7.1 Pulmonary circulation and systemic circulation

The circulation subserves functional interaction between the various systems of the body and between the organism as a whole and its environment. The rate of flow of the blood in the arteries is quite high, thus the time taken in communication between organs is fairly short, a very important factor in the synchronization of the various functions. The flow of blood through the capillary bed in the tissues is slow, providing functional and temporal match between the mass transport and metabolic processes in the extracellular and intracellular spaces.

Systemic circulation: The rate of flow of the blood in the large arteries is 40-50 cm/s on average, decreasing with each successive ramification because the total cross-sectional area of the vascular bed is constantly increasing. In the arteries the blood flow pulsates strongly, with considerable changes of pressure. These decrease greatly towards the periphery, particularly as a result of the high resistance in the terminal arteries and arterioles. The blood flow in the capillary network is regulated by the arterioles and the precapillary sphincters. The capillary bed has a very large total cross-section, resulting in a very low linear rate of flow of the blood (0.07 cm/s). The capillary walls are easily permeable; endothelial cells are permeable to water, gases, electrolytes, urea and glucose; intercellular links are permeable to plasma proteins, bacteria and small blood cells; the stomata are also permeable to larger cellular blood elements. The veins in the systemic circulation carry the blood back to the heart and accommodate changes in the total volume of blood: about 75% of the blood in the system is in the venules and small veins and only 25% in the arteries and capillaries. The capacitance function of the veins is probably under nervous regulation; the pressure in the right atrium is kept at a constant very low level. Regulation of the post-capillary resistance in the venules is important for filtration and the absorption of extravascular fluids (see 7.8).

Pulmonary circulation: The pulmonary circulation is linked in series with the systemic circulation. It is a low pressure system with few regulating mechanisms and low resistance to flow. The blood pressure is about a fifth to a seventh of that in the systemic circulation, due to the relationship between the blood flow and the size and elasticity of the vascular bed. The pulmonary blood vessels are highly elastic and larger than the corresponding systemic vessels. Such a vascular system is relatively sensitive to outside forces, e.g. gravity (see 6.5). The pulmonary vascular bed has no equivalent to the muscular walls of systemic arterioles which govern capillary perfusion, with consequent effects on blood pressure. The pulmonary capillaries differ from the systemic capillaries: thin walls, low flow resistance, anastomoses with the bronchial vessels. The pulmonary vascular bed has a very high perfusion capacity: the resistance to flow is about an eighth of that in the systemic circulation. The perfusion time of the pulmonary capillaries is 0.7-0.8 s at rest and 0.35 s during physical exertion. An increase in the pulmonary blood flow from 6 L/min at rest to, say, 40 L/min during work hardly causes any rise in pressure in the pulmonary artery because the increase of blood flow is accompanied by dilatation of the pulmonary capillaries. The pulmonary blood flow is pulsatile as far as the capillaries, varying during the cardiac cycle from 2 to 15 L/min. The most important function of the pulmonary circulation is the exchange of gases. It also serves as an equalizer of blood volume changes: alterations of 200 mL and more in the pulmonary blood volume can occur. The pulmonary capillary bed also removes any foreign bodies (fat, air, etc.) which have entered the systemic circulation on the venous side: this filter effect prevents systemic (cerebral) embolism. The pulmonary circulation also has a metabolic function, e.g. in surfactant metabolism (see 5.5).

References:
Murray JF. The normal lung. W. B. Saunders, Philadelphia, 1976
7.2 Pulsations and vascular control

Blood pressure, blood flow and blood volume, and their regional distribution, vary greatly during the cardiac cycle. The pattern of systolic pressure in the aorta differs only quantitatively from that in the pulmonary artery; the shape of the pressure curves are roughly the same, but the blood flow curves show distinct differences. Blood flow in the aorta quickly reaches a sharp peak, then drops slowly. In the pulmonary artery its pulsations are much smoother, as a result of the diameter and mechanical properties of the pulmonary blood vessels and the low resistance to flow in the pulmonary vascular bed (see 7.1). In the pulmonary circulation the relationship between blood pressure, blood flow and blood volume is dependent on the movements of the heart and lungs. There is no clear relationship between blood volume and resistance to flow: changes in the diameter of the vascular bed can occur without any change in resistance to flow, and resistance can change without altering the blood volume. Resistance to flow usually decreases with increase in volume of blood, but at high levels of lung inflation the resistance increases with blood volume. The pulmonary vascular bed is very elastic and apparently behaves like a passive organ: during systole the stroke volume is taken up by the great arteries, which have an "air-chamber" function for blood flow during diastole. The pulmonary vascular bed is a pulsating system, the pulsations reaching into the pulmonary veins. It is not certain how far the pulmonary circulation in man is regulated by the nervous system. The pulmonary flow resistance may be under the influence of sympathetic and parasympathetic stimuli; the mechano-sensors in the lung play a part in the regulation of the capillary circulation (see 11.6). On the other hand the small muscular component in the walls of the pulmonary arteries means that no great significance can be attached to pulmonary vascular reflexes, in contrast to the systemic circulation. The humoral regulation of the pulmonary circulation is much more important. Many substances have a vasoconstrictor effect: catecholamines, angiotensin, histamine, fibrinopeptides, prostaglandin F and perhaps serotonin. Vasodilatation is caused by substances such as bradykinin, acetylcholine and prostaglandin E. Pulmonary vasoconstriction is localised in the pre-alveolar vessels and can be reversed by sympathicomimetics, aminophylline and isoprenaline: a-receptor blocking substances decrease the effect of hypoxia, whilst beta-receptor blocking substances (propranolol) have the opposite effect. Vasoconstriction makes the walls of the larger pulmonary blood vessels more rigid, facilitating the transmission of pulsations.

The breathing gases can have great effects on the pulmonary circulation. Hypoxia causes pulmonary vasoconstriction, leading to a rise in pressure in the pulmonary artery. It is mainly a local reaction, probably involving a neuronal component consequent on chemical stimulation of the carotid body (Von Euler). Its mechanism is obscure. Histamine, which is present in large quantities in the perivascular mast cells, may play a part; dopamine, prostaglandin F and angiotensin have also been considered as mediators. Hypercapnia (increase of the CO₂ content of the blood) also causes vasoconstriction, though to a lesser extent than hypoxia. The mechanism of CO₂ vasoconstriction involves a change in the H⁺ concentration, and is quite different from that of hypoxia-based vasoconstriction.

References:
Best and Taylor's Physiological basis of medical practice. Brobeck J. R. (editor); Williams and Wilkins
Dirken MNJ, Heemstra H. *Quart J Exper Physiol* 1948;34:193
Murray JF. The normal lung. W. B. Saunders, Philadelphia, 1976
7.3 Pressure and flow resistance

The pressure in the pulmonary circulation is measured with a transducer which is connected by means of a cannula, needle or catheter to the blood in an artery, arteriole, capillary or vein. Some transducers are small enough to be built into the tip of a catheter (intravasal pressure transducers). Since determination of the pulmonary circulation involves measuring a pulsatile blood flow with varying pressures, the dynamic characteristics of a measuring system are important particularly when long flaccid catheters are used. A measuring system with a resonant frequency of 50 Hz is sufficient for clinical use. Intravasal pressure transducers have a very high intrinsic frequency (e.g. 1000 Hz) and bring about no disturbing effects from the catheter.

In the pulmonary vascular bed the following pressures are distinguished:
- The static pressure (‘blood pressure’) is measured relative to the atmospheric pressure and represents the potential energy at the point of measurement.
- The dynamic pressure (‘driving pressure’) is the intravasal pressure gradient in the direction of the bloodstream and represents kinetic energy.
- The hydrostatic pressure is the gravity (height difference) component of static pressure and is the difference in pressure between two equal, freely communicating blood vessels.
- The transmural pressure is the pressure gradient across the vascular wall, i.e. the difference between intravasal and perivasal pressure. The latter is the intrathoracic, alveolar or pulmonary parenchymal pressure, depending on the position of the blood vessel.

In a stationary medium the energy per unit volume is the sum of the static, dynamic and hydrostatic pressures: \[ W = P + \frac{1}{2} \rho y^2 + \rho gh, \] where \( P \) = static pressure; \( \rho \) = specific mass; \( y \) = average flow; \( h \) = height, and \( g \) = acceleration due to gravity. As the pulmonary vessels are very elastic and the blood flow pulsates, the pulmonary haemodynamics change during the course of each cardiac cycle. For the sake of simplicity, the pulmonary flow resistance (\( R_{\text{pulm}} \)) is defined as the quotient of the average dynamic pressure (driving pressure) (\( P_{PA} - P_{LA} \)) and the mean pulmonary blood flow (\( Q_{\text{pulm}} \)). The average pressure in the left atrium \( P_{LA} \) is measured as the pulmonary wedge pressure (\( P_{\text{wedge}} \)):
\[ R_{\text{pulm}} = \frac{P_{PA} - P_{LA}}{Q_{\text{pulm}}}. \]

The normal value for the average pulmonary flow resistance is: \( R_{\text{pulm}} = (14 - 5)/90 = 0.10 \text{ mmHg mL}^{-1}\text{s} = 13.3 \text{ kPa L}^{-1}\text{s}. \) The pulmonary vascular bed is a low-pressure system and thus heavily dependent on the environment. The following factors are relevant:
- As a result of gravity, the pulmonary intravasal pressure in a standing position is lower than when lying down: the transmural pressure in a standing position is thus less than when lying.
- Intravasal pressures are strongly influenced by alveolar pressures.
- Physical exertion in a young adult has comparatively little influence on pulmonary pressures; any effect increasing with age.
- Hypoxia causes a rise in the resistance to flow in the pulmonary vessels and thus an alteration in the distribution of the pulmonary pressures and blood flow (see 7.2).
- Metabolic and respiratory acidoses cause an increase in the pulmonary vascular resistance and thus a change in the pulmonary pressure and flow ratio.
- Drugs strongly influence the pulmonary circulation: administration of alpha-agonists, and adrenaline causes a rise in blood pressure; acetylcholine, atropine, beta-agonists, ganglion blocking agents and aminophylline lower the blood pressure (see 7.2). The effect of anesthetics on the pulmonary circulation is very variable: some mainly influence the pressure and others the blood flow. The effect also depends on whether respiration is spontaneous or assisted.

References
7.4 *Assessment of the Pulmonary Blood Flow*

To measure the pulmonary blood flow (cardiac output, minute volume) the following methods are among those available:

- **Fick's method**: the blood flow through the lungs is calculated on the basis of the oxygen uptake and the differences in oxygen concentrations in the arterial and mixed venous blood:
  \[
  Q_{\text{pulm}} = Q_c = \frac{\dot{n}_{O_2}/(c_{a,O_2} - c_{v,O_2})}{(c_{a,cO_2} - c_{v,cO_2})}
  \]
  The method requires the use of sampling catheters to determine the oxygen concentrations of the mixed venous blood in the pulmonary artery and of the blood in a systemic artery. The pulmonary circulation can similarly be determined with carbon dioxide:
  \[
  Q_{\text{pulm}} = \dot{n}_{CO_2}/(c_{a,cO_2} - c_{v,cO_2}).
  \]
  Carbon dioxide has the advantage that its concentration in mixed venous blood can be estimated by the non-invasive rebreathing method (Defares), although this is a relatively difficult procedure which has not gained general acceptance. Fick's method provides information about blood flow through the functioning alveoli but not about any existing cardiac or pulmonary shunt circulation.

- **Stewart-Hamilton's indicator dilution method**: the blood flow is calculated on the basis of the quantity of indicator added to the mixed venous blood and the quantity passing through a systemic artery in a given time (see 7.14). This latter figure is calculated from the area of the concentration-time curve:
  \[
  Q_{\text{sys}} = Q_{\text{pulm}} = \frac{(m_i/c_i)t}{},
  \]
  where \(m_i\) is the quantity of indicator added and \(c_i\) the average concentration (dilution) of the indicator during the time \((t)\) that it takes to pass. The indicator can be a dye, but could also be a change in temperature, acidity or electrolyte content. Continuous monitoring of the indicator concentration is necessary in order to distinguish the first circulation from recirculation.

- **Plethysmographic determination** of the pulmonary blood flow is a non-invasive method technically difficult to carry out and requiring expensive equipment (Lee and DuBois). The principle is as follows: the subject takes a breath of nitrous oxide/oxygen mixture. Nitrous oxide is very readily soluble in blood (\(\alpha_{N_2O} = 0.388\)) and does not combine chemically with it (see 8.1). The N\(_2\)O uptake from the alveolar gas in the capillary blood is a measure of the blood flow through the functioning alveoli (\(Q_c \approx Q_{\text{pulm}}\), see 8.5). The rate of N\(_2\)O uptake is measured using a plethysmograph as the decrease in lung volume when the airways are closed at the mouth:
  \[
  Q_c = \dot{n}_{N_2O} \times \alpha_{N_2O} \times P_{N_2O}
  \]

- The regional pulmonary circulation is usually determined with radioactive labeled substances (gases) (see 6.22-6.24). The regional perfusion (\(Q_r\)) is measured per unit of lung water (\(C^{15}O_2\)), gas volume (\(133\)Xe, inhalation), alveolus (\(133\)Xe, injection), or lung tissue (macro-aggregates).

The many other ways of measuring cardiac output are not discussed here.

References


7.5 **Lymph and fluid movement**

The perivascular and peribronchial interstitial tissues contain large numbers of lymph vessels and are therefore very effective in the transport of tissue fluids. These tissues are found deep in the lung, extending to arteries and veins with diameters of 100 μm, forming the chief connection between the lung parenchyma and the mediastinum. The perivascular and peribronchial cavities within the lung are analogous to the pleural cavity on the outside. They are connected with each other via the alveolar interstitial space. The forces in the interstitial spaces keep the blood vessels, lymphatics and airways open; the forces in the pleural space keep the lung expanded. The inner spaces contain only free connective tissue and no mesothelial cells and in this way differ from the outer space.

At least as much interstitial fluid is formed in the lungs as in other organs. The lymph vessels are essential for carrying it away, especially protein molecules. The endothelium of the lymph vessels shows many intercellular openings through which the tissue fluid can flow in practically unaltered form (see 7.8). The lymphoid tissue extends to the level of the terminal bronchioles and respiratory bronchioles and plays an important part in the pulmonary immune response and in cleaning the airways. The lymph flow is directed by valves from the visceral pleural lymph system to the deep parenchymal network and then through peribronchovascular structures to the hilus. The visceral lymph system is continuous, the densest network being in the basal parts of the lung, especially in the left lower lobe. The lymph circulation in man is probably maintained by contraction of the smooth muscle tissue in the lymph vessel walls. No lymph capillaries have been found in the interalveolar septa nor the alveolar-capillary membrane, but they exist in the connective tissue between the terminal alveolar units (juxta-alveolar lymph vessels, Lauweryns). In the left lung, 80% of the pulmonary lymph drains into the lymph glands in the vicinity of the bifurcation of the trachea; the drainage area of the right lung is much more extensive; the lymph drainage shows very wide individual variations.

References
7.6 ALVEOLAR AND EXTRA-ALVEOLAR BLOOD VESSELS

Alveolar and extra-alveolar blood vessels are distinguished on a functional basis. The alveolar vessels are subject to alveolar pressure and are compressed or dilated as the alveolar pressure becomes greater or less than the intravascular pressure. The diameter of these vessels is 30 μm or less. The small extra-alveolar vessels (30-100 μm) are subject to the interstitial pressure, and the large ones (>100 μm) are subject to intrathoracic pressure. As the lung inflates, the resistance in the extra-alveolar blood vessels decreases and that in the alveolar vessels increases. The total pulmonary vascular resistance is made up of both the alveolar and extra-alveolar components, it is least on the inspiratory side of the breathing level at rest and increases with both deep expiration (deflation) and maximal inspiration (inflation). The increase in vascular resistance seen when the lung is strongly inflated is due to the narrowing of the alveolar capillaries by stretching of the alveolar walls. The extra-alveolar capillaries become narrower when the interstitial pressure increases. This is the case with reduction of the degree of inflation of the lung tissue. Gravity brings about regional differences in lung expansion, associated with regional differences in interstitial pressure and thus with regional differences in the function (resistance, perfusion) of the extra-alveolar vessels. This perhaps explains the comparatively limited blood flow in the most basal parts of the lung (see 7.8, zone 4).

When lung inflation is a consequence of positive pressure at the mouth, alveolar pressure increases over vascular pressure (positive pressure inflation). This results in increased resistance, due to the change in transmural pressure (see 7.8). Inflation of the lung tissue also increases when the pressure on the outside of the thorax is reduced, so that thorax and lungs expand and the intrathoracic pressure drops (negative pressure inflation). The vessels are thus dilated and vascular pressure decreases. Positive and negative pressure inflation thus have different effects on the pulmonary circulation. This difference is important in lung pathology and the treatment of respiratory functional disorders.

References
7.7 Fluid Movement and Pulmonary Edema

The endothelial cells of the pulmonary capillaries are separated by slit pores. Fluid moves through these extracellular spaces as well as through the cell membranes and by endocytosis. The alveolar epithelial cells lie close together, making it difficult for fluid to penetrate into the alveolar cavity. The direction and extent of the fluid movements are determined by hydrostatic and colloid osmotic pressure differences (see 2.11). The hydrostatic pressure in the pulmonary capillaries is about +1.3 kPa (+10 mmHg), while the interstitial tissue pressure is 0.4-0.7 kPa (3.5 mmHg) lower than the environmental pressure. The hydrostatic pressure gradient over the pulmonary capillaries (filtration pressure) is thus about 1.7-2 kPa (13-15 mmHg). The colloid osmotic pressure of the blood is about 3.3 kPa (25 mmHg) and of tissue fluid and lymph about 2.5 kPa (19 mmHg). The effective colloid osmotic pressure is the difference between the two. As a result of the filtration pressure and effective colloid osmotic pressure there is a constant flow of fluid out of the capillaries and through the alveolar tissue to the lymph vessels.

The movement of fluid through the alveolar membrane depends on the alveolar surface tension: as this increases, so does the pressure gradient and with it the passage of fluid. In normal circumstances, passage of fluid through the alveolar membrane is slight.

Filtration and resorption of extravascular fluid are governed by changes in hydrostatic pressure, which depend on alterations in the ratio between the precapillary and post-capillary resistance in the venules. High venous resistance causes a flow of fluid from the blood to the extravascular fluid; high precapillary resistance results in dehydration. High hydrostatic pressure, for example as the result of a disturbance in the circulation, causes excessive formation of interstitial fluid. This causes the colloid osmotic pressure to drop, preventing the withdrawal of further fluid. When the endothelium is damaged and plasma proteins escape, the colloid osmotic pressure rises and extra water is drawn into the lungs. Non-cardiac pulmonary oedema is therefore more serious than cardiac pulmonary edema.

Abnormal fluid movement, whether resulting from abnormal formation of extracellular fluid or failure to remove it, appears first as a build-up of fluid in the interalveolar septa (interstitial oedema). Capillary leaks often play an important part here. The accumulation of extracellular fluid in the interstices impedes circulation through the pulmonary capillaries. In serious disorders the accumulation of fluid extends to the alveolar septa. The thick parts of these septa act as the interstitial buffer for fluids, the primary function of the thin parts is the transport of gas; the gas and fluid functions are thus separate. The accumulation of fluid in the interstices must be considerable before fluid appears in the alveolar spaces (alveolar oedema). Alveolar edema is associated with severe disturbance of alveolar ventilation and circulation and also of the diffusion through the thickened alveolar-capillary membrane. If the oedema extends to the bronchioles, alveolar function is completely eliminated at that point. As interstitial oedema often occurs before alveolar oedema, it is clinically very important that it should be diagnosed at an early stage. Physiological methods exist whereby the quantity of fluid can be estimated.

References
7.8 Regional perfusion and gravity

Gravity is an important determining factor in the regional distribution of blood flow through the lungs. A distinction must be made between the effects of gravity on the intra-alveolar and on the extra-alveolar blood vessels; perfusion of the alveolar vessels is influenced by the alveolar pressure and that of extra-alveolar vessels by the interstitial pressure (see 7.7).

With regard to the alveolar vessels, West has developed a model in which the lung is divided into four zones, the boundaries between which are to a large extent determined by the degree of inflation of the lung tissue.

Zone 1 is found in the uppermost parts of the lung in which the pericapillary pressure ($P_{pc}$) exceeds the pressure in the pulmonary artery and vein. The pericapillary pressure is slightly less than the alveolar (atmospheric) pressure because of the alveolar surface tension; thus it changes with the degree of inflation of the lung tissue (see column diagram $P_{pc}$).

In Zone 2 the pulmonary arterial pressure is greater than the alveolar (pericapillary) pressure, which in turn is greater than the venous blood pressure. The alveolar blood vessels act like a "Starling resistance"; they are collapsible tubes surrounded by a pressure chamber. The blood flow is determined by ($P_{PA} - P_{pc}$) and not by ($P_{PA} - P_{PV}$) (see column diagram); the pressure in the capillaries is almost the same as the pericapillary (alveolar) pressure.

Because of gravity, the arterial blood pressure increases, and with it the pressure gradient ($P_{PA} - P_{pc}$), in the direction of the basal parts of the lungs, bringing about a corresponding increase in blood flow; the number of open capillaries also increases in the same direction. The collapsible segments extend to vessels with a diameter of 30 μm; about half the vascular resistance is located in the alveolar vessels. The extra-alveolar vessels also contribute largely to vascular resistance (see 7.7).

In Zone 3 the pericapillary pressure is below the arterial and venous pressure and the blood flow ($Q_{c}$) is determined by the arterial-venous pressure gradient. This increases in the direction of the basal parts of the lung; as a result of gravity the arterial and venous pressures are greater than the pericapillary pressure. This results in greater capillary filling (capillary distension) and increased blood flow through the capillaries.

Zone 4 is found in the most basal areas of the lung where perfusion is less than in the adjacent upper part. This reduction cannot be explained on the basis of the mechanics of the alveolar vessels, but probably arises from the increase in the flow resistance of the extra-alveolar vessels in conjunction with the rather slight lung inflation and relatively high interstitial pressure in the basal parts of the lung (see 7.7).

The effect of gravity on the regional perfusion of the lung can be pictured as a "waterfall", with an "upstream pool" (arterial blood pressure), a "barrage" (pericapillary pressure) and a "down stream area" (venous blood pressure). In Zone 1 the barrage ($P_{pc}$) is higher than the level in the upstream pool ($P_{PA}$), so there is no blood flow. In Zone 2 the level of the pool ($P_{PA}$) is above the barrage ($P_{pc}$); the difference in height between the two determines the blood flow, independent of the level of the downstream area ($P_{PV}$). In Zone 3 both the level of the pool ($P_{PA}$) and that of the downstream area are above the barrage. The latter can play no part: the blood flow is entirely determined by the difference in hydrostatic pressure on both sides of the barrage. In Zone 4 the determining factors are other than these three elements. If the lung volume is small, the effect of compression of the lungs on the extra-alveolar vessels is probably dominant, resulting in a reduction in the difference between arterial and venous pressures.

References

G.J. Tammeling and Ph.H. Quanjer
7.9 Regional capillary blood volume

In the pulmonary capillary bed the blood is spread in a layer of about 10 μm in thickness spread over an area of 90-140 m² in more than 700 million capillaries; the pulmonary capillary bed covers 85-95% of the total alveolar surface. The effective blood volume is about 60 mL at rest and about 95 mL during work. Gravity gives rise to regional differences in capillary filling and perfusion. The functional zones of the lung (see 7.8) can also be distinguished morphologically (Glazier).

Zone 1: the alveolar (pericapillary) pressure is greater than the arterial and venous blood pressures. In this zone the capillary width is small: 2-3 μm; the capillaries are to a large extent collapsed. The red blood cells in these capillaries are distorted and comparatively few in number. In the corners of the alveoli the capillaries are kept open by surface tension. Perfusion depends on the diameter of the capillaries and on the intensity of the flow pulsations.

Zone 2: the pulmonary arterial pressure is higher than the alveolar (pericapillary) pressure; the capillaries act like a “Starling resistance” (see 7.8). The pulmonary capillaries vary from 3-7 μm in diameter and from 7-14 μm in length. There are 25-30 capillaries per mm of alveolar wall. The filling of these capillaries with erythrocytes is unequal: the number per mm of alveolar wall varies from 5 to 20, depending on the perfusion pressure. As the lung tissue stretches, the tension in the alveolar wall increases, the capillaries become narrower, and the number of erythrocytes per unit of alveolar wall decreases. This is probably what gives rise to the observation that pulmonary vascular resistance increases with the degree of inflation.

Zone 3: Both arterial and venous blood pressures are higher than the alveolar pressure; gravity causes dilatation of the alveolar capillaries. The alveolar wall contains many erythrocytes, some 10-30 per 100 μm septal length, depending on the perfusion pressure. The capillaries are thus relatively wide and much more homogeneously filled than in Zone 2.

Zone 4: There are not yet sufficient morphological data on this zone.

References
### 7.10 Factors determining regional perfusion

As a result of gravity, the regional perfusion per unit of lung volume increases from the apex to the base of the lungs (see 7.8). To a lesser extent the same applies to the ventilation per unit of lung volume. Under normal conditions the V/Q ratio decreases from apex to base (figure A). The following factors play a part: Increase in pulmonary blood flow is not accompanied by a change in the vertical perfusion gradient as long as the pressure in the pulmonary circulation does not increase (figure B). When the pressure increases, the gradient is reduced (figure D).

**Body position:** The apico-basal perfusion gradient characteristic of the vertical position almost completely disappears in a supine position (figure B). In addition, a position adopted earlier plays a part: the blood flow through the apex diminishes the longer the individual is upright. This change is due to a local vascular response.

**Stretching of the lung:** The more the lung tissue is inflated, the greater the difference between apex and base in the regional perfusion per unit of lung volume, except for the most basal parts of the lung, where the regional perfusion per unit of lung volume decreases (figure C).

**Age:** There are indications that the distribution of regional perfusion becomes more even with age as a result of changes in the mechanical properties of the lung tissue.

The regional perfusion of the left apex is greater than that of the right, possibly as the result of haemodynamically favourable branching of the left pulmonary artery. This difference is accentuated by a high blood velocity, as happens in stenosis of the pulmonary artery.

Arterial pulmonary hypertension is associated with a reduced vertical gradient of the regional perfusion. The normal apex/base ratio is 0.2-1.0. As the pulmonary pressure increases the ratio can shift to 0.9-1.0 (figure D). In hypoxia the relatively small vertical perfusion gradient is probably caused by the rise in pressure in the pulmonary artery and by selective vasoconstriction in the basal zones (Dawson).

Arterial pulmonary hypotension causes an increase in the vertical perfusion gradient: the upper zones of the lung are no longer perfused, resulting in a considerable rise in dead space ventilation. This occurs in acute blood loss and in Fallot's tetralogy.

Venous pulmonary hypertension is associated with a decrease in the vertical gradient of the regional perfusion ratio. In mitral stenosis the hypertension leads to reversal of the gradient: blood flow is directed mainly to the apex. The blood flow in the basal parts of the lung is impeded by the local perivascular interstitial oedema (zone 4); extension of this zone towards the apex is caused by a reduction in the diameter of the extra-alveolar vessels (Hughes). In long-standing pulmonary venous hypertension irreversible vascular changes occur, especially in the lowest parts of the lungs.

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**References**


7.11 Perfusion of the Pulmonary Capillaries

A variety of factors affect the function of the pulmonary capillary bed: blood pressure, blood flow and capillary blood volume. 35% of the pulmonary flow resistance is localised in the "arterioles" and 60% in the capillaries, as distinct from the systemic circulation where 70% of the flow resistance is localized in the precapillary arterioles, and 25% in the capillaries. Pulmonary capillaries are not very elastic but the degree of filling can change greatly. A change in perfusion is the result of a change in the degree of filling and/or the number of capillaries involved in the perfusion. Which factor predominates depends on the lung region (see 7.8).

The pulmonary vascular bed is a low pressure system and, as such, subject to the following mechanical factors (see also 7.3):

- Increase in pressure in the pulmonary artery is associated with a reduction in the pulmonary flow resistance; the greater the pressure in the left atrium, the less the effect.
- Increase in pressure in the left atrium is associated with a reduction in the pulmonary flow resistance; the greater the pressure in the pulmonary artery, the greater the effect.
- The effect of transpulmonary pressure on the alveolar blood vessels differs from that on the extra-alveolar vessels. The perivascular pressure of extra-alveolar vessels is connected with the degree of inflation of the lung tissue and that of the alveolar vessels with the surface tension of the alveolar membrane. An increase in surface tension reduces the perivascular pressure and thus promotes fluid movement (see 7.6-7.8).
- The pulmonary blood volume and blood viscosity (hematocrit) are also of significance in pulmonary flow resistance.

Depending on circumstances, pulmonary perfusion can show regional variations (see also 7.10).

A. Normal perfusion in a sitting position at rest. The vertical gradient of blood perfusion and capillary filling is normal: perfusion of the basal parts of the lung is considerable, while the apical zone is perfused but little.

B. Increased perfusion during work: all capillaries are perfused, with only slight regional differences. This situation is also found in a lung that is compensating for loss of function in the other lung or when perfusion increases due to a cardiac left-right shunt.

C. Greatly increased perfusion: caused by heavy work of severe cardiac left-right shunt: almost all capillaries show maximum filling. The blood pressure in the pulmonary artery is usually higher than at rest.

D. Decreased perfusion as the result of pulmonary hypotension or reduced cardiac output. In large parts of the upper regions of the lung, perfusion is reduced to practically zero flow. This is the result of gravity, possibly combined with local humoral regulating mechanisms.

E. A reduced capillary bed arises from destruction of capillaries (inflammation, degeneration, vascular obstruction, tumours etc.). The result is completely unequal perfusion.

F. Capillary blockage is caused by obstruction of venous return and is often associated with reduced circulation: regional differences in perfusion have disappeared.

References
7.12 Disturbances in the Capillary Blood Flow

Disturbances in the pulmonary blood flow can be demonstrated by functional and radiographic methods and by methods using radio-active indicators (see 7.4). These methods do not give exactly comparable results, so the choice of method is determined by the type of data required and the need for diagnostic intervention.

The lung consists of a large number of units differing in perfusion, blood volume and blood pressure gradient. These differences apply not only to the characteristics of the alveolar capillaries but also to those of the arteries and veins:

- Under normal conditions at rest (A), the capillary blood volume is 60–100 mL and the alveolar contact time is 0.5–0.7 seconds.

- During work (B), the capillary blood volume increases by some 25–50% and the contact time decreases to about 0.35 seconds. The capillary pressure gradient is roughly equal to that at rest and the blood flow increases by a factor of 3–4. The capillary perfusion capacity is thus considerably greater during work than at rest (opening and dilatation of capillaries).

- Disturbances in the arterial supply (precapillary) occur when the great pulmonary arteries are obstructed (thrombosis, embolism, compression and bending of the great pulmonary vessels) and in cases of precapillary pathology: microembolism, vasoconstriction or sclerosis of the vascular walls. Not only is perfusion abnormal but also the blood filling of the capillary bed. In cases of long-standing disturbance, perfusion of the pulmonary capillary bed is taken over by the bronchial circulation (see 7.13).

- Disturbances of the capillary bed (D) result from destruction of alveolar tissue (degeneration, tumours, inflammation, fibrosis) or from a local functional response to a disturbance of ventilation. Capillary perfusion shows marked regional differences.

- Disturbances in the (post-capillary) venous return system (E) occur in mitral stenosis, thrombosis and anomalies of the pulmonary veins, and in left-sided cardiac decompensation. The capillary blood volume increases and the capillary and pre-capillary vessels are overfilled. The regional distribution of perfusion is abnormal; cardiac output is frequently abnormally low and the alveolar contact time is lengthened. In long-standing venous congestion irreversible changes occur in the vessel walls.

- Disturbances in pulmonary circulation in a few pathological conditions are briefly described:

  - In pulmonary embolism, the circulatory defect can be localized by radio-active indicator gases. In the area concerned, ventilation is often slightly disturbed due to humorally induced bronchoconstriction (see 6.24).

  - In bronchial carcinoma, a circulatory defect may be caused by growth of tumours in the large blood vessels or by hypoxaemia due to bronchial obstruction (hypoxic vasoconstriction).

- In emphysema, the distribution of the circulation varies: in some patients the blood flow is displaced towards the apex, in others perfusion of the apical region is most affected. In cases of deficiency of α1-antitrypsin, blood flow in the basal zones is affected because it is here that white blood cells are primarily sequestrated in the pulmonary capillaries.

- In bronchial asthma, perfusion is reduced as a result of hypoxic vasoconstriction, especially in the basal areas of the lungs. Perfusion of relatively large areas of the lungs may be considerably reduced.

- In kyphoscoliosis, malformation of the thorax, with its attendant compression of a lung, directs the blood flow especially towards the apical regions of the lung.
7.13 Bronchopulmonary circulation

The pulmonary vascular bed is a low-pressure system, the main function of which is the exchange of gases; its secondary function is to provide for the metabolism of the terminal pulmonary units. The bronchial circulation forms part of a high pressure system supplying the lung tissue with blood down to the terminal units (see 2.12). At the arterial and capillary level there are only small bronchopulmonary anastomoses which are of little or no functional importance (see A). The bronchial and pulmonary veins are, however, closely linked; some two thirds of the bronchial venous blood is carried away by the pulmonary veins (see 2.12). In pathological conditions, bronchopulmonary links greatly influence the pulmonary blood circulation and gas exchange. The diagrams refer exclusively to the circulation in diseased lung tissue; the effects on blood flow in healthy tissue are not shown.

Circulatory disturbances due to abnormalities in the lung parenchyma (see B) vary according to the position and type of lesion. Usually disturbances to the pulmonary circulation are most evident: a great proportion of the pulmonary vasculature is out of action or there are unventilated or badly ventilated alveoli (functional R-L shunt). A parenchymal abnormality can also cause atypical arterial-venous connections in the pulmonary system, resulting in a considerable anatomical R-L shunt (see B2). In addition, disturbances of the parenchyma of the lung lead to abnormal bronchopulmonary capillary connections, causing the pulmonary capillary bed to be perfused with arterial blood from the bronchial circulation (pulmonary L-R shunt; see B1). Depending on circumstances, this blood enters the venous system or flows back into the pulmonary artery and from there reaches the circulation of the other lung (see D).

When one of the main branches of the pulmonary artery is blocked (congenitally, or due to thrombosis, embolism, bending, operative ligature or compression) the vascular bed of the lung concerned is wholly or partly perfused from the systemic circulation (see C). Usually this happens from the bronchial arteries and, exceptionally in cases of congenital abnormality, from arteries entering the lung through the pleura. The pulmonary vascular bed is thus perfused with oxygenated blood; the lung in question takes up no oxygen but gives off carbon dioxide. Such circulatory disturbances can be assessed by combining various methods (bronchospirometry, dye dilution curves, angiography) (see 6.26). The functional bronchopulmonary circulation can attain values of 1.0 litre per minute; the non-functional part is difficult to measure.

Abnormal bronchopulmonary circulation is associated with blocking or severe restriction of the venous flow. In figure D, this condition is shown in a patient with a venous obstruction whose pulmonary capillary bed is perfused from a systemic artery in the pleura. In this case the pulmonary artery in the lung concerned is perfused with oxygenated blood in the reverse direction. This was demonstrated by cardiac catheterisation and was analyzed quantitatively by bronchospirometry. A left to right shunt of this nature implies a considerable overloading of the vascular bed of the other lung, which has to carry the total circulation of the body plus the bronchopulmonary collateral circulation of the diseased lung.

References
7.14 Measurement of the shunt circulation

In normal circumstances almost all the blood, which follows the pulmonary vascular bed and participates in the external gas exchange in the lungs is involved in the internal gas exchange in the tissues (tissue metabolism). The systemic circulation ($Q_{\text{syst}}$) and the pulmonary circulation ($Q_{\text{pulm}}$) are calculated by Fick's method.

$$Q_{\text{syst}} = \frac{n_O_2}{(c_{SA,O_2} - c_{SV,O_2})} \text{ L/min}$$

$$Q_{\text{pulm}} = \frac{n_O_2}{(c_{PV,O_2} - c_{PA,O_2})} \text{ L/min}$$

where $n_O_2$ = oxygen uptake (mmol/min)
$c_{O_2}$ = oxygen concentration of the blood (mmol/L)
$SA$ = systemic artery; $SV$ = systemic vein
$PV$ = pulmonary vein; $PA$ = pulmonary artery.

A representative sample of systemic venous blood is usually obtained from the pulmonary artery. The portion of the circulating blood which does not participate in external gas exchange in the lungs is called a right-to-left shunt. The blood flow which is not involved in internal gas exchange in the tissues is called a left-to-right shunt. In normal circumstances these shunts form only a small proportion of the total circulation. As a result of abnormalities in the heart, the large central vessels, or the small peripheral vessels, the shunt circulation can increase considerably. The blood from the high pressure system always flows into areas where pressure is low.

Both categories of shunt are subdivided into different types which can be distinguished by dye dilution methods. The dye indicator is always introduced upstream from the abnormality and measured downstream. When the indicator is introduced into the pulmonary artery and the dye concentration is monitored in a systemic artery, the first part of the curve provides information on pulmonary blood flow. From this, the downward part of the curve after the first concentration peak is exponentially extrapolated to the base line. This extrapolation is necessary in order to separate the first circulation (A) from the recirculation peak (B). The pulmonary blood flow is calculated from:

$$Q_{\text{pulm}} = \frac{m_i}{(c_{\text{pulm}} \cdot t)}$$

where $m_i$ = quantity of dye indicator administered, $c_{\text{pulm}}$ = average dye concentration calculated from the area under the first circulation peak; and $t$ = duration of the first circulatory peak.

The area under the recirculation peak is not measured in normal circumstances. In a right-to-left shunt an abnormally large quantity of circulating blood fails to participate in external gas exchange in the lungs. This shunt can be located in the heart, in the great blood vessels, in the lungs as an arterial-venous aneurysm or other vascular anomaly, or as capillary perfusion of non-ventilated alveoli. When the R-L shunt involves a considerable vascular short circuit the concentration curve shows two peaks, the first peak (A) is caused by the rapid circulation through the vascular shunt ($Q_{sh}$) while the second peak (B) represents the circulation through the capillary bed of the lung ($Q_{\text{pulm}}$). The total area under both peaks is a measure of the systemic circulation (total circulation) ($Q_{\text{syst}}$). The ratio of the area under the first peak to the total area gives the extent of the right-to-left shunt as a fraction of the total (systemic) circulation.

References
Hamilton WF, Moore JW, Kinsman JM, Spurling RG. Amer J Physiol 1928; 85: 337.
7.15 Measurement of the shunt circulation II

In the case of a left-to-right shunt, part of the circulating oxygenated blood flows back to the right side of the heart or to a pulmonary artery without participating in tissue metabolism (internal gas exchange). This happens in congenital abnormalities of the heart (e.g., septum defects) or great vessels, but can also be caused by more peripheral vascular anomalies. Oxygenated and non-oxygenated blood are thus mixed.

The example given is that of a large left-to-right shunt between a systemic artery and a systemic vein. Only part of the blood from the left side of the heart reaches the tissues. For a satisfactory supply to be maintained to the tissues, the total circulation must be increased. The shunt then has little or no consequence for tissue metabolism. The extra circulation of oxygenated blood is an additional load on both sides of the heart and the pulmonary vascular bed, being especially heavy in cases of severe anomaly of the heart or blood vessels. When the vascular shunt connects a large systemic artery and the pulmonary circulation, blood flow through the right side of the heart is normal but it imposes an extra burden on the heart because of the raised pressure in the pulmonary vascular bed.

A left-to-right shunt can be measured by means of the dye dilution method. For this, the indicator is introduced into the pulmonary artery and its concentration is measured in a systemic artery (e.g., the brachial artery). The blood containing the dye passes through the lungs and left side of the heart without mixing. The first peak in the concentration-time diagram is thus a measure of the pulmonary circulation. The area under this peak is obtained by extrapolating the curve exponentially to the base line.

The pulmonary circulation is calculated as follows:

\[
Q_{pulm} = \frac{m_i}{t_{pulm}} \cdot c_{pulm}
\]

where 
- \(m_i\) = quantity of dye administered
- \(c_{pulm}\) = average concentration of dye during the first peak
- \(t_{pulm}\) = duration of the first peak

The dye in the blood that arrives early at the right side of the heart and pulmonary vascular bed via the shunt can be regarded as a second injection of indicator. This appears in the dye dilution curve as an early recirculation peak. This too is extrapolated exponentially to the base line and the area underneath is a measure of the left-right shunt.

The ratio of the area of the recirculation peak to that of the first peak is a measure of the L-R shunt circulation as a fraction of the total (pulmonary) circulation.

In some cases a R-L shunt and a L-R shunt occur at the same time. It is sometimes possible to distinguish them by simultaneously monitoring the dye dilution curve at two separate locations. A dye is usually used as indicator, although change in temperature or acidity can be used, provided the indicator does not leave the bloodstream while passing through.

References: See 7.14