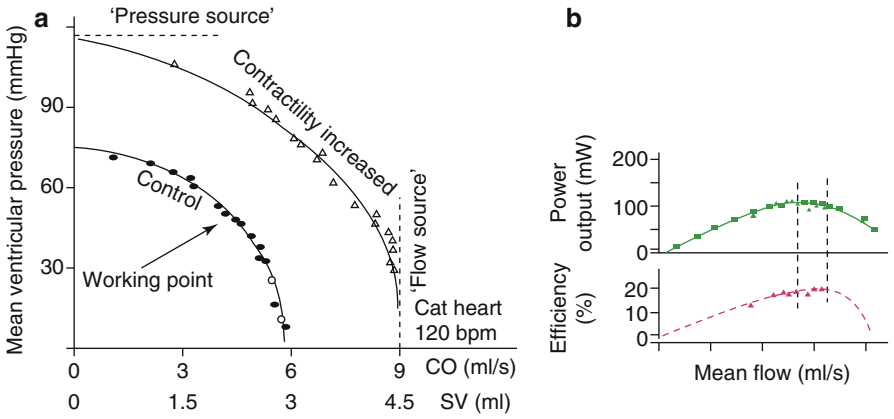

Fig. 16.8 (**a**) Pump function graph of the isolated cat heart at a fixed rate of 120 beats/min. The lower curve shows ventricular output under control conditions. As mean ventricular pressure increases, the output (stroke volume) decreases. Analogously to the hydraulic ram, the ventricle functions as a "pressure source" at high working pressures and becomes a "flow source" at low working pressures. The performance is optimal at "working point" where the heart is neither flow nor pressure source. Increase in contractility causes a parallel shift of the performance curve. (**b**) External power and efficiency of the isolated feline left heart. Similarity of the curves with poorly defined maxima suggests that the heart works close to maximal power and efficiency (around 20 %), with remaining energy dissipated as heat (Adapted from Ref. [16], used with permission of Springer)

graphically represented as a "pump function graph," which closely resembles a mechanical pump-head capacity curve (Fig. 16.8a). (An example of such a pressure-head capacity curve for a roller pump is given in Fig. 6.1.) It is evident from the graph that when working against increasing loads (aortic pressure), the isolated heart will generate smaller stroke volumes, eventually reaching the isovolumic state at maximal pressure and no flow. The reverse is the case at decreasing aortic pressures. The graph further shows that the working point of the ventricle falls roughly midway between the maximal flow and pressure. Accounting for the pressure differences, experiments on the right ventricle closely match those of the left [34, 35].

It is a remarkable fact that during a steady state, the working point of the heart is located near its *maximum* external power and efficiency (Fig. 16.8b). This has been a consistent finding in the isolated heart preparations [31, 36] as well as in intact animals [37, 38] and humans [39]. It will be recalled that a similar finding applies to the embryonic heart (see Chap. 10). Why should the heart work at the peak of its power during control (resting) condition? And what is the feedback mechanism which would control it? It surely goes against sound mechanical principles to design a mechanical pump in such a way that it would operate at its *maximum* power during *normal* working conditions. This paradox has certainly been noted by Elzinga and Westerhof, who were at a loss to explain it, namely:

> The implications of the idea that the ventricle is controlled to function either at optimum power or efficiency are not easily explained on the basis of current knowledge of cardiovascular control. For both variables, no known mechanism is designed to keep the ventricle at either of these optimum values. [30]

More importantly, they observed that the receptors which would detect power and/or efficiency have not been discovered and would be difficult to imagine since any value, lower than optimal, would have to occur twice[30] (see Fig. 16.8b).

A similar issue has been raised by others [31, 38, 40]. Is it possible that the isolated model heart does in fact function according to sound design (natural and mechanical) principles emulated, however, by a different mechanical model? It is proposed that this model is a hydraulic ram which can be made to operate at two extremes: at high load, by clamping the delivery pipe, when the ram generates maximum pressures, but no flow. This scenario, as demonstrated on the isolated cat heart preparation, is analogous to isovolumic contractions, where power, the product of pressure and flow, is zero. The reverse situation occurs when the ram pumps at low pressures and generates maximal flows at optimal power and efficiency. This state is comparable to the heart working against low aortic pressures [31, 38]. The often quoted statement by Starling that "the heart can only pump as much blood as it receives" certainly sounds ambiguous when used in the context of the heart as a pressure-propulsion pump but is an accurate observation if the heart is considered to function as a hydraulic ram.

16.4 Ventricular Elastance Model

An alternative way to represent the left ventricular pump function is by a time course of the ventricular pressure–volume relationship. What Frank was unable to demonstrate on a frog heart, namely, that a unique relationship exists for isovolumic and ejecting beats, was shown some seventy years later by Suga, who had an intuitive insight that the action of the left ventricle could be modeled by discharge of a capacitor, i.e., by a time-varying function. Suga tested the hypothesis on isolated, perfused, and denervated dog hearts by measuring ventricular volumes during a graded occlusion of the inferior vena cava until a volume was reached, when the ventricle could no longer generate pressure (V_d) (see Fig. 10.1a). In a separate set of experiments, the ascending aorta was occluded in a stepwise fashion, in order to control the pressure against which the ventricle was ejecting [41, 42]. The working cycle of a ventricle can thus be represented on a pressure/volume plane in which a data point moves in a counterclockwise direction and describes a loop for a given set of loading conditions and contractility. Suga showed that the relationship between pressure and volume in the LV is described by an elastance curve according to the following equation:

$$p(t) = E(t) \bullet \left[V(t) - V_0 \right] \tag{16.1}$$

where $p(t)$ and $V(t)$ are time-varying pressure and volume, respectively, $E(t)$ is time-varying elastance, and V_0 is volume at zero pressure (and assumed to be negligible compared to end-systolic volume). As is evident from the graph, the end-systolic/pressure–volume points of consecutive beats fall on a straight line, known as ESPVR, with a slope of maximal elastance (E_{max}) [43]. (Please note that, even if the

term E_{max} suggests a maximal ventricular end-systolic elastance, the ventricle attains its maximal stiffness.) Changes in preload (EDV) and afterload will normally result in variations of end-systolic volume and pressure, but not their ratio. According to Suga, the advantage of E_{max} over other purely phenomenological indices of contractility is that it has dimensions of volume elastance (mmHg/ml) which can quantify three-dimensional (i.e., stress–strain) property of the ventricular wall [44]. Over the years the elastance concept has gained a wide acceptance as a load-independent index of contractility.

It is of interest that, when normalized with respect to time and amplitude, the elastance curves $E(t)$ are almost identical in normal individuals and in patients with underlying cardiac disease, in spite of variations in contractility, heart rate, and loading conditions [45]. By application of continuous ventricular volume recording [46], remarkably similar normalized elastance curves have been found to exist in humans, cats, dogs, and mice, suggesting that mechanical and temporal activation of the ventricle is conserved across mammalian species [47]. The concept of elastance is a powerful tool which has afforded an unprecedented insight into the mechanical (and energetic) aspects of ventricular contraction. It appears that there is a "universal" elastance curve which has been widely adopted as a modeling tool of the circulatory system [48].

It transpired over the years that the ventricular elastance concept, despite of performing reliably within the physiological range of heart rate and loading conditions, has lost its status of being "the ideal" index of ventricular function. Numerous studies have shown its dependence on heart rate, load, geometric, and biochemical properties and contractility-dependent curvilinearity [49–52]. The latter is problematic since extrapolation of the ESPVR curve gives a negative value, with the volume axis (V_0 intercept), yielding virtual (less than zero) diastolic volumes. Opinions are divided whether single-beat P–V loop estimations of E_{max} [45] are reliable [53] or fail to predict ventricular contractility in vivo [54].

16.5 Energetic Aspect of Myocardial Contraction

The discovery by Schwan's in 1832 that the tension produced by the skeletal muscle depends on its initial length and by Helmholtz that contracting muscle produces both work and heat caused a sensation among the nineteenth-century physiologists who proceeded to analyze the newly discovered phenomena in terms of the fledgling new science of thermodynamics [4]. Schwan and later Weber (1846) also proposed that muscle behaves like a stretched spring whose strain–stress characteristics could be expressed in terms of mechanical equivalent of work and heat released during a contraction cycle [55]. As mentioned, it was Starling's intention to define the length–tension relationship of cardiac muscle in terms of mechano-energetics of the skeletal muscle, as was attempted by contemporary researchers. Starling's close collaborators, Evans and Hill, carried out a series of myothermic experiments on the amphibian striated muscle and showed that the total energy released by isotonically

contracting muscle (performing work and releasing heat) is equivalent to the energy turnover of the muscle contracting isometrically, when no work is done [56]. This work culminated in Hill's viscoelastic theory by which the stimulated muscle becomes "the new elastic body" with predictable (linear) mechano-energetic behavior [57].

Since the shape of muscle length–tension curves generated by Evans and Hill bore some similarity to the "Starling curves" obtained earlier on the isolated heart preparation by Patterson and Starling [10], Starling concluded that the newly discovered viscoelastic theory applies also to cardiac muscle. To Starling's satisfaction, his prediction that the energy expended during heart's contraction is a function of the length of muscle fibers (Starling's law of the heart) had, therefore, been experimentally verified [58]. Only 9 years later, in a dramatic turn of events, Fenn demonstrated that the energy output of the muscle was *not* constant, but depends on its load, and, more importantly, that the enthalpy (the sum of work and heat) released during isotonic contraction is about 30 % *greater* than the tension and heat produced isometrically [59]. Fenn's findings essentially disqualified Hill's viscoelastic theory of muscle contraction, although, according to Hill himself, "it took an unconscionable time dying" [59]. Moreover, Fenn's findings meant "death warrant for the Starling's law of the heart…Curiously enough, as was, the Law of the Heart never died. It disappeared for some time only to reappear many years later. In the meantime it has lost a limb, was no longer standing on a proper theory, and had acquired a new identity. Physicians did not recognize this old law in a new form" [17]. In what form, then, did the Frank–Starling law reappear?

16.6 Length-Dependent Activation in Cardiac Muscle

In the 1970s Suga introduced a novel method of relating ventricular mechanics and oxygen consumption by suggesting that the area of the P–V loop is proportional to the external mechanical work performed by the ventricle [26]. Without a doubt, this was one of the great discoveries in cardiac physiology, since none of the existing parameters of myocardial oxygen consumption could consistently predict its mechano-energetic relationship [60]. As mentioned, the concept was born out of the time-varying elastance model with assumption that the ventricle is equivalent to a spring in which the potential energy is stored during stretch (systole) and released as mechanical work in the course of diastole. The difference between the two being that during systole, the elastance (stiffness) of the ventricle increases gradually, whereas the elastance of the spring increases instantly at the beginning of its stretch [61]. It was subsequently validated – in a series of tightly controlled studies on the isolated, cross-circulated dog heart model ─ that during a given contractile state (E_{max}), the pressure–volume area (PVA) obtained by planimetry from P–V plots closely correlates with the total mechanical energy of contraction. Thus, the PVA consists of the external mechanical work (EW), which the ventricle performs during ejection and of the potential energy term (PE), stored in the LV during contraction.

It was further determined that an increase/decrease in contractility resulted in a parallel shift of E_{max} line in the corresponding directions (Fig. 10.1).

As already mentioned (Chap. 10), it is a remarkable fact of myocardial energetics that under a stable inotropic state, the slope of the relation between oxygen consumption VO_2 and the PVA is *constant* and does not depend on the type of contraction, i.e., isovolumic or ejecting. During isovolumic contraction, the PE stored in the ventricle is represented by PVA, and, since no external work (EW) is performed, PE is dissipated as heat. Increased E_{max} elevates the VO_2-PVA relationship, and decreased contractility (E_{max}) results in a parallel downward shift. The contractile efficiency (the ratio of PVA divided by oxygen consumption per beat, from which activation and basal components have been subtracted) has been shown to be consistently around 40 % across the range of mammalian species and humans, under a variety of physiological and pharmacological conditions [61] (see Fig. 10.1d). The slope of this isoefficiency line is independent of the preload and afterload as well as of the inotropic interventions [62], implying that a *constant* relationship exists between the generation of chemical energy (ATP production) and mechanical output [57]. It is further significant that within a constant PVA, almost all of the PE can be converted into EW during the relaxation period, without affecting VO_2 [63], indicating that the PE and EW are nearly energetically equivalent [64]. According to Suga, the PVA concept and the linear VO_2-PVA relation point to the autoregulatory mechanism which adjusts the energy output of the myocardium to load and represents the very parameter Starling was hoping to discover, when he proposed the "law of the heart," but failed [44, 61].

Although the most accurate index to date, the VO_2-PVA relationship, remains a purely phenomenological finding, many questions about cardiac energetics remain unanswered. The fact that in comparison to striated muscles, the non-beating myocardium exhibits about ten times the basal metabolic rate of the striated muscle (5 mW/g of tissue vs. 0.5 mW/g), of which some 30 % is dissipated as heat, continues to be one of the "physiological enigmas" [65, 66]. During contraction myocardial metabolic rate increases by three to four times, with about 75 % of consumed oxygen converted into heat. High resting and working metabolic heat production accounts for a relatively low mechanical efficiency (the ratio of oxygen consumption and work output) of cardiac muscle, in the range of 10–15 % [67, 68]. The fact that maximum energy expenditure in cardiac muscle occurs during isometric contraction makes it fundamentally different from the striated muscle. The classical Fenn effect does not exist for the cardiac muscle [65, 69]. This, however, has been disputed by proponents of the revived form of viscoelastic theory of cardiac muscle contraction based on VO_2-PVA concept. In a comprehensive review on the topic, Suga maintains that "the time-varying elastance model can simulate, although phenomenologically, the cardiac version of the Fenn effect…and is reconcilable with the energy consequence of the time-varying elastance model of the ventricle" [61].

The commonly accepted biochemical "feedback model" of tissue respiration predicts that changes in cytosolic phosphate metabolites (ATP and ADP and [Pi]) would be proportional to cellular respiration, i.e., oxygen consumption and the work done by the myocardium. However, numerous studies on cardiac energy metabolism in the intact and isolated hearts have failed to show significant

correlation between changes in workload and the high-energy phosphate metabolites and are at odds with this fundamental model (for review, see [70]). Neely et al., for example, demonstrated that increase in workload and oxygen consumption in the isolated, perfused rat heart occurs in the absence of measurable changes in ATP and creatine phosphate (PCr) [71]. In a similar study, Williamson et al., showed that during increased rate of ventricular filling (increase in EDV), the rate of oxygen consumption can increase by about 15–20 times above the basal, all at the approximately constant ATP turnover rate [72]. This remarkable metabolic stability, also known as the "stability paradox," has put in question the long accepted "calcium-only" hypothesis, according to which calcium liberated from the intracellular stores by calcium-induced release during excitation–contraction coupling activates the contraction cycle by binding of troponin C of the tropomyosin complex of the thin filaments [70]. Recent studies on effects of mitochondrial respiration in vitro and in vivo have confirmed that changes in calcium concentration can, at most, double mitochondrial respiration and cannot account for a large increase in energy flux, observed in cardyomyocytes (reviewed by [73]). It has also been shown that a disproportionally large ATP turnover rate is a function of length-dependent activation of myofilaments brought about by enhanced sensitivity of the thin filaments to calcium, caused by increased sarcomere length. (See [73] for further references.) Increasing evidence points to the fact that the mechanical loading of the ventricle (Frank–Starling mechanism) is in fact the direct cause of length-dependent activation of the myofilaments and, in turn, of linear increase in oxygen consumption (VO_2-PVA relationship) and ATP production, as mentioned above.

The concept of length-dependent activation is further linked to diastolic work which is performed "on the ventricle" by the blood returning to it during ventricular filling. Its magnitude is marked by the triangular area between the upper portion of the P–V loop and ESPV line and is referred to as "negative work" [61] (see Fig. 10.1e). According to Loiselle et al., this work has been "universally excluded" form the calculation of VO_2-PVA energy balance [55]. Evidently, this energy is imparted to the ventricle by the blood during "passive" filling phase. One could argue that this is a recaptured energy from the previous systole, but as we have shown, there is little reason to believe that such a direct hydrodynamic relationship exists between the functions of the left and the right ventricles. Loiselle et al. recently challenged the assumption that the rate of basal cardiac metabolism is independent of ventricular volume and that diastolic work should be included in the further refinement of the VO_2-PVA model [55].

At the conclusion of their review article on cardiac mechanics and energetics, published several years after discovery of the linear VO_2-PVA relationship, Gibbs and Chapman made the following comment:

> Thus, although one would expect the thermodynamic efficiency of potential energy generation to be significantly less than 100 %, one would not prima faciae expect it to be constant and independent of a wide variety of mechanical, physiological, and phenomenological conditions. Therefore, the experimental finding of a constant thermodynamic efficiency of potential energy (pressure-volume) generation in cardiac muscle suggests that some kind of optimally interactive autoregulatory mechanism is at work in the myofilaments, previously undiscovered but required to explain the otherwise puzzling findings of Suga and co-workers…. [57] (Used by permission of the American Physiological Society)

In a more recent comparative review, Gibbs reiterates the above quote and summarizes the outstanding problems to be solved in the field of myocardial energetic [65]. Could it be that the metabolic demands of the tissues expressed as the autonomous flow of blood returning to the heart and affecting the length-dependent ventricular activation via well-recognized endocardial endothelial signaling (for review, see [74]) are the actual missing piece of the cardiac energetic puzzle?

16.7 Limitation of Isolated Heart Models

The strength (and weakness) of ventricular function models can be appreciated from their applicability to a real life situation where an algorithm is applied to a device which wholly, or in part, replaces the function of the heart. For example, the interaction between a native ventricle and a ventricular assist device (VAD) is of great importance and determines its performance and, therefore, usefulness [75, -76]. A number of mathematical lumped parameter and computer models exist in which the pressure–volume loop analysis and the concept of elastance have been used to model the function of left ventricular assist devices (LVADs) [77, 78]. To determine the value of the ventricular elastance model, considered to be the "gold standard" [79] in predicting the interaction between the LVAD and the peripheral circulation at different levels of cardiac support, Moscato and coworkers implanted seven healthy sheep with LVADs and measured the hemodynamic response during normal heart function (with LVAD clamped off) and during various degrees of ventricular support. The baseline hemodynamic parameters were measured for each sheep and compared with different levels of arbitrarily chosen levels of pump support of around 12, 27, and 57 % above the basal COI (cardiac output index) values. Each pump condition was assessed for different heart rates, CVPs (preload), afterload (by infusion norepinephrine), and pharmacologically altered contractility (Ca-channel blocker). The results showed that an increase in preload (with infusion of additional fluid) during control conditions (LAVD off) caused an increase in EDV (22 %), no change in SV, and a decrease in contractility (E_{max}) and in systemic resistance (30 %). During low levels of pump support, COI stayed within control values but increased significantly at medium pump support, with decrease in LV volume. However, during the maximum pump support, COI decreased to near baseline with concomitant decrease in SVI and LV volume. The authors concluded that "Left ventricular SV and overall CO are, in the presence of mechanical support,(only) slightly determined by the pump support level" and noted that "almost fixed levels of CO" ultimately depend on metabolic requirements of the tissues. Multiple regression analyses showed that the cardiac assist device performs more physiologically during a steady state, when ESV change is a function of EDV, as predicted by the elastance model, rather than by the Starling-like model in which SV is a function of EDV. The elastance model, however, cannot account for a substantial interaction between the ventricle and the circulatory autoregulatory mechanisms, "which appear to oppose LVAD driving mode" [80].

In a similar study, Vandenberghe et al. tested the validity of the elastance model by assessing the interaction between the native heart and the two types of cardiac assist devices in experimental animals. Ventricle support with positive-displacement type of LVAD showed a high beat-to-beat variation in volume loading of the native ventricle and a marked variation of ventricular pressure and elastance curves which deviated significantly from the typical bovine curves. On the other hand, the circulatory support with a rotary pump showed that a progressive increase in pump flow results in decreased EDV and increase in LV pressure. In addition, there was an increase in LV elastance and mean aortic pressure, leading the authors to conclude that "the time-varying elastance theory insufficiently models the complex hemodynamic behavior of a left ventricle that is mechanically assisted" and call for an improved model which better simulates the heart–device interaction [81].

Danielsen and Ottesen developed a mathematical model which, unlike the elastance model, which is applicable to hearts with ejection fractions of less than 50 %, allows for separation of isovolumic (non-ejecting) and ejecting heart properties. The model describes the ventricle as a pressure source, determined by its volume, ventricular outflow, and time, and allegedly yields pressure and flow curves which are more representative of the normal ventricle [82, 83].

The ultimate test of modeling can be gleaned from performance and behavior of the total artificial hearts (TAHs) and ventricular assist devices in patients. The problems with these devices have been appreciated ever since DeVries implanted Jarvik-7 TAH into the first recipients in the 1980s, all of whom died of a combination of thromboembolic, hemorrhagic, and infectious events leading to multiple organ failure and cerebrovascular accidents. The core of the problem, as identified by the authors, was related to disturbed hemodynamics where, in spite of the fact that COs could be easily adjusted, they could not be matched with individual patient's (and organ's) requirements. DeVries noted that "Attempts to increase cardiac output by increasing the rate resulted in vasodilation, returning the output to the original levels. Cardiac outputs were extremely stable, including response to activity or febrile events….it is not understood how the artificial heart may interfere with the physiological mechanisms that regulate both blood pressure and sodium homeostasis" [84].

Thus, the initial enthusiasm over prolonged use of these devices has been dampened and is currently restricted in the USA to "the bridge to heart transplant" use. Though not as severe, blunting of the cardiovascular response to patient's global and regional metabolic requirements also occurs in patients with left ventricular support devices (VADs) [85], leading to secondary right ventricular failure in 10–20 % of recipients [76] and hepatic dysfunction [86]. Thus, the "insensitivity" of TAH's cardiac support devices to rapid changes (beat to beat) in loading conditions of the left as well as of the right ventricles results in complex baroreceptor and neurohormonal imbalance which can further exacerbate the preexisting heart condition [75, 78]. Remarkable improvement in technology and design in TAH during the past 50 years has benefited countless patients; however, Brecher's vision of "replacing the pump as a heart" for prolonged periods remains an elusive goal.

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Chapter 17
Cardiovascular Response During Exercise

In contrast to the hitherto revived studies mainly performed on anesthetized, open-chest animals or on isolated heart preparations, the physiological events that occur in exercising animals or humans provide a unique insight into the function of the cardiovascular system at the limits of its capacity. Under such conditions, the role of central and peripheral circulations becomes more clearly defined and affords us with, as yet, the strongest evidence for the primal role of the peripheral circulation. It is not surprising that, given the lack of a unifying paradigm on the hemodynamic response to exercise, this field is fraught with many inconsistencies which, in the face of new studies, are becoming increasingly more difficult to reconcile. Predictably the argument pivots on the already familiar question of the degree of contribution of central versus peripheral factors in the overall control of the circulatory response to exercise (for reviews, see [1–4]).

17.1 The Role of Peripheral Circulation

It has long been recognized by exercise physiologists that optimal muscular activity is a function of adequate supply of oxygen and metabolic substrate, as well as of efficient dissipation of heat and metabolic by-products. Even a few seconds of sustained muscular exertion depend on the adequate blood flow to the skeletal muscle. A typical response to an incremental exercise consists of doubling of the HR, a four to fivefold increase in CO, and a moderate increase in MAP. In addition to a profound increase in blood flow to active skeletal muscles, know as exercise hyperemia, there is an increase in vascular resistance of the skin, viscera, and other tissues not directly supporting muscular effort [5] (Fig. 17.1). Muscle perfusion is linearly related to workload and both are, in turn, proportional to oxygen consumption up to the peak levels of exertion [6] (Fig. 17.2).

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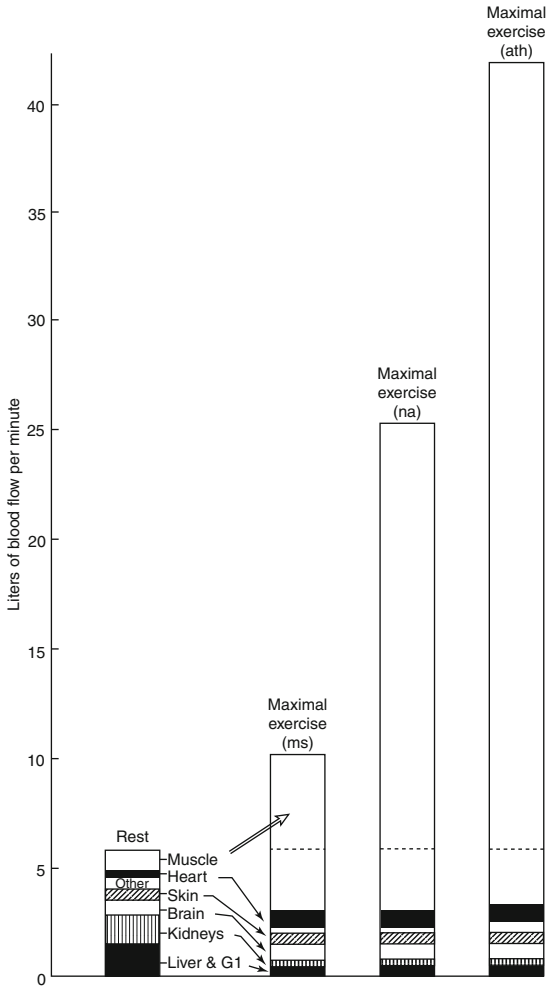

Fig. 17.1 Blood flow distribution at rest and during maximal exercise in patients with mitral stenosis (*MS*), in normal individuals (*NA*), and in highly trained athletes (*ATH*). Note that at rest and during exercise, blood flow to skin and viscera is similar in all three groups, whereas muscle perfusion varies greatly (Reproduced from Ref. [5], used with permission of the American Physiological Society)

17.1.1 Skeletal Muscle Pump Hypothesis

Quantitative changes in blood flow in the forearm muscles during sustained contractions were first measured by occlusion plethysmography in 1930s by Grant who noted a small increase in the volume of the limb during contraction and a larger one during muscular relaxation, when the blood rapidly filled the veins [8]. In the subsequent decade several reports were published on the circulatory changes during muscular activity which led to the muscle pump hypothesis in the 1940s (for review see [9, 10]). The next phase of research on skeletal muscle blood flow focused on the rapidity of its onset. Rushmer, for example, performed a series of studies on dogs with chronically implanted Doppler transmitters across the left ventricle and demonstrated that the increase in CO occurs within a single heartbeat of the onset

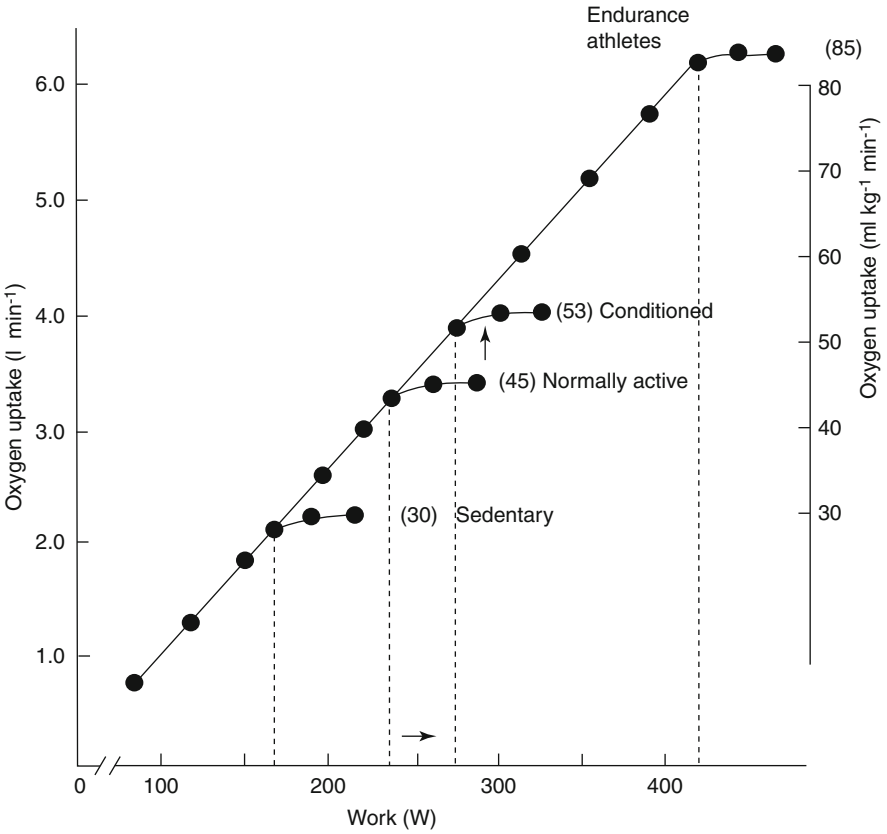

Fig. 17.2 The relationship between exercise intensity and oxygen uptake is similar in individuals with different levels of physical conditioning, but their maximal uptake varies widely (Reproduced from Ref. [7], used with permission of Oxford University Press, USA)

of exercise [11]. Similarly, Guyton et al. showed a sudden threefold increase in CO in anesthetized dogs with spinal cord transection in which hind leg muscles and sciatic nerves were stimulated with cyclical current, simulating muscle activity. Since the increase in CO occurred in the absence of nervous (and cardiac) stimulation, it was ascribed to a combination of metabolically induced muscle vasodilation and to translocation of blood into the central compartment, with resulting increase in MCP. Without significant augmentation from the periphery, argued Guyton, the heart itself cannot increase CO more than a few percent [12]. On the basis of rapid refilling of lower leg veins during exercise observed by venographic imaging, Almen and Nylander proposed that the contracting muscle works similarly to a "bellows pump" [13] in which changes in muscle length, in turn, affect the length and diameter of the veins [14].

Over the years several revisions and refinements were added to the muscle pump concept, and in their review Rowell et al. specify three requirements for its effective

operation: intact venous valves, maintenance of low blood volume within muscle veins, and increase in "driving pressure" [15]. Similarly, Delp and Laughlin characterized activity of the muscle pump as "contraction-induced, rhythmic propulsion of blood from skeletal muscle vasculature which facilitates venous return to the heart and perfusion of skeletal muscle." It is implicit in this characterization that muscular action *adds* hydraulic energy to the circulating blood and that any degree of increased blood flow due to metabolic increase in vascular conductance and blood flow is *not* due to the action of the pump [16].

Because of dramatic increase in CO with concomitant shifts of the blood volume into the working musculature, Rowell et al. suggested that the muscle pump can be viewed as the *second heart* at the venous return part of the circuit, having the capacity to generate blood flow rivaling that of the left ventricle [15]. On the basis of extensive analysis of the central and peripheral factors which limit the circulatory response to exercise, Rowland likewise contends that, in addition to a central cardiac pump which supplies the muscles, a second or peripheral pump, responsible for systemic venous return, is indispensible for the following reasons: (1) to assure adequate cardiac diastolic filling, due to gravitational sequestration of blood at the onset of upright exercise; (2) because of large outputs, e.g., in the order of 1,000 ml/s at maximal exercise, the output of the peripheral pump must be equal to the central (cardiac) pump, since "the heart cannot expel the blood it does not receive"; and finally (3) maximal response to exercise is determined by the peripheral pump, which "drives the system," unlike the central pump, which "sustains it" [1]. This view is further echoed by Sheriff in whose analysis a large, as yet unexplained, discrepancy existing between the levels of blood flows achieved by maximal chemical vasodilation and through voluntary exercise cannot be explained [14].

Despite the above listed, seemingly well-grounded imperative for muscle pump hypothesis, some researchers have argued that the evidence for its existence is at best circumstantial [17], sparking a lively debate on the topic [14, 18, 19]. As noted by Laughlin and Scharge, one of the major difficulties with the theory lies in the fact that there is no satisfactory method to directly measure the variability of venous pressure within the contracting muscle itself [20]. In addition, animal models in which direct or indirect electrical stimulation of the muscles has been applied – to show the effect of muscular contraction on muscle hyperemia – have proven just the *opposite*, namely, that the volume of blood expelled from the muscle during contraction is small in comparison to blood displaced by the arterial inflow [17]. More significantly, the changes of blood flow through the muscle in response to exercise are far greater than those accounted for by measuring local arterial and venous pressures [21]. The validity of the mechanistic pressure–suction model of muscle-activated blood flow has been further questioned on grounds of virtually instantaneous, contraction-linked surge in muscle blood flow with the onset of exercise [22, 23], followed by metabolically induced hyperemia [24, 25]. This view is supported by findings which suggest that, in the absence of vasodilation, muscle contractions per se do not elicit an increase in blood flow [26]. In their review on

blood flow dynamics in the working muscle Tschakovsky and coworkers proposed an exponential model of exercise-induced muscle hyperemia with an early perfusion peak within 5–7 s (phase I), followed by the second increase reaching plateau in 15–25 s (phase II) and a gradual transition during sustained, heavy exercise into the third phase, with maximal blood flows [27].

17.1.2 Metabolic Control of Muscle Blood Flow

At rest, skeletal muscles exhibit very low perfusion rates. For example, an individual weighing 75 kg has about 30 kg of muscles containing 750 ml of blood (14 % of total blood volume, TBV). In comparison, the liver, a highly vascular organ weighing 1.5 kg, contains 500–600 ml of blood (10 % of TBV) [15]. Historically, pronounced basal tone of the skeletal muscle vessels was thought to have been maintained by local and systemic vasoconstrictors. Gaskel, the first to describe an increased blood flow with the onset of muscular activity in 1870s, ascribed it to neurogenic origin [9]. Well over half a century later, Lofving and Mellander demonstrated that the resistance to flow in an acutely denervated cat muscle was decreased by 80–85 % with an arterial injection of ATP, or acetylcholine, but did not substantially change to infusion of epinephrine, norepinephrine, serotonin, angiotensin, and vasopressin [28]. Over the years the much sought for evidence over control of muscle blood flow regulation has shifted to the interaction between the locally formed vasoactive substances and their local as well as systemic sympathetic modulation. In the 1980s, the pivotal role of vascular endothelium – and its response to sheer stress and production of endothelium-derived factor (NO) and prostaglandins – was recognized (for review, see [4]). Since the already-known vasodilators, such as acetylcholine, adenosine agonists, and antagonists, and NO synthase inhibitors failed to exhibit significant muscle blood flow regulation, a search was on for “a missing vasodilator” [4].

It is currently understood that in resting muscle the vasomotor tone is determined by an inherent myogenic activity of the resistance vessels, modulated by a relatively high (sympathetic) myogenic tone [16]. During exercise, on the other hand, the primary determinant of the skeletal muscle blood flow, and hence of perfusion, is the increased metabolic rate of the muscle which plays a central role in exercise hyperemia [16, 29].

Muscular exercise is accompanied by a general increase in sympathetic activity – a response known as the “exercise pressor reflex,” directed to active as well as to resting muscles [30, 31]. In inactive muscles, the “pressor reflex” causes vasoconstriction, whereas in active muscles, the effect of increased sympathetic activity has no measurable effect and vasodilation is maintained despite of high levels of circulatory catecholamines. This phenomenon, known as “functional sympatholysis,” is believed to play a pivotal role in the distribution of cardiac output between the maximally dilated vessels in working muscles and other organ systems [6, 16].

A review by Joyner and Halliwill suggests that, at least in humans, neurally mediated vasodilation in active muscle does not play a significant role [32]. There is increasing evidence that intraluminal ATP, released from the RBCs, plays a pivotal role in promoting local skeletal muscle blood flow regulation directly by causing vasodilation and indirectly by the inhibition of vasoconstrictive effect of norepinephrine mediated by endothelial purinergic receptors [31, 33, 34].

To differentiate the effects of muscle pump from pharmacologically induced muscle vasodilation at rest and during exercise, Gonzalez-Alonso and coworkers conducted a study in which local and systemic hemodynamic parameters were measured in response to femoral artery/vein infusion of ATP in male subjects [35]. It was proposed that pharmacologically induced hyperemia, in the absence of muscular pump, would significantly compromise venous return, cardiac filling, and, in turn, cardiac output. The second aim of the study was to ascertain the contribution, if any, of the skeletal muscle pump on local and systemic hemodynamics during active, one-legged knee-extensor exercise and of the hemodynamic effect of passive, external muscle compression. To separate out the metabolic effects of exercise-induced hyperemia from hyperemia caused by external, rhythmic compression and/or passive motion, the leg blood flow, O_2 delivery, and $D(a\text{-}v)O_2$ (arteriovenous oxygen difference) were measured. Results of the study are shown in (Fig. 17.3) and demonstrate a number of important points:

During incremental arterial infusion of ATP, there was an increase in CO which closely matched the increase caused by the active leg exercise, whereas the vascular conductance, stroke volumes, and MAPs were significantly higher during ATP infusion than with the active exercise. In contrast, no changes in CO, leg blood flow, or MAP occurred during venous infusion of ATP, suggesting that increases in CO during exercise or ATP infusion are brought about by increased blood flow through the muscle. Of further interest is the fact that ATP infusion did *not* affect metabolism of the tested leg as indicated by unchanged leg VO_2, glucose uptake and lactate release, and femoral venous temperature, suggesting that an activation component, which triggers the metabolic changes in the muscle, is not activated by intraluminal ATP. The authors concluded that the skeletal muscle pump is *not* obligatory for sustaining CO or maintaining muscle blood flow during one-legged exercise in humans. Moreover, the contribution of muscle pump and of mechanically induced vasodilation is small in comparison with the effects of limb muscle vasodilation [35]. High vascular conductance with ATP infusion confirmed previous reports in which ATP infusion increases vascular conductance during maximal exercise by a further 17 % [36] and overrides sympathetic vasoconstrictor activity in human skeletal muscle [37]. It appears that matching of metabolic demands of the contracting myocytes is brought about between locally formed vasoactive substances (ATP, ADP, AMP, and adenosine) [31, 38] and increased perfusion caused by intraluminal ATP released by the circulating erythrocytes [34, 39, 40]. A growing body of data suggests that ATP is the key modulator of local and systemic hemodynamics during exercise. Its brief half-life (less than 1 s) and immediate availability from the circulating red blood cells make it a likely candidate to be the "the missing vasodilator" [3, 41].

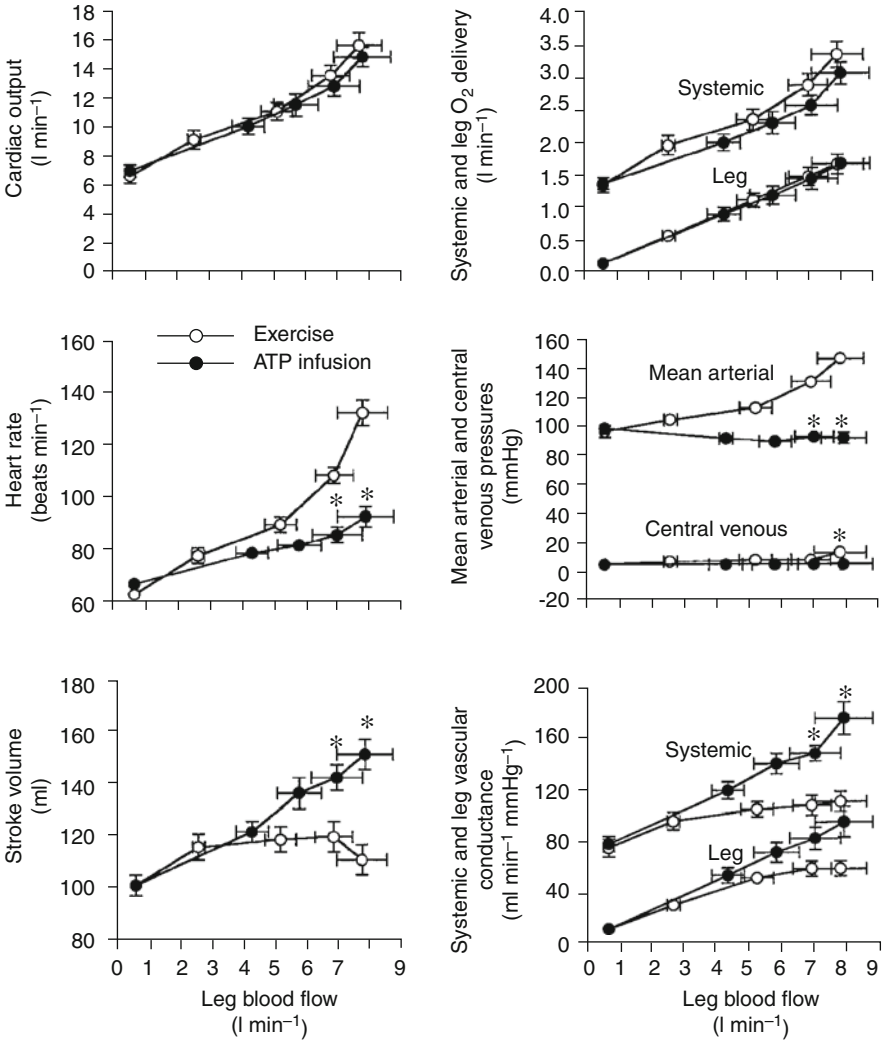

Fig. 17.3 Lower extremity and systemic hemodynamics during incremental exercise and graded femoral artery infusion of ATP. *Open circles* depict systemic hemodynamics and *filled circles* represent leg hemodynamics. Data points are mean ± S.E.M for nine subjects. * different from exercise, $P < 0.05$ (Reproduced from Ref. [35], used with permission of John Wiley and Sons)

17.2 The Heart in Exercise

The heart represents less than 5 % of body weight and during basal conditions receives around 60–70 ml of blood per 100 g of tissue. The high capillary density (exceeding that of the striated muscle by a factor of 8!) facilitates diffusion and extraction of oxygen, which reaches the range of 60–80 % of available arterial

oxygen content. Therefore, the heart can meet increasing energetic demands of exercise only by increasing coronary perfusion which, at peak exertion, parallels that of the skeletal muscle. Due to considerable interspecies variation detailed pathways of the "metabolic" increase in (human) coronary blood flow to exercise have not been elucidated. For example, studies in dogs suggest that "metabolic dilation of canine coronary resistance vessels is regulated via a myriad of vasodilator systems that act in concert to match coronary blood flow to myocardial oxygen demand so that when one system fails, back-up systems ensure an adequate oxygen supply to the myocardium" (Duncker and Bache [42]). Since there are no venous valves in cardiac veins, existence of a muscle pump in the myocardium has not been proposed as a mechanism which maintains its perfusion [4].

The remarkable ability of the heart to increase its performance by four to six times in the course of incremental exercise is attributed to increased contractility (E_{max}) due to beta-adrenergic stimulation and an enhanced ventricular diastolic compliance which improves diastolic filling in the order of 60 % [43]. Untrained subjects typically demonstrate an initial rise in SV averaging 28 % (range 13–46 %), before reaching a plateau that remains unchanged to the point of exhaustion (see [44] for review). In highly trained endurance athletes, in contrast, the SV may continue to rise progressively to the point of maximal exercise [45]. The increased diastolic chamber compliance is, therefore, the single most important mechanism for increasing SV, noted particularly in endurance athletes, in whom, surprisingly, the contractility is no greater than in nonathletes [46].

Apical displacement of the AV (valve) plane during diastole represents 60 % of the total SV at rest [47] and increases significantly even after short-term endurance training [48]. There is a reciprocal relationship between the heart rate and SV, i.e., as the HR doubles, the SV halves, which limits CO. This effect is ameliorated by adrenergically controlled force–frequency relation (FFR), an intrinsic mechanism of the myocardium by which the strength of contraction is markedly enhanced, allowing the maintenance of SV in the face of decreased diastolic filling times [49]. There is a linear relationship between HR and intensity of exercise up to maximum rates which can increase up to two and a half times in untrained and up to five times in trained athletes [50]. Thus, an immediate response to exercise is marked by a 30–40 % increase in SV; however, the value differs with position in which the exercise is performed, i.e., supine, sitting, or upright. Stroke volumes reach similar values, regardless of position, after exercise stabilization and remain the same to exhaustion [2]. Similarly, LV end-diastolic dimensions remain stable or possibly decline with exercise intensity [2]. The lack of incremental change in SV and ventricular size in progressive exercise is remarkable, considering the large increase in venous return. Linden proposed that changes in HR constitute the basic mechanism for controlling the heart volume and size [50]. As the heart rate increases during maximum exercise, the diastolic filling time progressively shortens to the point of becoming *shorter* than the systolic ejection time, indicating a remarkable rate of diastolic filling [44]. Theoretical and experimental studies by Lauboeck demonstrate, moreover, a progressive shortening of isovolumic contraction period at increased heart rates, until it disappears entirely at the rate of about 140 beats/min. Conditions

thus prevail during strenuous exertion where the blood begins to flow through the aortic valve even *before* the closure of the mitral valve, suggesting a *continuous* flow of blood through the heart [51, 52].

It is imperative that the size of the heart is kept small, since in accordance with LaPlace's Law, at constant wall thickness, the heart with greater diameter would have to work at increased wall tension [1]. This would constitute an energetic disadvantage and pose a danger of right ventricular overdistension [53]. It is apparent that the pericardium also plays a crucial role in controlling the size of the heart during periods of large-volume throughputs. Studies in pigs have shown that the removal of pericardium results in 33 % increase in EDV and a 29 % increase in CO within 2–3 weeks of treadmill exercise [54]. Increase in SV and EDV was also demonstrated in untrained, pericardiectomized dogs [55]. Exercise-induced endurance training leads to "physiological" LV hypertrophy, i.e., athletic heart, characterized by increased LV cavity dimension and mass and preserved contractility [56–58], which distinguishes it from hypertrophic cardiomyopathy, responsible for up to a third of sudden deaths in young athletes [59].

Helical orientation of myocardial fibers, as discussed in Chap. 13, adds significantly to the heart's ability to "hold up" against the increasing momentum of the moving blood in aerobic exercise. During systolic contraction the ventricular chamber undergoes a counterclockwise torsion of the apex relative to its base, followed by untwisting (clockwise rotation) of the apex during the isovolumic relaxation and early diastole [60]. Tischler and Niggel reported an increase in systolic twist (apical minus basal rotation) by 8.4 ± 2.8° (86 %) during a short bout (60 s) of maximal treadmill exercise in young adults [61], and Notomi et al. measured an increase in systolic twist from 11.4 ± 4° at rest to 24 ± 8° during submaximal supine bicycle exercise [62]. Compared to age-matched, non-trained individuals, professional soccer players have a reduced angle of left ventricular twist and torsion velocities at rest [63], suggesting that larger hearts, with more inertia, interrupt the flow of blood more efficiently. It is of interest that patients with hypertrophic cardiomyopathy show an increased LV twist at rest when compared with normal subjects, however, with apical and basal rotation in the *same* direction (rather than in the opposite, as is the norm). These differences are enhanced during exercise, where patients fail to respond with an increase in LV twist from baseline and have a significant delay in untwisting [62], thus predisposing them to a potential catastrophic reduction in forward flow.

17.3 Changes in Pulmonary Circulation

It is a given that any increase in systemic flow during progressive exercise is paralleled by a matching increase in pulmonary blood flows. Unlike in the systemic circuit where, due to blood redistribution, the muscles are super-perfused at the "expense" of other organ systems (which receive less blood than during basal conditions), the pulmonary vessels respond to increased functional flows by

recruitment of the capillary bed. In adult lung, flow can be increased threefold before any change in the pulmonary artery pressure can be detected. Once "fully recruited," further increase in flows results in linear increase in pulmonary artery and venous pressures [64] and activation of intrapulmonary arteriovenous pathways [65]. Large increase in flow results in distension and recruitment of pulmonary microcirculation [66] and a twofold decrease in mean capillary transit time [67] reflected in linear increase in PAm (mean pulmonary artery pressure), from an average of 14 to 25 mmHg at maximal exercise [68]. In spite of highly compliant vasculature, systolic PA pressures up to 60 mmHg and higher have been reported in trained athletes [69–71]. The excess flow is further indicated by additional arteriovenous shunting, as seen in progressive rise in $A–aDO_2$ (alveolar–arterial oxygen difference) [72]. Increase in exercise intensity results in increased rate of oxygen uptake by the lung which is similar in trained and untrained subjects; however, the *maximal* rates are significantly greater in trained athletes [20] (Fig. 17.2). A slight but significant deterioration in pulmonary gas exchange (in the range of 10–15 %) due to shunting reaches peak values immediately after the onset of exercise and remains stable to exhaustion [73].

The factors which lead to such marked increase in PA pressures during exercise are not fully understood and cannot be accounted for in the context of the pressure propulsion theory, considering the fact that PVR (pulmonary vascular resistance) does not rise in exercise and may even decline [74, 75]. It is not clear whether increase in pressure is the result of increased pulmonary flow, a change on PVR, or the combination of both, leaving the clinicians to question the significance of PA pressures as such [71]. The situation is further compounded by data which indicate that left atrial (LA) pressure can exceed 20 mmHg and pulmonary capillary wedge pressures (PCWP) can reach up to 36 mmHg or higher during strenuous exercise, the values which significantly *exceed* Starling equilibrium at the alveolocapillary membrane and the threshold for the generation of pulmonary edema [76]. It is well known that progressive exercise and increased pulmonary flows are linearly related to the degree of tricuspid valve regurgitant flows. Sonographic assesment of regurgitant flow has become a standard noninvasive screening method for the assessment of PA pressures at rest and during exercise in normal subjects and in those with suspected pulmonary hypertension. One would expect that increasing diastolic incompetence of the tricuspid valve during strenuous exercise would work *against* the pumping action of the RV at the time when it is most critical. Or, is it possible that the thin-walled RV is overdistended by the large increase in venous return, generated by the opened muscular loops?

17.4 "The Sleeping Giant"

The blood flow to exercising muscle increases up to 100-fold above the basal values, or 2.5 l kg^{-1} min^{-1} in quadriceps muscle [77, 78] and can reach up to 3–4 l kg^{-1} min^{-1} in trained athletes [79]. Concern has been raised that this level of perfusion could overwhelm the "pumping capacity" of the heart, with

concomitant drop in CO and blood pressure, if similar level of hyperemia would be achieved in most muscle groups during the whole body exercise [3, 77]. Calbet et al. demonstrated that during submaximal exercise in well-trained athletes, i.e., cross-country skiers, the legs receive 60 % and the arms 35 % of CO (CO values ranged around 27 l min^{-1}). When compared to baseline conditions the mean, systolic, and diastolic arterial pressures were lower by 14, 11, and 34 %, respectively. To *maximally* perfuse all limbs, the calculated CO should have been 33–34 l min^{-1} or some 4 l *more* than the measured values. In case of maximal exercise, the calculated CO of 37–40 l min^{-1} would be needed to perfuse the arms and legs, without compromising systemic blood pressure and perfusion of other vascular beds. In view of these remarkable discrepancies the authors (rightfully) concluded that "The combined conductance of arms and legs exceeded the pumping capacity of the heart…implying that muscular vasodilatory response during maximal exercise must be restrained to maintain perfusion pressure" [80], the problem being that the mechanism of this "restraint" has yet to be identified.

We are clearly faced with a paradox here in the sense that even in moderate degree of exercise blood flow to the muscle can easily exceed what the heart could actually supply as a propulsion pump. Hence, the theory arose that the CO is the limiting step in the capacity of the cardiovascular system to deliver oxygen to the muscles [81]. This is the situation in the best case scenario in a dynamic exercise, when the (hypothetical) muscle pump is doing at least as much work as the heart. Is the heart performing a double role of impelling, i.e., accelerating and "restraining," the blood at the same time? A profound decrease in peripheral resistance as seen in exercise can cause a drop in MAP, jeopardizing perfusion of the brain and heart and, ultimately, of the working muscles. It is of interest that exercise-related syncope, due to hypotension and cerebral hypoperfusion, shares many similarities with advanced degrees of vasodilatory shock. The latter is associated with *decreased* myocardial contractility (in spite of increased cardiac outputs) and exhibits resistance to vasopressors [82] (cf. Chap. 21).

A further problem concerns the abovementioned immediate, substantial increase in blood flow after the release of the first muscle contraction, i.e., faster that could be accounted for by the "metabolic vasodilation" [24, 25]. A related question concerns the inertia of some 5 l of blood which has to be moved within a matter of seconds up to remarkable flow velocities, invoking an image of a row of cars, which all drive off at the same time rather than being pushed from behind resulting in a pileup. The exercising muscle has aptly been referred to as "the sleeping giant, whose blood flow must be under tonic vasoconstrictor constraint if hypotension is to be averted" [4]. In a recent review on the subject, Calbet and Joyner submitted that "Despite the effort made by several generations of physiologists over the past 150 years, many questions remain on the regulatory mechanisms that elicit and maintain skeletal muscle hyperemia and how cardiac output and muscle hyperemia are coupled during heavy exercise in humans" [3]. The existing problems of exercise hyperemia have been summarized by Tschakovsky and Sheriff [25] and were subject of a thought-provoking editorial [83].

It is proposed that the conflicting observation can be resolved only when the blood is assumed not to be an inert fluid "pumped" around the circuit by the heart but a "self-moving" agent with flow directly coupled to the metabolic needs of working muscles. The existence of muscle pump serves the same purpose as the heart, namely, to "restrain" the massive increase in venous return, with venous valves protecting against the backflow and peripheral congestion. Performance of the heart during exercise is perhaps the best example of the fact that the heart sets itself *against* the flow of blood and impedes rather than propels it. Enhanced systolic torsion (counterclockwise rotation of the apex relative to the base) [44, 62, 84], increased myocardial mass, and enlarged ventricular cavities are physiological adaptations to increased flow. In keeping with the greatly increased venous return, the mean arterial pressure is kept low to accommodate for increased oxygen requirements by the working muscles and, yet, is adequate to sustain perfusion of vital organs. Only when seen as an organ of impedance can the heart place itself effectively against the "runaway train" of oncoming blood to generate only moderately increased MAP even during maximal exercise. It does this by increasing its diastolic compliance (which markedly improves diastolic filling) and increased contractility, which increases maximal systolic contraction and, thus, ejection fraction. Both of these mechanisms allow the heart to maintain normal (or near normal) dimensions and protect it from overdistension in the face of greatly increased blood flow ("cardiac throughput").

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Chapter 18
Hemodynamic Effects of Aortic Occlusion

Mechanical occlusion of the aorta has been considered one of the classical interventions in cardiovascular physiology in the study of models of circulation. It is characterized by a complex hemodynamic response of great interest not only to cardiovascular physiologists but also to clinicians in the fields of vascular surgery and anesthesia. According to the pressure-propulsion model of the circulation, one would expect that a break of continuity between the pump and the system of vessels would result in an immediate decrease in flow. This, however, is not the case. A progressive occlusion of the proximal aorta in a dog results in increase in peak ventricular systolic pressures (PVP) and a concomitant increase diastolic pressure–volume (LVEDP and LVEDV), without change in CO (the phase of *complete compensation*). During the subsequent stage (*partial compensation*), there is a further increase PVP, LVEDP, and LVEDV and only a slight drop in CO. Only during the final phase is there a sharp drop of CO and a maximal increase in PVP pressure (200–250 mmHg) and a progressive rise in LVEDV and LVEDP (phase of *decompensation*) [1]. It is little surprising that in spite of the large number of animal and clinical studies, information regarding the underlying pathophysiology and regulation of cardiac output during aortic occlusion remains contradictory, with some reporting increase, decrease, or no change (for a review see [2]). We will now briefly examine some of the major circulatory effects of aortic occlusion on the peripheral circulation and on the heart.

18.1 Systemic Circulation

Historically, as early as 1986 de Jager ascribed the rise in carotid and central venous pressures in response to aortic occlusion in anesthetized dogs to the shift of blood from arterial to venous compartments, caused by "elastic energy accumulated in the coats of arteries." De Jager also noted that occlusion of the inferior vena cava results in a drop of arterial pressure to about half of normal values and of the central venous pressure to zero. He thought it particularly significant that after a temporary release

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Table 18.1 Arterial pressures, systemic flows, and right atrial pressures in dogs at control conditions and after sequential occlusions of thoracic aorta, superior vena cava, inferior vena cava, and brachiocephalic artery

	Control	Thoracic aorta occluded	Superior vena cava occluded	Inferior vena cava occluded	Brachiocephalic artery occluded
Arterial pressure (mmHg)	70	140	50	32	100
Systemic flow ($ml \cdot min^{-1}$)	792	990	360	125	792
Right atrial pressure (mmHg)	5.1	5.8	4.1	3.2	4.1

Reproduced from Ref. [6], used with permission of John Wiley and Sons

and re-occlusion of the IVC, there was a rise in CVP which he interpreted as venous stasis due to weakening and inadequate diastolic suction of the right ventricle [3].

In the 1930s Barcroft was the first to demonstrate the peculiar phenomenon of an increase in systemic blood flow by some 25 % above the control levels after occlusion of the thoracic aorta in anesthetized, open-chest, vagotomized dogs [4]. Barcroft further showed that a marked increase in arterial pressure and flow did not, in fact, result from the "increased pumping action of the heart" or on account of central neurogenic or local vascular reflexes but was caused by an additional volume of blood, transferred from the splanchnic compartment [5]. In an effort to clarify the puzzling hemodynamic response, Barcroft sequentially occluded the thoracic aorta, SVC, IVC, and the brachiocephalic artery and measured hemodynamic parameters during each state (Table 18.1).

The findings showed that in spite of profound changes in flows and arterial pressures affected by occlusion of the great vessels, there was relatively little variation in the corresponding RAPs [6]. In order to confirm that the heart indeed "reacts to all changes in the peripheral circulation by maintaining the central venous pressure constant" – as corroborated by Starling and coworkers only a few years earlier on the heart–lung preparation – Barcroft repeated the vessel-occlusion experiments in animals whose heart had been replaced by a mechanical pump [7]. The results indeed showed that, during aortic occlusion, the pump flows had to be increased by up to 60 % above baseline to maintain constant RAPs. The pump flows during occlusion of other great vessels, on the other hand, were comparable to baseline flows before occlusion. In view of his findings, Barcroft made the following comment: "The striking thing is that the healthy heart maintained the venous pressure practically constant in the face of flow changes from 990 to 125 c.c. per min., and arterial blood pressure changes of 140 to 32 mm of mercury. Broadly speaking this suggested that, in these experiments, the heart maintained the venous pressure at zero, pumping away what returned to it irrespective of arterial pressure" [7].

Barcroft therefore concluded that the increase in CO following aortic occlusion results from factors related to the peripheral circulation, citing the model proposed by Krogh by which the blood is transferred from a large, highly compliant

hepatosplenic reservoir into the low-compliance, upper-body compartment with concomitant increase in venous return [8].

These experiments were repeated almost half a century later on anesthetized, atropinized dogs by Stokland and coworkers [9]. In addition to implanting snares around the descending thoracic aorta and IVC, the internal mammary artery and the azygos vein were ligated to prevent vascular communication between the upper and lower parts of the body. Left ventricular dimension, i.e., the myocardial cord length (MCL), was monitored via a pair of miniaturized ultrasonic probes implanted on the anterior aspect of the LV wall. The results showed that occlusion of the descending aorta results in doubling of SVC flows, while the flow through IVC stabilized at 10 % of control. Unlike in Barcroft's experiments where aortic occlusion resulted in a marked increase in CO, the combined flow through SVC and IVC reached only about 80 % of control value. The left ventricular systolic pressure (LVP) increased from 102 ± 7 to 188 ± 11 mmHg and LVEDP rose from 3 to 8 mmHg, the latter corresponding to an increase in MCL by 10 %.

Simultaneous occlusion of the descending aorta and IVC resulted in the cessation of flow in the IVC and caused MCL to diminish by an average of 38 %, while LVP and flows in the SVC remained the same as during the aortic occlusion. Remarkably, after reaching a "steady state," the systolic LVPs and SVC flows during combined aortic and SVC occlusion were virtually the same as during control (pre-occlusion) state.

A heightened "sensitivity to blood volume" during combined aortic and SVC occlusion was demonstrated by the infusion of 50 ml aliquots of blood into the jugular vein to the total cumulative volume which restored myocardial dimensions and SVC flows to pre-IVC occlusion levels. Subsequent withdrawal of blood from the upper-body compartment to pre-infusion control values suggested that about 7–8 % of total blood volume was transferred from the lower to upper-body vascular compartment, presumably via venous communications in the spinal canal. On the basis of their data, Stokland and coworkers concluded that redistribution of blood volume due to "vascular collapse" and the activation of the Frank–Starling mechanism via increase in LV end-diastolic volume "completely accounted for hemodynamic responses" during descending thoracic aortic occlusion [9].

Unlike Barcroft's and several other reports, which demonstrated an increase in CO following the occlusion of the thoracic aorta, the study by Stokland et al. showed an actual *decrease* in CO. The question was therefore posed as to what factors could account for such a discrepancy in COs between the two studies. Did large LV pressures and distension of the LV cause a weakening of the LV, leading to decreased output, or was there a significant but unrecognized backing up of blood before the right heart, since no values of RAPs were reported in Stokland's study? To clarify the issue, Stene et al. repeated Barcroft's aortic occlusion – right heart bypass experiment [10]. In place of the total cardiopulmonary bypass, where the "heart–lung preparation" of another dog served as a source of oxygenated blood, Stene et al. used the right heart bypass (RHB). The pump flows were maintained at rates slightly above venous return to keep consistent drainage of the RA (Fig. 18.1). Estimates of the MSP (mean systemic pressure) were obtained by temporarily stopping the pump

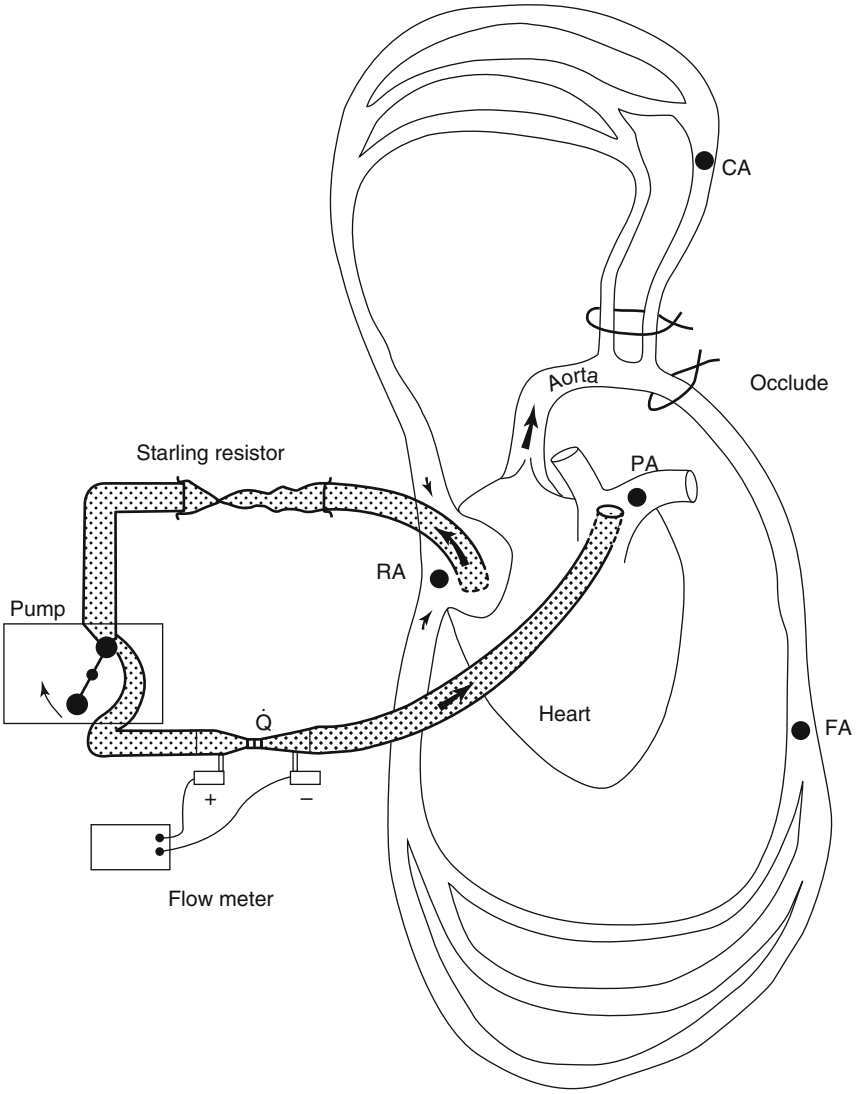

Fig. 18.1 Right heart bypass preparation used for descending aortic occlusion experiments in a dog by Stene and coworkers. Blood returning to the right atrium flows via Starling resistor to control right atrial pressure and is delivered into the pulmonary artery, bypassing the right ventricle. Snares show levels of aortic and brachiocephalic artery occlusion. Right atrium (*RA*), pulmonary artery (*PA*), carotid artery (*CA*), and femoral artery (*FA*) (Reproduced from Ref. [10], used with permission of the American Physiological Society)

and measuring the plateau pressures for 7–9 s. The latter served as an index of overall compliance changes in the peripheral circulation during AO (aortic occlusion).

The results showed that occlusion of the descending thoracic aorta with constant RHB in anesthetized, paralyzed dogs resulted in 47 % increase in mean carotid

pressure and a 43 % increase in CO above the control, with values of MSP remaining at baseline levels. Stene et al. concluded that the increase CO in their study resulted solely from the increase in venous return to the heart, which was "unmasked" by adjusting the pump flows to control RAP at near-zero values. In their words, "The fine-tuning of CO can only occur if RA is competent to maintain RAP constant," which is to say, that the heart can only pump away the blood that is delivered to it, as already observed by Barcroft. Thus, any increase in RAP would constitute a "resistance to venous return" and, according to Guyton's model (see Sect. 14.3.), diminish CO.

As to the causes of increase in CO during AO, Stene et al. considered two possibilities, namely, the alterations of vascular tone and changes in blood volume distribution from the splanchnic veins to the vascular system drained by SVC. The splanchnic vascular bed is considered to be the most important reservoir for blood relocation during thoracic aortic occlusion [11]. The constant values of MSP before and after AO suggested a redistribution of blood from a large-compliance splanchnic compartment to low-compliance upper-body vascular compartment, as originally proposed by Krogh and later reformulated by Caldini et al. [12, 13].

18.2 Cardiac Effect of Aortic Occlusion

In addition to affecting the distribution of blood in the periphery, aortic occlusion in an intact animal exerts significant effect on the action of the heart. The magnitude of these changes naturally depends on the level of aortic occlusion but invariably result in a large increase in afterload and adaptive changes in ventricular preload and contractility. The function of the LV in the isolated heart preparation under conditions of increased afterload has already been considered (see Sect. 16.3).

While changes in heart rate during aortic occlusion can be eliminated by the administration of atropine, it is conceivable that baroreceptor reflexes could play a significant role in modifying of cardiac contractility, in particular during proximal aortic constriction. To assess the significance of cardiac and reflexogenic effects of proximal and distal aortic occlusion, Ilebekk and coworkers performed a study on open-chest, atropinized dogs, in which a stepwise constriction of proximal and distal aorta was performed during baseline conditions and during increased inotropic state (isoproterenol infusion), until systolic LV pressure increased by 50–70 mmHg. Aortic and ventricular pressures were recorded and LV wall parameters and aortic dimensions were sampled by means of implanted ultrasonic probes [14].

The results showed that *proximal* aortic constriction during control conditions and during increased inotropic state raised the systolic pressure by an average of 49 mmHg and reduced SV by 18 % but, surprisingly, affected neither LVEDP, EDMCL (end-diastolic myocardial cord length), or contractility. In contrast, SV during *distal* aortic constriction was no different from controls but rose by 42.5 % during isoproterenol infusion. Inotropic intervention caused, moreover, a marked increase in left ventricular diastolic dimensions (dilation) and an increase in contractility. (It should be noted that the authors used (dP/dT), the first derivative of

LVP divided by instantaneous ventricular pressure, as an index of myocardial contractility.)

The finding of a decreased SV during proximal aortic constriction was paradoxical, since the ventricle was ejecting at greater pressures (afterload) during distal occlusion. To clarify the mechanism which would account for the differences, the authors repeated proximal aortic occlusion experiments. Increments of low molecular weight dextran were now infused in the amount which would restore SV to control levels. Additional volume was thus able to restore SV during proximal aortic occlusion without affecting ventricular flow and pressure parameters. Analysis of LV pressure and flow patterns indicated that alterations in aortic compliance and volume are, in effect, independent of afterload, as is the case in the isolated heart preparation and that increase in ventricular filling (preload) solely accounts for the changes in SV during proximal and distal aortic occlusion [15] (see Sect. 16.3). Of further interest is the observation that during proximal aortic constriction, the pressure in the aorta (distal to the snare) fell from the mean of 97 to mean of 85 mmHG, in contrast to the aortic pressure beyond the distal aortic occlusion, which fell to 20 mmHg [14]. The mechanism which would maintain such relatively normal pressure during high aortic occlusion is not understood.

It is certainly difficult to imagine by what mechanism the heart as a pressure-propulsion pump achieves increased CO in the face of an occluded aorta without any increase in its contractile power. Ilebekk and coworkers' study confirms what has been observed repeatedly ever since Starling, namely, "that the heart pumps out all of the blood which it receives" [16] and in this respect behaves mechanically like a hydraulic ram.

What then are the factors which control the CO during inimical state of aortic occlusion? It has been observed that decreased blood flow distal to the aortic occlusion is associated with a decrease in oxygen consumption in ischemic tissues [2]. One would not expect, however, that oxygen uptake in tissues *above* the occlusion is also reduced. Magnetic resonance studies show a decrease in muscle creatine phosphate levels in the skeletal muscles above the level of aortic occlusion and are consistent with muscle ischemia which starts immediately after application of the cross clamp [17]. A decrease of total body oxygen consumption during aortic occlusion is further indicated by consistent findings of increased mixed venous oxygen saturation and content [18, 19] and has been attributed to *increased* arteriovenous shunting in the tissues above the occlusion [20].

It appears that, in the face of such inconsistencies, the circulating blood forms "a unity" and is subject to a lawfulness that differs substantially to that for inert fluids.

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Chapter 19
Increased Pulmonary Flows

The hemodynamic response to exercise is characterized by a combination of peripheral and central factors brought about by increased metabolic activity. Conversely, there are a number of conditions in which a hyperdynamic state exists in the absence of "metabolic cause" such as in congenital heart disease with communication between systemic and pulmonary circulations, in AV malformations, and in traumatic or acquired arteriovenous (AV) fistulas. Because of varied clinical presentation and a wide-ranging symptomatology, the "short circuit" between the arterial and venous circulations has been of interest to physiologists and clinicians alike for well over a century and offers a unique insight into the relationship between central and peripheral circulations. We will first consider the hemodynamic perturbations of AV fistulas.

19.1 Arteriovenous Fistula

A typical adaptive response to opening of a "mature" (3 weeks post-procedure) femoral AV fistula in a dog is marked by a 5 % drop in mean arterial pressure (MAP) and an increase in SV(18 %), HR (24 %), and CO (37 %) [1]. There is a partial transfer of the circulating blood volume from arterial to venous side of the circulation with increase in CVP. Similar changes occur in dogs lacking spinal and autonomic innervation [2]. The creation of a more proximal fistula, i.e., by placement of a 10 mm diameter graft between infrarenal aorta and vena cava in dogs, results in an immediate doubling of HR (97–173 beats/min) and CO (250 %) and concomitant increase in SV and EDV [3]. Ventricular (load-independent) contractility index (E_{max}) was maintained in the immediate period of fistula opening but became significantly depressed during a week-long experiment. In spite of the compensatory hypertrophy (an average increase in heart mass of 10 %), the animals experienced signs of severe congestive heart failure (ascites, limb edema, high LVEDP, and pulmonary edema) [3]. Fujisawa et al., on the other hand, noted an

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immediate increase in contractility (E_{max}) in dogs after the opening of a large aortocaval fistula [4].

When the initially large fistula flows are "within the limits" of cardiovascular compensation, a chronic condition ensues, characterized by a gradual return of HR and MAP to control levels, with concomitant increase in heart mass (hypertrophy) and expansion in extracellular fluid and blood volumes, resulting in progressive hemodilution. Huang and coworkers showed that in rats with large fistula flows (equaling about 50–77 % of baseline CO), there was a progressive increase in CO over a 5-week period, reaching values over three times of control; however, when adjusted for increase in weight (due to increased blood volume), the cardiac index (CI) was the *same* as in the control group. The mean arterial pressure and systemic flow (determined by subtracting fistula flow from CO) initially decreased but gradually returned to normal. The persistence of near-normal HR in the face of greatly increased CO indicated a large increase in SV [5]. This observation has been confirmed by several other reports in which increases in SV of up to 80–90 % were observed in acute and chronic AV fistulas. With time, the circulation through the fistula continues to increase with further expansion of arterial and venous collaterals, leading to a vicious cycle of escalating cardiac outputs and CHF [6, 7]. In terms of cardiac biochemical and energetic changes, Gibbs and coworkers found only a small increment (13 %) in basal metabolic activity and no change in mechanical efficiency in the hearts of rabbits subjected to chronic volume overload (12 weeks of aortocaval fistula flows). This was in contrast to chronic pressure overload studies in which partial obstruction of aorta resulted in marked *depression* of myocardial metabolic activity, leading the authors to conclude that "It seems clear from both our pressure- and volume-overload studies that in vivo cardiac failure can occur regardless of whether many of the intrinsic contractile and biochemical processes of cardiac cells are relatively unimpaired" [8].

Conventional explanation of circulatory effects caused by AV fistulas is invariably based on the concept of a drop in peripheral resistance. For example, Guyton and Sagawa initially maintained that LV hypertrophy is a response to increased workload on account of increased venous return and filling pressures [2], whereas in a later study by Guyton's group, the authors submitted that the cause of LV hypertrophy is not completely understood. However, the fact that blood flow to individual organs is eventually *normalized*, in the face of decreased peripheral resistance, suggests that increased flows are dictated by the metabolic demands of the tissues [5].

In addition to the systemic effects listed above, a variety of peculiar local phenomena have been observed in connection with acquired or created AV fistulas, such as thickening of the intima and media (arterializations) of the vein proximal to the fistula, elongation and increased tortuosity of the proximal artery, flow reversal in the distal artery [9], peripheral ischemia due to "stolen" perfusion or increased limb growth. (For review, see [10].) Some of these phenomena, such as the *retrograde* flows in veins, have eluded explanations based on conventional circulation model.

High-output cardiac failure is a known complication of aortocaval fistula in experimental animals [7] and in humans [11, 12] and is relatively common in renal

patients on hemodialysis [13, 14]. Recent data moreover suggests that dialysis patients with high fistula flows develop pulmonary hypertension (PHT) [15, 16]. It is noteworthy that closure of the fistula in experimental animals [1] and end-stage renal disease (ESRD) patients, say, after receiving of a donor kidney, reverses the changes [17, 18]. Massive diuresis has been reported in a patient after closure of chronic aortocaval fistula [19].

Several physiologists have remarked on a striking similarity between the acute circulatory response to exercise and the opening of a large AV fistula in the sense that a large decrease in peripheral resistance is met by increased CO (references quoted in [20]). However, as shown in Sect. 14.1, numerically derived "peripheral resistance" from Poiseuille's equation [20] or Ohm's relationship [10] reflects neither global nor local state of organ perfusion. As mentioned, a surge in CO seen in aerobic exertion is a physiological stimulus to increased metabolic demands that calls for a parallel rise in pulmonary blood flow and differs markedly from the increased pulmonary flows due to AV fistula. The final increase in volume flow in AV fistula comes from two sources, namely, from the shunt and from the expanded blood volume due to misdistribution of systemic perfusion, with concomitant increase in plasma levels of renin and atrial natriuretic peptide (ANP) [5]. The real difference between the two conditions, however, becomes apparent during chronic cardiovascular adaptation to increased fistula flows which invariably lead to increased pulmonary resistance and pulmonary hypertension.

19.2 Eisenmenger Syndrome

In addition to AV fistulas, a number of congenital cardiac abnormalities exist which lead to pulmonary vascular disease due to increase in pulmonary flows. Eisenmenger syndrome (ES), the most advanced form of pulmonary hypertension, is typically associated with a large communication between the pulmonary and systemic circulations at the atrial, ventricular, or aortopulmonary levels. The current understanding of ES goes back to 1950 when Paul Wood characterized the underlying pathophysiology of the condition in his classical paper as "pulmonary hypertension due to high pulmonary vascular resistance with reversed or bidirectional shunt" under the collective eponym of the Eisenmenger syndrome [21].

As noted by Wood, the starting point for understanding of the ES should begin with normal fetal circulation. Briefly, the oxygenated blood ($SpO_2 \sim 85$ %) from the placenta reaches the fetus via the umbilical vein and flows into the RA via the IVC. Of the 69 % of total cardiac output (TCA) that enters the RA via the inferior vena cava, 27 % is shunted through the foramen ovale into the LA. The LA in addition receives deoxygenated blood returning from the lung (7 % of TCA). The LV thus receives only 34 % of TCA, which is ejected into the aorta to supply mainly the upper part of the body. The balance of blood entering the RA via the IVC (69 % − 27 % = 42 %) and blood from the SVC (21 % of TCA) and the coronary sinus (3 %), totaling 66 % of TCA passes through the tricuspid valve into the right

ventricle and is ejected into the pulmonary artery. The vast majority of RV output (59 %) is shunted via the widely opened ductus arteriosus into the descending aorta and only 7 % continues to flow via the pulmonary artery to perfuse the lung [22] (Fig. 19.1a).

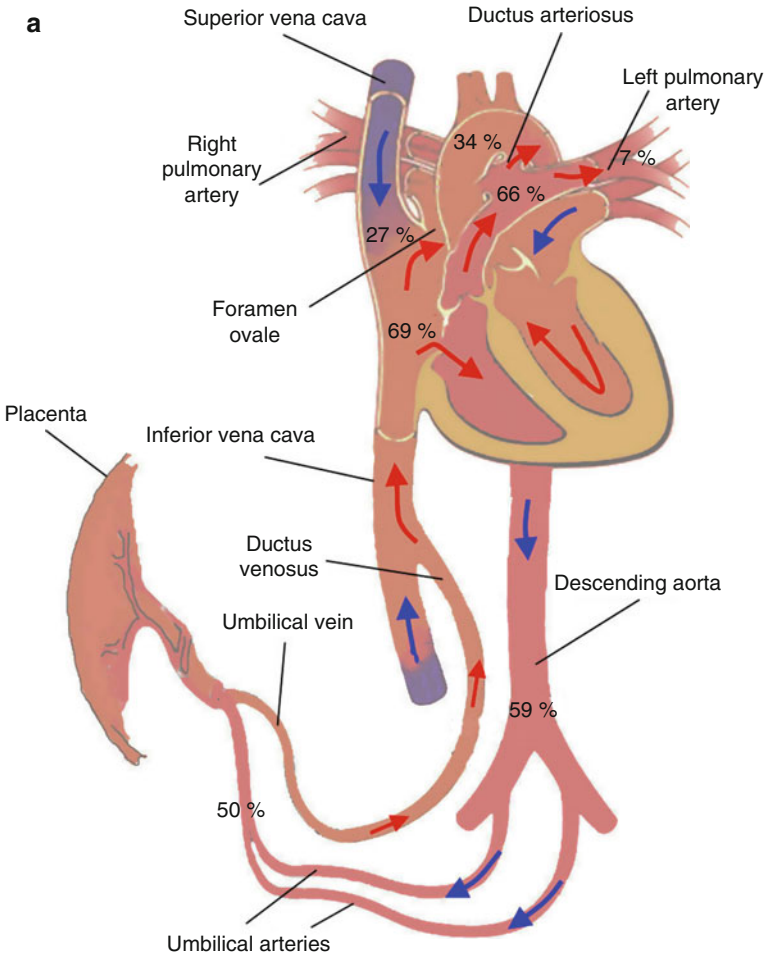

Fig. 19.1 Distribution of cardiac output in fetus. Percent distribution of cardiac output at selected checkpoints (values in *black*). See text for explanation (**a**). Percent saturation of fetal blood at selected sites (values in *black*) and oxygen tensions in mmHg (values in *white*) at selected sites (**b**). Note that the fetus lives in a relatively hypoxic environment (Data from Ref. [22])

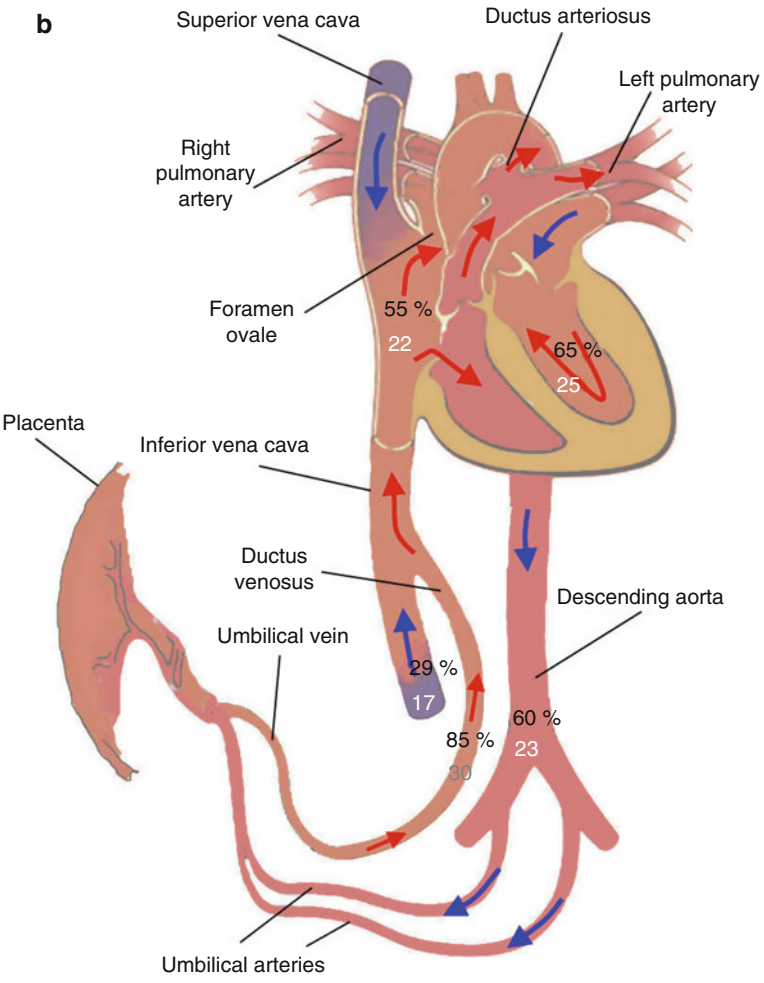

Fig. 19.1 (continued)

Of note is the fact that a relatively hypoxic environment of the fetus is critical for the development of fetal lungs and pulmonary vasculogenesis. The near-term pulmonary vasculature actively responds to vasoactive agents and to changes in oxygen tension. Unlike the systemic vessels, which relax in response to hypoxia, the pulmonary vessels react with marked constriction. Hypoxic pulmonary vasoconstriction (HPV) is a physiological response by which the circulating blood is diverted away

from hypoxic alveoli, in order to match perfusion with ventilation. The presence of low arterial PO_2 in utero increases, while maternal hyperoxia decreases, fetal PVR. Increasing evidence suggests that the fetal pulmonary circulation is actively maintained in a vasoconstricted state by HPV. (For review, see [23] and [24].)

Because of extensive communications between the left and right side of the heart, the pressures throughout the cardiac cycle are essentially equal. In terms of pressure generation, the ventricles can be considered to be a *single* functional unit; however, in respect of volume throughput, the RV receives 2/3, and the LV only 1/3 of the TCA. The two ventricles, moreover, differ in the quality of blood they receive, i.e., the blood in the LV is more oxygenated than the blood in the RV (SpO_2 65 % vs. 55 %). Finally, the placenta, the fetal "respiratory organ," receives about 50 % of TCA. Its efferent vessel, the umbilical vein, directs the oxygenated blood back to the fetus via ductus venosus (Botalli) directly into the inferior vena cava, bypassing the liver. It is significant that the PO_2 in fetal "oxygenated" blood is lower than the venous PO_2 during air respiration. (The placenta receives venous blood with a PO_2 of about 23 mmHg from the fetus and oxygenates it to levels of 30–35 mmHg – compared to PO_2 of 40 and 100 mmHg, for venous and arterial bloods, respectively, for lung respiration.) The fetus therefore thrives in a predominantly venous milieu (Fig. 19.1b). The existence of communication between the atria (foramen ovale) and the pulmonary artery/aorta (ductus arteriosus) ensures equal systolic and diastolic pressures in the ventricles as well as in the aorta and the pulmonary artery (Fig. 19.2).

Cardiopulmonary adjustments at birth are marked by separation and shedding of the placenta and expansion of the lungs with the first breath, the defining event in the life of the newborn. The pulmonary circulation which hitherto received only 7 % of TCA now receives the entire CO and replaces the placenta as the organ of respiration. Other changes within the first few hours of birth include closure of the ductus venosus (Botalli) which marks the beginning of portal circulation, with full perfusion of the liver. Closure of the foramen ovale prevents direct shunting of blood between the right and left atrium. Immediately after birth the ductus arteriosus remains open; however, it no longer conducts the flow of blood from the pulmonary artery to the aorta, but in the *opposite* direction, i.e., from the aorta to the pulmonary artery. It is patent for about a week after birth and remains functionally opened for up to a month, after which it becomes permanently closed and is reduced to a fibrous band (ligamentum arteriosum) [22].

19.2.1 Who Gets Eisenmenger Syndrome?

As mentioned, the ES occurs only in patients with large, nonrestrictive communications between the pulmonary and systemic circulations. Anatomical defects which most likely lead to development of ES have been classified in relation to the tricuspid valve. Pre-tricuspid defects are proximal to or above the tricuspid valve and

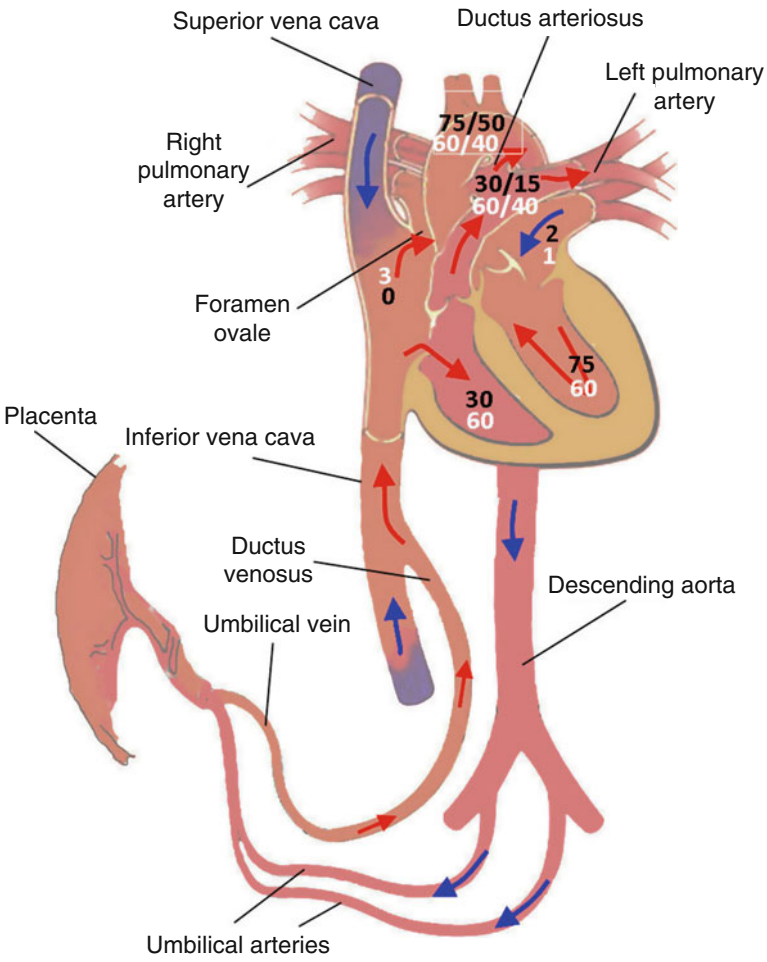

Fig. 19.2 Pressures in fetal and neonatal heart chambers and great vessels. Note equal right and left ventricular pressures due to large, nonrestrictive communication between the two circulations via patent foramen ovale and ductus arteriosus. Consequently, the right and left ventricular walls have similar thickness. Numbers in *white* denote fetal pressures in mmHg. Numbers in *black* are postnatal pressures (Data from Ref. [22])

include all types of ASDs and defects of the sinus venosus and the common atria. Post-tricuspid defects, on the other hand, are located distal to the tricuspid valve and comprise all types of VSDs, hypoplastic (single) ventricles and aortopulmonary communications (PDAs and aortopulmonary window). In the former group the ES is uncommon and occurs in adult life, whereas in the post-tricuspid group the

syndrome already begins in infancy and typically manifests in a severe form [25]. Patients with ES frequently survive into their third or fourth decade and present with progressive symptoms of dyspnea, cyanosis, fatigue, syncope, and cardiac arrhythmias and have reduced life expectancy. Epidemiological studies indicate that virtually all of the patients with unrepaired complex congenital heart disease with unobstructed pulmonary flow, and 50 % of patients with large VSD, or PDA develop ES. On the other hand, only 10 % of patients with large ASD will develop Eisenmenger physiology and do so only later in life [26]. It should be noted that before the days of surgical correction, the development of ES was actually lifesaving, giving the patients with severe cardiac defects a reasonable chance of survival into the fourth or fifth decade [25].

The "Eisenmenger reaction" (the term used by Wood to describe the changes in the pulmonary circulation of the affected patients) begins in infancy with a progressive left-to-right shunt and increasing pulmonary blood flow, resulting in elevated pulmonary vascular resistance (PVR) [21] (Fig. 19.3). Hyperdynamic pulmonary flows (Qp to Qs ratios 3:1 to 5:1) can lead to temporary heart failure in patients with large, uncorrected defects [27, 28]. Increase in PVR causes bidirectional shunt with reduction of pulmonary flows and *resolution* of heart failure [29]. Further progression of the condition is marked by shunt reversal, deepening cyanosis, polycythemia, systemic hypoxemia, and severe pulmonary hypertension [21]. A striking feature of ES is that the right and left ventricular, as well as aortic and pulmonary artery, pressures are equal throughout the cardiac cycle [29] with pulmonary artery pressures often *exceeding* the systemic [21]. Characteristically, the aorta and the pulmonary artery receive blood at the same pressure head from the ventricles which are anatomically distinct but physiologically function as one unit [28, 30]. The right ventricular function in patients with established ES is surprisingly well preserved, in spite of the greatly increased pulmonary artery pressure (afterload). As in the fetal heart, the thickness of the RV wall closely matches that of the LV. This is in stark contrast to patients with primary pulmonary artery hypertension (PAH) and pulmonary hypertension secondary to vascular, hypoxic, and embolic disease of the lung, which are commonly associated with RV dysfunction and failure, in spite of PA pressures and pulmonary vascular resistance (PVR) values, similar to those found in ES [25, 31]. For example, the median survival in patients with untreated symptomatic idiopathic pulmonary hypertension is 2.5 years, and the 2-year survival in patients with portopulmonary hypertension or thromboembolic pulmonary hypertension is only about 20 % [28, 29]. Surprisingly, patients with primary and secondary PAH develop early signs of RV dysfunction and failure in the *absence* of a cardiac defect, uncorrectable hypoxemia (due to left-to-right shunt), and a number of other aggravating factors characteristic of ES patients.

So why then do patients with ES fare so much better than patients with other forms of PAH? The current pathophysiological interpretation of ES originated with Wood who suggested that "During the first day of life, the physiological and anatomical findings are identical with Eisenmenger's syndrome…and that after birth a powerful right ventricle, as big and as strong as the left, pumps its contents into the system of vessels which differs little from the systemic circulation; it is only natural

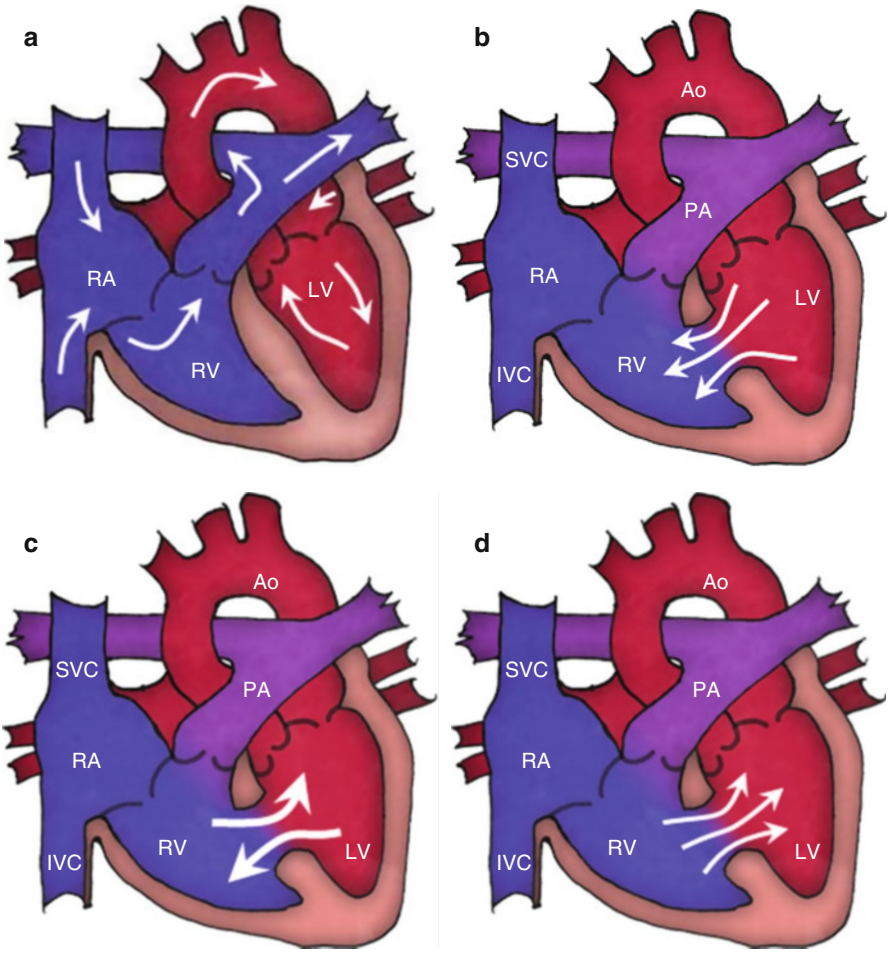

Fig. 19.3 An example of hemodynamic progression leading to Eisenmenger syndrome. Direction of blood flow (*white arrows*) in normal heart (**a**). Uncorrected ventricular septal defect causes persistent L to R shunt and increased pulmonary flows (**b**) with possible early hyperkinetic heart failure. Increase in pulmonary vascular resistance (PVR) may lead to bidirectional shunt with temporary improvement of heart failure (**c**). Established pulmonary hypertension causes shunt reversal (R to L), cyanosis, and fully developed clinical picture of Eisenmenger syndrome (**d**). *RA* right atrium, *SVC* superior vena cava, *IVC* inferior vena cava, *PA* pulmonary artery, *LV* left ventricle, *RV* right ventricle, *Ao* aorta

therefore that pulmonary and systemic resistances should be similar" [21]. Thus, the "persistence of fetal morphology" with preservation of right ventricular function (increased wall thickness) into adolescence and adulthood, in association with the abovementioned shunt reversal and interim heart failure, is still offered as the most likely hypothesis for development of ES [28, 29]. Moreover, according to the same theory, the presence of high pressure (and resistance) in the pulmonary circuit is an

essential component of the Eisenmenger reaction. Should there be a drop in PVR, as is the case in patients with large ASD (see below), higher flows are necessary to maintain high pressures [21]. This is in contrast to patients with other forms of severe PAH and patients with ASD who undergo *regression* of the right ventricular wall during infancy, with subsequent development of PAH and secondary RV hypertrophy and failure [28].

The prevailing model which supposedly explains the development of Eisenmenger reaction is based on the unique capability of the RV to overcome "the astronomical resistance" of the pulmonary vasculature at birth [21] and its subsequent "exceptional ability" to maintain the pulmonary circulation at pressures that equal or even surpass the systemic [28, 29]. However, resorting to the heart's ability to create high pressures in the face of patent communications between the systemic and pulmonary circulations, and the presence of reversible shunts, offers little in the way of understanding the rapidly changing (normal) hemodynamics at birth and is difficult to reconcile with protean manifestations of Eisenmenger physiology. For example, Dexter and coworkers performed hemodynamic measurements in three "compensated" patients with Eisenmenger complex (a large VSD with dextroposition of the aorta). The systolic and diastolic pressures in the RV and LV were essentially identical, as were the pressures in the pulmonary and brachial arteries (mean of 119/75 mmHg). The mean pulmonary capillary (wedge) pressures (PCWPm) were in the normal range (8–13 mmHg), which makes the average gradient between the PA and PCWP of 79 mmHg. In spite of extreme PA pressures, the pulmonary flow was normal or even decreased (range 2.3–4.1 l/min) and, surprisingly, there were no signs of pulmonary edema. The calculated PVR values were in the range of 1,365–3,090 dynes sec cm^{-5} (in comparison, PVR in normal subjects is around 60 dynes sec cm^{-5}, and SVR in the range of 1,000 to 1,200 dynes sec cm^{-5}). The authors commented on the puzzling nature of the "protective mechanism" which keeps the pulmonary capillaries intact, in spite of extreme PA pressures and high PA to LA gradients. In the presence of a functionally single ventricle, and pulmonary and systemic circulations placed in parallel, the SVR and PVR would have to be exactly matched or the blood would soon be pumped into the circuit offering lesser resistance [30].

19.3 Atrial Septal Defect

In the light of the above discussion, the question has naturally been raised as to why patients with large ASDs follow such a different clinical course. The thick-walled right ventricle at birth surely possesses enough power to shunt the blood across the existing defect in the atrial wall and maintain high pulmonary pressures, as is the case in other types of large defects between the two circulations [21]. This, however, does not occur, and the ventricle in these patients continues to involute as is the case in normal circulation. According to the prevailing theory, the PVR in patients with ASD first drops precipitously at birth and then continues to drop

(as is the case in normal population) until a left-to-right shunt flow develops. At a certain stage of progression, patients with large enough (uncorrected) defects become subject to "adverse hyperkinetic factor" [21] and begin to develop high pulmonary to systemic flow ratios (Qp–Qs). Why do only a small proportion of patients with ASD develop Eisenmenger reaction? According to Wood, those patients are subject to "a powerful hyperkinetic factor" operating within the pulmonary circulation *before* complete involution of the muscular arteries has taken place. They continue to develop large pulmonary flows with Qp–Qs ratios ranging from 3:1 to more than 5:1. Hyperdynamic pulmonary flows (in the absence of PH) typically lead to CHF and demise. Significantly, only early surgical correction of a large defect, i.e., before the Qp–Qs ratios reach 2:1, can prevent the development of fully expressed ES in adulthood [21].

19.4 Overview

In summary, we are confronted with a paradox in the sense that patients with large, unrestricted shunts between the pulmonary and systemic circulations have more favorable hemodynamics compared to patients with primary and other forms of PAH. Moreover, how is it possible that such a diverse number of cardiac conditions should share a common denominator in a complex clinical presentation of ES? It is proposed that this intricate hemodynamic web can be unraveled when, rather than the right ventricle, the passage of blood through the pulmonary vascular beds is seen as the primary source of blood propulsion. (This will become more apparent in the next chapter when circulation without the right ventricle will be considered.) The normal right heart complex plays a similar (mechanical) function as the left, namely, of rhythmically interrupting the flow of venous blood, albeit at significantly lower pressures than the left.

The "adverse hyperkinetic" and "self-perpetuating factors" active in the pulmonary microcirculation which, as suspected by Paul Wood, play the essential role in the pathogenesis of ES, can be identified as the physiological forces (inherent in the oxygenated blood itself) responsible for increased blood flows at the level of the pulmonary circulation. Their formidable power is particularly obvious in the case of a large ASD where pulmonary flows up to 24 l/min have been measured [21]. The phenomenon of "self-perpetuating" flow of ASD can be compared to accelerating, i.e., self-feeding flows in systemic AV fistulas, as discussed above. In this context, the cause of premature circulatory failure in patients with primary PAH and in those with certain other forms of pulmonary vasculopathies can be understood as failure at the source of blood propulsion itself.

Studies in animal models suggest that increased pulmonary flows in utero lead to endothelial dysfunction and PAH with characteristic histological changes of arterializations of the pulmonary arteries [32, 33]. In addition, maternal hyperoxygenation has been shown to increase pulmonary blood flows in near-term human fetuses [34] and increases the proportion of RV output distribution to fetal lung by 50 %

[35]. As mentioned, an increase in oxygen tension markedly dilates, while a decrease in oxygen tension constricts pulmonary vessels in near-term fetal sheep, suggesting that fetal pulmonary circulation can acutely respond to changes in oxygen tension [36]. The presence of higher oxygen tensions in the pulmonary arteries can therefore significantly accelerate pulmonary flows, resulting in increased ratios between pulmonary and systemic flows. The latter, as shown, depend on metabolic demands of the tissues, while the former are functional in nature. In the light of foregoing, the "function" of the lung needs to be redefined to include the "kinetic momentum" imparted to venous blood during its transition from venous to arterialized state. This is supported by an increasing body of evidence, which suggests that pulmonary veins are not only passive conduits but play an active role in the regulation of pulmonary circulation. For example, in a number of species the pulmonary veins are more muscular than the arteries and demonstrate significantly greater vasoreactivity to a variety of agents, including EDNO (endothelium-derived NO), prostaglandins, thromboxane, PAF (platelet-activating factor), and endothelin-1. The release of some of these agents is modulated by oxygen. It appears that the major part of the resistance to flow under normal and hypoxic conditions is regulated by the venous side of the pulmonary microvascular segment [37].

As discussed, with transition to air breathing at birth the normal separation between the systemic and pulmonary circulations is not possible in infants with large defects at the level of the heart and/or the great vessels. The predominantly venous fetal circulation, now "primed" to air breathing, is unable to make appropriate anatomical adjustments of switching from the parallel to in-series arrangement. The increased flows generated by the passage of blood through the pulmonary vessels are shunted back to the pulmonary circulation (left-to-right shunts) with progressively increasing Qp:Qs ratios. Since the anatomical defect prevents the heart to keep the red and the blue blood separate, the pulmonary arteries now assume a role of "restraining" the hyperkinetic circulation by increasing PVR. Collectively, the above phenomena suggest that the development of increased pulmonary resistance is a *compensatory* response on the part of the lung which, in an effort to normalize excessive flows, transforms from an organ with low to an organ with high impedance. The vicarious role that the normally low-resistance pulmonary circulation now assumes, however, comes at a cost. The progressive increase in pulmonary arterial resistance leads to a pathological state where PA pressures approach the systemic pressures, eventually manifesting as ES. The persistence of RV wall thickness in these patients should therefore be viewed as a compensatory hypertrophy for increased flows and pressures, rather than their cause.

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Chapter 20
Single-Ventricle Physiology

Hypoplastic left heart syndrome (HLHS) is a rare developmental abnormality of the left-sided heart structures that accounts for 3.8 % of congenital cardiac malformations. It comprises a range of defects characterized by a single functional ventricle belonging either to the left or to the right heart complex. A common presentation of the HLHS is a small or nonexistent left ventricle, stenosis of aortic and mitral valve, and hypoplastic ascending aorta. The circulation is achieved by way of the pulmonary artery which supplies the lungs and the systemic circulation via the ductus arteriosus [1] (Fig. 20.1). Unlike in the normal circulation where the two circuits are separated and said to be placed *in series*, the systemic and pulmonary circuits are arranged *in parallel*, giving rise to significant mixing of arterial and venous bloods. The increase in pulmonary blood flow tilts the balance between the normal ratio of pulmonary and systemic circulations (Qp:Qs) and results in progressive shunting of the blood away from the systemic circuit. Ductal closure results in a sudden decrease in systemic perfusion, leading to acidosis, oliguria, and shock [1]. As a "duct-dependent" lesion, the condition was universally fatal within days to weeks after closure of the duct and was therefore not amenable to therapeutic intervention until the duct patency could be maintained by administration of PG_{E1} in the early 1980s [2]. The empirical approach for palliation of HLHS and associated anomalies with a single-ventricle physiology has evolved gradually over the past 40 years and is based on the pioneering work of Fontan and Baudet in the 1970s who were the first to succeed in anatomical separation of the two circulations [3].

Their work came in the wake of extensive experimentation in the 1950s when the feasibility of shunts between the caval system and pulmonary arteries was tested on animals [4]. Of note is the fact that complete bypass of the right heart was pursued by several groups at the time but was fraught with failures in animals and yielded poor results in infants [5]. While connection between the SVC and PA was tolerated well (the bidirectional cavopulmonary or Glenn shunt), direct connection of the IVC to pulmonary artery resulted in a large amount of pooling in lower parts of the body, in particular, in the splanchnic bed, and was found to be incompatible with long-term survival. In spite of the fact that, at the time, the complete cavopulmonary

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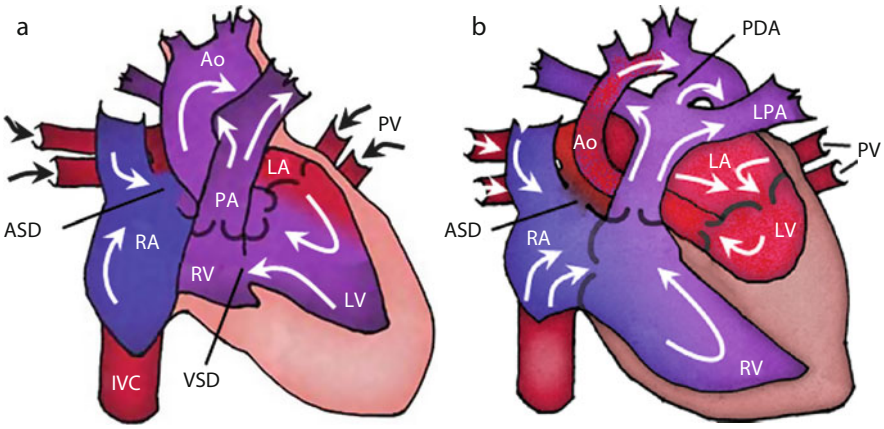

Fig. 20.1 Anatomical features of "single-ventricle" hearts. Tricuspid atresia (**a**) is marked by complete absence of tricuspid valve and a rudimentary right ventricle. Communication between the atria (*ASD*) enables the blood to reach the left ventricle, which subserves the pulmonary and systemic circulations. The salient features of the hypoplastic left heart syndrome (HLHS) include an aberrant left ventricle and hypoplastic aorta (**b**). The pulmonary and systemic circulations are placed *in parallel* and are supplied by the only functional (right) ventricle. A mixture of arterial and venous blood reaches the systemic circulation via the patent ductus arteriosus ("duct-dependent disease"). *Arrows* indicate the direction of blood flow. *ASD* atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus, *RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle, *PA* pulmonary artery, *PV* pulmonary veins, *LPA* left pulmonary artery, *IVC* inferior vena cava, *Ao* aorta

anastomosis was known as "a procedure for which a disease was yet to be found," it nevertheless became the cornerstone of Fontan repair [5].

As is evident from their report, the dilemma continued in the early 1970 when Fontan and Baudet initially attempted the right ventricular bypass in three patients with tricuspid atresia. "We were of the opinion," they reported, "that the right atrium of a normal heart could not provide the required work, whereas a hypertrophied atrium, as in tricuspid atresia could supply the additional work represented by pulmonary arterial pressure higher than the left atrial pressure" [3]. In other words, will the right atrium be able to supply enough *pressure* to overcome greatly increased pulmonary resistance and effectively "drive" the systemic venous return to the left atrium in spite of adverse pressure gradients?

It transpired that Fontan and Baudet had, in fact, misplaced their misgivings about importance of the right atrium for the success of their novel procedure. Circulation model experiments by de Leval and coworkers in the 1980s showed that interposition of a compliant atrial chamber between the systemic venous and pulmonary compartments *dissipates*, rather than enhances the propulsive force needed to overcome pulmonary resistance [6, 7]. This, together with frequent observations of chronic atrial distension and long-term arrhythmias, led to conclusion that the hemodynamic importance of the right atrium (in atriopulmonary connection) has been overestimated, and by the mid-1990s, the technique of total cavopulmonary

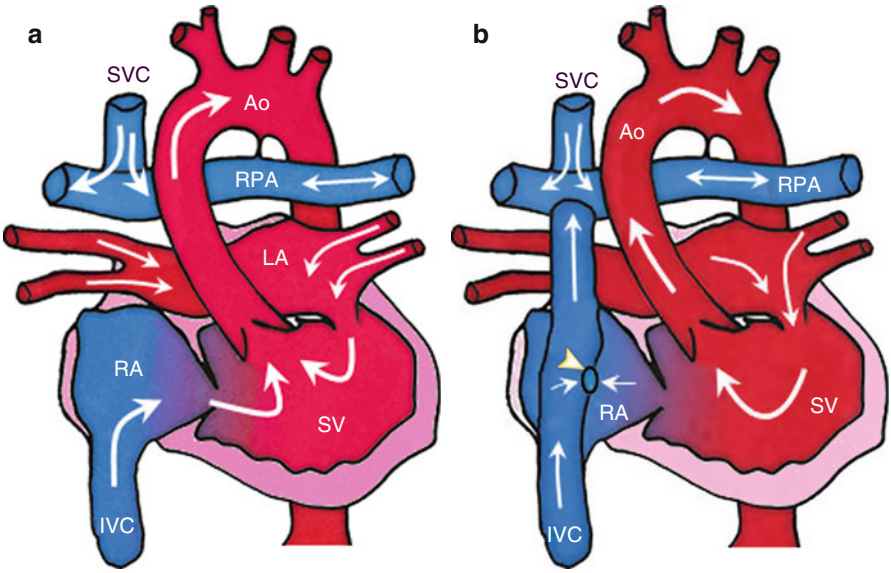

Fig. 20.2 Two-stage Fontan repair. After optimization of pulmonary and cardiac blood flows, i.e., the first-stage repair, hemi-Fontan (Glenn shunt) is achieved by connecting the superior vena cava to the right pulmonary artery (**a**). Chronic volume overload results in remodeling (strengthening) of the (single) ventricle. The final stage of Fontan repair consists of connecting the inferior vena cava to the pulmonary artery. The extracardiac cavopulmonary connection, schematically depicted in (**b**), is generally used in children older than 3 years. Fenestration (marked by *arrowhead* in **b**), a 3–6 mm communication between the extension of inferior vena cava (the baffle) and the atrium, is often added to vent excessive systemic venous pressures. *Arrows* indicate direction of blood flow. *SVC* superior vena cava, *IVC* inferior vena cava, *RA* right atrium, *LA* left atrium, *RPA* right pulmonary artery, *Ao* aorta, *SV* single ventricle

connection was widely adopted in most patients with functionally univentricular hearts [8].

It is generally accepted that surgical correction of the HLHS will have a better outcome if the pulmonary vascular resistance is low and the left atrial pressure can be maintained at low levels [9]. The ultimate goal of staged repair of any HLHS defect is the separation of pulmonary and systemic circulations and bringing their flow ratios (Qp:Qs) as close to unity as possible. The repair typically proceeds in three stages. The initial aim is to achieve unrestricted flow from the heart, i.e., by reconstructing stenotic part of the aorta (Norwood repair). Excessive blood flow to the lung, if present, is optimized by pulmonary banding. In case of a deficient flow, say, due to stenotic pulmonary artery, a systemic to pulmonary artery shunt (Blalock–Taussig) is placed. As a rule, the heart is now subjected to chronic volume overload which, incidentally, improves the development of pulmonary vasculature.

The next stage of repair (at the age of 4–12 months of age) is the connection of the superior vena cava to pulmonary artery (bidirectional Glenn shunt or hemi-Fontan) (Fig. 20.2). This intervention further increases the volume load to the ventricle with flows up to 2.5–3.5 times higher than in normal hearts [9].

The combination of chronic volume overload caused by the creation of Glenn's shunt and expansion of plasma volume due to increased levels of ANP (atrial natriuretic peptide) secreted by the distended atrium [10] is a potent stimulus for dilation and hypertrophy of the weakened ventricle [11]. With typically low arterial oxygen saturation values (SpO_2 % in the low 80s), the systemic oxygen delivery now depends on a delicate balance between the pulmonary and systemic flows (Qp–Qs) with little, if any, functional reserve.

The final, crucial stage of repair consists of the complete separation of pulmonary and systemic circulations achieved by joining the inferior vena cava to the pulmonary artery. In addition, any existing anastomoses between the aorta and the pulmonary artery are ligated. A dramatic reversal of hemodynamics follows in which previously chronically overloaded ventricle now operates at a fraction of its previous load (in the range of 25–75 %) [9]. The combination of hypertrophied ventricular wall and reduced filling can result in enhanced systolic thickening (contractility–afterload mismatch) with early-diastolic dysfunction and markedly reduced CO [12].

The long-term outcome in single-ventricle Fontan repair patients is characterized by decreased cardiac output (range of 60–70 % of normal controls) and mildly to moderately reduced exercise capacity. It is not clear whether the exaggerated fall in BP during exercise is primarily due to reduced CO or due to decreased vasomotor tone [13]. It has been observed that during exercise Fontan patients employ a strategy of taking more frequent, shallow breaths to harness the beneficial effect of negative inspiratory phase and thus improving the pulmonary blood flow and, in turn, CO by up to 30 % [14]. Furthermore, the minute ventilation at the same given intensity of exercise is greater in Fontan patients than in normal controls [15]. Studies of pulmonary blood flow patterns at rest reveal an exaggerated flow response during the respiratory cycle and point to the importance of the "respiratory pump" as an important auxiliary source of blood propulsion. Doppler flow studies by Redington and coworkers demonstrated a *cessation* of blood flow in the PA and flow *reversal* in SVC during short periods of forced expiration (Valsalva maneuver) and a considerable augmentation of forward flow during forced inspiration (Mueller maneuver) [12, 16].

During early years after palliation, there is partial regression of ventricular hypertrophy with persisting ventricular dysfunctions which, in the absence of residual rhythm and conduction disturbances, rarely presents significant cardiovascular limitation (New York Heart Association class I or II) [17, 18].

The systemic complications of Fontan circulation are mostly related to increased venous pressure and congestion and include protein-losing enteropathy (3–15 %), hepatomegaly with ascites and peripheral edema, interstitial pulmonary edema, pleural effusion, and predilection to thromboembolic events (pulmonary embolism, stroke, myocardial infarction) [17, 19]. It is of interest that (as mentioned in Part I) ontogenetically, the left ventricle is a relatively late evolutionary gain of adaptation from the gill-based water respiration to lung respiration. The amphibians already have two atria but a single ventricle, which serves systemic and pulmonary circulations (cf. Fig. 11.7b). The parallel arrangement of systemic and pulmonary circuits

and "pulmonary hypertension" are physiological in amphibians where, in addition, the excessive lymph production is cleared by accessory (lymph) hearts. It has been suggested that the HLHS can be viewed as a "developmental arrest" at the stage of amphibian circulation [20] with far-reaching consequences affecting not only the macrocirculation but also the microcirculation [21].

Chronic effects of total systemic to pulmonary drainage (in the absence of the right heart) on the pulmonary circulation are less well understood and appear to be related to steady rather than pulsatile flow, to loss of normal ventriculo–vascular coupling, and to abnormal endothelial reactivity, possibly related to reduced endothelial NO production [12, 21]. Overt and silent pulmonary embolic episodes may contribute to increase in pulmonary vascular resistance and adversely affect long-term survival [22]. Notwithstanding the radical deviation from what is considered a "normal" circulatory anatomy, the vast majority of (about 90 %) hospital survivors with Fontan circulation nevertheless enjoy remarkably normal lives [23].

20.1 The Fontan Paradox

As mentioned, the Fontan "correction" comprises of placing the systemic and pulmonary circulations in series, as is normally the case. However, the pressure generated by the single ventricle is now considered the sole source of blood propulsion for systemic as well as the pulmonary circulations. In terms of the hydraulic (or electrical) analogue, the circuit resistances are now the sum rather than the reciprocal of their values. The question naturally arises whether the weakened ventricle, operating at *reduced* preload, would be capable of generating high enough pressure to overcome the vastly increased peripheral resistance. The answer, of course, is affirmative, or these patients would never survive the radical anatomical rearrangement of their circulations. Paradoxically, rather than presenting with signs of left ventricular failure with pulmonary congestion and increased LV filling pressures, the Fontan patients exhibit signs of *right* ventricular failure (hepatic congestion and peripheral edema) in the *absence* of the right ventricle! In other words, too much blood is being "pushed" (by the single ventricle!) into the systemic venous reservoir. Unlike in the biventricular circulation, where CVP is normally low (0–5 mmHg), patients with Fontan circulation have significantly higher central pressures (in the range of 15–20 mmHg), and placing a "relief valve," by creating a communication between the systemic and pulmonary circulations (fenestration) (see Fig. 20.2), has been found to be an effective way to improve survival and reduce congestion-related complications [24, 25]. In addition, placement of fenestration has been shown to improve ventricular preload and augment CO [26]. Evidently, the ensuing cyanosis due to R–L shunting is tolerated better than complications related to increased venous pressure.

No doubt, the Fontan circulation presents one of the biggest challenges to conventional pressure-propulsion model of circulation, and some interesting suggestions have been proposed to solve it, for example, "The paradox of the Fontal circulation is that it imposes a caval hypertension and a pulmonary arterial

hypotension. In terms of hemodynamics, a mechanical device capable of a step down in pressure energy of 5 mmHg in the inferior vena cava and producing a step up in pressure energy of 5 mm Hg in the pulmonary arteries would reverse the Fontan paradox" [8, 27].

While it remains doubtful whether "the paradox" will yield to a simple mechanical measure, a number of related phenomena have been described which, it is believed, form a rational basis for its understanding. They can be conveniently grouped into those related to the heart and to pulmonary circulation and have been summarized in a recent review by Gewillig and coworkers [26]. It has been frequently observed by clinicians, for example, that in the acute postoperative period, the "Fontan operation leaves the child's cardiac output nearly totally dependent upon pulmonary blood flow" [28]. In addition, in spite of reduced ventricular contractility, the Fontan patients fail to increase CO in response to inotropes, the situation observed in several other forms of acute or chronic heart failure [29]. Similarly, the indices of ventricular performance do not improve by decreasing systemic vascular resistance (by administration of vasodilators) and may even worsen exercise performance [30].

On the basis of gathered evidence, Gewillig and coworkers have made a compelling argument that the single most important factor limiting CO in Fontan patients is reduced ventricular filling (preload). They proposed a conceptual model by which chronic "preload deficiency" in Fontan circulation leads to weakened ventricle by a mechanism of chronic "deconditioning" as seen, for example, in severe mitral stenosis where lack of preload is the major contributing factor to diastolic dysfunction [26]. The problem has been aptly summarized (from the surgical perspective), thus:

> Apart from a few exceptions, pulmonary vascular resistance will control the cardiac output. The circuit runs on 'autopilot', with little interference by the clinician. This has frustrated many cardiologists as they have experienced that 'their organ' no longer controls cardiac output. Cardiac output can be increased by improving flow to and into the lungs, or by bypassing the lung with a fenestration. The effect of pulmonary vasodilators is usually very modest. [23]

However, the proposed model fails to take into account the fact that the reduction of cardiac output in Fontan circulation is *primarily* due to failure on the part of the pulmonary microcirculation to generate adequate systemic flows, rather than due to failure of the ventricle to pump the blood. The maintenance of arterial pressure as the primary function of the (systemic) ventricle is, in fact, adequately preserved. As mentioned, all HLHS patients initially present with extensive shunting between the two circulations. The flow is further increased after the creation of SVC to PA anastomosis (bidirectional shunt). In principle, the situation is similar to any other condition with increased pulmonary to systemic flow ratios, such as is the case in large AV fistulae or a large ASD/VSD. With completion of the Fontan circuit, the pulmonary flows are significantly reduced, resulting in amelioration of further "damage" to the pulmonary circulation and, more importantly, in averting a further rise in pulmonary pressures leading to Eisenmenger syndrome. Nevertheless, the absence of the right heart complex (and of non-pulsatile flow) continues to exert its toll, and, in spite of its "physiological incompatibility" [5], the Fontan repair provides an

excellent long-term palliation for the majority of patients with a single-ventricle heart [19]. The fundamental mismatch between the (reduced) pulmonary flows and the systemic circulation "driven" by metabolic demands of the tissues remains. It presents clinically with reduced pulmonary and overfilled systemic venous compartments.

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Chapter 21
Blood as an Organ

Medical men, indeed, only pay attention to human blood, taken in phlebotomy and contained in cups and coagulated.

W. Harvey, 'On the Generation of Animals', 1651

In order to bring the hitherto discussed material into a broader perspective, it may be helpful to review some of the salient phylogenetic features discussed in Part I. We have seen that in the single-circuit vascular system of the fishes, the gills are placed in series with the systemic circulation (see Fig. 11.11). This is a low-pressure, predominantly venous circulation, where the highly efficient "membrane oxygenator" system of the gills extracts oxygen, dissolved in water, to satisfy the relatively meager metabolic demands of poikilothermic aquatic species. The two-chambered heart is placed *before* the gills and generates pressure in the branchial circulation which, unlike in the case of mammals and birds, *exceeds* the systemic.

The existence of a differential sensitivity in the gill and in the systemic vessels to hypoxia, points to a highly conserved vascular response, shared across the vertebrate taxa (see Sect. 11.4.2). The coexistence of lung and skin respirations in amphibians represents a transitional stage and marks the beginning of separation of pulmonary and systemic circulations. The emergence of lung calls for development of a new heart chamber – the left atrium. The pulmonary and the systemic circulations are now *in parallel* with the heart and are subject to *equal* pressures generated by a *single* ventricle. The prospect of generating metabolic energy by harnessing of oxygen directly from air, rather than water, has created "new evolutionary opportunities" [1], such as the development of limbs, of wings, and of the weight-bearing skeleton. After a long lineage of vertebrate phylogeny, the two circulations are, once again, placed *in series*. This, however, is not just a modification of the former gill respiration but its metamorphosis and an enhancement.

The achievement of an independent, inner thermal environment with adaptation to terrestrial life by virtue of lung respiration is possible only with total separation of the systemic and pulmonary circulations, as extant in mammals and birds. Not only the rates of oxygen consumption but also the ranges of achieved cardiac outputs far surpass what was possible in gill breathers. The newly acquired left heart together with arteries with thicker elastic walls, able to withstand higher pressures and flows, are only some of the many anatomical adaptations to the earthly

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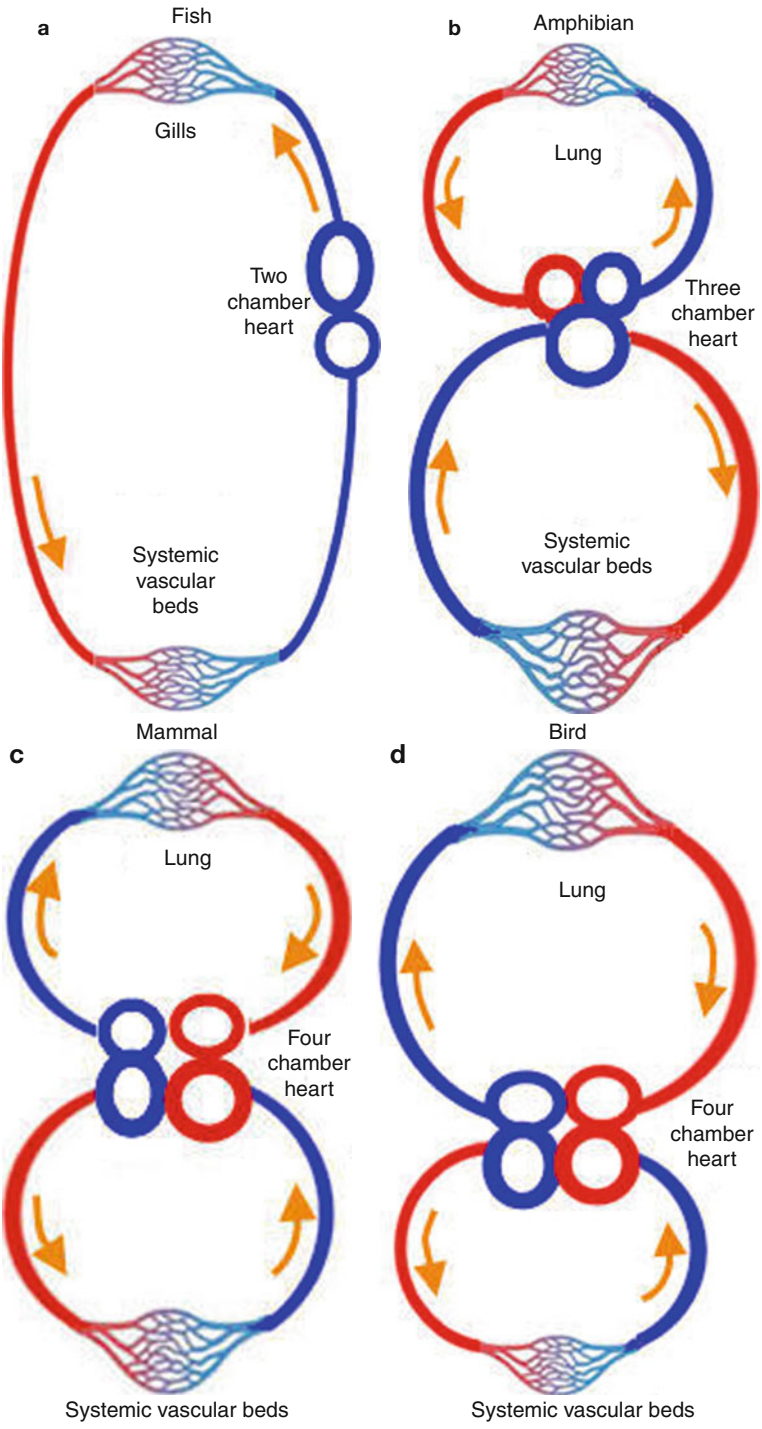
environment. They have been brought to extreme, for example, in birds in which, from the mammalian perspective, hyperthermia and hypertension are physiological (Fig. 21.1).

It was further shown that the long evolutionary development of the mammalian circulatory system (ontogeny) in effect recapitulates former evolutionary steps but, in pursuit of a higher evolutionary goal, leaves them behind as unsuitable. Should they emerge as atavistic forms – as is the case in congenital heart conditions – they fall short of optimal performance and may be incompatible with life without surgical correction. They serve, however, as instructive evolutionary models of

Fig. 21.1 Circulatory systems as the pivot for the evolutionary development in vertebrates. Unlike in plants, where growth and reproduction are bound to the *external* environment in the course of the yearly cycle, the animals have *separated* themselves from the surroundings and have, to various degrees, developed species-specific *inner* environments. (**a**) In fish, the single-circuit circulatory system, the gills and the heart are placed in series. The two-chambered heart is located in the venous limb downstream from gut and liver and supplies the gills with blood at pressures that *exceed* those in the arterial limb of the circuit. Largely devoid of gravity, fish depend on water for respiration, fluid balance, thermoregulation, reproduction, and fin development. (**b**) The amphibians are adapted to life in water only during early stages of their development. Transition to land (and gravity) is marked by loss of fins and gills and the emergence of limbs. Adaptation to air respiration marks a fundamental change in the structure of the cardiovascular system. In contrast to fish, the circulatory loops *cross* and assume the shape of a lemniscate (figure of 8). The heart and the lung are joined by a newly formed pulmonary circulation placed in parallel with the systemic. The heart acquires a new chamber, the left atrium, while a common ventricle is shared between the pulmonary and systemic loops. Amphibians continue to depend for temperature, reproduction, and part of their respiratory needs on water (skin respiration). (**c**) Through development of sophisticated organ systems of thermoregulation, respiration, excretion, inner reproduction, and locomotion, the mammals have attained a high degree of environmental emancipation. The cardiovascular system consists of two anatomically separated but functionally unified parts – the systemic and pulmonary circulations, placed in series ("balanced" lemniscate). In addition to an independent *inner* watery environment, the mammals have developed an "inner atmosphere," reflected primarily in the partial pressure of oxygen and nitrogen in the blood that parallels the atmospheric pressure. The essential new feature of the mammalian circulation is a pressurized arterial compartment. The similarity of arterial pressure across the mammalian species suggests that the pressure as such does not serve the blood propulsion (It is of interest that the arterial blood pressure in a giraffe is about twice that of other mammals, with the same body mass. The pressure must be sufficient to overcome gravitational and hydrostatic pressure exerted on the heart by the vertical height of the column of blood in the arteries above the heart. The height of the pressure is proportional to the length of the neck, and the mean arterial pressures in the range of 200 mmHg are needed to maintain adequate perfusion of the head. In the adult giraffe (average wt 1,400 kg), the heart weighs about 6–7 kg; a value consistent with other mammals of similar weight [23]. A unique feature of the giraffe's heart, however, is its length (up to 30 cm), a morphological trait, possibly related to generation of high arterial pressures. Note that the heart in birds, also known to be physiologically hypertensive, has thickened walls and oblong shape (cf. Fig. 11.10).) (**d**) Finally, the circulatory system in birds exemplifies an environmental adaptation that goes beyond the terrestrial balance reached by mammals. The largest heart-to-body weight ratio of all species, physiologic hypertension, and hyperthermia, coupled with a remarkable adaptation to low-oxygen environments during flight at high altitudes, demonstrate that the birds have "overcome" gravity and become creatures of air (Note that the predominance of cardiorespiratory function in birds is depicted by a "top-heavy" lemniscate)


a
Fish
Gills
Two chamber heart
Systemic vascular beds
Mammal
b
Amphibian
Lung
Three chamber heart
Systemic vascular beds
Bird
c
Lung
Four chamber heart
Systemic vascular beds
d
Lung
Four chamber heart
Systemic vascular beds

circulation. The persistence of a communication between the pulmonary and systemic circulations at the level of the heart and/or the great vessels after birth disqualifies the heart to perform its primary role of separating the two circulations and of its primary function as a damming-up, pressure-generating organ. Recirculation of the oxygenated blood through the lung, as is the case in a left-to-right shunt, creates a condition where the blood continues to accelerate through the pulmonary circuit. Unchecked by the heart and out of balance with the systemic oxygen demands, the increased pulmonary flows lead to "arterializations" of the pulmonary vessels and to increased pulmonary vascular resistance (Eisenmenger reaction). The opposite is the case in systemic AV fistulas, where increased fistula flows and related phenomena of flow reversal, such as "arterializations" of the venous fistulous segments, signify a dearth of oxygen and hence perfusion, in the affected tissues.

The ability of vascular beds to meet and sustain metabolic demands of the tissues is known as vascular autoregulation. Multiple mechanisms have been identified which contribute to changes in vascular tone, such as intraluminal pressure (myogenic response), local metabolite concentrations, and the effect of shear stress on endothelial lining, to name a few. A number of theoretical models have been developed which consider different combinations of tissue blood flow regulators [2, 3]. Increasing evidence suggests that local biochemical and mechanical factors work in conjunction with a key blood component, the erythrocytes. While a close relationship between the tissues' need for oxygen and the cardiorespiratory response has been recognized for well over a century, the mediator, or the "sensor," in this demand–supply loop has been, until recently, one of the great physiological unknowns. Ellsworth and coworker were the first to suggest in the 1990s that, in addition to carrying oxygen, the red blood cells serve as oxygen "sensors" and may be the prime regulators of vascular tone. According to the proposed model, the metabolic needs of the tissues are communicated to the microvascular network and are closely matched by the release of ATP from the RBCs which, in turn, affects vascular tone via the endothelial purinergic (P_{2y}) receptors [4, 5] (Fig. 21.2).

Several studies suggest that RBCs release ATP at higher rates when oxygen is depleted and that the vascular response to ATP is conducted by way of the endothelium in the direction *opposite* of flow, i.e., from venules to arterioles, traversing the intervening capillaries [5]. In addition to playing the essential role in arterial vasodilation [6], as well as mediating coronary [7] and muscle perfusion during exercise (see Chap. 16), the RBC-released ATP may also play a pivotal role in the regulation of pulmonary flow [8]. Well known, for example, is the capacity of the RBCs to inactivate NO – which is continuously produced by the pulmonary vascular endothelium and airway epithelium – and thereby augment HPV [9, 10].

Recent theoretical models of blood flow autoregulation which include the RBC-based ATP response of vascular beds to metabolic needs of the tissues show that RBC-mediated vasodilation opposes and thus balances out the myogenic and

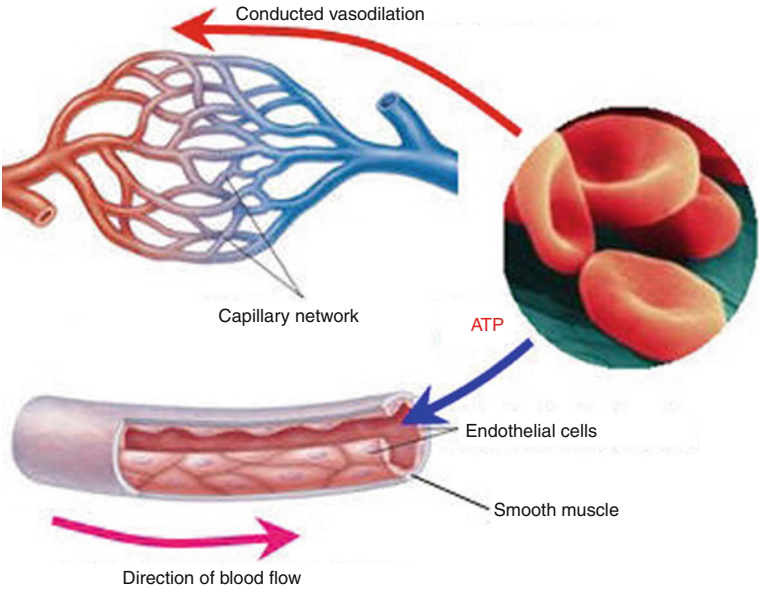


Fig. 21.2 Erythrocytes as oxygen sensors and modulators of vascular tone. During entrance of erythrocytes into the region with high oxygen demand, the release of oxygen from the RBCs causes a drop in oxygen–hemoglobin saturation (SO_2) and stimulates the release of ATP, proportional to the fall in SO_2. The RBC-derived ATP reacts with endothelial purinergic receptors, causing production of mediators that initiate vasodilation in the direction *opposite* to the flow of blood, resulting in increased blood flow in areas of increased oxygen demand

shear-dependent vasoconstriction [2, 3, 11]. It is believed that these models more realistically represent the pivotal role of blood – as a mediator between the metabolic demands of the tissues and the uptake of oxygen in the lung – and thus support the thesis proposed in this monograph.

However, the forward and backward communication between the red blood cells, the endothelium, and the tissues beyond becomes significantly impaired during critical illness. The development of novel techniques for intravital microscopy, namely, the orthogonal polarization spectral imaging (OPS) and sidestream dark field imaging (SDF) in animal models and in patients, has afforded new insights into the microvascular beds that were off limits to conventional in vivo light microscopy (for review, see [12]). Numerous studies over the past several decades have shown that microvascular hemodynamics is altered in patients with sepsis, hemorrhage, cardiogenic shock, or multiple trauma, as well as during cardiopulmonary bypass. Unlike in the normal state where a fine balance exists between the metabolic demands of the tissues and its perfusion, the equilibrium between myogenic, metabolic, and neurohumoral mechanisms is disturbed in patients with critical illness.

Experiments on animal models show that administration of endotoxin results in endothelial injury, capillary leakage, and interstitial edema with progressive reduction in total number of perfused capillaries, technically referred to as decreased functional capillary density (FCD). The loss of capillary function is heterogenous, with some areas affected more than others, resulting in progressive decrease in arteriolar diameter, shunting, increase in mixed venous oxygen saturation (SvO_2), and acidosis.

The purported mechanism for transition to heterogeneity in perfusion is excessive red blood cell formation of ATP and NO produced by inducible nitric oxide synthase[1] (iNO) [13] during states of tissue hypoxia, resulting in an override of the normally occurring regulatory mechanisms and leading to loss of microvascular tone and diminished responsiveness to vasopressors [14]. Significantly, these changes can occur in the presence of *increased* cardiac outputs and oxygen delivery values (hyperdynamic circulation) [15].

The severity in decrease of the FCD is proportional to the time of exposure to the causative agent, i.e., the endotoxin and/or the duration of low flow condition, in cases of hemorrhage or cardiogenic shock. Should the critical window, during which the microcirculatory changes can potentially be reversed by resuscitative measures, be missed, the inhomogeneity in perfusion will be exacerbated by the inflammatory response (reperfusion injury), leading to multiple organ failure and death. Microcirculatory dysfunction is one of the most sensitive predictors of outcome in critical illness [16] – and at least in animal models of survival after cardiac arrest [17] – and the restoration of its function has become the principal focus of goal-directed therapy [18]. The microcirculation is thus positioned at the crossroads of the abovementioned pathophysiological events and has been aptly called the "integrative compartment" [12], or the "motor of sepsis" [15].

In view of the pivotal role of the microcirculation in acute circulatory failure and various types of distributive shock, some researchers have called for reexamination of the commonly assumed link between the microcirculatory function and global hemodynamics. Since an apparently adequate organ perfusion occurs during a relatively wide range of mean systemic arterial pressures (60–100 mmHg) [19], it is believed that the microcirculatory flow is relatively *independent* of global hemodynamic variables [20]. Notwithstanding the fact that there must be a minimal pressure, below which tissue perfusion during normal and pathological states becomes compromised, such values have yet to be defined and appear to vary widely among individuals. Significantly, the response of the microcirculation in critical illness is often blunted to therapeutic intervention with vasopressors (tachyphylaxis) and can

[1] To be distinguished from the NO produced by nitric oxide synthase produced normally by the endothelial cells (eNOS) and neurons (nNOS). In sepsis, the formation of NO from arginine is increased on account of cytokine-mediated induction of inducible NO synthase (iNOS) in cells that normally do not have this ability, such as in the heart myocytes and vascular smooth muscle cells [13].

lead to greater inhomogeneity in perfusion of the microvascular beds with adverse outcome. A recent therapeutic trend in "recruiting" the microvascular beds by using vasodilators, such as nitroglycerin, rather than "pushing" more flow via already overperfused vessels, is a radical departure from conventional thinking, and yet it seems to be the logical next step (for review, see [20]). Collectively, these observations point to a relative "independence" of the microvascular bed in the overall circulatory dynamics, lending further support to the thesis advanced in this monograph.

In the light of forgoing discussion, it appears that in the case of microcirculatory failure, we are once more faced with a facet of an already familiar phenomenon of reciprocity between the pulmonary and peripheral circulations (see Sects. 19.1 and 19.2). According to the proposed model, the heterogeneity in perfusion and shunting in the microcirculatory beds with increase in SvO_2 causes the pulmonary circulation to be perfused by the blood with *higher* than normal oxygen content, thus serving as a trigger for accelerated flow. This could explain the curious phenomenon of hyperdynamic circulation (high CO and low SVR) in patients with various types of distributive shock (except in cases of hypovolemia), even in the face of globally *decreased* myocardial function [21].

In summary, an attempt has been made to review the current status of the pressure-propulsion model of circulation and highlight a number of inconsistencies which have been either explained away or tailored in order to fit its mold. According to the mechanistic (cardiocentric) model, the blood is considered an inert fluid, impelled along the vessels by the pressure gradient created by the heart. Experimental and phenomenological evidence presented in this monograph suggests exactly the opposite, namely, that the blood is a "fluid organ," with *self*-movement as its inherent characteristic. 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 (Table 21.1).

As discussed in Chap. 12, the ontogenetic origin and morphology of the cardiovascular system indicate that it can be considered an organ, whose function is rhythmic mediation between the nerve–sense (form) and the metabolic poles of the organism. Its mobile component, the blood, fulfills this function (cf. Fig. 12.2).

During the long evolutionary course, the red blood cells, as oxygen carriers, have become devoid of a nucleus and mitochondria and are no longer able to synthesize proteins – a possible oxygen-sparing adaptation – but have retained a unique form of "sensitivity" to the metabolic needs of the tissues. In addition to being a "mobile sensor" for oxygen requirements of the tissues [22], the red blood cells also play a key role in matching ventilation to perfusion in the lung [8]. It is often forgotten that the blood as an organ possesses *its own* metabolic requirements and that, as venous blood, it too needs to be replenished with oxygen. The blood thus plays a dual role of "serving itself" but, above all, the organism as a whole. The dynamic tension existing between the oxygen source in the lung and its sink in the tissues is, therefore, bridged by the (autonomously) circulating blood.

Table 21.1 Comparison of hemocentric and cardiocentric models of circulation

	Hemocentric	Cardiocentric
Blood *flow* control at the level of:		
(a) Macrocirculation	Heart; via flow restraint	No known mechanism
(b) Microcirculation	Tissue metabolism RBCs as O_2 "sensors"	Driven by pressure head
Maintenance of *pressure* in arterial circulation	Heart as hydraulic ram	Heart as pressure-propulsion pump
Blood propulsion affected by:	Blood on contact with O_2 in lung/gill	Heart as a pump
Blood properties	"Liquid organ"	Inert fluid

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