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Robert P. Frantz *Editors*

Diagnosis and Management of Pulmonary Hypertension

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Preface

Over the last few decades, the study of pulmonary arterial hypertension (PAH) has become one of the most rapidly developing fields of cardiopulmonary medicine. This may seem surprising considering the relatively small number of patients who carry this diagnosis, but like many rare diseases that were once untreatable, interest in PAH has been spurred on by an intense desire to improve the outcome of those who are affected. At the same time, numerous discoveries in the field of pulmonary vascular biology have led to a marked shift in how we view the pulmonary circulation. Many of these discoveries have led directly to the development and licensing of over a dozen drugs in the last 20 years.

When we began our training in pulmonary and cardiac medicine, primary pulmonary hypertension, as the disease was known then, had no approved treatment and less than 50 % of patients survived more than three years after diagnosis. Nitric oxide and endothelin had not yet been discovered and there were no genetic defects that were known to be associated with familial pulmonary hypertension. In less than 30 years, a staggering number of cell signaling pathways vital to the maintenance of normal pulmonary vascular tone and remodeling have been found to be impaired or deregulated in PAH and point mutations in a single gene have been found to be responsible for nearly 80 % of patients with heritable PAH and up to 25 % of those with no known family history. Although no cure has been found yet, four distinct classes of drugs are available for treatment and recent registries from the USA, China, and Europe suggest that five-year survival now exceeds 60 %. Many of the therapies that are presently available for the treatment of PAH were newly discovered agents that we tested in animals with experimental models of pulmonary hypertension in the lab not so long ago. The rapid increase in our understanding of the disease and the rapid development of effective therapy are very much a part of the intense interest that PAH has generated.

Today, the diagnosis and treatment of pulmonary vascular disease has become an important part of cardiopulmonary medicine. Most major medical centers have faculty and staff who have received specialized training in this area or who have devoted a major part of their practice to this disease. Many institutions have developed pulmonary hypertension centers that specialize in the evaluation and care of patients with

pulmonary hypertensive disease. Recently, the Pulmonary Hypertension Association (PHA), a nonprofit organization created by patients and their families for the advancement of research and treatment of PAH, has embarked on an accreditation initiative that aims to identify centers with special expertise in PAH. Pulmonary hypertension programs across the nation will be designated as Centers of Comprehensive Care or Regional Clinical Programs. This program aims to improve the overall quality of care by ensuring that PAH patients are able to find experienced medical care close to home and establish referral patterns that can provide rapid access to more invasive testing and aggressive treatment options when needed.

Presently, health care providers face several major challenges in the field of pulmonary vascular disease. The first is the need for earlier diagnosis. Despite the marked increase in awareness of PAH that has been brought about by advances in its understanding and treatment, the delay in diagnosis has not improved. In fact, the median time between symptom onset and diagnosis of PAH remains greater than two years and has not decreased since the initial NIH registry reported this data in the 1980s. Delay in diagnosis is due to the rarity of the disease, its nonspecific symptoms, and lack of readily available and highly sensitive screening tools. To improve the time to diagnosis and ultimately response to treatment, practitioners must have a high level of suspicion and stay alert to the possibility of PAH in any patient with unexplained dyspnea. The second challenge is proper clinical classification. Although PAH is rare, pulmonary hypertension is not. From 1980 through 2002, the estimated number of hospitalizations with pulmonary hypertension as any-listed diagnosis tripled for the total US population from 87,000 to 260,000. However, epidemiologic studies suggest that less than 3 % of patients with elevated pulmonary arterial pressure have PAH. In one well-known study, three-quarters of cases of elevated pulmonary artery pressure on echocardiogram were found to be due to left-sided heart disease and another 20 % were attributed to chronic lung disease. Less than 3 % had PAH. The most recent disease classification system developed during a series of meetings sponsored by the World Health Organization divides pulmonary hypertension into five distinct groups. Proper identification of which type of pulmonary hypertension a patient has is absolutely essential to proper management. Some patients have complex phenotypes with what appear to be multiple contributors to their pulmonary hypertension. It is our hope that future research will further elucidate the pathophysiology and best management of these challenging cases. Finally, health care providers may struggle with the large number of options that are rapidly becoming available for the treatment of PAH. This is an issue complicated by the high cost of most medications and recent data suggesting that combinations of PAH-specific medications may be more effective than single-drug therapy.

In *Diagnosis and Management of Pulmonary Hypertension*, we have tried to provide the reader with an overview of the pulmonary hypertensive diseases, the current understanding of their pathobiology, and a contemporary approach to diagnosis and treatment. Chapters 1 and 2 discuss the definition and classification of the pulmonary hypertensive diseases and the epidemiology of PAH. Chapters 3 through 11 review the approach to diagnosis and evaluation and discuss the considerable

body of data that has stemmed from the broad use of echocardiography, right-heart catheterization, and, more recently, cardiopulmonary exercise testing to diagnose and monitor the progression of PAH. Each of the major drug classes used to treat PAH and the cell signaling pathways that they target are described in Chaps. 12 through 15. Adjunct treatments and investigative therapies that are likely to herald the next generation of PAH medications are explored in Chaps. 16 and 17. Finally, the book concludes with several chapters that discuss special situations that have been particularly challenging in the management of PAH including perioperative evaluation and treatment of the critically ill patient with PAH. Each of the chapters is written by experts in their respective fields, many of whom have helped to shape the face of the modern-day approach to the diagnosis and treatment of PAH. We are indebted to the authors for their outstanding contributions and hope that you will find their chapters as helpful and as insightful as we have.

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Chapter 1
The Pulmonary Circulation

Victor F. Tapson

Abstract The pulmonary circulation carries oxygen-depleted blood from the right heart to the lungs and returns oxygenated blood to the left heart for delivery to the systemic circulation while serving as a source of humoral mediator production and a barrier to the exchange of fluid and solutes. This chapter discusses several aspects of this unique circulation, including a brief history of its discovery and the tools used to explore it; an overview of pulmonary hemodynamics and how they affect right ventricular function; structure and mechanical properties of the pulmonary circulation; and neural/humoral regulation of the pulmonary vascular tone and barrier properties that prevent leakage of fluid and solutes into the alveolar space. The chapter is written to highlight those unique properties of the pulmonary circulation that are involved with the pathogenesis of pulmonary hypertension and the response of the right ventricle and pulmonary blood vessels to disease development. The overall aim is to prepare the reader for an in-depth discussion of pulmonary hypertensive diseases that follows in the subsequent chapters.

Keywords Pulmonary circulation • Right ventricle • Pulmonary vascular disease • Pulmonary hypertension

Abbreviations

ACE	Angiotensin-converting enzyme
CO	Cardiac output
LA	Left atrium
LAP	Left atrial pressure
MDCT	Multidetector row computed tomography
mPAP	Mean pulmonary artery pressure

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PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RV	Right ventricle
VCO_2	Carbon dioxide output
VO_2	Oxygen uptake

Introduction

The pulmonary circulation carries oxygen-depleted blood from the heart to the lungs and returns oxygenated blood back to the heart to be delivered to the systemic circulation. Specifically, the pulmonary arteries carry *venous* blood to the capillaries so that carbon dioxide can diffuse out of the blood cell into the alveoli, and oxygen can diffuse out of the alveoli into the blood. Blood leaves the capillaries and enters the pulmonary veins, which carry *arterial* (oxygen-rich) blood to the left atrium, left ventricle, and then aorta.

In addition to delivering the entire cardiac output, the pulmonary circulation also serves as a source of humoral mediator production and processing. Finally, this vasculature serves as a barrier to the exchange of fluid and solutes, thus maintaining pulmonary fluid balance.

The pulmonary circulation is not the only blood supply to the lungs; the bronchial circulation supplies systemic arterial blood to ensure nutrition to the airways [1]. While the bronchial arterial supply is only a small percentage of the cardiac output, it is capable of extensive proliferation when pulmonary blood flow is compromised or in the setting of chronic pulmonary inflammation [2].

The pulmonary vasculature can be profoundly affected in certain disease states. Our goal is to discuss certain aspects of this unique circulation, particularly as they relate to pulmonary hypertensive disease. A number of topics in this textbook potentially overlap with this chapter, including pathogenesis of PAH, hypoxemic PH, pulmonary vascular remodeling from chronic lung and heart disease, and pulmonary hemodynamics and right heart catheterization. Our focus is a historic overview, followed by a description of the normal pulmonary circulation, but also includes some pathogenetic concepts as they relate to PH and certain aspects of its evolution.

Historical Aspects

The discovery and characterization of the pulmonary circulation is a fascinating story. The Greek anatomist Erasistratus, in the mid-200's B.C., was credited with discovering that the heart was a pump and described the valves of the heart [3].

However, he believed that the arteries and the left side of the heart were empty, and functioned to convey the "spirit of life" to the body. This concept remained until Galen proved that blood emanated from any living mammal when an artery was pierced [4]. His theory was that blood from the right side of the heart passed to the left side through invisible pores in the cardiac septum. There, it mixed with air to "create spirit" and was distributed to the body. He indicated that a small portion of the blood passed back from the left side into the lungs to be cleansed of its "soot." He did believe that a small portion of the blood on the right side passed through the *vena arteriosa* to the *arteria venosa*, and on to the left side. Thus, Galen understood certain basic principles of the pulmonary circulation (Fig. 1.1).

For at least the next 1,000 years, there were no apparent major discoveries involving the pulmonary circulation. Michael Servetus, the Spanish physician and theologist, was credited with the first description of the pulmonary circulation in his book "Christianismi Restitutio," published in 1553 [5]. "The vital spirit has its origin in the left ventricle of the heart, the lungs especially helping towards its perfection. It is generated through the commingling which is effected in the lungs of the inspired air with the elaborated subtle blood communicated from the right ventricle to the left [5]." Servetus trained in Paris with Vesalius and was considered an exceptionally skilled dissector [4–7]. Sadly, he was regarded as a heretic and was ultimately tried in Geneva and burned at the stake [8]. His contributions were substantial. Only three surviving copies of the original document are known, although it was translated into a number of languages.

In 1924, an Egyptian physician, Muhyo Al-Deen Altawi, studying the history of medicine discovered a treatise by a physician, Ibn al-Nafis, entitled "Commentary on the Anatomy of Canon of Avicenna" in the Prussian State Library in Berlin [9]. These writings covered human anatomy, physiology, and pathology [9]. They were translated by two Syrian physicians, and it was learned that al-Nafis had made essentially the same observations as Servetus, in the thirteenth century, prior to several hundred years [9–11]. This work of Ibn al-Nafis was believed to be the earliest description of the pulmonary circulation.

Al-Nafis, a Syrian physician, trained in Damascus and ultimately practiced and researched in Egypt in the thirteenth century. He became the Sultan's personal physician. Al-Nafis was credited as the first person to challenge the long-held belief of Galen that blood could pass through the cardiac interventricular septum; he was emphatic that all the blood that reached the left ventricle passed through the lungs [9–11]. He also stated that there must be small communications or pores between the pulmonary artery and vein (this concept preceded Marcello Malpighi's discovery of the pulmonary capillaries by four centuries). Al-Nafis also postulated that nutrients for the heart are extracted from the coronary arteries [9–11]. Thus, Ibn al-Nafis and another prominent physiologist of the period, Avicenna (approximately 1000 A.D.), were among very few physician researchers to link the Galenic period in the second century to the European scientific Renaissance in the sixteenth century. The Haddad translation published in the Annals of Surgery in 1936 offers detailed descriptions of Al-Nafis' discoveries [9]. In summary, Ibn al-Nafis should be regarded as a major influence and as the primary forerunner of Servetus, Vesalius, Colombo, and Harvey in the description of the pulmonary circulation as we now know it.

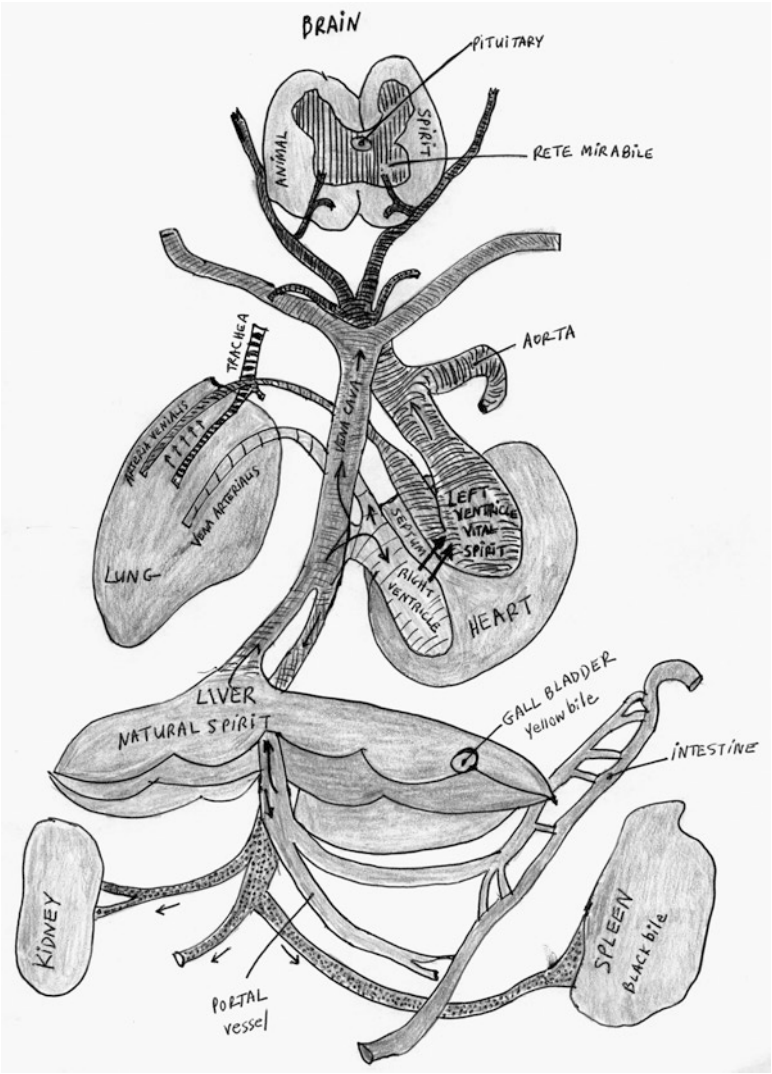

Fig. 1.1 A reproduction of Galen's scheme. In Galen's schema, the venous, arterial, and nervous systems, with the liver, heart, and brain as their respective centers, were separate, and each distributed through the body one of the three pneumata: respectively, the natural, vital, and animal spirits. Blood was carried both within the venous system and the arterial system. The heart and lungs worked together, with some of the blood passing through the pulmonary artery into the lungs; there it nourished the lungs and also mixed with the air breathed in. Some of the blood in the heart passed from right to left through "pores" in the interventricular septum. It was bright red because it had the vital spirit infused within it; from the left heart, it went out via the aorta to warm up the body

In the sixteenth century, in his book, "De Fabrica," Vesalius described the pulmonary circulation in a way that very much resembled the description of Ibn al-Nafis [12]. In the first edition of his book in 1543, Vesalius agreed with Galen that the blood "… soaks plentifully through the septum from the right ventricle into the left …" [12, 13]. When he published his second edition in 1555, he omitted the above statement and wrote instead "… I still do not see how even the smallest quantity of blood can be transfused through the substance of the septum from the right ventricle to the left …" [12, 13]. Colombo, who studied under Vesalius at Padua, ultimately queried this concept, and determined through vivisection and dissection of human cadavers that "almost everyone assumes that the blood passes from the right ventricle to the left ventricle across this wall … But they are completely wrong. For the blood is conducted to the lungs by the pulmonary artery, where it is diluted and together with air is led to the left ventricle by the pulmonary veins, which no one has noticed until now, nor described in writing …" [12].

The work by Ibn al-Nafis, Servetus, and subsequently Vesalius and Colombo, paved the way for Harvey's elegant description of the pulmonary circulation. "*Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*" (An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings) is the best known work of William Harvey [14–17]. The book was first published in Latin in Frankfurt in 1628 and remains one of the most important works establishing concepts of the circulation of the blood. Harvey's methods combined observations and experimental methods; among them were the examination of the effect of ligatures on blood flow. The book taught that blood was pumped around the body in a "double circulation," so that after being returned to the heart, it was recirculated in a closed system to the lungs and back to the heart, where it was returned to the main circulation [14–17]. There was, however, one portion of the circulation which Harvey could not characterize, although he did postulate it, i.e., the way in which the veins and arteries subdivide into a capillary network. As alluded to above, it was in 1660, 3 years after Harvey's death, that Marcello Malpighi of Bologna saw the blood moving in the capillaries of the frog's lung, and thus the missing link that Harvey needed to fully characterize the circulation of the blood [18]. The period of the Islamic Golden Age, the long influence of the teachings of the Galen School, and the European Renaissance are shown on a timeline in Fig. 1.2.

Subsequent relevant discoveries included the demonstration by Boyle with his air-pump experiments in 1666 that air was essential to life [7]. The next year, Hooke demonstrated that it was the supply of air *to the blood* that was crucial to respiration [19]. In 1669, Lower found that the difference between arterial and venous blood was the change in color and that this change took place in the lungs and not the heart. In 1668, Mayow discovered that only part of the air, the "spiritus nitro-aereus," was necessary for life [19]. Priestley, in 1774, called oxygen "dephlogisticated air." In 1777, Lavoisier further clarified these concepts, demonstrating for the first time that during respiration, the air that was breathed in lost oxygen and gained "fixed air of Black." (Black had discovered carbon dioxide 20 years prior.) Spallanzini subsequently characterized concepts involving tissue respiration [19].