

## Chapter 2

# Microcirculation of the Lung: Functional and Anatomic Aspects

Joan Gil

**Abstract** The fixed pulmonary vascular anatomy differs from the systemic anatomy in the arrangement and shape of the capillary segments, but an even more striking peculiarity of the lung is that it needs to adapt itself to three different pressures, which leads to considerable adaptations and changes in morphology. Because of the pressure changes required by respiratory mechanics, the morphology differs both at the level of the capillaries and at the level of the extraalveolar small arteries and veins as a function of the existing mechanical conditions, adapting them in a way that is best suited to fulfill their respective functions. The configuration of the pulmonary capillary network markedly differs from that in the systemic capillary bed. The gas exchange needs are different in the systemic and in the pulmonary capillaries. In the periphery, the capillaries are longitudinal and their number and density in the tissue reflect local needs; in the lung, their purpose is to be capable of picking up from the outside as much oxygen as possible to fulfill the most extreme conceivable needs for gas exchange (the “diffusing capacity”). This capacity is normally not reached and the capillaries tolerate recruitment, de-recruitment, and changes in configuration that support variable quantitative levels of gas exchange.

**Keywords** Gas exchange • Small pulmonary arterioles • Capillary • Flow kinetics • Microvascular circulation

### 1 Introduction

Long gone are the times when the *pulmonary circulation* was absurdly referred to as the *lesser circulation*. No other organ circulation, not even when the systemic circulation is studied as a whole, raise issues as complicated and unexpected as those encountered in the lung. This is not limited to the

biochemical, cellular, and reactive properties of the vessels, but includes the fixed and functional vascular anatomy [1–6]. The fixed anatomy differs from the systemic anatomy in the arrangement and shape of the capillary segments, but an even more striking peculiarity of the lung is that it needs to adapt itself to three different pressures, which leads to considerable changes in morphology.

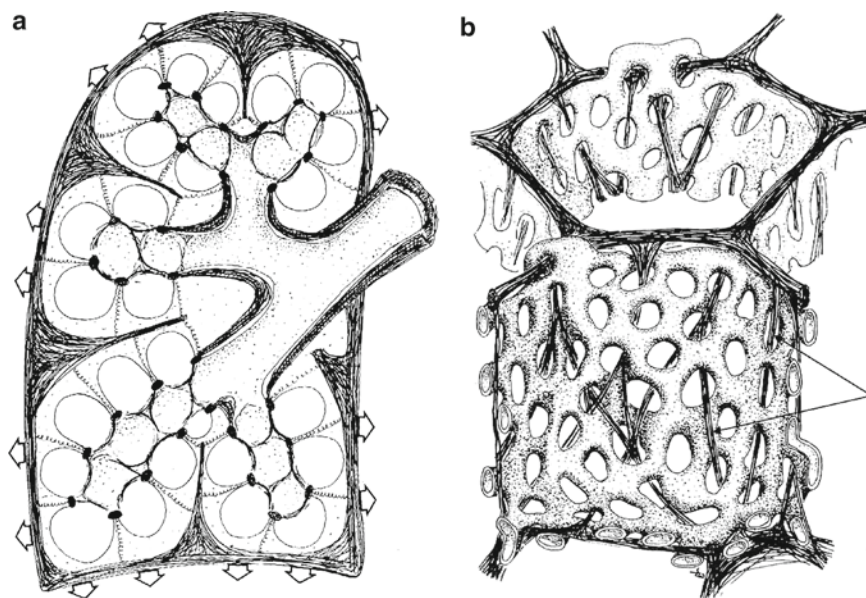
Because of the pressure changes required by respiratory mechanics, the morphology differs both at the level of the capillaries and at the level of the extraalveolar small arteries and veins as a function of the existing mechanical conditions, adapting them in a way that is best suited to fulfill their respective functions. A pulmonary-specific structure required to understand the process is the *connective tissue* (“*fibrous*”) *continuum* [7] (Fig. 1), which inserts itself proximally in the hilum, which is relatively fixed like a fulcrum. At the distal end, however, the visceral pleura is not mechanically fixed, as it moves in solidarity with the parietal pleura and the chest wall only by virtue of the existing subatmospheric air pressure without physical contacts between both of them. While several elements contribute to the generation of recoil pressure of the lung, only the pleural pressure helps to keep the healthy organ open. The connective tissue continuum connects both visceral pleura and hilum, becomes tensed during inhalation, and distributes subatmospheric pressure throughout all interstitial points of the lung. This has many consequences. Nowhere else in the body are capillaries normally exposed to changes in pericapillary pressures.

More important yet, the configuration of the capillary network markedly differs from that in the systemic capillary bed. The gas exchange needs are different in the systemic and in the pulmonary capillaries. In the periphery, the capillaries are longitudinal and their number and density in the tissue reflect local needs; in the lung, their purpose is to be capable of picking up from the outside as much oxygen as possible to fulfill the most extreme conceivable needs for gas exchange (the “diffusing capacity”). This capacity is normally not reached and the capillaries tolerate recruitment, derecruitment, and changes in configuration and in velocity of the fluid that support variable quantitative levels of gas exchange.

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**Fig. 1** The fibrous continuum of the lung. **a** The fibrous continuum extends from the hilum to the visceral pleura extending into all the alveolar wall. **b** Hexagonal capillary network in the alveolar septum supported by an incomplete layer of elastic and collagenous fibrils and fibers. Occasional interstitial cell elements are not shown. (Reproduced with permission [7])



The lung exhibits two different circulations [1]: (1) a *systemic* component arising mostly from the aorta and its intercostal branches that supplies the bronchial walls and the pleura and provides them with nourishment and oxygen and (2) the narrowly designated *pulmonary circulation* originating in the right ventricle which exchanges gas (oxygen intake and  $\text{CO}_2$  elimination) to serve the entire body and exhibits the complex properties described by others in this book. Remarkably, both components distally anastomose at the level of their venules in the wall of the small bronchioles and to a lesser extent in the pleura, which creates a permanent right-to-left shunt of variable flow intensity. Pulmonary shunts are about the most perplexing problems of the pulmonary vascular morphology [8].

## 2 Technical Fixation Problems: Vascular Perfusion

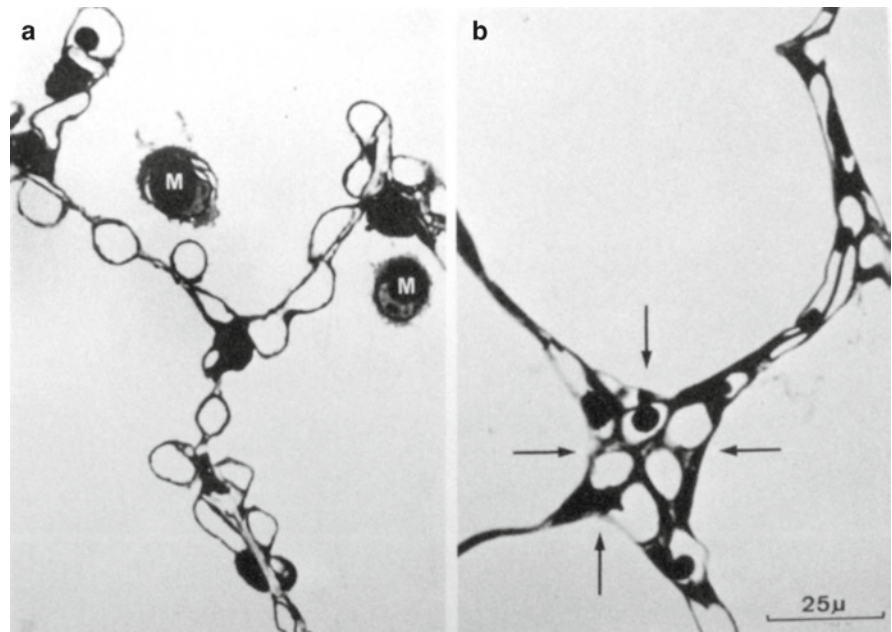
The lung does not have a rigid, really fixed shape or size: it is a semiliquid organ. Its shape depends in part on the container. It is not easy to determine its true outside anatomy after removing the lung from the chest and placing it on the dissecting table, but the difficulty doubly applies to the internal configuration, raising a complex methodological issue [3] discussed by many authors, as the original morphology is lost when the subject dies and the chest is opened. What should be done to preserve the real anatomy? Supravital microscopy through a chest wall window is appealing but is limited and precludes study of deeper areas [9]. Many in the past [10–12] tried to visualize the “true” *in vivo* morphology by applying a rapid freezing technique [13]. Liquid  $\text{CO}_2$  was the medium of choice. Liquid nitrogen is generally not desirable, as it forms a mantle of boiling fluid and insulating gas around the tissue, resulting in slow cooling and poor fixation. In both

cases, unless the lung has been pretreated with a cryoprotector, which frequently defeats the purpose, the slow penetration of the cold temperature results in an unacceptable number of artifacts, in particular large ice crystals and torn membranes, which cast doubt on the quality of the preservation and the dependability of the observations. Generally, only a thin peripheral layer of tissue will be preserved for interpretation, which renders the possibility of representative sampling impossible and limits all observations to the surface.

Chemical fixation [3, 6, 7] is a more desirable approach to the preservation of the lungs for light- or electron-microscopic study because it allows unrestricted sampling of well-preserved tissue. Buffered aldehyde (formalin for light microscopy, glutaraldehyde for electron microscopy) is rapidly instilled into the trachea or a stem bronchus following pneumothorax. The use of a controlled instillation pressure in the fluid, some 20 cm  $\text{H}_2\text{O}$  [7, 14], is advisable and results in the adjustment of a reproducible and well-defined lung volume, corresponding to the plateau of the pressure–volume curve of the fluid-filled lung. Morphologically, this simple approach yields outstanding results, requires little preparation and modest training, and it is currently the method of choice for most morphology studies, for instance, of lung injury.

But airway flooding with fixatives is clearly unsuitable for correlative studies of morphology with pulmonary mechanics or lung circulation [3, 6]. At the very least, the alveolar surface tension is abolished and the pressure–volume curves of air- and water-filled lung are very different, so the morphology must also be suspected of being different. For the purpose of this chapter, we are naturally interested in the air-filled natural condition. As repeatedly shown by us [3, 4, 15], this preservation can be achieved only by inflating the lung with a known air volume after an  $\text{O}_2$ -wash-induced atelectasis, full air inflation, subsequent deflation, and adjustment and stabilization of the desired final pressure. This is followed by flush of the pulmonary

**Fig. 2** **a** Rabbit, fluid-filled lung fixed by vascular perfusion. Note the empty capillary spaces and the undulated appearance of the surface. **b** Rabbit, air-filled lung fixed by vascular perfusion under zone II conditions. Note the smooth surface and the rectangular internal capillary luminal outlines. (Reproduced with permission [4])



circulation through a catheter inserted in the pulmonary main artery and perfusion of the fixative also at a well-known and controlled pressure. Most workers perfuse with buffered, isotonic glutaraldehyde as the fixative, followed by block immersion of the entire or a large fragment of lung and very careful dicing. We [3, 4, 15] believe that a perfusion with 1% buffered  $\text{OsO}_4$  yields superior results, but it must be warned that osmium emanates highly toxic, dangerous fumes and handling of large volumes of that substance requires training, exhaust equipment, precautions, and great care. Most of our studies and descriptions rely on findings in lungs fixed by vascular perfusion. Figure 2 shows three alveolar walls of two perfusion-fixed rabbit lungs (the capillaries are empty) photographed at the same magnification. The lung in Fig. 2a has been filled with saline, whereas the lung in Fig. 2b is filled with air under zone II conditions (to be discussed later). The difference is striking.

### 3 Systemic Component of Circulation in the Lung: Bronchial and Pleural Circulation

The *bronchial arteries* arise from the descending thoracic aorta and from the posterior intercostal arteries [16]. They supply with oxygen and nutrition the mediastinal bronchi and the following conducting airways all the way to the terminal bronchioles. In the wall of the large bronchi they form two plexuses, one in the incomplete muscle layer and the other in the submucosa.

The *bronchial veins* are much smaller and have a lower flow volume. Some of them are deep veins that arise parallel to the bronchial arteries but run in the opposite direction, increasing in volume only modestly because they drop much of their blood in the abundant anastomoses, with the

pulmonary veins returning it to the left atrium. Other veins are superficial and arise in the pleural surface. The bronchial venous blood is drained in the azygos or hemiazygos veins.

The *lymphatics* are also a vascular component. There are none in the alveolar walls, because the overflow compartment of the capillaries is the alveolar space. The pulmonary lymphatics do not arise from closed sacks, as they do in the systemic beds, but instead arise from connective tissue spaces in the periarterial sleeves, partly lined by *boundary cells* that appear to be either fibroblasts or endothelial cells [17] (Fig. 3). The periarterial lymphatic vessels are barely visible unless the lung is edematous. Lymph nodes are frequently found in the subpleural and peribronchial parenchymal areas.

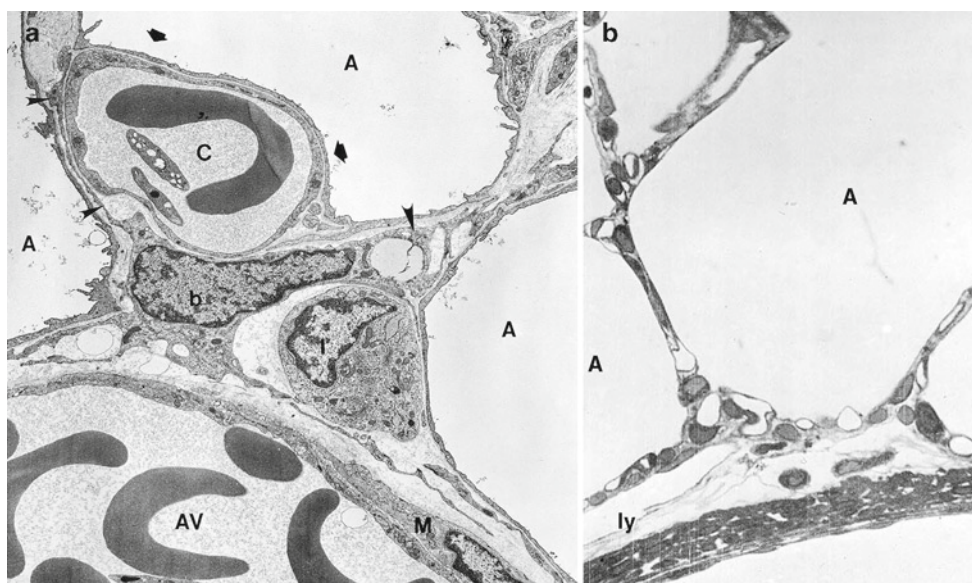
### 4 Role of the Connective Tissue Continuum of the Lung in Relation to the Capillaries

A *connective tissue continuum* of connective tissue of fibers, ground substance, and a few cells extends from the visceral pleura and septa to the hilum [7]. The continuum is fundamental in pulmonary mechanics [18].

Throughout the body, blood vessels and nerves are embedded in the connective tissue stroma of the organ, a filling and supporting component which might be compared to a soft tissue skeleton. In the alveolar walls, however, the pulmonary stroma exhibits peculiar characteristics.

The connective tissue continuum (Fig. 1) mostly consists of elastic and collagen fibers and fibrils, generally of type 3, is resistant to traction but is thin and malleable, and fulfills the function of connecting the hilum with the visceral pleura [1, 7].





**Fig. 3** **a** Rat lung fixed by instillation of fixative fluids into the airways following pneumothorax. Note that blood vessels are filled with blood. **A** represents air spaces, **C** is a capillary, **AV** is an extraalveolar vessel surrounded by its own thin sheath of connective tissue, and **B** is an interstitial cell, probably a fibroblast of an

endothelial cell giving rise to a lymphatic of an incomplete wall. **b** Rat lung fixed by vascular perfusion under zone II conditions. Note that the extraalveolar vessel (bottom) contains a lymphatic (**Ly**) and a muscular medium. **A** represents alveolar spaces. (Reproduced with permission [17])

During inhalation, the subatmospheric pressure generated in the pleural space pulls on the visceral pleura and causes an expansion of the lung parenchyma. The pull counteracts the effects of the alveolar surface tension and any connective tissue resistance due to overstretching and results in the generation of an interstitial subatmospheric pressure throughout the organ. The opposite happens during expiration.

The extraalveolar arteries and veins, like the alveolar capillaries, are embedded within the continuum, although the arrangement and consequences are markedly different in both of them.

## 5 Blood Vessels Inside the Lung but Outside the Alveolar Parenchyma: Extraalveolar Arteries and the Connective Tissue Continuum

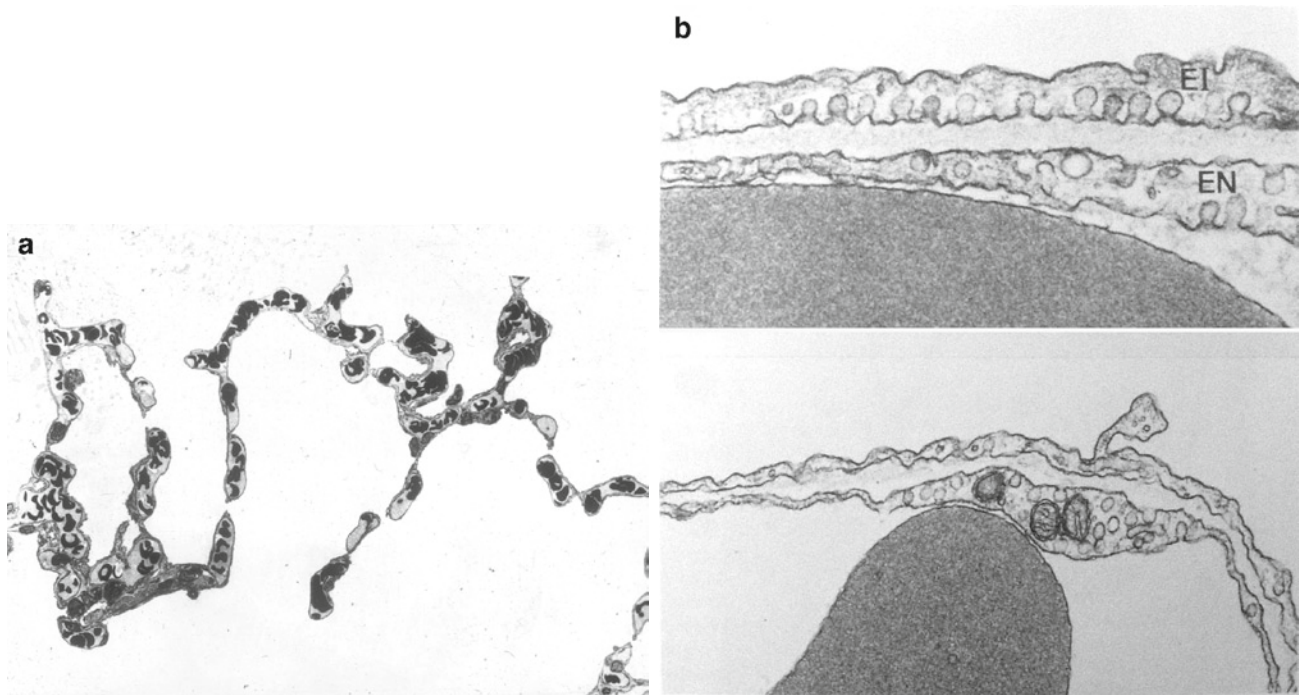
We have already described how the pulmonary arteries become surrounded with adipose and connective tissue upon their entering the hilum. Structurally, they continue to differ from systemic arteries of comparable caliber only in the smaller thickness of their medial walls. Because of this they stay functionally and anatomically separated from the alveolar wall (Fig. 3), which is occupied mostly by capillaries (Fig. 4) (blood vessels consisting only of an endothelium without a muscle cell layer). Therefore, a major difference exists between the environment in which arteries and veins function and the situation surrounding alveolar capillaries. Unlike the alveoli and the

bronchioles, arteries, despite the smooth muscle which serves different purposes, lack surface tension to actively retract but the surrounding connective tissue sheath with its changes of pressure allows them to participate in pulmonary mechanics in association with the respiratory movements. The important characteristic (Figs. 3, 5), however, is that unlike the alveoli arteries and veins are never directly exposed to air pressure. During inflation, the alveolar walls radially inserted in the periphery of the connective tissue sheaths are pulled out of the sheath's perimeter and cause an enlargement of the vascular diameter and therefore an increase of their volume. During expiration, as the alveolar volume is reduced, the radial alveolar wall anchors are somewhat relaxed and the diameter and the volume of the extraalveolar blood vessels accordingly decrease [12]. As we shall see later, this result is exactly the opposite of what happens to the alveolar capillaries, whose volume decreases as the alveolar air pressure compresses them during inspiration. During inspiration, arteries and veins therefore become a blood reservoir.

## 6 Pulmonary Circulation: Conducting Arteries

### 6.1 Arteries Outside the Lung

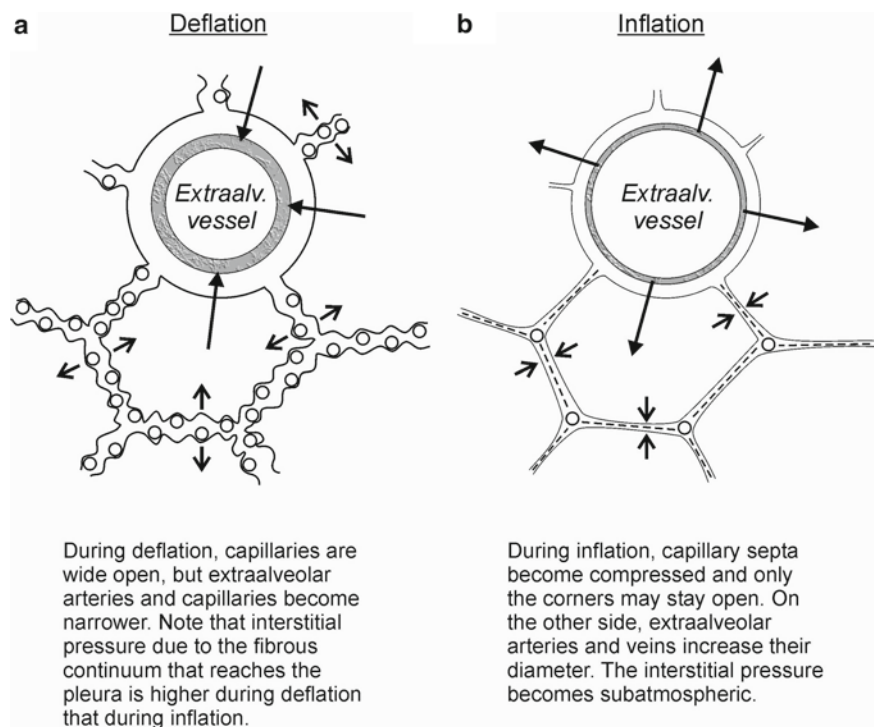
The main pulmonary artery arises directly from the conus arteriosus of the right ventricle. It and its main branches are of the elastic type. This means that the medium is made up of parallel



**Fig. 4** **a** Dog lung fixed by instillation of fixatives into the airways and photographed with the electron microscope at very low power. **b** High-power electron micrograph of two air-wall barriers of lung fixed by instillation of the airways. Note the dark erythrocytes at the *bottom*, and

the thin endothelial and epithelial layers containing many pinocytotic vesicles. EI, epithelial cell; EN, endothelial cell (Reproduced with permission [7])

**Fig. 5** The difference between extraalveolar and alveolar vessels during respiratory movements, deflation **a** and inflation **b**



elastic lamellae connected to each other by smooth muscle cells inserted obliquely to the lamellae but parallel to each other. As in the systemic circulation, smaller branches become muscular, with a solid medium made up of smooth muscle and

a well-developed intimal layer. The most peculiar characteristic of pulmonary arteries is the relatively thin medial wall when compared with the luminal diameter, which reflects the small prevailing pulmonary pressure. Once they penetrate into the



pulmonary parenchyma and the hilum, the pulmonary arteries and veins become surrounded by a loose adipose connective tissue which frequently contains lymph nodes.

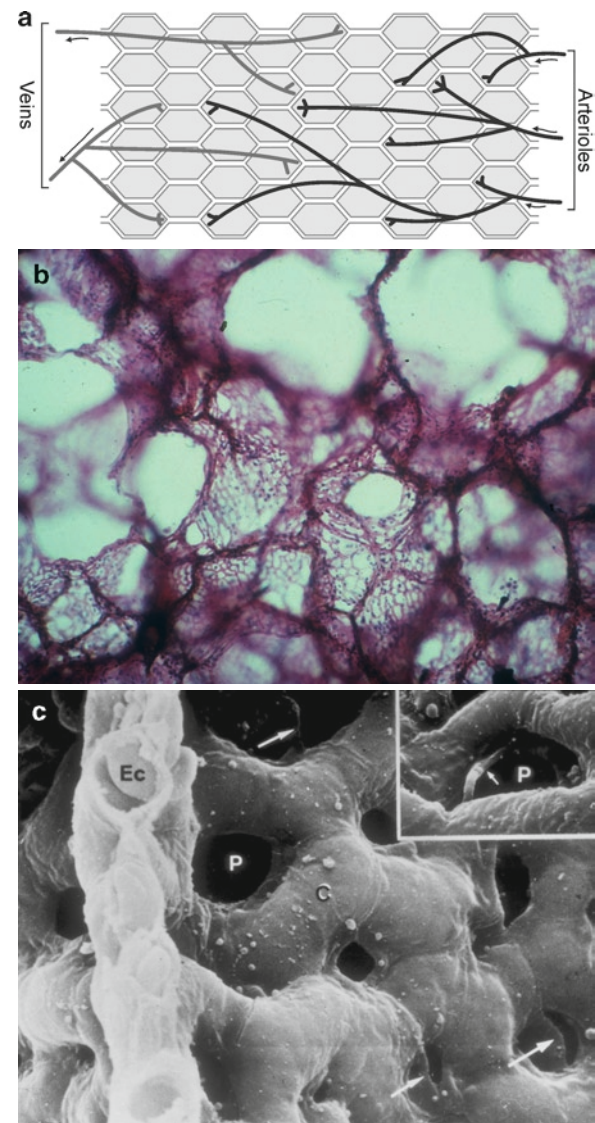
An arterial branch that runs in parallel to the bronchial walls is named an *axial* artery. Evidently, there are as many generations of axial arteries as there are of conducting airways, on average 18 in the human lung [14]. Most parenchymal lymphatics arise in the connective tissue sleeve that surrounds the artery rather than the bronchi. In the bronchiolar peripheral territory, the connective tissue sheaths are frequently separated from the bronchiolar sheaths, but are close to them. Additionally to their dynamic changes of volume in association with mechanics, the periarterial sheaths are also the site of the earliest accumulation of interstitial lung edema [6, 18].

The axial arteries are not the only extraalveolar arteries. Hislop and Reid [19] demonstrated that although they are frequently ignored, numerous *supernumerary* arteries additionally exist and exceed in number the axial ones. Supernumerary arteries branch out of an axial artery and run into the parenchyma surrounded by a connective tissue sheath and enter the alveolar wall and the alveolar capillaries in a way that has never been clarified but probably approaches the scheme shown in Fig. 6a, feeding the hexagonal network of capillary segments in the area of the corner vessels as demonstrated in Figs. 6b and c and 7, at intervals.

In the systemic circulation, *arterioles* (small arteries where the endothelium is surrounded by a single layer of smooth muscle cells) are located between the last arteries and the capillaries and they are responsible for most of the resistance to blood flow and the drop of pressure. Such anatomically distinct arterioles are absent in the lung circulation, which raises the issue of the location of the main site of resistance to flow. In some cases it may well be the capillary corner capillaries (see later), which, if this assumption is correct, would represent the universal entry point of the arterial blood into the alveolar capillaries. At any rate, in many cases of pulmonary hypertension small extraalveolar vessels of minimal caliber with an abnormal layer of smooth muscle cells can be recognized.

The *veins* inside of the lung rarely receive much attention, but they are also extraalveolar vessels because they are surrounded by connective tissue. They typically originate in the subpleural areas and are located in the interlobular septa, where they increase in size and advance toward the hilum (Fig. 7). Their wall is still thinner than that of the arteries of the same caliber and is frequently less well organized.

Finally, the existence of numerous anastomoses between the pulmonary and the bronchopleural systemic circulation needs to be pointed out. They are located at the venular origins of the bronchiolar and the pleural circulations. The existence and possible reversibility of blood flow through these anastomoses is credited with the relative rarity of lung infarcts when compared with the frequency of embolisms.



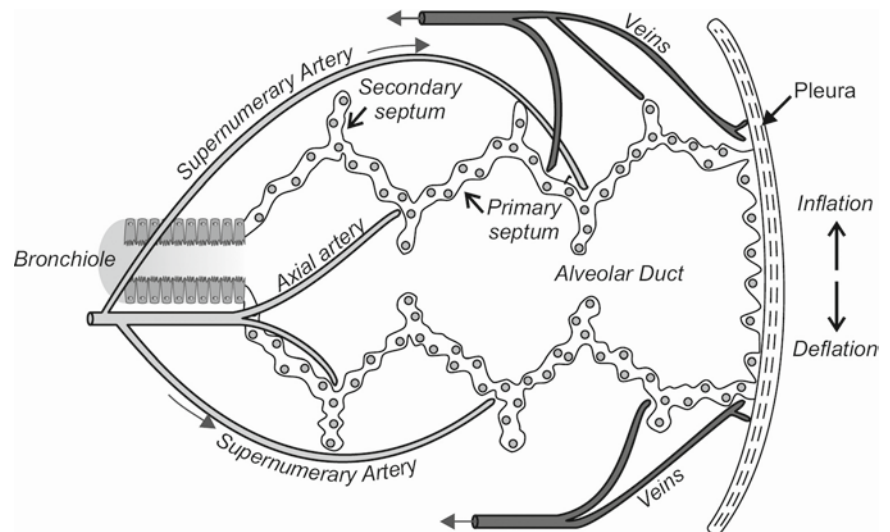
**Fig. 6** a The hexagonal capillary network of an alveolar wall shown as a continuum being drained and fed at intervals by small arteries and veins. b Flat view of the alveolar wall (comparable to a) where capillaries have been filled with a red stain. c Scanning electron micrograph of alveolar walls showing protruding filled capillaries. *P* is a pore of Cohn. Compare with a and b. (Reproduced with permission [7])

## 7 Inside the Alveolar Septa: Static Capillary Alveolar Microcirculation

### 7.1 The Hexagonal Capillary Network

The small *systemic* arteries branch out into arterioles which split into a brush-like bundle of capillaries. Their blood is immediately collected by a mirrorlike assembly of venous capillaries soon assembled into a venule that leads to a drainage vein. This is not so in the *pulmonary* circulation.

**Fig. 7** Longitudinal section through an alveolar duct showing the relation of axial and supernumerary arteries to alveolar walls and the difference between primary and secondary alveolar walls. Not shown is the fact that arteries and veins are connected by the corner vessels which act as shunts



The first realistic description of the arrangement of the alveolar capillary segments in the alveolar wall was offered by Weibel [14] in his seminal book *Morphometry of the Human Lung*. Determined to quantify everything quantifiable, Weibel, needing a realistic model, pointed out the major difference between the systemic and the pulmonary capillary networks: the capillaries are in the form of a dense anastomosing mesh of capillary segments, which for modeling purposes approach hexagons (Fig. 6). Weibel [7, 20] later revealed the extraordinary size of the capillary endothelial surface, slightly smaller than the epithelial surface, in an average human lung some  $120 \text{ m}^2$ . In referring to surface areas, however, it is necessary to consider fractal effects. In other words, the size of an area always depends on the magnification at the time of the measurement

## 7.2 Primary Versus Secondary Alveolar Walls

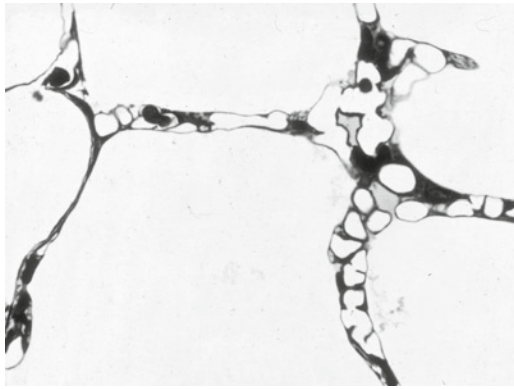
Before discussing the intraseptal capillary morphology, we need to point out another anatomic characteristic. Because more than 90% of the alveolar walls is occupied by pulmonary capillaries, it follows that the architecture, geometry, and relationships of alveolar walls must have a decisive influence on the geometry of alveolar capillary networks. In Fig. 7, note two important details: (1) only a small part of the alveolar capillaries are located close to the bronchioles, where the front of bulk air transport normally ends and where gas exchange should logically reach its maximum and (2) there are two different types of alveolar walls [21] — the *primary septum* at the bottom of alveoli, which separates alveoli open to different ducts (and sometimes possibly to different bronchioles), and the *secondary septum*, which

arises from the primary septum to separate two neighboring alveoli belonging to the same duct. At the end of the last duct, whenever the final insertion of the alveolar ducts into the pleura or a septum is near, the secondary walls taper off slowly and disappear, simplifying the ductal morphology and transforming alveolar ducts into cones or cylinders [21]. Considering the capillary flow, on a flat section one could be tempted to view the secondary alveolar wall as collateral of the primary wall: the blood that penetrates it will have to rise and fall back, causing considerable turbulence inside the hexagonal capillary segments. On the other hand, if the flow is viewed from a cross section of the duct, the impression would be that of a complex single layer of capillaries flowing constantly from the bronchiolar end toward the pleura, describing a zigzag motion in the secondary septa and a relatively straight line in the primary septa. Both alternatives are difficult to analyze from the hydrodynamic point of view.

## 7.3 Corner Capillaries

*Corner capillaries* are those located in the corners of alveolar walls, where three septa meet. The word “corner” in this case is based on two-dimensional flat sections (Fig. 7). In the undisturbed three-dimensional space, they are likely to represent long lines at the junctions between primary and secondary septa. They have been observed by multiple authors when attempting to fix the dry lung at different degrees of inflation with high intraalveolar air pressures [21–28]. As we shall discuss below, high-pressure alveolar inflation (with air pressures above the local pulmonary arterial pressure) invariably results in the total collapse of the septal capillaries, which are mounted on the connective tissue continuum (Figs. 8, 9a, b) but lack any rigid supporting protective



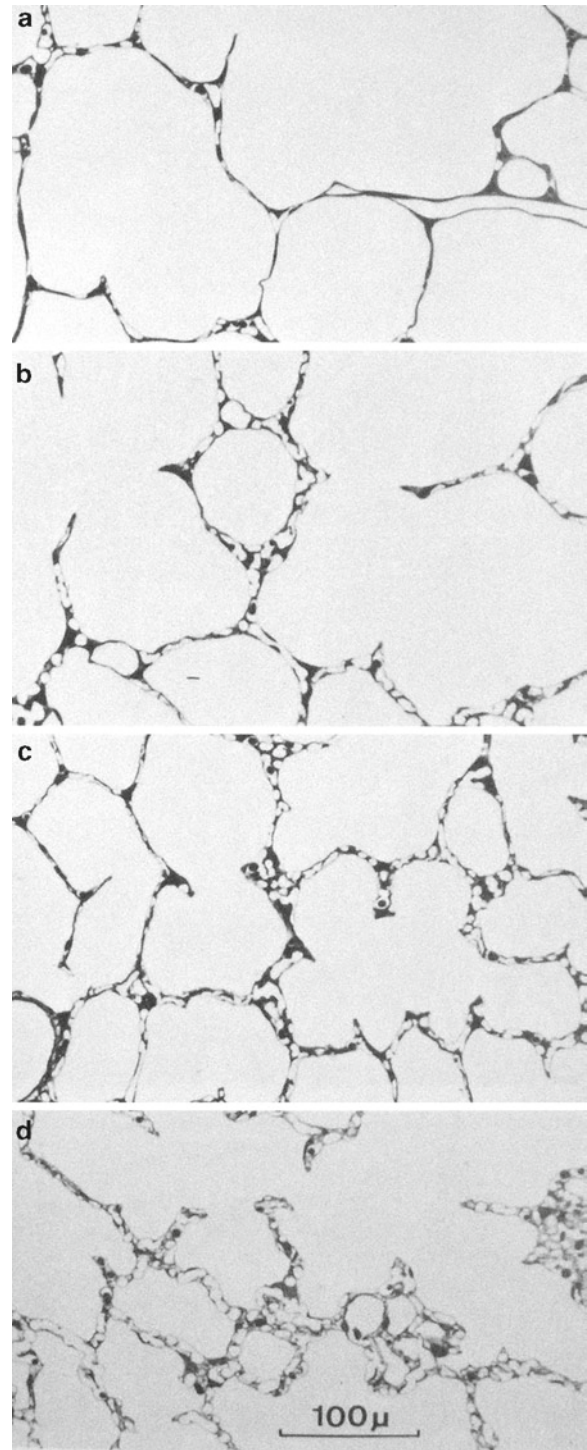


**Fig. 8** Rat lung fixed by vascular perfusion under zone II conditions. To the *right* note septal pleat and open capillaries, to the *left* note a dilated corner vessel opening into a capillary

structure. At the same time, as discussed already, the extraalveolar arteries and veins dilate because of the radial pull of the periarterial alveolar walls. This results in the alveolar blood being squeezed out of the septa and pushed into storage in the extraalveolar vessels. Yet this situation would appear to be unstable as it might conceivably prevent the blood from returning to the veins and the left atrium. It is therefore necessary to have a mechanism capable of maintaining the patency of the lung even when the air pressure collapses most of the alveolar network. This is the function of the corner vessels (Figs. 8, 9a, b). They frequently appear dilated, which enables them to carry an increased flow volume possibly at higher velocity [29] and they are not affected by the high air pressure because of their corner location. The alveolar spaces acquire a more or less rounded structure that leaves the corner capillaries well protected in dead spaces. Corner capillaries are the most striking anatomic characteristic of West's zone I.

#### 7.4 Corner Pleats

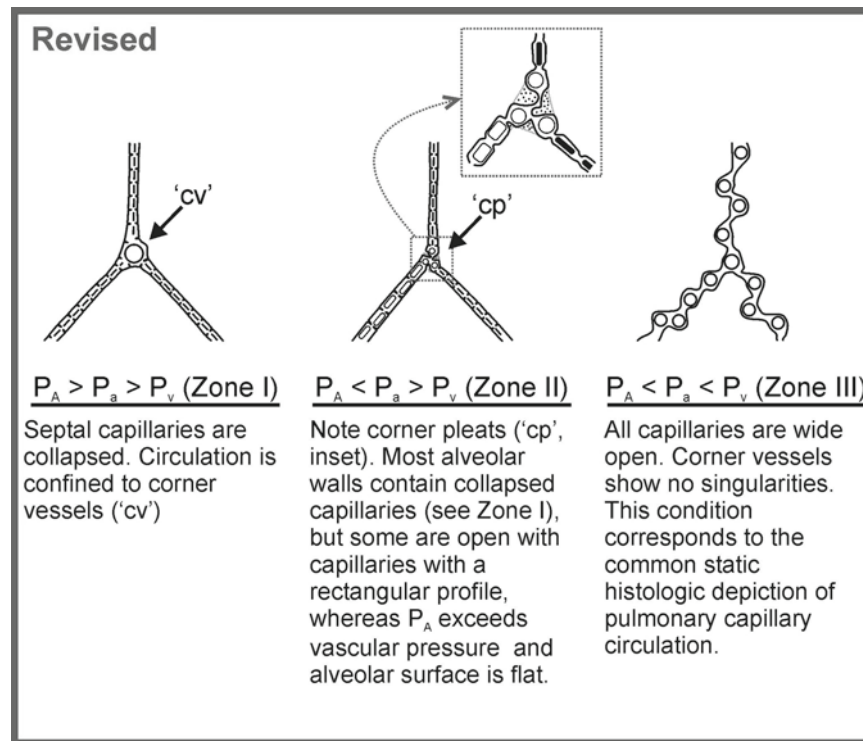
Gil and Weibel [4, 5, 15] first described in rat lungs fixed by vascular perfusion of chemical fixatives the existence of a reversible alveolar wall feature named "*corner pleat*" (Figs. 8, 9c) also located, like the corner vessels, in alveolar junctions. This caused confusion, as it was originally interpreted as a mechanism of pulmonary mechanics permitting the relaxation of alveolar corners tensed during inflation [5] and therefore the reduction in volume of the alveolar space. This interpretation is attractive because there is nothing in the alveolar wall to suggest that it might be particularly extensible and because areas of microatelectasis morphologically look like progressions of these pleats with the same structure. Pleats consist of nicked alveolar walls with capillaries folded over themselves and minute gaps filled



**Fig. 9** Rabbit lungs fixed by vascular perfusion **a, b** under zone I, **c** under zone II, and **d** under zone III conditions. (Reproduced with permission [4])

with a surfactant-like fluid. It was later observed that alveolar pleats only appear under what is called zone II in West's nomenclature, which is when the arterial pressure exceeds the air pressure and flow is driven by the difference between air and venous pressures. In this situation many alveolar





**Fig. 10** Summary of the findings in the three zones

walls are also collapsed and it can be assumed that the alveolar pleats fulfill a function similar to that of the corner vessels. In collapsed lumps it can be observed that pleats serve as needs for microatelectasis. Presumably the presence of surfactant reduces the retraction force arising from such areas.

## 8 Functional Adaptation of Alveolar Capillary Networks to Respiratory Movements

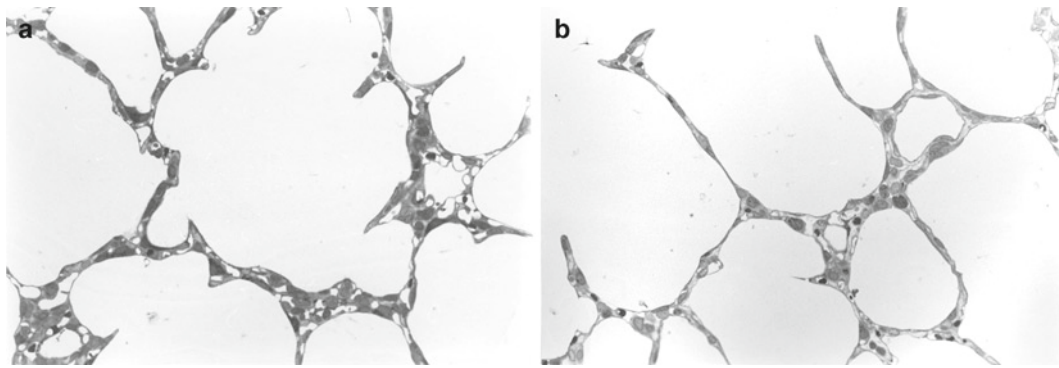
In all organs of the body except the lung, vascular anatomy is generally fixed. Even if the number or the diameter of open capillaries varies as a function of the local functional or oxygen requirements, the structural arrangements remain unchanged. The reason for that difference is twofold: first, the very limited connective tissue support available to the alveolar structures, which renders them vulnerable to the effects of pressures, and secondly, the existence, in addition to the arterial pressure  $P_a$  and the venous pressure  $P_v$ , of a third player, the alveolar air pressure  $P_A$ .

It was West who first pointed out three different pressure combinations (named by him “zones”) that result in major changes of the alveolar and capillary configurations. Neither the connective tissue support nor the thin epithelial and

endothelial cells confer any stiffness. Here is a summary of the conditions and the findings [29] (Figs. 9, 10). In all cases it is understood that the alveolar pressure  $P_A$  is identical to the pleural subatmospheric pressure:

**Zone I:**  $P_A > P_a > P_v$  (Figs. 9a, 10), where the air pressure is higher than the arterial pressure, which itself is higher than the venous pressure. In the systemic circulation the arterial flow is driven by the difference between arterial and venous pressure, but here the driving force for the circulation is the difference between  $P_A$  and  $P_a$ . The air pressure (including that generated by the alveolar surface tension) overwhelms any plastic tissue or intracapillary adaptations related to the perfusate and causes an ironing out or flattening of the entire alveolar surface. The exception is, of, course the *alveolar corners*, where a hidden space remains between the three rounded-off alveolar spaces, occupied by dilated capillaries named “*corner vessels*,” which most likely are equivalents of arterioles. These corner vessels are hidden from the alveolar pressure and will remain open and permit flow at any extreme alveolar air pressures (for instance, when using the abdominal press or during forced expiration), therefore ensuring a patent path between the right and left chambers of the heart. These corner vessels have similarities with the corner pleats discussed below.

**Zone II:**  $P_a > P_A > P_v$  (Figs. 2b, 9b, c, 10, 11a, b), where the arterial pressure is the highest and the air pressure (including pressure generated by the surface tension) is intermediate



**Fig. 11** a Zone II rat lung showing at the *bottom left* pleated capillaries. b Zone II lung remarkable for a large, dilated corner vessel (*top right*)

between the arterial and venous pressures. Here the appearance of the tissue and vessels is the result of the balance between the arterial and the air pressure. There are areas where the arterial pressure prevails slightly and the alveolar septa are therefore perfused. Other alveolar septa, however, contain only collapsed capillaries. The alveolar epithelial surface remains smooth and the outline of the open capillaries is rectangular, not round (Fig. 10). This finding may result from the small difference between the values of the arterial and air pressures. Even small variations of intracapillary pressures seem to be able to turn the balance toward perfusion of the alveolar wall (when  $P_a$  prevails) or total collapse (when  $P_A$  is locally higher than  $P_a$ ). It is remarkable that an entire alveolar wall will show either empty capillaries or open capillaries but never isolated open capillaries in the middle of the wall. This suggests that folds at the intersection of septa may act as flood gates for an entire side of an alveolar wall. Finally, single, dilated, corner vessels are generally absent, but their place is taken by small corner pleats, infoldings of septal walls containing capillaries that acquire the appearance of a bundle and fill the space between the three rounded alveolar walls. The narrow gaps between folded-over alveolar walls are filled with a fluid thought to be alveolar surfactant. We [14] reported in a reconstruction of sections of rabbit lungs fixed by perfusion with osmium that these corner pleats can be seen connected to both an artery and a vein, making it clear that they represent shunt mechanisms aimed, like the corner vessels, at permitting the passage of blood regardless of high alveolar air pressure. The morphology of this zone is important because it corresponds to the situation prevailing in intubated patients with positive end-expiratory pressure. It is relevant to note that the alveolar wall owing to the alternative stitching of the basement membranes of epithelial and endothelial cells to the epithelium of both sides has little capability for distension. The small spaces between capillaries contain only connective tissue and some rare cells, such as pericytes or fibroblasts, which may predispose them to folding. It is impossible to determine if these pleats are related or not to the hexagonal pattern. All the above applies only to

air-filled lungs. If the alveolar spaces are flooded with edema fluid, or surfactant the smoothening of the alveolar epithelial surface by alveolar pressure does not happen regardless of pressure relationships, as the pressure is equally transmitted to all points of the surface as described by the principles of solid mechanics [4].

**Zone III:**  $P_a > P_v > P_A$  (Figs. 9d, 10), where both the arterial and the venous pressure exceed the alveolar air pressure. This is the case when the alveolar morphology approaches the textbook description of the pulmonary circulation and the situation encountered in systemic organs, with the flow driven by the difference between  $P_a$  and  $P_v$ . Since  $P_v$  exceeds  $P_A$ , the alveolar surface is undulated, no longer ironed out, with each alveolar capillary protruding into the alveolar space. No corner vessels and no alveolar pleats can be recognized and all available capillaries appear completely filled.

In summary, the study of the morphological equivalents of the three zones of West is difficult and can be achieved only in lungs fixed by vascular perfusion of the fixative (preferably osmium). It is not known whether pressure alone is responsible for all observations described here or whether other factors, for instance, contractile cells also play a role. The observations appear to have the capability of profoundly affecting the functionality of the circulation, but also appear relevant to pulmonary mechanics. In the perspective of a dense hexagonal network of capillary segments fed and drained at regular intervals with a maximal endothelial surface of some 120 m<sup>2</sup>, without terminal vessels the corner pleats of zone II and the corner vessels seem to represent the secure and uncollapsible entry and exit points of the arterial and venous pulmonary circulations, whereas in zone III the entire morphological capillary network is available to exercise its gas-exchanging and metabolic functions without interference from the alveolar air pressure.

Of interest are also the hydrodynamic properties and singularities of the system as described as it concerns flow velocity, pressure distribution and turbulence, and particularly the interplay with pulmonary mechanics. The capillary pulmonary pressure is believed to be of the order of 10 mmHg

[13, 30–34]. Years ago, there was a popular discussion between the followers of the tube flow theory under Poiseuillian conditions and the theorists of the sheet flow [9, 11, 13, 33, 34], where alveolar flow would be compared to circulation inside a parking garage with a low ceiling interrupted by posts (the center of the hexagons). The sheet flow theory seems to accommodate certain findings in zone II, whereas the tube flow theory suits best the mainstream zone III circulation pattern.

## 9 Gas Exchange

Few physiological functions are as dependent on physical properties as gas exchange. The morphometric basis of diffusing capacity has been repeatedly described [7, 20]. A simple way to approach the problem is that a tissue barrier or membrane is interposed between gas mixtures of different concentrations (Fig. 4). This barrier consists of thin layers of alveolar epithelium, interstitium, and capillary endothelium. This always applies, although one should additionally consider the distance to the front of inspired air. We have described three different configurations of the relevant gas-exchanging structures and it is reasonable to assume that all three of them support this essential function.

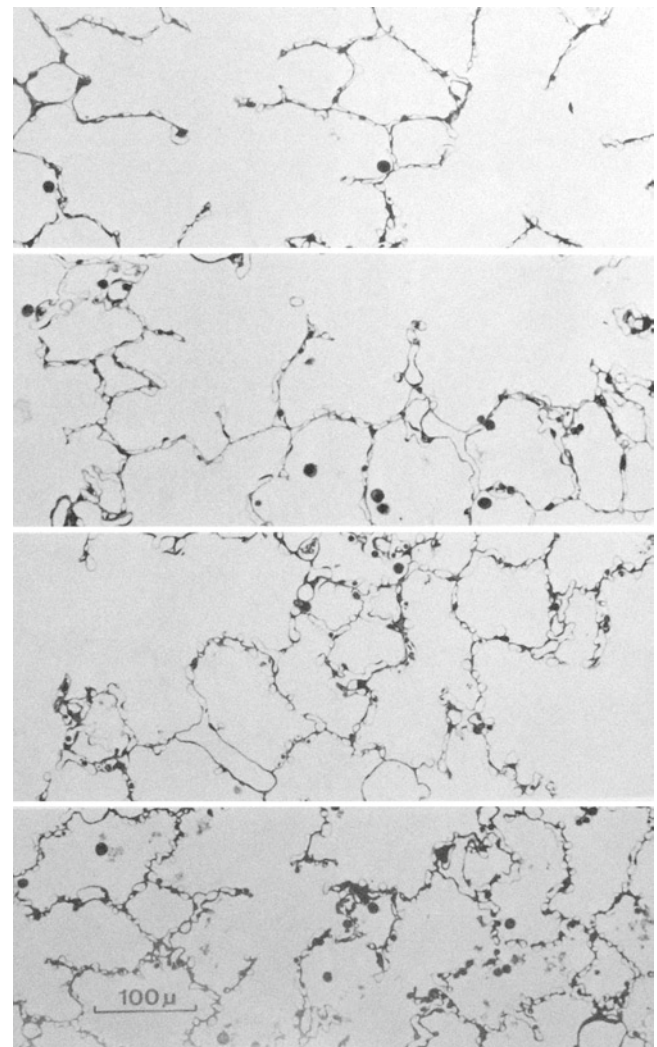
The most striking characteristic of zone I is that only corner vessels are open. Lamm [26, 27] showed that zone I lungs are capable of gas exchange. From our point of view, we note that the gas-exchanging membrane that surrounds the corner vessels is locally as thin as in other alveolar capillaries. Corner vessels are shunts that connect the arterial to the venous circulation, bypassing all septal vessels. It stands to reason that if they absorb all the circulation in the corners, additionally to some widening they need to be associated with a higher *flow velocity* of the blood. When all capillaries are open (Zone III) one would assume that their location is the site of capillary drainage.

Similar considerations can be made with regard to zone II, which is particularly important in medicine. As described, the alveolar walls, if dry, that is, without alveolar edema, are smooth. Some alveolar walls will include patches of closed and open capillaries which typically have a quadrangular profile, whereas most of the alveolar wall capillaries are compressed and closed. The patches always extend from corner to corner, but we cannot explain the reason for this configuration. These are evidently suitable for gas exchange under all conditions. Regarding the corner pleats which represent a more or less circumferential (in two dimensions) convoluted bundle of capillaries inside folded alveolar walls, we have shown that they represent arteriovenous shunts which evidently allow some blood to escape and penetrate into the alveolar septa [15]. They have at least superficially some similarity with the glomerular capillaries in the kidney

which produce only minimal resistance to perfusion and are therefore suitable for the function. The considerations presented for the corner vessels apply fully: the cluster of capillaries on several sides offers very thin air–blood barriers suitable for gas exchange.

Finally, zone III, where the flow is driven only by the pressure difference between arteries and veins, is the model of the commonly shown pulmonary anatomy: the alveolar walls no longer appear flattened out because of the capillary bulges and all capillaries are open and it is also configuration where the diffusing capacity would reach its maximum.

One should add that whenever alveolar edema exists and the air spaces are filled with fluid, the surface tension is abolished and the configuration is always that of zone III regardless of the pressures. This is shown in Fig. 12, which shows saline-filled rabbit lungs fixed under pressure conditions identical to those in the air-filled lungs shown in Figs. 3, 5, 8, 9.



**Fig. 12** Counterpart to the micrographs of air-filled rabbit lungs shown in Fig. 9, but this time, prior to the perfusion with fixatives, the alveolar spaces of the lungs having been filled with saline, thus simulating the conditions of alveolar edema. (Reproduced with permission [4])



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Textbook of Pulmonary Vascular Disease

Yuan, J.X.-J.; Garcia, J.G.N.; Hales, C.A.; Rich, S.; Archer,  
S.L.; West, J.B. (Eds.)

2011, XXXII, 1658 p. 345 illus., 224 illus. in color.,

Hardcover

ISBN: 978-0-387-87428-9