Pulmonary Vascular Anatomy

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Abstract

The pulmonary circulation is a highly specialized vascular system that has evolved in order to allow for the high volume of gas exchange that is necessary to facilitate oxygen delivery to the organs and tissues of the human body. To achieve this, the pulmonary circulation differs from the systemic circulation in several key aspects. The pulmonary circulation receives the entire cardiac output during each cardiac cycle, more than any other organ in the body. However, despite this incredibly high capacitance, the pulmonary circulation maintains both a low pressure and low resistance, properties that are critical to preventing damage to the delicate gas exchange barrier and optimizing the efficiency of the right ventricle. Additional challenges facing the pulmonary circulation include (1) maintaining low pressure in the face of dramatic increases in cardiac output during normal exertion as well as disease states, (2) converting the pulsatile blood flow from the right heart into steady-state flow in the capillary bed, and (3) organizing the vascular network in such a way to optimize the surface area around the alveolar epithelium. Here we will discuss the complex structural properties of the pulmonary vasculature that allow it to simultaneously accomplish all of these critical tasks. Additionally, we will briefly describe the bronchial circulation, the systemic component of blood delivery to the lung tissue,

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with a focus on understanding the structural and functional relationships between these two circulations.

Abbreviations

ARDS	Acute respiratory distress syndrome
CO	Cardiac output
EM	Electron micrograph
HPV	Hypoxic pulmonary vasoconstriction
P_AO_2	Alveolar partial pressure of oxygen
P_aO_2	Arterial partial pressure of oxygen
PAP	Pulmonary arterial pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance

Introduction

The pulmonary circulation differs dramatically from the systemic circulation in its biophysical and hemodynamic properties, structural organization, and physiology. These differences ultimately stem from the fact that the purpose of the pulmonary circulation is substantially different from that of the systemic circulation. While the systemic vasculature is designed to deliver nutrients and oxygen to the tissues, the pulmonary circulation is designed to maximize oxygen uptake in the blood that will ultimately nourish the rest of the body (Fig. 1). In order to maximize gas exchange, the pulmonary circulation has an extremely high capacitance, receiving 100 % of cardiac output during each cardiac cycle. The pulmonary circulation distributes this enormous volume of blood through a complex system of arteries to a capillary bed designed to optimize gas exchange, before circulating the blood volume back to the left heart for delivery to the systemic circulation. However, despite the expansive volume of blood present, the pulmonary circulation maintains a low pressure and a low resistance (Yuan and Rubin 2001). These hemodynamic properties allow the right heart to effectively and efficiently pump this large volume of blood through the pulmonary vascular circuit, despite its relatively thin walls, compared with the left ventricle (Lammers et al. 2012). Additionally, the low pressure in the pulmonary vasculature protects against vascular leak across the pulmonary capillaries. This

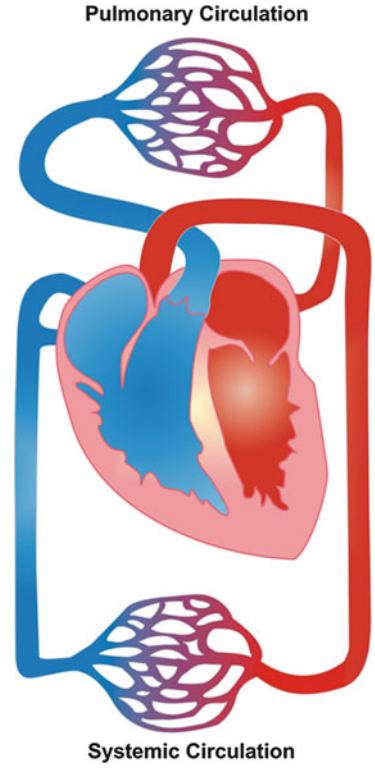

Fig. 1 Pulmonary and systemic circulations. Schematic diagram showing the parallel connection of the pulmonary and systemic circulations in which the pulmonary circulation is fed from the right ventricle to the pulmonary artery. The pulmonary capillaries drain into the pulmonary vein and left heart. The circulation then passes into the aorta and systemic circulation in which the circuit ends with drainage from the superior and inferior vena cava into the right heart

is particularly important due to the extremely fragile nature of the blood-gas barrier and the immense surface area of the pulmonary capillary network, which predispose the pulmonary circulation to devastating vascular leak, exemplified by acute respiratory distress syndrome (ARDS) (Effros and Parker 2009; Matthay et al. 2012; Ware and Matthay 2000). In addition to the pulmonary circulation, the bronchial circulation also delivers blood to the lung. However, in contrast to the pulmonary circulation, the bronchial circulation is part of the systemic circulation, and thus, it is connected in parallel to the vasculature of the other organs and tissues of the body and is maintained at a high pressure and high resistance. Although its primary purpose is to deliver nourishment to the large conducting airways

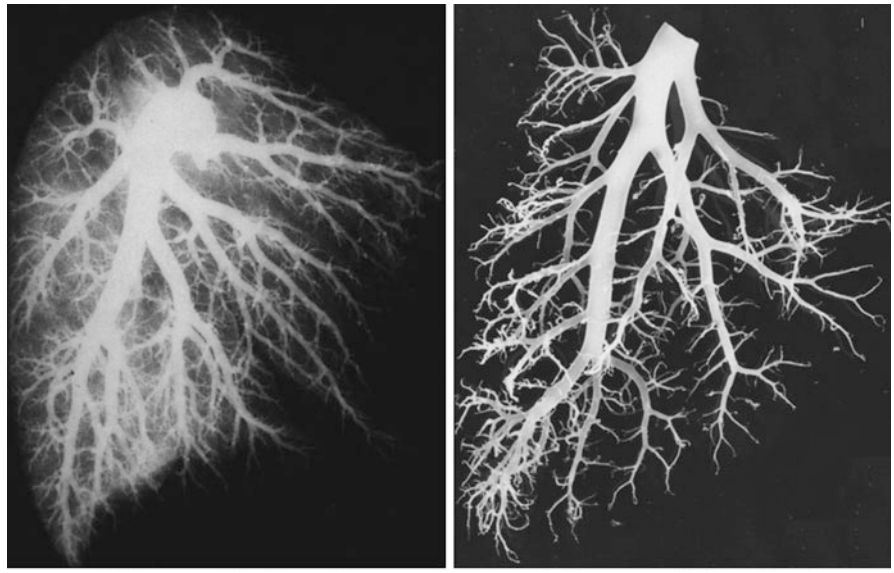

Fig. 2 Organization of the pulmonary vascular tree. Shown is a contrast angiogram of the pulmonary arterial tree as well as a pulmonary artery cast. Extensive branching of the pulmonary arteries are demonstrated (Reproduced with permission from Mandegar et al. (2004))

of the lung, it also plays a critical role in heat and water exchange with the environment as well as the recruitment of inflammatory cells to the airways (Horvath and Wanner 2010).

At a gross level, contrast arteriograms of the pulmonary vasculature allow us to begin to appreciate the incredibly complex organization of this system (Fig. 2). However, a full appreciation of its structure and function requires rigorous analysis of each of its components. In this chapter we will discuss the anatomy of the pulmonary vasculature with an emphasis on how its structure serves to optimize gas exchange at the alveoli. In doing so, we will review the hemodynamic and biophysical properties of the pulmonary vasculature, as well as the unique structural properties present at each segment. We will also briefly describe the bronchial circulation, while focusing on the functional relationship between these two systems. Additional details regarding how the structure of the pulmonary vasculature facilitates the unique functions of the lung, as well as how these functions are impaired in disease states, including pulmonary hypertension (PH) and ARDS, will be discussed in the subsequent chapters.

Hemodynamics of the Pulmonary Circulation

As mentioned above, the pulmonary circulation is a high capacitance, low resistance, and low pressure system. The maintenance of these hemodynamic properties is absolutely critical to pulmonary vascular function as increases in pulmonary pressures can cause vascular remodeling, put additional stress on the right heart, and damage the delicate gas exchange barrier (Naeije and Westerhof 2011). In this section we will discuss the biophysical properties and physiologic mechanisms that enable the pulmonary vasculature to maintain these hemodynamic properties.

Pulmonary Arterial Pressure and Pulmonary Vascular Resistance

Although interindividual variation exists, the upper limit of normal mean pulmonary artery pressure (PAP) in disease-free lowlanders is approximately 20 mmHg, compared with

approximately 100 mmHg in the aorta (Yuan and Rubin 2001). Elevated PAP is found in disease states, including PH, as well as numerous physiologic situations, including individuals living at altitude, divers, mountain climbers, and athletes (Mandegar et al. 2004). PAP is calculated as the product of cardiac output (CO) and pulmonary vascular resistance (PVR), which describes the resistance of the whole pulmonary circuit, including the arteries, capillaries, and veins, as indicated in Eq. 1:

$$\mathrm{PAP} = \mathrm{CO} \times \left[\mathrm{PVR}_{\mathrm{arteries}} + \mathrm{PVR}_{\mathrm{capillaries}} + \mathrm{PVR}_{\mathrm{veins}}\right] \quad (1)$$

According to this equation, a dramatic increase in CO, such as during intense exercise, would be expected to cause an increase in PAP. However, contrary to this prediction, in healthy individuals, PAP does not dramatically increase in parallel with an increase in CO. This phenomenon is due to compensatory changes that occur to prevent large fluctuations in PAP. Specifically, in response to an increase in CO, an additional reserve of un-perfused pulmonary capillaries opens. This increases the cross-sectional area of the pulmonary vascular bed, which decreases PVR and ultimately minimizes changes in PAP. The physiologic mechanisms of this response were investigated by Solbert Permutt, who proposed that the pulmonary vascular bed is composed of parallel vessels with a range of collapsing pressures, which he likens to a "vascular waterfall" (Permutt et al. 1962; Permutt and Riley 1963). Subsequently, it was demonstrated that vascular wall distension also contributes to the maintenance of PVR in response to changes in CO (Naeije and Westerhof 2011; Nelin et al. 1993; Zhuang et al. 1983).

In order to fully appreciate how the physiologic properties of vascular wall distension and capillary recruitment stabilize PVR in the face of dramatic changes in CO, it is necessary to discuss the mathematical determinants of PVR. Poiseuille's Law is commonly employed to explain the profound influence of vascular distension on PVR and is reproduced below in Eq. 2:

$$\mathrm{PVR} = 8L\eta/\pi \times 1/\mathrm{r}^4 \quad (2)$$

Here, L is the length of the vessel, r is the vessel radius, and η is the coefficient of viscosity of the blood. The relationship of PVR with r^4 explains the profound influence that vascular distension can have on PVR. The effects of capillary recruitment on PVR can be understood by considering the circuit properties of the vasculature with successive orders of vessels organized in series and same order of vessels organized in parallel (Mandegar et al. 2004). To quantify the resistance of the entire circuit, the resistances of vessels connected in series are calculated as the sum of each individual element as indicated in Eq. 3, whereas the resistance of vessels connected in parallel is calculated by Eq. 4:

$$R_{\mathrm{series}} = R_1 + R_2 + R_3 + \ldots + R_n. \quad (3)$$

$$1/R_{\mathrm{parallel}} = 1/R_1 + 1/R_2 + 1/R_3 + \ldots + 1/R_n. \quad (4)$$

These equations demonstrate that parallel elements reduce overall resistance, while elements in series add to the overall resistance. Thus, the recruitment of additional capillaries in parallel with those that are already being perfused, as described by Permutt's vascular waterfall model, will decrease PVR, which is ultimately responsible for allowing PAP to be maintained despite increases in CO.

Biophysical Properties of the Pulmonary Vasculature

Although fundamental to the hemodynamics of the pulmonary circulation, the PAP and PVR calculations discussed above vastly oversimplify the complex biophysical properties of the pulmonary vasculature. Of particular concern is the fact that these equations assume steady-state flow throughout the vasculature, which due to the pulsatile nature of ventricular contraction is absolutely incorrect. Notably, the pulsatile nature of flow in the pulmonary circulation is even more pronounced than that of the systemic circulation

(Naeije and Westerhof 2011). The dissipation of pulsatile flow, which serves to alleviate stress on the ventricle and prevent damage to the pulmonary capillaries, is accounted for by the elastic nature of the large arteries that enables them to act as a pressure reservoir (Lammers et al. 2012). In order to quantify the effects of elasticity on the pulmonary circulation, it is necessary to consider the complex biophysical properties of impedance, stress, and strain.

Impedance and Pulmonary Vascular Stiffness

In order to quantitatively account for the pulsatile nature of blood flow from the heart and the effects of arterial compliance, it is necessary to consider the property of pulmonary vascular impedance, which is expressed as the ratio of the amplitude of the oscillatory arterial pressure to flow rate at a given frequency (Mandegar et al. 2004). Although the calculations of pulmonary vascular impedance are beyond the scope of this chapter, it is critical to note that stiffening of the elastic arteries, which can occur secondary to vascular remodeling in PH, characteristically alters the vascular impedance, reflecting a decreased capacity to buffer the pulsatile blood flow (Lammers et al. 2012). Thus, in recent years there has been an increased effort to quantify these changes and correlate them with outcomes in PH patients. This work has established that consideration of pulmonary vascular impedance and PAP together is more predictive of clinical outcomes in PH than PAP alone, thus necessitating further investigation into this complex property of the vasculature (C. T. Gan et al. 2007; Hunter et al. 2008; Rodés-Cabau et al. 2003).

Stress, Strain, and the Zero-Stress State

Additionally, in accounting for the elastic properties of the vasculature, it is important to consider the properties of stress and strain that occur within the vessels, which can be described by the constitutive equations (Fung and Liu 1993). These equations define the strain (ε) (5) and stress (σ) (6):

$$\varepsilon = \Delta l / l_o \tag{5}$$

$$\sigma = F/A \tag{6}$$

Here, Δl is the change in vessel length due to stretch and l_o is the initial length of the vessel. F is the total force applied and A is the cross-sectional area of the vessel. After quantification of these forces, the relationship between stress and strain can be calculated to determine the elastic properties of the vessel, which are described by the elastic modulus (E) according to Eq. 7:

$$E = \sigma / \varepsilon \tag{7}$$

Although the elastic modulus allows us to better understand the stress and strain imposed by blood flow through the pulmonary circulation, it is still an oversimplification of the complex biophysical forces operating in the pulmonary vasculature. Notably, even when all loads are removed, i.e., isolated pulmonary artery rings devoid of blood, residual stress and strain exist within the walls of the vasculature. Experimentally, an incision in the wall of an isolated vessel results in the circular shape opening up and becoming a sector, termed the zero-stress state (Fig. 3) (Vaishnav and Vossoughi 1983). This concept demonstrates the existence of residual stress and strain in an intact blood vessel even when all loads are removed. Additionally, it has been established that these stresses differ across the vascular bed as the opening angle at the zero-stress state varies between third- and ninth-order human pulmonary arteries (92–163°) and veins (89–128°) (Huang and Yen 1998). Furthermore, it has been demonstrated that the tissue remodeling characteristic of PH alters the opening angle at the zero-stress state (Fung and Liu 1991; Huang et al. 2001). While it is clear that these residual stresses play an important role in the normal structure and function of the pulmonary circulation, the implications of these residual stresses in normal and diseased vessels have not yet been fully elucidated and are currently under investigation.

Distribution of the Pressure Differential in the Pulmonary Circulation

An additional biophysical property of the pulmonary vasculature that differs substantially from the systemic vasculature is the distribution of the

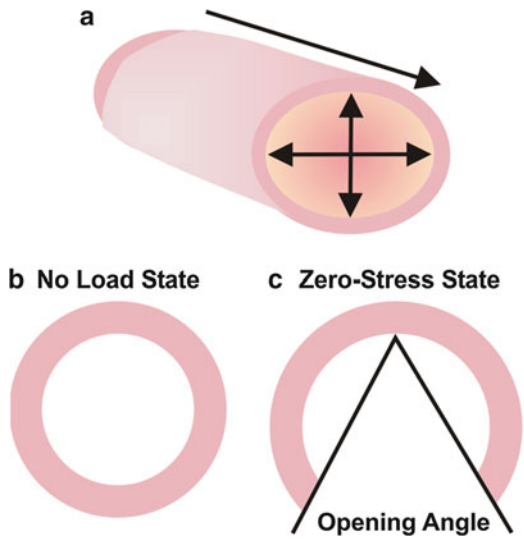

Fig. 3 Pulmonary vascular stress and the zero-stress state. (**a**) Schematic diagram of the cross-sectional and longitudinal stressors induced by blood flow. (**b**) When the internal loads are removed, the internal pressure, external pressure, and longitudinal stress are all zero. (**c**) Zero-stress state exists when the vessel is allowed to open into a sector as seen in cross section. The opening angle has been shown to vary between normal vasculature and various disease states

pressure differential across the circuit. The flow of blood through the circulatory system relies on passive movement of blood from high to low pressure. In the systemic circulation the largest proportion of the pressure decrease across the circuit occurs at the level of the small muscular arterioles due to the high resistance of these vessels. However, multiple groups have confirmed that in the pulmonary circulation the pressure differential is relatively constant across the vasculature (Fig. 4) (Brody et al. 1968; Fronek and Zweifach 1974; Hakim et al. 1982; Zhuang et al. 1983). Owing to this property, changes in pulmonary venous resistance may have equally important consequences to similar pressure changes in the pulmonary arterial bed.

Structure of the Pulmonary Circulation

At the gross structural level, the pulmonary circulation, like the systemic circulation, is a series circuit composed of arteries, capillaries, and veins. However, each of these components is immensely complex in order to satisfy the purpose of the pulmonary vasculature, gas exchange. At the histologic level, the pulmonary arterial and venous circulation is composed of a simple squamous endothelial monolayer surrounded by vascular smooth muscle cells and supported by an extracellular matrix rich in fibroblasts. At the level of the pulmonary capillary bed, the simple squamous monolayer of endothelial cells runs in close apposition to the alveolar epithelial layer with only a very thin interstitial layer separating them. These descriptions however remain lacking in that the pulmonary circulation also relies heavily on structural and functional contributions from several other cell types including smooth muscle cells, fibroblasts, intermediate cells, pericytes, neurons, mast cells, and macrophages, as well as matrix components, including collagens, elastins, fibronectin, glycosaminoglycans, and proteoglycans (Townsley 2012). The cellular and matrix components of the vasculature differ at the various portions of the pulmonary vascular circuit in order to best support its complex functions. Of additional functional importance is the presence of a connective tissue continuum composed of fibers, ground substance, and cells that supports the lung structure and serves to distribute the subatmospheric pressure, ensuring even inflation of the lung (Lai-Fook 1993). Although morphometry studies, conducted in several species over many years, have helped to quantify and conceptualize our understanding of the structure of the pulmonary vasculature, the branching patterns and overall organization of each of these components remain incompletely understood (Horsfield 1978; Huang et al. 1996; Michel 1982; Singhal et al. 1973; Weibel 1963; Yen et al. 1983).

Structural Classification of the Pulmonary Vasculature

Three models conceptualizing the structure of the pulmonary circulation have been established: the Weibel model, the Strahler model, and the Diameter-Defined Strahler's system (Fig. 5). The first model proposed to describe the branching

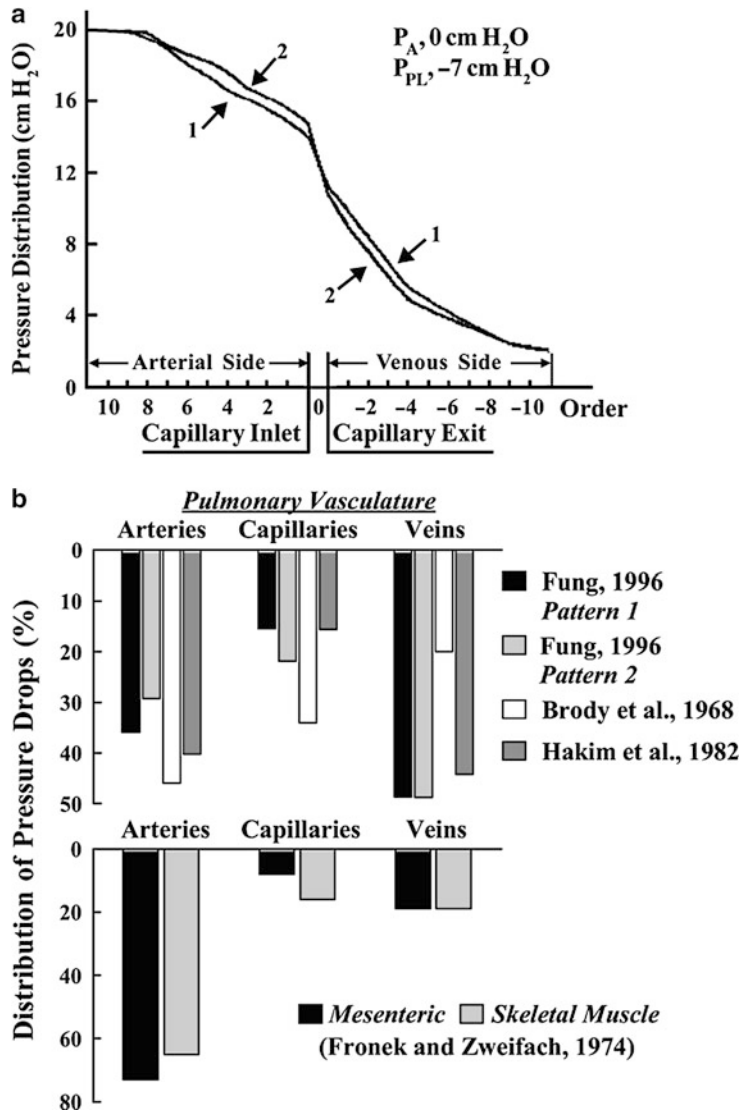

Fig. 4 Pressure difference across the pulmonary circulation. (**a**) Represents the pressure difference that occurs as blood progresses through the pulmonary circulation. This representative tracing occurs at alveolar pressure of 0 cm H_2O and pleural pressure of −7 cm H_2O. Numeral 1 indicates the pressure drop in a symmetric branching pattern, while numeral 2 identifies a nonsymmetric pattern. (**b**) Bar graphs illustrating the distribution of pressure drop in arteries, capillaries, and veins of the pulmonary vasculature (*upper panel*) and systemic vasculature (*lower panel*). P_A indicates alveolar pressure; P_{PL}, pleural pressure (Reproduced with permission from Mandegar et al. (2004))

system of the pulmonary vasculature was developed by Ewald Weibel in 1963. In his model the largest vessel is designated as generation one, and each bifurcation projects superseding vessels of equal luminal diameter and length which are designated as generation n + 1 (Weibel 1963; Weibel et al. 1993). Using this method to classify the human pulmonary vascular tree, he reported that there are a total of 28 generations of arteries and 23 generations of veins (Weibel and Gomez 1962). However, this classification method relies on the assumption of symmetrical dichotomy in branching, thus making it an imperfect model for understanding the complexities of the pulmonary vasculature.

Subsequently, Arthur Strahler developed a classification system to avoid the assumption of symmetric dichotomy encountered by the Weibel model. The Strahler model defines the smallest non-capillary vessels as order one, and when two vessels of the same order coalesce, the resulting vessel is designated the order number n + 1. In this system, if a smaller order vessel merges with a larger order vessel, the order number does not increase (Mandegar et al. 2004). At this point, it is critical to point out the difference in

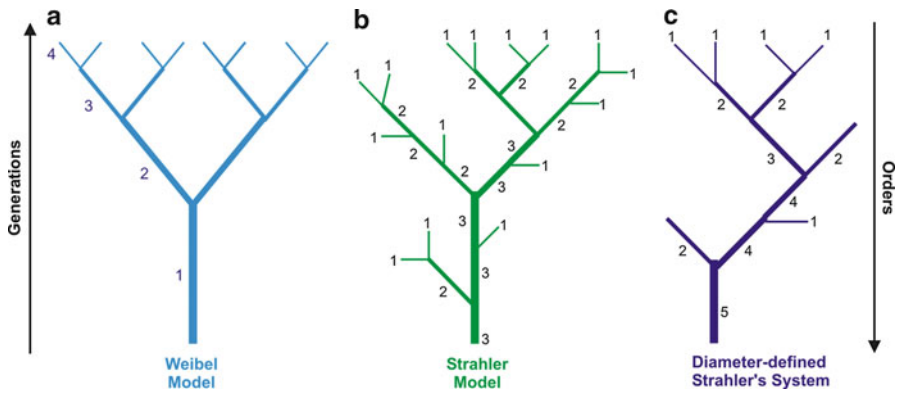

Fig. 5 Classification of pulmonary vascular branching patterns. Three proposed schemes to describe the branching pattern of the pulmonary vascular tree are the Weibel model (**a**), the Strahler model (**b**), and the Diameter-Defined Strahler's system (**c**). In each of these models, generations are considered as branching from the central to the peripheral lung, while orders are counted from the periphery toward the center

terminology that has been put in place to differentiate successive vessel branches counted from the center to the periphery, termed generations, from those counted from the periphery inward, termed orders (Horsfield 1984). Although the Strahler model overcomes the assumption of symmetric dichotomy of the Weibel model, morphometric studies in multiple animals using this model have not yielded accurate measurements of pulmonary resistance (Roldan-Alzate and Chesler 2011). These inaccuracies are attributed to substantial overlap in the diameters of successive order vessels when applying this model (Gan et al. 1993; Jiang et al. 1994; Singhal et al. 1973; Yen et al. 1983, 1984).

In a model designed to avoid the pitfalls of each of these models, the Diameter-Defined Strahler's system delineates that when two vessels coalesce the order number will only increase when the diameter of the ensuing vessel exceeds the standard deviation of the preceding order vessels (Jiang et al. 1994). Thus, an order increase only occurs when $D_{n+1} > D_n + (S_n + S_{n+1})/2$, where S_n and $S_n + 1$ are the standard deviations of the diameter of orders n and $n + 1$. In each of these models, vessels of successive order or generation are conceptualized to be connected in series, whereas those of the same order or generation are conceptualized to be connected in parallel, which allows for calculation of vascular resistance (Gan et al. 1993; Huang et al. 1996; Jiang et al. 1994; Singhal et al. 1973; Yen et al. 1983, 1984). Using the Diameter-Defined Strahler's system, 15 orders of vessels have been identified in both the arterial and venous systems (Huang et al. 1996). This work has revealed that the diameter and length of individual pulmonary artery branches decline exponentially as order number increases, while the cross-sectional area does not follow an exponential curve (Fig. 6). Based on this data, 25.5 %, 44.4 %, and 30.2 % of the total cross-sectional area are attributed to large (diameter >0.6 mm), medium (0.2–0.6 mm), and small (<0.2 mm) diameter vessels, respectively (Roldan-Alzate and Chesler 2011).

Pulmonary Arteries

The main pulmonary arteries arise from the right ventricle and travel in subsequent branches from the hilum of the lung to the capillary bed as part of a bronchovascular bundle, which includes the arteries, veins, their paired airways, and the pulmonary lymphatic vessels. The bronchovascular bundle is surrounded by interstitial tissue; however, the exact components enclosed in this structure vary between species (Kay 1983; McLaughlin et al. 1966). In addition to the main branching pattern of the arterial tree discussed above, supernumerary arteries are

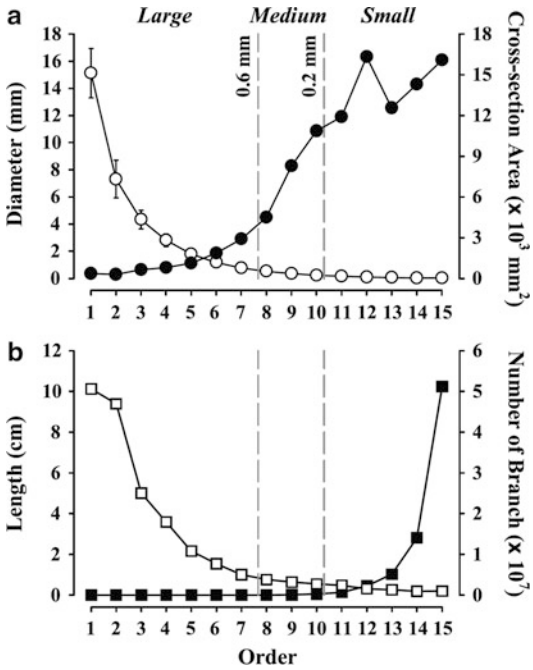

Fig. 6 Branching in the pulmonary vasculature. (**a**) Indicates the changes in diameter (*open circles*) and total cross-sectional area (*closed circles*) through increasing generation of pulmonary artery branches. This indicates that a majority of the cross-sectional area of the pulmonary arterial system exists in the small- and medium-sized vessels. (**b**) Shows that the length of the vessels (*open squares*) declines as the generation increases, though more branches exist (*solid squares*) (Reproduced with permission from Mandegar et al. (2004))

also present. These are short, thin-walled arteries that arise perpendicular to the axial arteries and serve to supply the alveoli that are in close proximity to the large airways and arteries (Elliott and Reid 1965; Hislop and Reid 1978; Horsfield 1978). The subdivisions of main branches of the arterial tree are classified based on the composition of the media into elastic, transitional, muscular, and nonmuscular arteries (Townsley 2012). Similar to the systemic circuit, the large arteries that originate from the ventricle have a large amount of elastic tissue, which allows them to accommodate the pulsatile flow that occurs in these segments due to the rapidly contracting ventricle. Later generations of arteries are composed of decreasing amounts of elastic tissue. Medium-sized arteries are predominantly transitional and muscular arteries. The smooth muscle cells in the walls of these arteries allow for the vasoreactivity that serves to regulate blood flow, which is critical to ventilation-perfusion matching in the lung in a physiologic process known as hypoxic pulmonary vasoconstriction (HPV). This function will be discussed in more depth in the following chapter entitled (▶ Chap. 157, "Pulmonary Vascular Physiology and Pathophysiology"). Lastly, as the branching continues, approaching the alveoli, the muscular component of the vascular wall decreases and the arteries are mainly classified as nonmuscular. The paring down of smooth muscle cells, as well as other cellular and matrix components, near the alveoli serves to transition the arterial circulation into the capillary network.

Pulmonary Capillaries

The pulmonary capillary bed is composed of a non-fenestrated endothelial monolayer, which is critical to the barrier function of the lung, and ultimately to the prevention of vascular leak and pulmonary edema (Mehta and Malik 2006). Notably, the transendothelial electrical resistance across human lung microvascular endothelial cells is approximately ten times higher than that of human pulmonary artery endothelial cells (Blum et al. 1997; Dudek and Garcia 2001). This is surprising given the extremely thin nature of the blood-gas barrier, which is the thinnest capillary barrier in the body (West 2013a). The barrier function of the pulmonary vasculature will be discussed further in the next chapter entitled (▶ Chap. 157, "Pulmonary Vascular Physiology and Pathophysiology"). Here we will focus on the structural organization of the capillaries, the alveolar septa, and the blood-gas barrier.

Sheet Flow Model

In contrast to the organization of pulmonary arteries and veins as multiple series and parallel components, the pulmonary capillaries are best thought of as an organized network consisting of a thin sheet of blood flowing over the alveolar framework (Fung and Sobin 1969, 1972a, b). In

the system of "sheet flow," developed by Fung and Sobin, the pulmonary capillary bed is comprised of a sheet of blood flow that is held in place by a vast number of extremely small-caliber vessels (~3 μm diameter) termed "posts" (Fig. 7) (Fung and Sobin 1969). In this model, the endothelial cells that comprise the capillary sheet are abutted to alveolar epithelial cells on both sides. These capillary sheets provide the structural basis for the alveoli and, thus, represent a majority of the volume of the lung. Studies of blood flow through this capillary network under varying transmural pressures indicate that the thickness of the capillary sheet varies with blood pressure, whereas the dimensions of the posts remain unchanged (Sobin et al. 1972). Additionally, it is critical to note that in determining the total peripheral resistance of the pulmonary circulation, sheet flow resistance replaces $PVR_{capillaries}$ (Fung and Sobin 1969).

Organization of the Alveolar Septa

The high volume of gas exchange across the pulmonary capillaries necessitates optimization of contact surface area between the alveolar epithelium and the capillary endothelium, suggesting a highly complex geometric relationship between these two structures. Morphometric analysis of the geometry of this system has been conceptualized as an irregular 14-sided tetrakaidecahedron (formed by cutting the six corners off a regular octahedron), a shape that maximizes space filling and ultimately gas exchange (Fig. 7) (Fung and Sobin 1969). The complex interplay between the branching structure of both the airways and the vasculature is also critical to the optimization of contact surface area. The alveolar branching structure consists of a primary septum, separating alveoli that branch into different ducts, and a secondary septum, which subdivides each duct into multiple alveoli (Gil 2011).

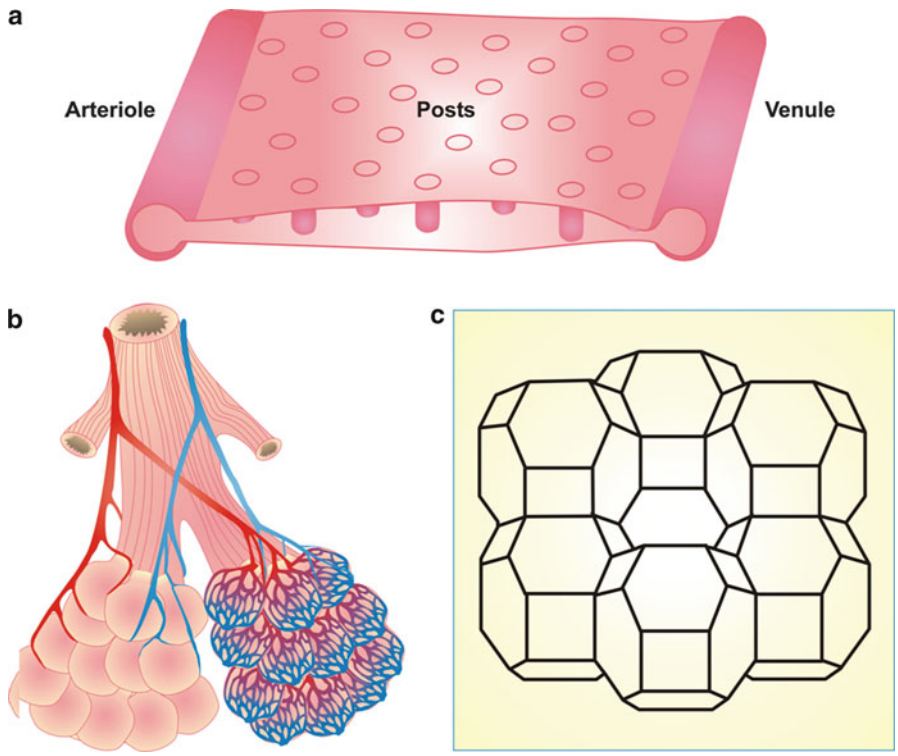

Fig. 7 Pulmonary capillary structure. (**a**) Schematic diagram of an alveolar sheet in which capillary-alveolar membranes are connected by posts allowing a sheet flow to maximize cross-sectional area ensuring adequate gas exchange. (**b**) Diagram of terminal bronchioles and subsequent alveolar structure in which pulmonary capillaries completely surround alveoli and are organized as a 14-sided tetrakaidecahedron (**c**)

Structure of the Blood-Gas Barrier

The first electron micrographs (EMs) of the blood-gas barrier were taken by Frank Low in the 1950s; however, as electron microscopy techniques have become more developed, these EMs have been improved upon dramatically (Fig. 8) (Low 1952, 1953; West 2013a). These studies have revealed the thickness of the blood-gas barrier to be only 0.3 μm, with approximately 0.1 μm thickness each from the alveolar epithelium, the capillary endothelium, and the extracellular matrix (West 2013a). Thus, the pulmonary capillaries constitute the thinnest capillary network in the body. The reasons for this have been elucidated by comparative studies across many species. As eloquently described by John B. West, over the course of evolution, the blood-gas barrier has become thinner in parallel with increasing oxygen demands of organisms due to the inverse relationship between diffusion capacity and thickness of the gas exchange barrier (West 2011, 2013a, b). However, although the thinning of the gas exchange barrier has vastly improved oxygen delivery capacity, it has also made the gas exchange barrier extremely delicate and prone to pulmonary capillary stress fracture under certain circumstances, including extreme exercise and high altitude (West 2013b).

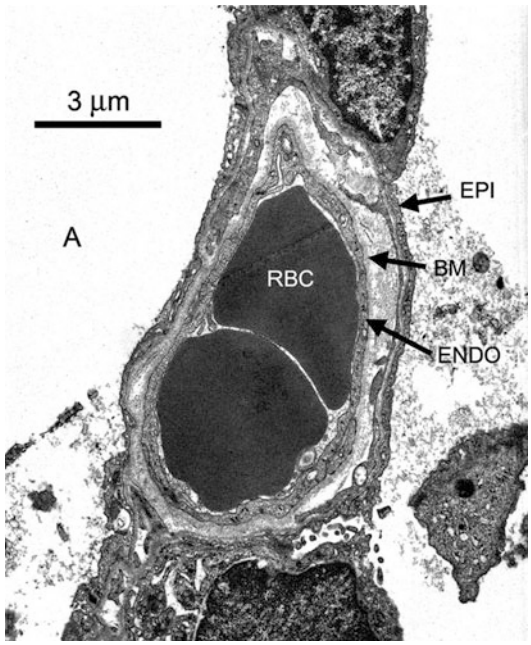

Fig. 8 Blood-gas barrier. A high-power electron micrograph image of the blood-gas barrier in which alveolar epithelium and vascular endothelium are separated by a very narrow sheet of basement membrane in order to facilitate efficient gas exchange. *A* indicates alveolar space, *EPI* epithelium, *BM* basement membrane, *ENDO* endothelium, *RBC* red blood cell

Pulmonary Veins

The pulmonary veins have received significantly less attention than the pulmonary arteries and capillaries; however, there are a few key structural features that have been characterized. The structural classification systems described at the beginning of this section, the Weibel model, the Strahler model, and the Diameter-Defined Strahler's system, have also been used to describe the branching pattern of veins arising from the pulmonary capillary network as they have been found to closely mirror the pulmonary arteries (Townsley 2012). The pulmonary veins originate in the subpleural region and coarse within a connective tissue sheath that is found in the interlobular septa (Gil 2011). Similar to the pulmonary arteries, the pulmonary veins are composed of an intima, media, and adventitia; however, the relative contributions of the various cellular and matrix components of these structures differ between arteries and veins in order to best fit their function. Notably, the pulmonary veins contain significantly less elastin and significantly more collagen than their corresponding arteries (Gao and Raj 2005; Mackay et al. 1978). Additionally, the muscular layer of the veins, as well as the vessel wall as a whole, is much thinner than that of their corresponding arteries (Michel 1982; Schraufnagel et al. 1997; Townsley et al. 1999). The pulmonary veins ultimately drain into the left atrium for delivery to the systemic circuit. Notably, significant anastomoses have been described between the pulmonary veins at their origin near the pleural surface and the bronchial veins, which create a permanent right-left shunt (Gil 2011). The significance of this will be discussed in the following section on the bronchial circulation.

The Bronchial Circulation

The primary purpose of the bronchial circulation is to supply oxygen to the conducting airways of the lung, the large pulmonary vessels, the pulmonary lymph nodes, the visceral pleura, and the hilar portion of lung parenchyma (Horvath and Wanner 2010). In line with its function in oxygen delivery to tissues, the bronchial circulation is part of the systemic circulation. As such, the hemodynamic properties of the bronchial circulation differ dramatically from those of the pulmonary circulation. Thus, the bronchial circulation is a high pressure and high resistance circuit that runs in parallel to the blood supply to the rest of the organs of the body. Additionally, the volume of blood contained within the bronchial circulation constitutes only approximately 1–3 % of the body's total cardiac output, compared with the 100 % of cardiac output received by the pulmonary circulation (Wagner 2009). However, although this seems like a trivial amount of blood flow, it is actually quite a large amount relative to the weight of the tissue that this circulation supplies. This facilitates oxygen delivery that is critical to maintaining the significant metabolic activity of the airways (Wagner 2009). Nutrient delivery, however, is not the only function of the bronchial circulation, as this system also supports diverse physiologic functions including heat and water exchange across the vasculature, inflammatory cell recruitment, and the clearance of bioactive substances from the airways (Deffebach et al. 1987; Serikov and Fleming 2001).

The bronchial arteries typically arise directly from the descending aorta or as a branch of an intercostal artery (Liebow 1965). Before entering the hilum of the lung, the bronchial arteries form a bronchomediastinal plexus that provides nourishment to hilar structures (Baile 1996). The bronchial arteries divide at the level of the main stem bronchi and then track along the airways of both lungs. In the airway parenchyma the bronchial capillaries form anastomotic networks in the subepithelium and adventitia to deliver oxygen to the various components of the airway wall (Baile 1996). These capillary networks converge to form bronchial veins, which drain to the azygos vein, superior vena cava, and ultimately the right atrium (Horvath and Wanner 2010). However, this venous drainage pathway is not the only route for return of bronchial blood flow to the heart, and a prominent system of anastomoses with the pulmonary circulation has been described (Fig. 9) (Baile et al. 1987). This system ultimately leads to drainage of bronchial circulation to both the right and left atria, creating a permanent physiologic shunt that allows for reversal of blood flow. Estimates of the fraction of bronchial blood draining to the left heart range from 66 % to 80 % (Baile 1996; Tobin 1952).

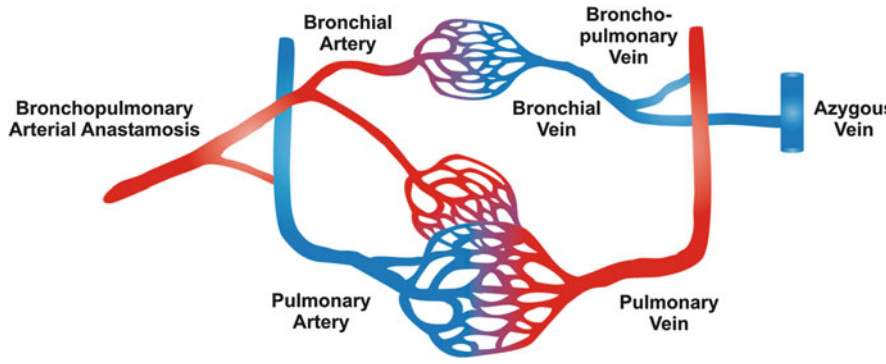

Fig. 9 The bronchial circulation. Schematic diagram showing the relationship between the bronchial and pulmonary circulations. The bronchial artery supplies capillary networks that drain into the systemic venous circulation (*azygos*) as well as the pulmonary venous circulation (*bronchopulmonary veins*). Additional anastomoses are present between the systemic and pulmonary circulations at the arterial level (*bronchopulmonary arterial anastomosis*)

It has been speculated that this shunt explains the infrequency of infarcts relative to thrombosis in the lung (Gil 2011).

Innervation of the Pulmonary Vasculature

The innervation to the pulmonary circulation is complex and multifaceted with inputs from the autonomic nervous system, both sympathetic and parasympathetic components, as well as the somatic nervous system (Barnes and Liu 1995). This innervation is derived from branches of the vagus nerve and the cervicothoracic sympathetic trunk (Townsley 2012). Although the sympathetic innervation is denser than the parasympathetic innervation, both of these nervous inputs are most prominent in the large vessels and decrease moving toward the periphery of the lung (Kummer 2011). The principal function of the sympathetic innervation to the lung is to mediate reflexive vasoconstriction in response to a decrease in PaO_2 as sensed by arterial chemoreceptors, which lead to activation of α_1 adrenergic receptors (Liu and Barnes 1997). It is critical to note that sympathetic vasoconstriction that occurs in the large and medium vessels in response to low *arterial* PO_2 (PaO_2) is a completely separate response from the hypoxic pulmonary vasoconstriction (HPV) that occurs in response to low *alveolar* PO_2(PAO_2) (Szidon and Flint 1977). This is underscored by the finding that sympathectomy does not block HPV (Tucker 1979). The mechanisms of HPV will be discussed separately in the chapter entitled (▶ Chap. 157, "Pulmonary Vascular Physiology and Pathophysiology").

The parasympathetic innervation of the pulmonary vasculature, similar to the parasympathetic innervation of other organs, is composed of a chain of two cholinergic neurons. The first neuron has its cell body in the nucleus ambiguous of the brainstem and sends its axons to the parasympathetic ganglia that lie in close proximity to the large airways and hilar vessels (Hadziefendic and Haxhiu 1999; Kummer 2011). The function of this innervation is to oppose the sympathetic inputs and relax the pulmonary vasculature. Lastly, there is a small population of sensory neurons that innervate the pulmonary vasculature. These neurons express a variety of neuropeptides, including substance P, neurokinins A and B, and calcitonin gene-related peptide (Kummer 2011). Similar to the parasympathetic nerve fibers of the pulmonary vasculature, the somatic nerves serve to vasodilate the pulmonary vasculature (McCormack et al. 1989; McMahon and Kadowitz 1993; Pedersen et al. 2000). However, the exact functions of this innervation are still incompletely characterized and remain under investigation.

Summary

In summary, the pulmonary circulation is a highly specialized vascular system that has evolved to facilitate the high volume of gas exchange necessary to oxygenate the blood. This task requires that the entire blood volume be delivered to the pulmonary circulation in each cardiac cycle, making it a high-capacitance system. However, in contrast to the systemic circulation, the pulmonary circulation maintains both low pressure and low resistance in order to prevent damage to the gas exchange barrier and optimize the efficiency of the right ventricle. Future work in the area aims to better characterize the unique structural properties at each level of the pulmonary vasculature and determine how these features facilitate pulmonary vascular function.

Cross-References

▶ Pulmonary Vascular Physiology and Pathophysiology

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