Congestive Heart Failure and Cardiac Transplantation

Clinical, Pathology, Imaging and Molecular Profiles

Daniel J. Garry
Robert F. Wilson
Zeev Vlodaver
Editors

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This book is dedicated to our wives:
Mary Grace Garry
Betsy Wilson
Dalia P. Vlodaver
For their encouragement, support, and inspiration

Preface

This book is a comprehensive overview of heart failure and the only curative therapy for this disease, heart transplantation. Since heart failure is so prevalent in our society and has such a profound impact in our healthcare system, we have targeted a diverse audience ranging from the student to the clinical trainee as well as the research investigator and the practicing clinical expert. As the title and table of contents outline, a unique feature of this book is its breadth. The intent is to produce a single book that comprehensively examines the field of heart failure and the therapeutic strategies, including cardiac transplantation, that would be of interest to the molecular biologist, the pathologist, the practicing clinician, the radiologist, and the surgeon.

Introductory chapters are provided as a platform for the depth of the subsequent chapters. Chapter 1, which presents an extensive historical perspective, provides a unique beginning to the book. Subsequent chapters in Part I explore the basic concepts in the physiology, molecular biology, pathology, and epidemiology of the normal and failing heart and also highlight emerging research discoveries that are having a significant impact on the field. Part II addresses the known causes of heart failure, such as right heart failure, valvular cardiomyopathy, molecular mechanisms of sarcomeric cardiomyopathies, and neuromuscular cardiomyopathy. These chapters serve as an outstanding resource for the practicing clinician and the research investigator. In Part III, the progression of heart failure is outlined, with chapters devoted to cardiorenal syndrome, neurohormonal activation, remodeling, and arrhythmias in cardiomyopathy. Advanced therapies for the heart failure patient are discussed in Part IV, including cardiac resynchronization, ventricular assist devices, and cellular strategies for structural and hemodynamic improvement of the failing heart. An area of intense interest is the field of regenerative medicine and Chap. 23 highlights the state-of-the-art research strategies and their potential clinical impact for this field. Part V addresses the field of cardiac transplantation. These chapters detail the rich history of surgical, immunobiological, and therapeutic discoveries that are the signature for this field and target the clinical management of the heart transplant recipient. Topics include the cardiac transplant procedure, the early and late management of the post-transplant patient, allograft rejection, heart-lung transplantation, and xenotransplantation.

A unique feature of this compendium is the authors' expertise and national and international reputations. Many of the authors direct research programs focused on heart failure and cardiac transplantation and these initiatives complement their outstanding clinical expertise in the field. They have further distinguished themselves as founders or leaders of institutes, cardiovascular programs, pulmonary hypertension programs, neuromuscular programs, physiology departments, robotic surgical and transplant programs, adult congenital heart programs, structural heart disease programs, regenerative medicine programs, and start-up cardiovascular companies. The expertise of the authors and the comprehensive nature of this book serve as an important resource both for the practicing clinician in her/his daily practice and for trainees and research investigators. Importantly, it is the editors' hope that this scholarly effort inspires the next generation to pursue innovations and discoveries that will bend the path of heart failure and cardiac transplantation and lead to cures for these diseases.

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Acknowledgements

The editors are grateful for all the efforts and insights provided by the authors of the respective chapters in this book. The research and clinical expertise of the authors is unparalleled and serve to distinguish this book.

The editors recognize the foundational impact of the innovative contributions to cardiovascular medicine that is reflected in our book by the following pioneers.

C. Walton Lillehei, MD, internationally renowned as the "Father of Open-Heart Surgery," was professor of surgery at the University of Minnesota under Dr. Owen Wangensteen. In 1952, Lillehei participated in the world's first successful open-heart surgical procedure using hypothermia, which was performed at the University of Minnesota. In 1954, he performed the world's first open-heart surgery using cross-circulation and these procedures provided the platform for use of the heart lung machine. In 1958, Dr. Lillehei was responsible for the implantation of the world's first small, portable, battery-powered pacemaker; he also developed and implanted the world's first prosthetic heart valve in 1966. Thousands of cardiac surgeons across the world were trained by Dr. Lillehei and his colleagues at the University of Minnesota and revolutionized the field of cardiovascular surgery. Dr. Garry pays special acknowledgement to the late Dr. Lillehei who together with his late spouse, Kaye Lillehei, established the Lillehei Heart Institute, which is led by Dr. Garry.

Jesse E. Edwards, MD, was a world-renowned pioneering cardiovascular pathologist. He was professor of pathology at the Mayo Clinic in Rochester, Minn., and at the University of Minnesota, Minneapolis. He taught many medical students, pathologists, cardiologists, cardiac surgeons, and visiting medical experts from around the world. Dr. Edwards housed an enormous collection of autopsied hearts at United Hospital, St. Paul, Minn., known as the Dr. Edwards' Cardiovascular Registry that became a principal resource for his illustrated reference books: *An Atlas of Acquired Diseases of the Heart and Great Vessels* (1961), and *Congenital Heart Disease* (1965). He also coauthored nearly 800 journal articles and 14 books. Dr. Vlodaver pays special acknowledgment to Dr. Edwards who was his teacher, mentor and "inspirational force in his medical life."

Howard B. Burchell, MD, cardiologist, professor of medicine at the Mayo Clinic in Rochester, and the inaugural chief of cardiology at the University of Minnesota. He was editor-in-chief of the journal *Circulation* from 1965 to 1970. Scholarship and education with a central theme of sound scientific evidence were hallmarks of Dr. Burchell's career. Drs. Garry and Wilson pay special acknowledgement to Dr. Burchell as they led the Cardiovascular Division at the University of Minnesota in the same spirit of innovation, discovery, and the delivery of outstanding cardiovascular care.

Jay N. Cohn, MD, Professor of Medicine at the University of Minnesota, discovered much of the basic physiology of heart failure and its relationship to afterload and vascular tone. Dr. Cohn created an integrative conceptual framework for understanding heart failure that shaped our understanding of the pathophysiology and guided a revolution in therapy. Today, he is widely recognized as the Father of Heart Failure as he founded the Heart Failure Society of America and served as the inaugural editor-in-chief for the *Journal of Cardiac Failure*. Dr. Cohn also served as the chief of cardiology for 22 years and established one of the world's leading heart failure programs in the world. Dr. Wilson pays special acknowledgement to Dr. Cohn who recruited him to the University of Minnesota and was supportive in his studies of sympathetic reinnervation after transplantation.

The editors wish to acknowledge all the trainees that they have worked with throughout their careers. It is our hope that the discoveries and discussions we shared together will serve as a platform to inspire you to further impact the field.

We acknowledge and thank Jane Hutchins-Peterson for her outstanding assistance and for handling the flow of material from the writers to the publisher.

We recognize with deep appreciation Barb Umberger for her dedication in the editing of the manuscript in the minutest detail to ensure the high quality of this project.

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We extend our gratitude to Michael Griffin, Development Editor for Springer Publishing, for his outstanding efforts, support, and attention to the details needed for publication of this book.

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History and Basic Mechanisms of Heart Failure

A Historical Overview of Cardiovascular Medicine and Heart Failure

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1

Introduction

» For as long as we have been self-aware, we have been in awe of the fact that there is something so vital, so alive, within our bodies: a relentlessly active core with a will of its own. An animating essence that does not obey our commands the way our hands do, or our eyelids, or even our lungs. A link to the universal motion surrounding us, the tides and stars and winds, with their puzzling rhythms and unseen sources. Once this awareness dawned, it would have been impossible for us ever again to look at ourselves or the world the same way. S. and T. Amidon [1]

These lines from *The Sublime Engine* are a good place to begin any historical excursion into the heart's role in the history of medicine. They remind us that, from the earliest moments of self-awareness at the dawn of humanity, the heart has been a constant companion of motion within us. Whatever that may have meant for our early ancestors is anyone's conjecture, but we do know that it was on people's minds from the very outset of our human journey. While the study of the heart has a rich and dynamic history, it also provides a platform for research that would focus on the pathophysiology of the failing heart and the discovery of therapies that would impact the course of this disease. Here, we provide a historical overview of the studies of the heart and heart failure as a foundation for the emerging technologies that are described throughout the remainder of this textbook. As Sir Winston Churchill stated, "Those who fail to learn from history are doomed to repeat it."

A Brief History of the Heart and Cardiovascular System

Recent research into Ardèche cave dwellings in France from the Aurignacian and Late Magdalenian cultures of the Paleolithic Era (35,000–10,000 B.C.) has shown that, among the wall etchings and paintings of hunting parties and the hunted, of spirits that lurk in the forces of nature, a vocabulary of symbols may exist literally. Among these is a surprisingly unmistakable outline of a heart or cordiform shape [2]—an almost childlike rendition of a valentine (Fig. 1.1). Whatever this may reflect in symbolic value, it could reasonably signify the organ so often seen in a butchered catch, a horrifically injured hunter, or in any accident that rendered the heart bare and exposed to the unsparing milieu of prehistory.

Ancient Egyptians

As we move forward in time to the ancient Egyptians, we find a culture that fully embraced the heart not only medically and physiologically but psychologically as well. Although there is

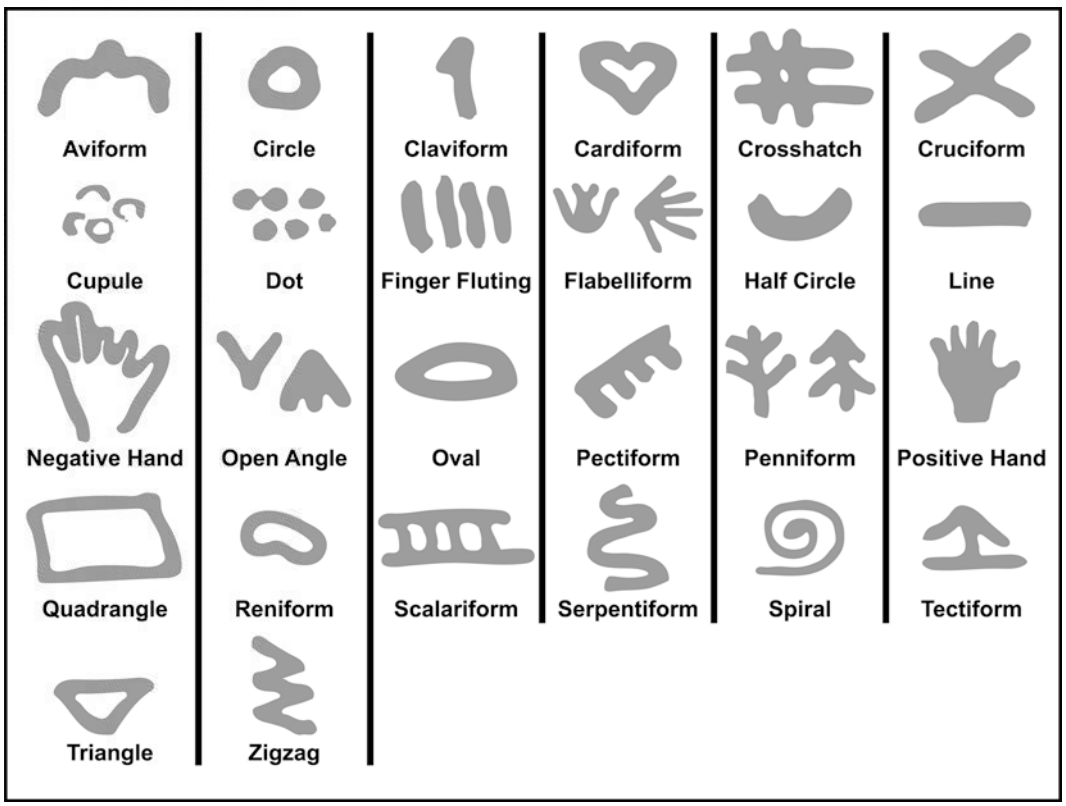

Fig. 1.1 Twenty-six signs all drawn in the same style but compiled from 146 prehistoric sites in France covering 25,000 years—from 35,000 to 10,000 B.C. These symbols may represent a written form of code transmitting information. While the cordiform symbol is heart-shaped, its symbolic meaning remains open to interpretation. *Source*: www.ancient-wisdom.co.uk/caveart.htm

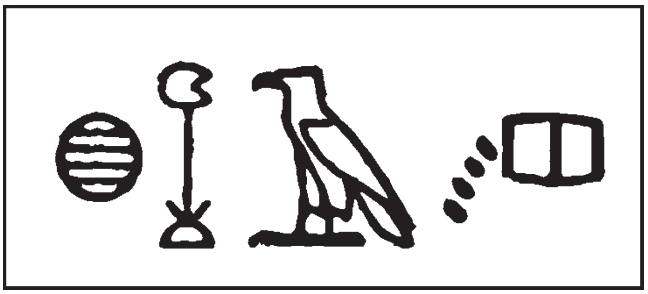

Fig. 1.2 The hieroglyphic characters from the Edwin Smith Papyrus, ca. 1700 B.C., portrays the "counting" or "measuring" of the pulse. The symbol on the *right* is a depiction of counting seeds or beads from a container. These characters represent the first account of tabulating the rate of the pulse and would later be replaced by water vessels in which incremental loss of water could be correlated with the pulse and a reference to time. *Source*: Brewer LA 3rd. Sphygmology through the centuries. Historical notes. Am J Surg. 1983;145(6):696–702

no defined structure of a circulatory system proper, the Edwin Smith Surgical Papyrus (c.1600 B.C.) does record its author's awareness that the status of the heart can be assessed by the pulse. It also records the first written observation of the heartbeat (Fig. 1.2). From the beginning, the papyrus' text suggests that: *The counting of anything with the fingers* [*is done*] *to recognize the way the heart goes. There are vessels in it leading to every part of the body. When a Sekhmet priest, any sinw doctor…puts his fingers to the head…to the two hands, to the place of the heart…it speaks…in every vessel, every part of the body* [3]. Furthermore, it was believed that all the "inner juices of the body" (e.g, blood, air, mucous, urine, semen, and feces) flowed through channels that extended from the heart and were distributed peripherally throughout the body in harmony and collected at the anus and recirculated [3]. Any disruption of the flow resulted in illness.

References to the anatomy and physiology of the heart are also evident in the Ebers Papyrus (circa 1550 B.C.). Aside from its biology, the papyrus described the heart as bearing the ponderous role as the center of emotion, memory, thought, will, and personality. As such, it was the final arbitrator in the afterlife by which one's integrity and eventual fate were determined. In this final judgment, unlike the other organs that were removed during mummification and placed in canopic jars to be buried with the body, the heart remained in the body. And according to the prescriptions of the Egyptian Book of the Dead, it was weighed in a balance against an ostrich feather, called the feather of Ma'at (Fig. 1.3). If found worthy, one would join the gods in the Fields of Peace. If the heart of the deceased weighed more than the feather—that is, more evil than good—the heart was immediately devoured by the chimeric demon Ammit. In effect, this condemned the bearer to dying a second death that signaled complete annihilation.

Egyptian medical knowledge of the heart would diffuse through time and eventually influence the early Greeks, including Praxagoras, the Cnidians, and the Sicilians in seeing the primacy of the heart, even as the seat of intelligence [4]. Nevertheless, much of Egypt's religion-based medicine was largely abandoned by the Greeks for a more rational approach to disease and medicine.

Ancient Greece

In Greece's Homeric period (1100–750 B.C.), aspects of cardiovascular anatomy were largely known in the traumatic context of battle wounds and lesions, including the well-known account in Homer's *Iliad* (760–710 B.C.) about the dying Alcathous and his still-pulsating heart: "… *while fighting Idomeneus stabbed at the middle of his chest with the spear, and broke the bronze armor about him which in time before had guarded his body from destruction. He cried out then, a great cry, broken, the spear in him, and fell, thunderously, and the spear in his heart was stuck fast but the heart was panting still and beating to shake the butt end of the spear*" [5].

Although later in the Archaic period, Hippocrates (460–355 B.C.) would hold a prestigious position within Greek medicine because of his compendium of medical practice which sought a rational basis for disease. Actual knowledge of the cardiovascular system within the Hippocratic Corpus was limited and, in many cases, erroneous, including its description of the heart as "a firm thick mass so richly supplied with fluid that it does not suffer harm or manifest pain [6]." Nevertheless, anatomical detail was not only useful but would historically help to define the organ with greater precision, including the heart's description as four-chambered. Other details included its unidirectional flow of blood through the aortic valve, the shape of the pulmonary valve, and the pericardial sac and fluid.

In the Classical Period (480–323 B.C.), Greek contribution to cardiology was modest, as reflected in the work of Diocles of Carystus (400 B.C.), who is attributed with distinguishing the aorta from vena cava, and Aristotle (384–322 B.C.), who took a cardiocentric position regarding the heart. He noted it as three-chambered and the seat of the soul. He also described the heart and great vessels as the source of all vessels.

Paraxagoras (ca. 340 B.C.) proposed a distinction between arteries and veins, with the former arising from the heart, transporting air, and the latter arising from the liver and transporting the blood. While Herophilus (335–280 B.C.) would further characterize and distinguish arteries and veins, noting that the arterial wall was thicker and pulsated, it was his colleague Erasistratus (304–250 B.C.) who championed the Greek contribution to cardiology with his observations on the nature of vessels, the valves of the heart, and his conceptualization of the vascular angioarchitecture.

Galen and Erasistratus

Most of what has been preserved about circulation theories comes by way of Galen. Judging from Galen's references to Erasistratus' works, Erasistratus was not far from an

1

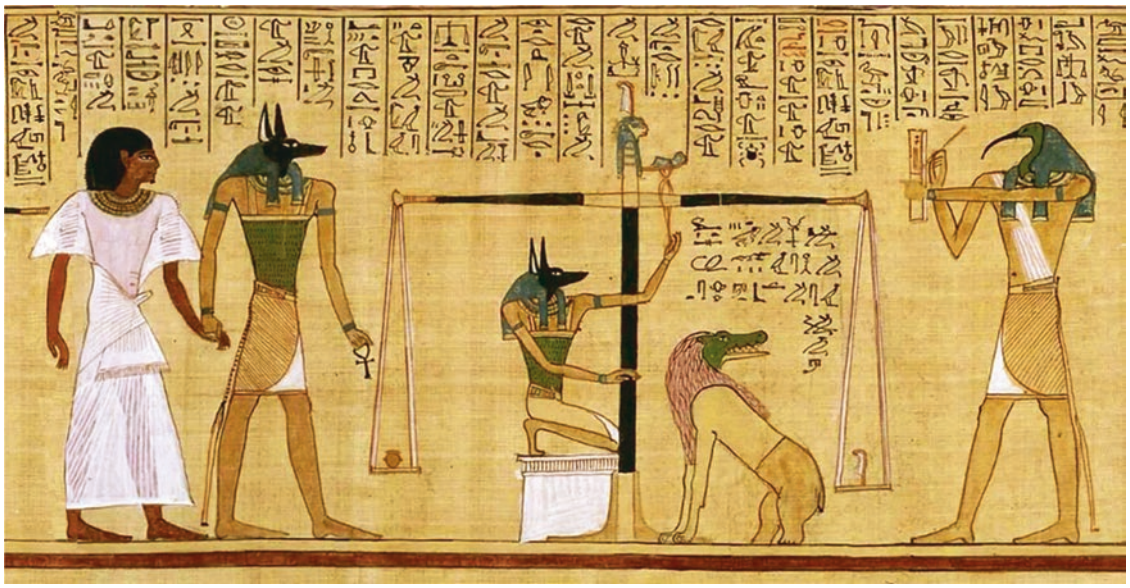

Fig. 1.3 A hieroglyphic and graphic representation of the ritual of the weighing of the heart from the Papyrus of Hunefer. Anubis, the jackal-headed god associated with mummification and the afterlife, takes Hunefer, dressed in white, by the hand to lead him to the ritual. Anubis is shown a second time checking the scale to assure its accuracy, while Ammit stands below the scale awaiting the results. The Ibis-headed god Thoth, the record-keeper and arbiter of godly disputes, stands on the right ready to record the outcome. Hunefer's heart is placed on one side of the balance and Ma'at's feather on the other. If the heart weighs less, reflecting the good life that Hunefer embraced while alive, he will join the gods in the Fields of Peace. If it weighs more, indicative of an evil life, the heart will be consumed by an anxious and hungry Ammit. This action condemns the lost to dying a second time, signaling complete annihilation. Fortunately, Hunefer's heart weighed less and will be presented to Osiris for admission into the afterlife and granted eternal life in Aaru

understanding of circulation—and, certainly, a more contiguous relationship between arteries and veins, both of which he believed arose from the heart: *The vein* (*pulmonary artery*) *arises from the part where the arteries*, *that are distributed to the whole body*, *have their origin*, *and penetrates to the sanguineous* [*or right*] *ventricle*; *and the artery* [*or pulmonary vein*] *arises from the part where the veins have their origin*, *and penetrates to the pneumatic* [*or left*] *ventricle of the heart* [7]. Furthermore, he held that arteries contained exclusively air and, when punctured, the air escaped. Blood seeped in from arteries to fill the space which was observed to spill from the cut vessel. Like Herophilus, Erasistratus believed that veins contained and transported blood only.

As Aird (2011) points out in his elegant analysis, the focus of the Greek school of cardiovascular thought was understanding how nourishment is disseminated to all parts of the body [8]. Erasistratus described an open-ended vascular system (Fig. 1.4a) where absorbed nutrients were converted in the liver into blood that flowed via the hepatic vein to the vena cava, and from there, to the rest of the body. A portion of the blood was directed to the right ventricle and, ultimately, to nourish the lungs. Conversely, he said the pulmonary veins take up air and transport it to the left ventricle and ultimately carry it to the tissues by arteries. Although flawed, such a system explained what he thought he observed in his dissections and would continue to influence cardiology until the time of Galen.

Galen (129–216 A.D.), whose name and theories alike would come to cement medical knowledge for thirteen centuries, was a Greek physician born in Pergamon. His seemingly unlimited knowledge of medical science likely was derived from his firsthand knowledge as court physician to several Roman emperors, surgeon to the gladiators, and avid dissector of numerous animal species including the Barbary ape and pigs. His cardiological work builds on a refinement of Greek physiology that relied heavily on the four bodily humors (blood, black and yellow bile, and phlegm). The underlying principle is that, although the heart is the source of innate heat that gives life and soul to the body, it must be cooled. In Aristotle's interpretation, cooling was the brain's task, while Galen held the novel idea that the lungs provided this activity. Galen provided an open-ended theory of the vascular system that expanded upon Erasistratus' scheme—providing an innovative way the blood flowing in both arteries and veins (Fig. 1.4b).

In Galen's scheme, the heart and arteries stood in parallel with the liver and veins, and the brain and nerves to form a tripartite system of governance. Each provided a functional component of the living system: brain and nerves brought sensation and thought, the heart and arteries replenished life-giving energy, and the liver and veins provided nutrition and growth. Each also generated a pneuma (πνεῦμα, an ancient Greek word for "breath") or spiritual substance that animated and nourished the body. He believed the heart

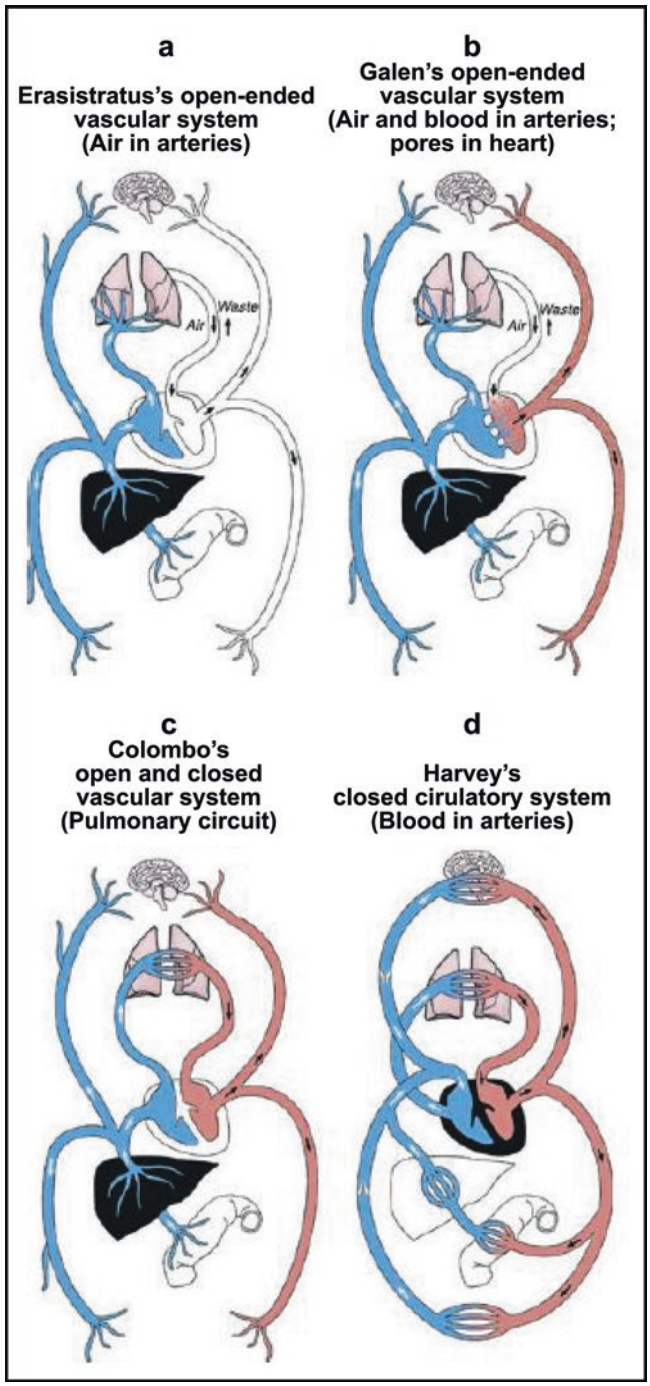

Fig. 1.4 A schematic of the circulatory system, comparing major advances in the conception of the cardiovascular system. (**a**) The work of Erasistratus illustrates his belief that the arterial and venous systems were separate. The venous system transported blood, while the arteries carried air. Food absorbed from the intestines was transported via the portal veins to the liver where the nutrients were transformed into blood that was delivered to the rest of the body via the vena cava. (**b**) Galen's scheme was designed around the arteries that carried blood—derived from venous blood that passed through pores of the interventricular septa. (**c**) Colombo's scheme provided for an accurate pulmonary circulation but maintained the Galenic distribution of most venous blood passing directly to the tissues of the body and only a portion to the right ventricle. (**d**) Harvey's system expanded the pulmonary route to include the entire body whereby all venous blood passes from the tissues and lungs to the right ventricle, and arterial

produced vital pneuma, the liver a natural pneuma, and the brain an animal pneuma.

The actual flow of blood via the Galenic system has not been without debate due to translation and the interpretation that comes with translation. Foibles also arise from Galen's own ambiguities which can be found in his descriptions. As Henri de Mondeville (1260–1320) would later note, "God did not exhaust all his creative power in making Galen [9]." That said, the following is a simple and generalized scheme of the Galenic system.

His scheme begins with the intake of food. Once digested, it is transported from the intestines to the liver via the portal vein (Fig. 1.5). In the liver, the nutrients were changed to blood which was suffused with natural pneuma that endowed it with the power of growth and nutrition—signaled by the dark red color of the newly formed blood. From the liver, the vitalized blood passed to several destinations. One portion flowed through the vena cava and downstream veins and throughout the body to bring the nutrient potential to muscles and organs. Some blood, however, diverted from the inferior vena cava to the right ventricle of the heart. Here, some flow continued to the lungs via pulmonary arteries (*arteria venialis*), while a portion of the flow filling the right ventricle passed through invisible pores located within the interventricular septum and into the left ventricle. Here, the blood mixed with air transported from the lung via *arteria venialis* and pulmonary vein by ebb and flow motion and infused with the vital spirit. The imbued blood, now bright red, was transported via pulsatile arteries to the rest of the body where it was consumed by the tissues and a portion of flow to the brain. The latter blood diverted to the brain was further vitalized by the animal pneuma, a rarefied pneuma that vitalized the brain and flowed peripherally via nerves to bring power to the muscles and perception via the senses.

Finally, as to pulsation, while Erasistratus saw the heart as a suction-and-force "bellows" that produced a passive distention of the artery due to the expulsive force of pneuma from the left ventricle during its contraction [10], Galen believed the pulse was generated by the active contraction and dilation of the muscular coats within the arterial wall. The stimulus arose in the heart and propagated down the wall [11]. Both were incorrect. For Erasistratus, the pulse arose from the action of the heart, but it was pneuma, not blood, that pulsed through the arteries. For Galen, it was blood that flowed through the arteries—but due to the pulse produced by the arterial wall.

Many clinicians today have asked why Galen, a scientist of discerning and incisive insight, failed to deduce the obvious role of the heart within a circulatory scheme. Many have

Fig. 1.4 (continued) blood passing from the lung is pumped to the rest of the body. Although no direct evidence existed in William Harvey's time for capillary beds to link the closed system, Marcello Malpighi later wrote of a porous transfer between the two. *Source*: Aird WC. Discovery of the cardiovascular system: from Galen to William Harvey. J Thromb Haemost. 2011;9(Suppl 1):118–29

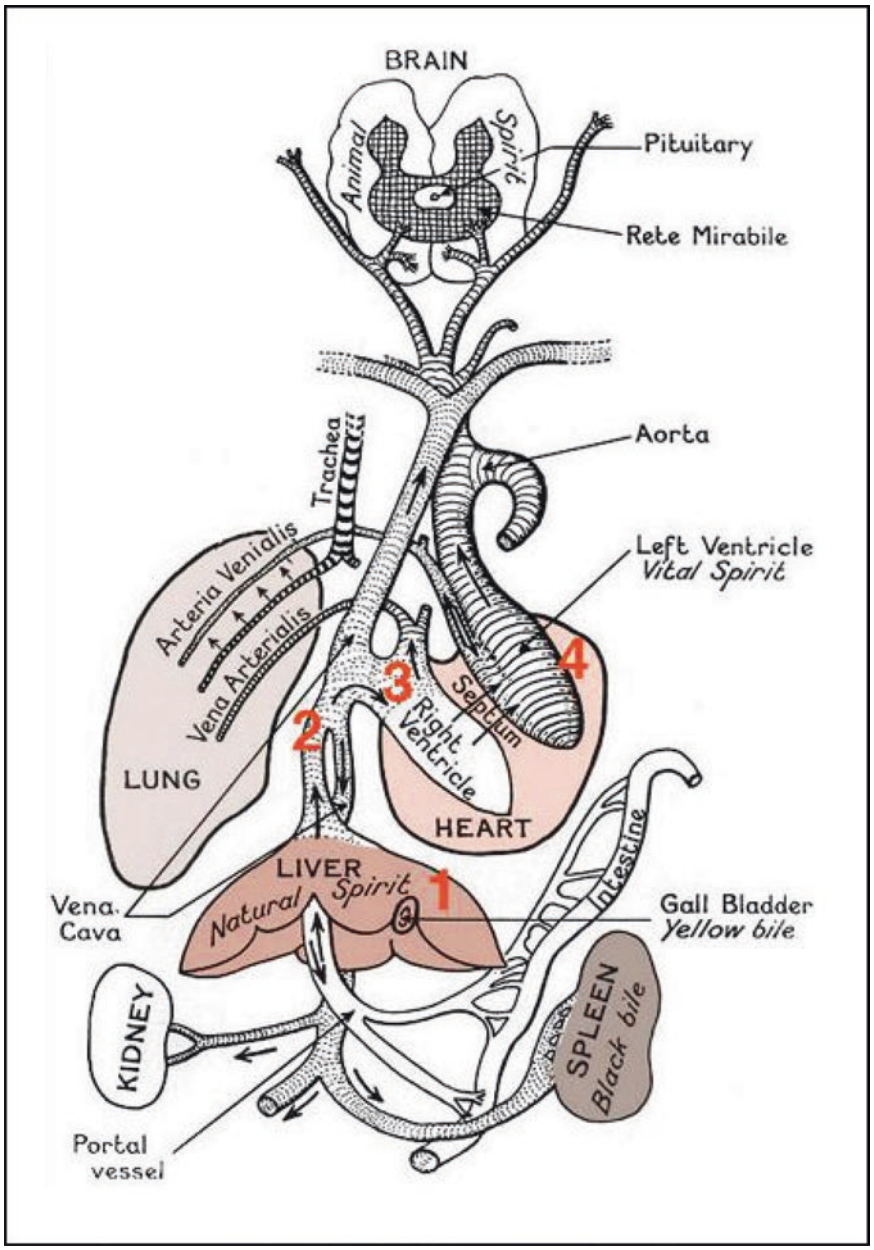

Fig. 1.5 A schematic representation of Galen's concept of circulation. Nutrients passing by way of the portal veins were carried to the liver (*1*) where, mixed with the natural pneuma, formed blood was distributed to the entire body by the vena cava (*2*) and a small portion to the right ventricle (*3*) by the ebb and flow motion from the liver. Some blood in the heart flows to the lungs to emit "sooty vapors," while some flows through pores of the interventricular septum where it is suffused with "vital spirits" from the pneuma and transported via the trachea. Blood flowing further into the brain was imbued with animal spirits before being distributed to the body via nerves considered to be hollow. *Source*: Singer C. A Short History of Anatomy and Physiology from the Greeks to Harvey. New York: Dover; 1957

also proposed answers to this puzzling question. An increasing number support the thesis that Galen became consumed and distracted by his ongoing dispute with the Stoics [12]. His agenda became a polemical dialectic to discredit the Stoics' concept of an indivisible soul while maintaining his own allegiance to the Platonic concept of the tripartite soul. The intensity of the debate allowed little option of moving beyond this defensive position. The Galenic system would become the predominant paradigm that would influence and guide medical practice and education down through the subsequent ages as it was further emulated and canonized during the Middle Ages.

The Galenic system would eventually be challenged in the thirteenth century by physicians of the Islamic world who had greater familiarity with the ancient Greeks. This included the Arab physician Ibn al-Nafis (1210–1288), who took clear exception to the existence of invisible pores within the interventricular septum that enabled blood passage from right to left ventricle and, furthermore, provided an accurate basis of pulmonary circulation. While the West continued to embrace and teach Galenic principles, new developments in the twelfth century would eventually lead to a reevaluation of Galen's all-pervasive influence.

Italy

Although it has been referred to as a "Civitas Hippocratica," the School of Salerno represented a fresh and integrated approach to medicine and medical education in an otherwise unresponsive era. Beginning the in the tenth century and arising in the context of Benedictine monasticism,

including Monte Cassino, it became the first medical school in the world and, subsequently, an outstanding secular institution. It returned to the earlier historical practice of animal dissection as one of its chief merits. As Castiglioni points out, "up to that time anatomy had been taught simply *sicut asserit Galenis* ('thus does Galen declare')" [13]. At Salerno's peak in the twelfth century, anatomic dissection, particularly of the pig, was systematically undertaken, and although still steeped in Galenic perspective, faculty members were beginning to embrace the importance of independent observation.

The first public dissection of the human body for medical instruction was performed by Mondino de Luzzi (1275–1326) at the University of Bologna in 1315. Dissection of the body was evident as well in the work of the great Italian Renaissance artists who were less confined by the ideas of Galen or even Aristotle or Hippocrates. They sought to examine firsthand what the visually impoverished medical texts of the period failed to relay. Human dissections, including those of da Vinci, provided the anatomic and mechanical basis that conferred dynamics of motion and function to the body in life. Leonardo da Vinci (1452–1519) has only recently been properly acknowledged for his impressive knowledge of the heart, both in terms of function and anatomical features.

Our temptation is to regard Leonardo exclusively as an artist or illustrator, but he was much more. He was a scientist at heart, driven by an inquisitive nature, open to novel ideas and explanations, and heavily dependent on firsthand observation and experimentation. From age 14, he apprenticed in art and art history in the workshop of Andrea del Verrocchio and at the age of 33 was appointed director of the Academy of Science and Art in Milan. For 17 years, da Vinci undertook numerous engineering and architectural projects for the Duke of Milan. He explored and studied the elements of city planning, military engineering, mathematics, hydrodynamics, and the physics of optics and motion.

The principles applied in these studies and projects were ultimately focused on his abiding interest in anatomy—dynamic anatomy—and recorded in his notebooks anatomical dissections which he had planned to publish. His anatomical works spanned two intervals: 1480–1497 and 1506–1509. Of his 5000 known pages of notes and illustrations largely on mechanics, 190 recorded the anatomy of autopsied human subjects and animals, of which 50 were devoted exclusively to the heart [14]. Aside from the amazingly detailed surface features of the heart (Figs. 1.6 and 1.7), Leonardo explored the inner aspects of the chambers and conduits, noting the architecture of the valves, papillary muscles—even the moderator band obvious in the ox heart and more difficult to distinguish in the human that he correctly identified as a muscular bridge stabilizing the right ventricle from over-distention. His drawings astutely record and analyze the physics of motion through the trileaflets of the aortic and pulmonary valves.

Aside from the intricacies of the heart itself, Leonardo regarded the heart as a muscle, not flesh, as stated by Galen. He clearly characterized for the first time the heart as four-chambered with atria distinct in configuration and function as they contracted to fill the ventricles. He also elegantly traced and defined the course of the coronary arteries as those that supplied the muscle of the heart itself and provided cogent demonstrations of the bronchial arteries (Fig. 1.8). Nevertheless, all this wealth of knowledge issued from the pen and drawings of da Vinci would never see the light of his age. With his death, his rich insights into the anatomy and function of the heart would be lost for almost 400 years.

During the century of Leonardo's death, several distinguished anatomists would prove essential to the continuing evolution of cardiology. Perhaps the most well known of these would be the Flemish anatomist Andreas Vesalius (1514–1564) who would publish his *De Humani Corporis Fabrica* and *Epitome* in 1543. This was a startling collection of dissected images of the human body illustrated by Jan van Calcar, his friend and pupil of the artist Titian, and unlike anything published to date. Despite the exquisite drawings, including those of the vascular system, his heart images remained modest and illustrated the interventricular pores of Galen (Fig. 1.9). On the other hand, the sentiment expressed in his text would indicate otherwise:

> The septum of the ventricles, composed of the thickest substance of the heart abounds on both sides with little pits impressed in it. Of these pits, none, so far as least as can be perceived by the senses, penetrate through from the right to the left ventricle, so we are driven to marvel at the handiwork of the Almighty, by means of which the blood sweats form the right to the left ventricle through passages which escape human vision. [15]

Whether the sarcasm was deliberate or unintentional, da Vinci simply had nothing else to substitute for Galen's explanation. Nevertheless, his instincts as a precise and careful scientist led him to conclude otherwise. In his second edition of the *Fabrica* (1555), he does assert no evidence for the pores. "*Not long ago I would not have dared to turn aside even a hair's breadth from Galen. But it seems to me that the septum of the heart is as thick, dense and compact as the rest of the heart. I do not see, therefore, how even the smallest particle can be transferred from the right to the left ventricle through the septum*" [15].

In addition to the work of Vesalius, others would provide strategic insights in moving forward the study of the heart. Michael Servetus (1511–1553), a Spanish physician, suggested evidence of a pulmonary circulation. While this was new to the West, it had been firmly articulated earlier by the Arab physician, Ibnal-Nafis, who clearly described the flow of blood from the right ventricle via the pulmonary artery to the lung and from the lung via the pulmonary veins to the heart and through the aorta to the rest of the body. Unlike Ibn al-Nafis' observations that were based on autopsies and human dissections [16, 17], the thesis proposed by Servetus was mainly based on his observations—primarily on the color of the blood and ventricular and pulmonary dimensions. Furthermore, his work was largely unknown because it

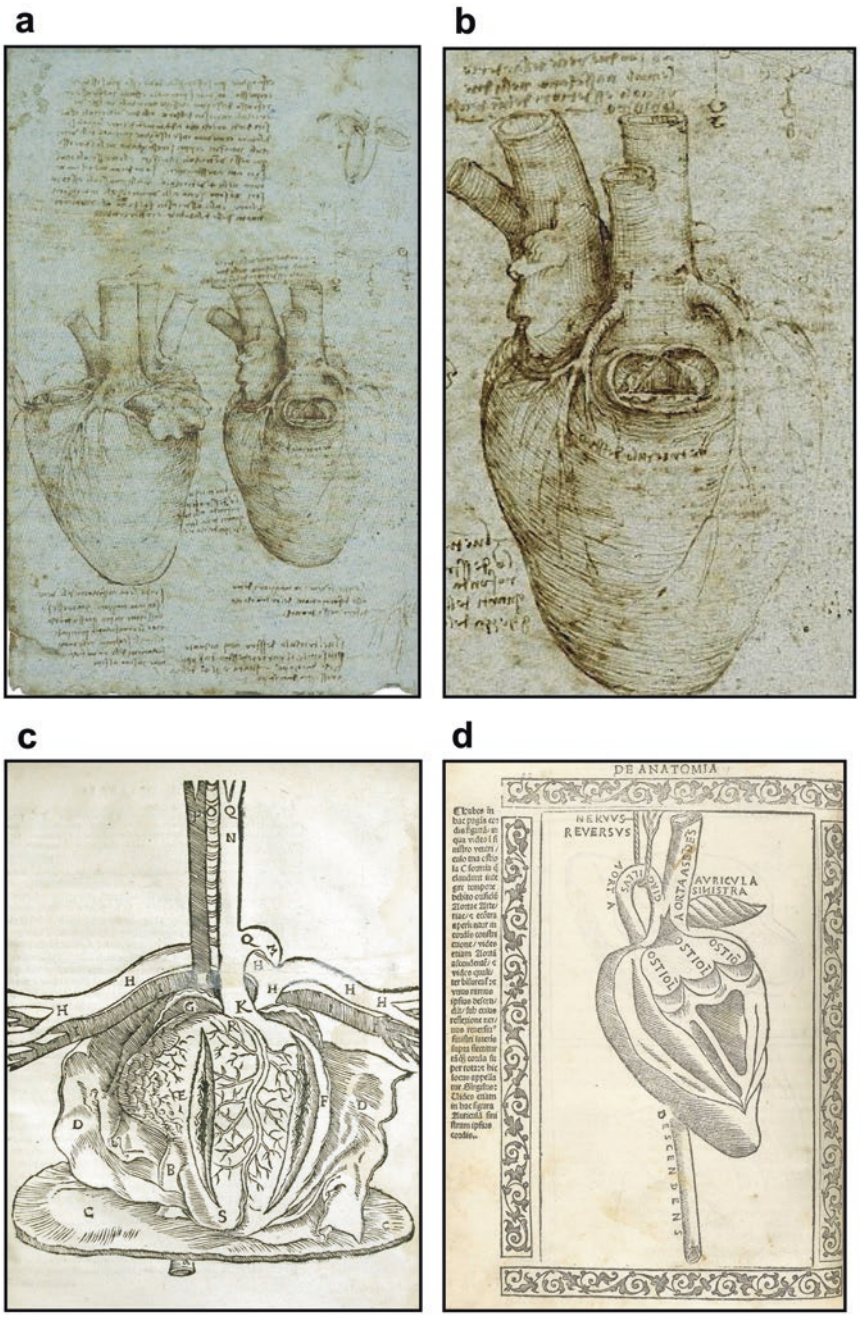

Fig. 1.6 A comparison of heart drawings by Leonardo da Vinci and contemporaries. (**a**) Leonardo's drawing of the ox heart, showing detailed images of the coronary arteries, the atria, as well as the great vessels. (**b**) An enlarged image showing the posterior facet of the base of the aorta with the pulmonary trunk cut away (1511–13). (**c**) The graphic representation of dissected hearts drawn by Mondino di Luzzi (1541) and (**d**) Berengario da Carpi (1523)

was found within his theological treatise, *Christianismi Restitutio*. He wrote it to clarify the origins of the Holy Spirit in the air-blood interface of the heart, "*Ab aere inducit Deus anima*" [From the air, it induces the soul].

Andrea Cesalpino (1519–1603), an Italian physician and contemporary, was interested in the dynamics of blood flow within the veins. For the most part, he understood that blood in veins flow in a single direction, and the distinctive differences between pulmonary artery and vein, and aorta and vena cava. He demonstrated in his *Quaestionum Peripateticum* (1593) the disposition of the blood above and below the point of a ligature placed on the arm. In showing the dilation below and the collapse above the ligature and, thus, a centripetal flow in the veins, he became the first to publish such experimental data and the first to have used the term circulation in print. His exact meaning of the term, however, is still debated. Some believe it referred exclusively to the cooling of blood in the heart [18] or that is was chemical (distillation) rather than physical in nature [19]. Others, taking a de novo translation and analysis of the original Latin text, concluded that "it is inescapable that this author, several decades before William Harvey, had a clear general understanding of the circulation of the blood [20]."

It would come as no surprise that the latter opinion could be true because Cesalpino was a student of the next major figure of this era. Realdo Colombo (1516–1559), a surgeon

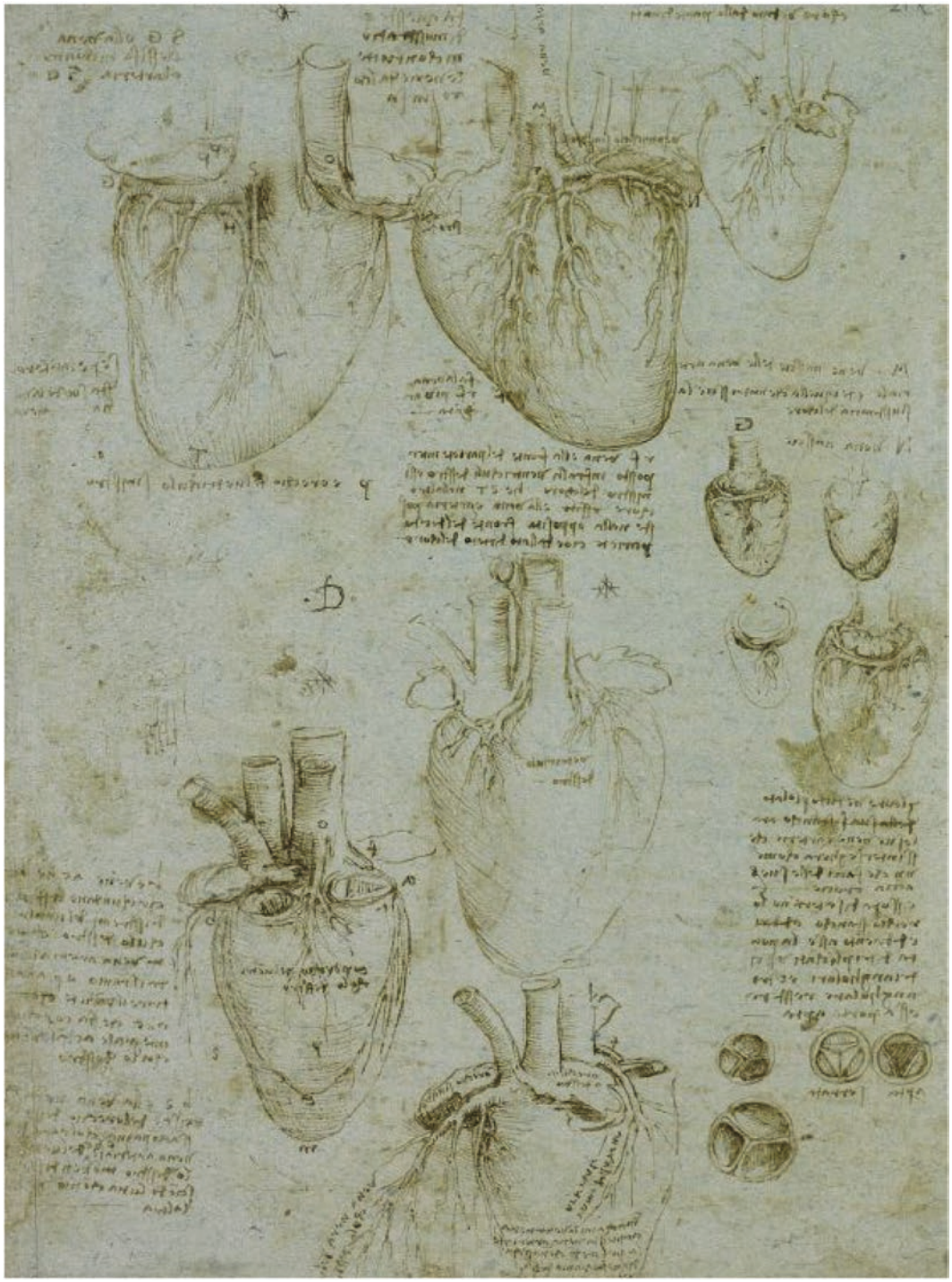

Fig. 1.7 Da Vinci's drawings of the human heart—both surface features and a study of the open and closed aortic valves—shown in the lower right margin of his notebook. Harvey asserted that the pulse was felt throughout the body and correlated with the heartbeat. As he stated, "And the same thing happens in the bodies of animals by means of the beating of the heart which generates a wave of blood through all the vessels, which continually dilate and contract. And dilatation occurs on the reception of superabundant blood, and diminution occurs on the departure of the superabundance of the blood received. This, the beating of the pulse, teaches us when we touch the aforesaid vessels with our fingers in any part of the living body"

and professor of anatomy, was a student and then colleague of Vesalius and, later, his successor at Padua. Later in Colombo's career, he would criticize Vesalius who, reacting strongly to the critique, ended their relationship [21]. Colombo would prove to be a sentinel, signaling that the full understanding of systemic circulation was at hand. Unlike his contemporaries, Colombo clearly presented his observations in a straightforward and scientific manner, which is

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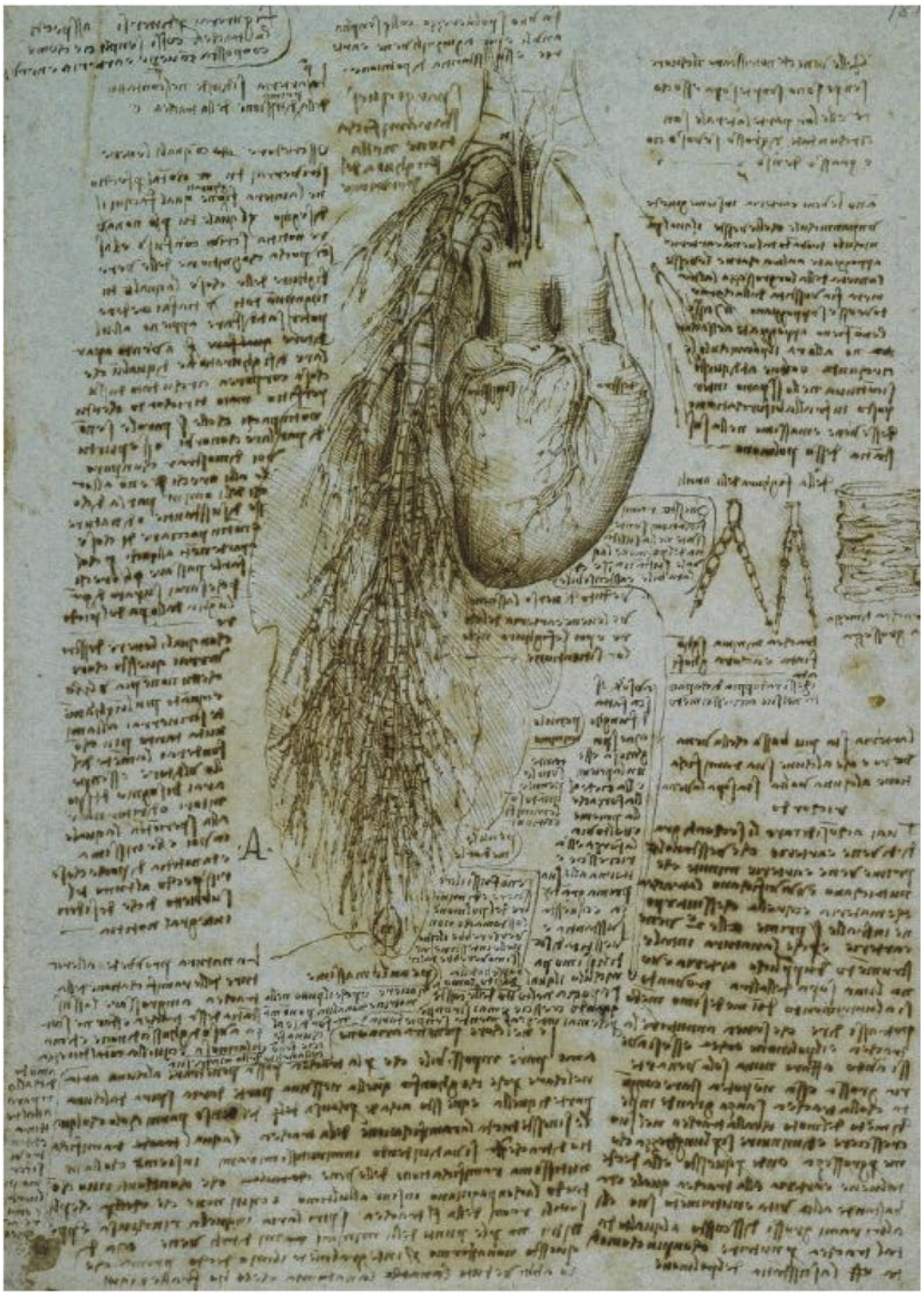

Fig. 1.8 Da Vinci's drawings of the bronchial arterial blood supply. Leonardo's views indicated an awareness of a perfusion of blood within the bodily organs for normal function. This included the size and the function of the organ

apparent in his *De Re Anatomica* (1559), published shortly after his death.

For example, much of Servetus' work, obfuscated by theological interests, was clearly articulated in Colombo's scheme of circulation, although he makes no mention of his name or work. Much of Colombo's scheme is Galenic, with veins arising from the liver, but no pores present in the interventricular septum. He dismisses the pulmonary vein as the conduit of air and fuliginous vapors and, given the true function of the cardiac valves, denies access of arterial blood retrogradely to the lungs:

» Between these ventricles there is a septum through which most everyone believes there opens a pathway for the blood from the right ventricle to the left, and that the

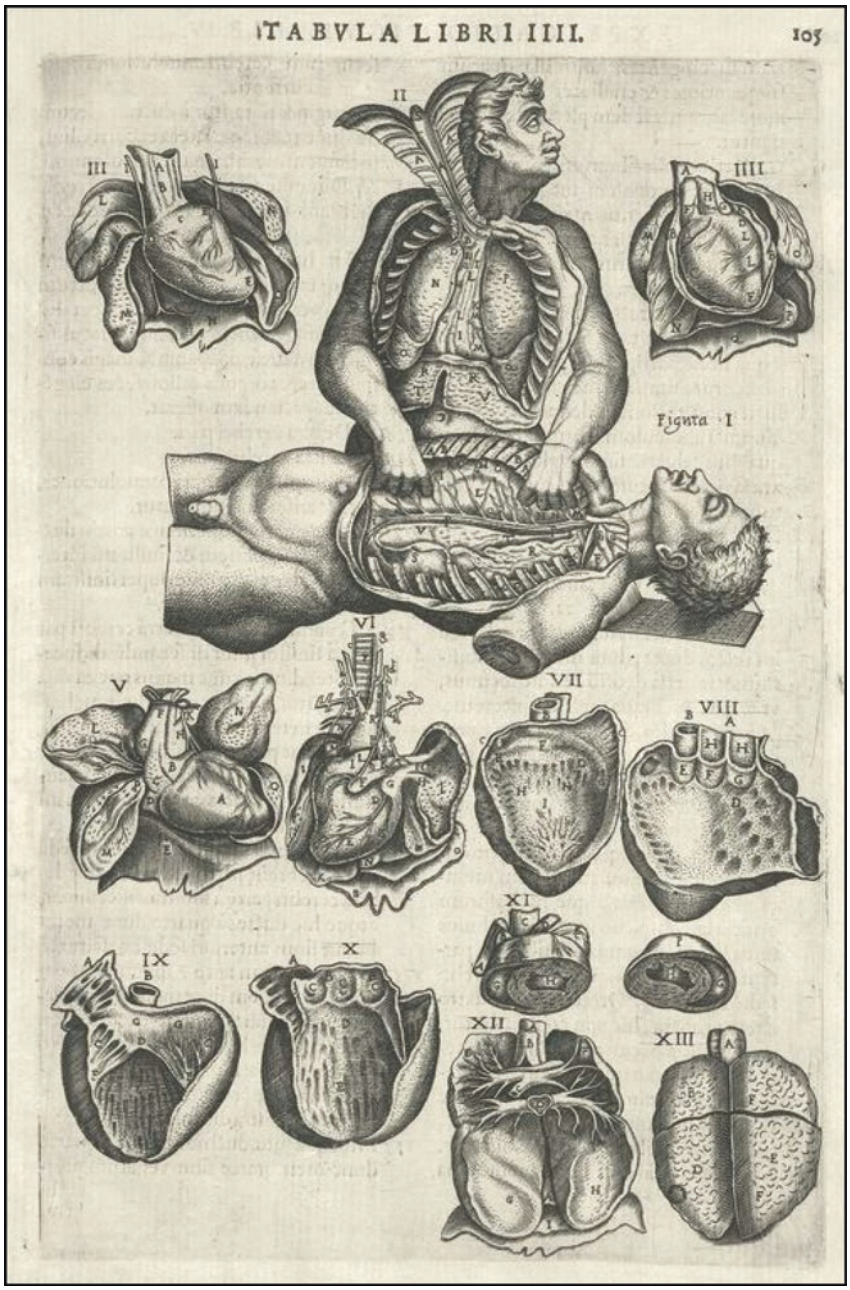

Fig. 1.9 The illustration of the heart dissected free of the chest and presented to show its various facets. In the first edition of *Fabrica*, the small pits were shown within the interventricular septum across which the blood passed from the right to left ventricle. This Galenic version of blood flow was omitted in this later edition (1566) of Andreas Vesalius' work

> blood is rendered this so that this may be done more easily for the generation of vital spirits. But they are in great error, for the blood is carried through the pulmonary artery to the lung and is there attenuated; then it is carried, along with air, through the pulmonary vein to the left ventricle of the heart. Hitherto no one has noticed or left in writing, and it especially should be observed by all [22].

Colombo's schema gave rise to both an open and closed system circulatory schema—open in the lungs but closed elsewhere in the body (Fig. 1.4c). Such a proposal clearly stood in contrast to but did not dismantle the Galenic system and was not unlike that proposed earlier by Ibn al-Nafis and Servetus. Colombo did not know of either man and arrived at his conclusions independently.

Colombo's successor at Padua was Girolamo Fabrizio (1537–1619), Italian anatomist and surgeon, also known as Fabricius. In addition to making remarkable discoveries, he taught a generation of notable anatomists and physicians including William Harvey, who succeeded Colombo at Padua. Fabricius was interested in circulation as well but focused his work on the valves present in walls of large veins. As shown in his *De venarum ostiolis* [On the Valves of the Veins], he proposed the hemodynamic feature of valves in facilitating the progressive flow of blood through a vessel and preventing retrogressive movement. Much of his work on the

tricuspid valves had already been described in da Vinci's work but went unknown to contemporaries.

All of these sixteenth-century physicians, anatomists, and professors contributed to a formative and fomenting period for cardiology. Their work led to the definitive moment when the undisputed center, the heart, would be ultimately understood as the source of motion that propelled the blood throughout a closed cardiovascular system. If we ask who discovered the pulmonary circulation, the reply would have to be all three: Ibn al-Nafis, Michael Servetus, and Realdo Colombo. Although followers have long favored their own candidate, the work of Meyerhof [23] and Temkin [24] in the 1940s spurred a general agreement that all three arrived at their conclusions independently, largely based on a comparison of their own commentaries. Later, Wilson [17] would concur due to all three sharing a common knowledge of Galenic physiology, but each using different evidence to support their observations and conclusions.

Many have suggested that Cesalpino discovered systemic circulation because of his comprehensive understanding of the circulation of blood based on careful empirical observations presented in his *Quaestionum peripateticarum* (1571) and *Quaestionum medicarum* (1593) [25]. He was the first to use the expression "circulatio sanguinis" in a hemodynamic sense. His physiological demonstrations with ligatures on the arm present in a compelling way as progenitors of Bauhin's iconic presentation of valves later used by Frabricus and still later by Harvey as the only illustration in his *De Motu* (Fig. 1.10).

But like many of his contemporaries, Cesalpino's work was a crucial footstep toward a definitive understanding of systemic circulation. That understanding would arrive very shortly with a work that struck literally at the very heart of the issue: *De Motu Cordis*. The very title, *On the Motion of the Heart*, cut to the chase. The heart was the source of the motion that systemically circulates the blood within a closed system.

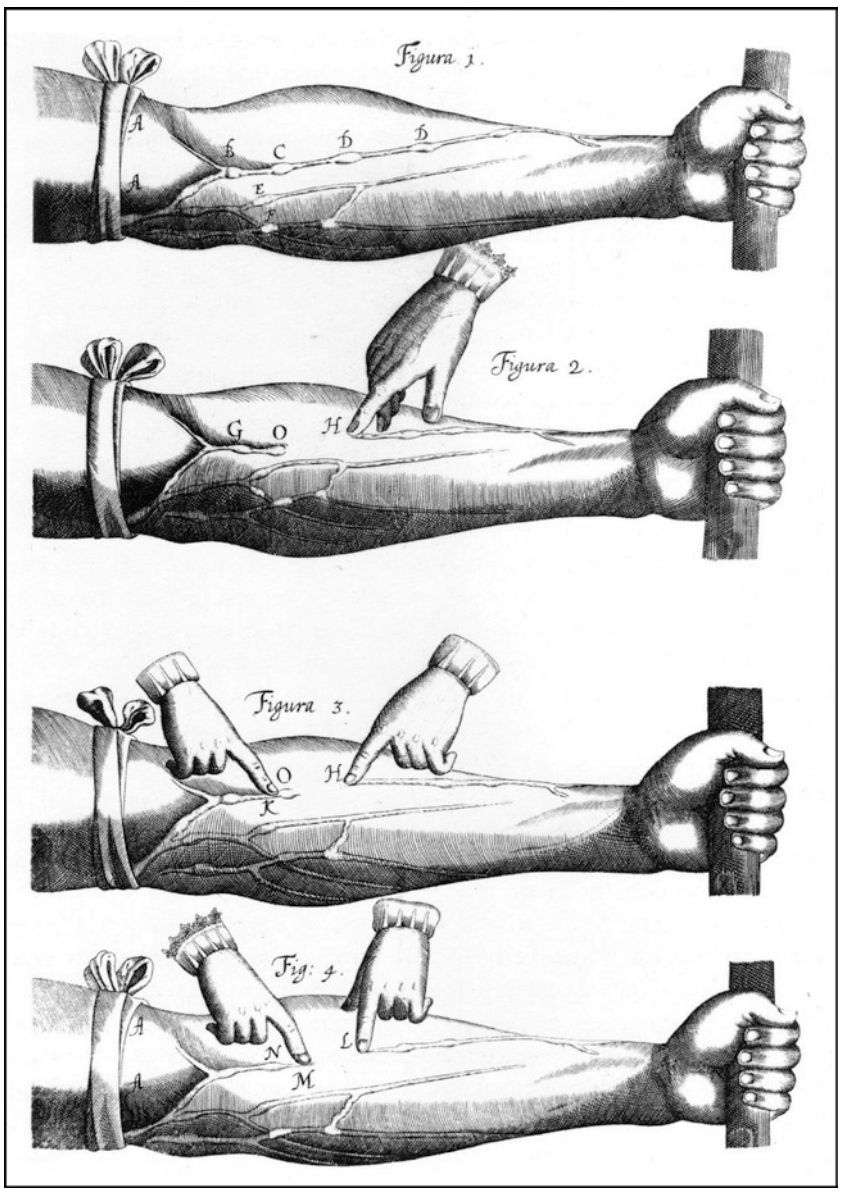

Fig. 1.10 The illustration used by Harvey in his *De Motu Cordis*, showing ligatures placed on the arm for the collection of blood. The original appeared in Bauhin's anatomical textbook (*Theatrum Anatomicum*, 1605) and later used by Fabricius. Before Harvey's use of the illustration, no one noted or addressed the obvious conflict. If the blood flowed centrifugally from the liver to the extremities, as it was held from the time of Galen, then the vein on the proximal side of the ligature should have showed swelling

William Harvey

Between 1597 and 1602, William Harvey (1578–1657) studied at and received his doctorate of medicine from the University of Padua. While a student there, he studied under Fabricus of Aquapendente. Fabricus would have a lasting influence on Harvey and, in particular, his appreciation of the venous valves. Harvey later intimated to Robert Boyle that this appreciation formed the basis of his interest in circulation [26].

After his return to England in 1602, Harvey was appointed Lumleian lecturer at the Royal College of Physicians. The gradual synthesis of his lecture notes and numerous experiments led him in his understanding of veins and blood flow. He may have initially shared his theory of circulation with his students between 1617 and 1619 when he most likely began to write. Experimental work including ligature experiments, jugular experiments, and heart dissections of deer and other animals to quantify flow-rate dynamics and intrinsic movement of heart muscle ensued for nearly another 10 years. Finally, the publication of his *Exercitatio Anatomica de Motu Cordis et Sanguinis Animalibus* in 1628, generally known simply as *De Motu Cordis*, made his theory of circulation known to all. Harvey began his work with a preface acknowledging his teacher Fabricus as "a venerable old man" and acknowledged his work, *De Respiratione* (1615).

Harvey maintained some of Colombo's ideas, including the assertion that the primary motion of the heart is contraction (systole), which propels blood into the arteries, which dilate (pulse) in response to the contraction of the heart and propulsion of blood. The pulse as demonstrated by Harvey was not blood being pulled into the heart but rather the blood being propelled by the heart into the arteries. Harvey had no role for interventricular septal pores since the blood of the right ventricle is propelled into the lungs by the pulmonary artery and from the left chamber into systemic circulation. Completing this circuit during diastole, blood flows from the great veins into the atria and ventricles. Unlike those who had gone before, Harvey believed the arteries transported nutrients throughout the body and, although undefined within the periphery of the tissues, blood passed from artery to vein, providing a circular basis of flow (◘ Fig. 1.4d) where the flow of venous blood is essentially centrifugal. Thus, the blood was not consumed by the tissues, as conjectured by the Galenists, nor by the liver, per generation de novo. The anatomical design of the veins with their valves is oriented toward the heart, with the heart as the source of the blood's movement, not the liver.

It has been suggested that this circular pattern came to Harvey because of his admiration of Aristotle who regarded circular motion as a symbol of perfection, perpetuity, and embodied qualities of preservation [8]. It was still remarkable that the definition of the circulatory system had so long eluded even the most skilled of physicians and the most astute of philosophers. Yet controversy arose as soon as *De motu cordis* was published. Harvey was not hailed as a hero but even as a scorned "circulator" (traveling quack) by his most vitriolic of opponents, Jean Riolan (1577–1657), who could not forgive Harvey's disrespect for Galen. Even more outspoken was Guy Patin (1601–1672) who stated that Harvey's theory was "paradoxical, useless, false, impossible, absurd, and harmful" [27]. Despite these and other vocal critics, Harvey had his supporters, including many eminent colleagues like Richard Lower (1621–1691) who, in his own work, demonstrated Harvey's system to be empirically sound. In addition to the negative reaction to his work, Harvey's troubles did not end in academic contention alone. He had served as court physician to King Charles I, who had kindly provided Harvey with deer from the royal parks for his experiments. Because he remained loyal to Charles even after his beheading in 1649, Harvey's residence was ransacked during the Cromwellian Civil War [Third English Civil War (1649–1651)], and many of his notes and papers were destroyed. Although Harvey died of a stroke in 1657, his legacy formed much of the basis for modern cardiology and its continuing evolution into modern times.

A History of Heart Failure

Heart failure was a recognized disease from ancient Greece, India, and Egypt, but mechanistic insights were limited until Harvey's description of the circulation, Rontgen's discovery of x-rays (1895), Einthoven's development of the electrocardiogram (1903), the discovery of echocardiography by Inge Edler (1953), the discovery of cardiac catheterization by Werner Forssmann (1929), and other medical interventions. These interventions initially used leeches for bloodletting (by the "barber-surgeons" of the day; ◘ Fig. 1.11) and later used Southey's tubes (established by Dr. Reginald S. Southey in 1877) to drain peripheral fluid from the patient with heart failure [28]. The practice of bloodletting continued up to the middle of the twentieth century when diuretics became available.

Diuretics

In addition to bloodletting, paracentesis was also used to remove fluid from the abdominal cavity. Dr. William Withering introduced the use of Digitalis purpurea in 1785, as outlined in his book, *An Account of the Foxglove*. Toward the end stage of the disease, patients were noted to be incapable of lying flat and were reclining in a semi-upright state. Heart failure patients were typically described as having dropsy (from the Greek word for water) which reflected the edematous state of the patient [28]. Various therapies were implemented including mercury (i.e., Mercupurin, Thiomerin, Mercuhydrin, Salyrgan), which served as a diuretic as outlined by Dr. John Blackall (1771–1860) in his book, *The Nature and Cure of Dropsies* [28]. During this time period, patients were primarily managed with bed rest, fluid restriction, and diuretic therapy.

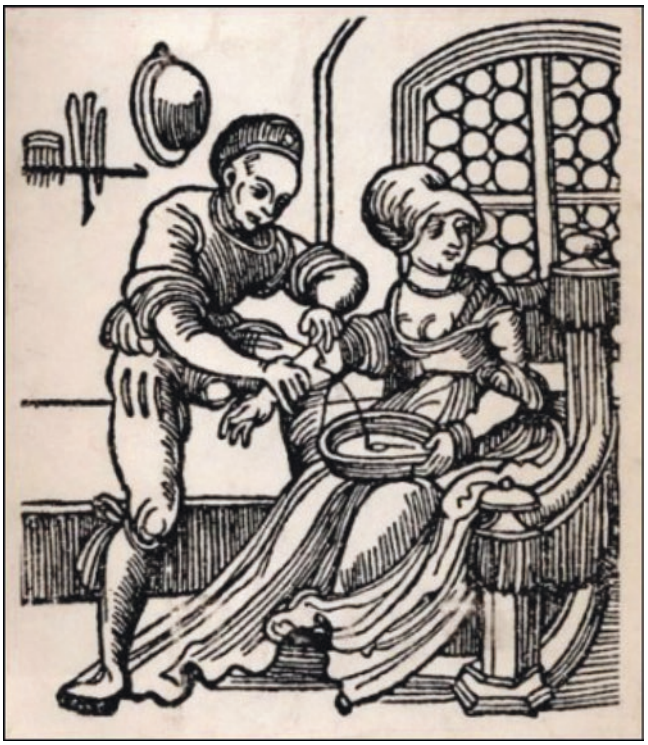

Fig. 1.11 The surgeon-barber provided health care for the community. The barber-surgeons performed a number of duties ranging from haircuts, beard trimming, teeth pulling, wound treatments, amputations, and bloodletting. Drawing emphasizes the bloodletting by the barber-surgeons. Barbers and surgeons remained part of the same trade guild until the mid-1700s

In a small study in 1957 of 15 patients with heart failure, a benefit was observed following sublingual nitroglycerin [28, 29]. Additional diuretics were discovered and used in the 1950s. (Karl Beyer led a team of scientists at Merck that synthesized chlorothiazide in the late 1950s.) The mechanisms of action for loop diuretics were examined in the 1960s and shown to impact those with heart failure.

Pump Failure

It was not until the mid-1980s before pump failure (systolic dysfunction) was recognized as a major contributor to heart failure. In response to systolic dysfunction, investigators realized the patient had a decrease in cardiac output, vasoconstriction, sodium and water retention, impedance, and increased peripheral resistance [29]. Vasodilator Heart Failure Trial (V-Heft) investigators led by Jay Cohn and colleagues introduced the benefit of vasodilator therapy, including hydralazine and nitrates [30].

In the early 1990s, research focused on the neurohormonal system and the renin-angiotensin-aldosterone system (RAAS) as many patients with heart failure had elevated peripheral catecholamines [29, 31, 32]. Collectively, numerous trials have established the predictive value of neurohormonal measurements (baseline and serial measurements) as reliable indicators for risk stratification in patients with heart failure [30, 33, 34]. Plasma brain natriuretic peptide (BNP), plasma renin activity (PRA), aldosterone, atrial natriuretic factor (ANF), and endothelin-1 are markers for morbidity and mortality in heart failure patients. Clinical trials (SOLVD, Studies of Left Ventricular Dysfunction; CONSENSUS, the Cooperative North Scandinavian Enalapril Survival Study) established the important role for angiotensin-converting enzyme inhibitors (ACE-I) in the reduction of morbidity and mortality in adults with dilated cardiomyopathy [33, 35, 36]. Angiotensin receptor blockers (ARBs) were shown to be similarly effective.

Drug Therapies

After Raymond Ahlquist discovered functionally distinct catecholamine receptors in the adult heart muscle in 1948 (termed alpha- and beta-adrenoceptors), intense effort focused on drug development. For example, a number of beta blockers were synthesized including pronethalol (1960), propranolol (1962), practolol (1964), and atenolol (1968) and shown to impact the treatment of angina and hypertension [37–44]. One of the first clinical studies using beta blocker therapy (i.e., practolol or alprenolol) was performed in the early 1970s and shown to improve heart function [43, 44].

In the 1980s, a number of laboratories, including those directed by Bristow and Lefkowitz, conducted biochemical studies and demonstrated perturbed signaling pathways following beta blockade in animal models and humans with heart failure compared to controls. Multicenter studies such as the MDC (Metoprolol in Dilated Cardiomyopathy), the US Carvedilol Heart Failure Study (led by Drs. Milton Packer, Michael Bristow, Jay Cohn, Wilson Colucci, and others), CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) trial, COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial, MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure), and CIBIS II (Cardiac Insufficiency Bisoprolol Study II) demonstrated improved mortality and morbidity in patients with heart failure.

These studies ultimately led to the approval of carvedilol in 1997 for the treatment of heart failure. Continued mechanistic studies regarding adrenergic receptors in the heart and the impact of beta blockers have been detailed by a number of laboratories. Robert Lefkowitz received the Nobel Prize in 2012 for his contributions to the field. Collectively, these and many other studies have established that beta adrenergic receptor blockers such as carvedilol and long-acting metoprolol have been shown to promote reverse remodeling of the left ventricle (structural regression of the dilated failing heart), improve cardiac function, and decrease the risk of sudden cardiac death [33, 37–42].

Targeted Therapies

The notion of subpopulations of patients that might derive a greater benefit from selected therapies emerged from subgroup analysis of large clinical studies. Jay Cohn, Anne Taylor, and the A-HeFT (African-American Heart Failure Trial) investigators demonstrated the benefit of combining hydralazine and isosorbide dinitrate with standard heart failure therapy to increase survival of black patients with advanced heart failure [45].

Furthermore, Bert Pitt and colleagues demonstrated a survival benefit from the aldosterone blocking agent spironolactone on morbidity and mortality of patients with end-stage heart failure via the RALES study (Randomized Aldactone Evaluation Study) [46]. In addition, other mineralocorticoid receptor antagonists (e.g., eplerenone, in the EPHESUS, or the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) were also shown to have a survival benefit in patients with advanced heart failure and mild symptoms (using the New York Heart Association Functional Class II guidelines) [47].

Moreover, detectable cardiac troponin T (cTnT) levels in patients with heart failure have been shown to be predictive of adverse outcomes [48, 49]. Depressed left ventricular ejection fraction and evidence of left ventricular remodeling (increasing left ventricular internal diastolic dimension, LVIDd) have been shown to be strong predictors of morbidity and mortality risks in heart failure patients [30, 33]. In addition to these pharmacological therapies, device (defibrillator and/or cardiac resynchronization) therapies have been reported to further reduce heart failure mortality and are now conventional therapy for adult heart failure patients who have a reduced ejection fraction [50–52].

Risk models stratify adult heart failure patients. In 1928, the New York Heart Association established a classification of patients with heart disease to reflect their clinical status and prognosis. Since then, the classification has been revised several times but continues to describe a patient's functional capacity, from NYHA Class I to IV [53]. In addition to the New York Heart Association classification, the American College of Cardiology and the American Heart Association jointly prepared a set of guidelines in 2005, based on research and medical evidence to classify patients with heart failure (Class A–D). Furthermore, the Seattle Heart Failure Model is a commonly used multivariable risk model for heart failure [54]. This model incorporates age, gender, ischemic etiology, ejection fraction, systolic blood pressure, diuretic use, statin use, allopurinol use, hemoglobin, percent lymphocyte count, uric acid, sodium, cholesterol, and diuretic dose per kilogram as significant predictors of survival. This model has been validated in five cohorts of patients and provides an accurate estimate of 1-, 2-, and 3-year survival [55]. Collectively, these classification systems are an essential tool for the clinician and scientist alike in the classification of patients with heart failure.

In 1948, the National Heart Institute launched the Framingham Heart Study. The study examined a cohort of "normal" patients (5209) living in the town of Framingham, Mass., and the incidence of heart failure (since 1948). In addition to the original cohort, their descendants were added to the heart study in 1971. These longitudinal studies enhance our understanding of heart disease and heart failure and have provided a foundation for studies focused on heart failure prevention [56].

Summary

The history of the heart and cardiovascular medicine is dynamic and marked by tremendous innovations and discoveries that challenged existing philosophies and practices. This rich history of innovation also provided an important springboard for addressing the mechanisms of heart failure and the discovery of therapies. Bench science and clinical science have contributed to the pharmacotherapies and devices that have had a tremendous impact on the quality of life and have extended the life expectancy of adults living with heart failure.

The University of Minnesota has emerged as a leader in this field with its participation in the discovery of therapies such as the use of vasodilators, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, which improve the failing heart function and the survival of patients. The University of Minnesota team has further established the Heart Failure Society of America, *The Journal of Cardiac Failure*, and the Minnesota Living with Heart Failure Questionnaire [57]. The questionnaire monitors the quality of life of those with heart failure and heart failure prevention strategies and is widely used in clinical trial/study practice. These and many other advances over the past 150 years have redirected and improved the morbidity and mortality of those suffering from heart failure.

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