101 Pulmonary Gas Exchange

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101.1 Introduction

In the original sense of the Latin word, “respiration” means repeated inhaling and exhaling of air with the associated movements of the thorax. Respiratory movements produce air flow for the transport of O₂ into lungs, and of CO₂, the end product of oxidative metabolism, out of the lungs. But respiration in today’s meaning includes all the processes involved in the transport of O₂ and CO₂ between the environment and body tissues, performed by pulmonary ventilation, pulmonary O₂ and CO₂ exchange, blood circulation, and O₂ and CO₂ exchange in tissues. Gas exchange in tissues is intimately related to the consumption of O₂ and production of CO₂ by oxidative tissue metabolism whose main purpose is provision of energy for life processes.

Obviously, the definition of where respiration stops and other processes start (e.g., circulation, tissue metabolism, energetics, etc.) is more or less arbitrary, like most subdivisions in physiology, but it is necessary for analysis and understanding. Taking respiration as the sum of the processes subserving (or related to) O₂ and CO₂ exchange and transport between the environment and body cells, respiration is treated in this and the following two chapters (Chaps. 102, 103). The emphasis will be on the basic principles of qualitative and quantitative functional analysis. What is practically excluded are the varied humoral and nervous control mechanisms (control of lung ventilation, cardiovascular function, acid-base balance, hemoglobin homeostasis, etc.) and cell physiological and molecular aspects, because these topics will be treated in other chapters.

The lungs are the site of gas exchange of the body with the environment, i.e., of uptake of O₂ and output of CO₂ (only about 1% of the gas exchange in man takes place across body skin).

The human lung airways (Fig. 101.1a) represent a tree-like structure, formed by repetitive branching of bronchi down to terminal bronchioles which give rise, by branching, to several generations of alveoli-carrying respiratory bronchioles and, finally, to alveolar ducts whose walls are entirely occupied by alveoli (about 3 x 10⁹ in human lungs) ([28]; see also Chap. 100). The alveoli are surrounded by a blood capillary network, fed by pulmonary arterioles and discharging to pulmonary venules. The multiple branching of airways and blood vessels leads to a very large air/blood exchange surface area (about 80 m² in human lungs). This and the extreme thinness of the tissue layers separating blood and gas (alveolar epithelium, interstitium, capillary endothelium), of about 0.1 μm, create favorable conditions for diffusive gas exchange. The efficient transport of O₂ and CO₂ by blood is ensured by the high blood flow to the lungs (equal to total cardiac output) and the rapid reversible chemical combination of O₂ and CO₂ in blood.

The simplest functional model for lung gas exchange function is shown in Fig. 101.1b. Pulmonary gas exchange includes three steps:

- **Ventilation** (air flow) bringing O₂ into, and removing CO₂ from, lung air spaces
- **Diffusion** across the air/blood barrier (and within pulmonary capillary blood, including chemical reactions in red cells and plasma)
- **Perfusion**, i.e., blood flow transporting O₂ from the lungs to body tissues and CO₂ from body tissues to the lungs.

R. Greger/U. Windhorst (Eds.)
Comprehensive Human Physiology, Vol. 2
© Springer-Verlag Berlin Heidelberg 1996

2037
The primary task of lungs is to provide adequate arterialization of blood, by achieving physiological values of \(O_2\) and \(CO_2\) partial pressures \((P_{O_2}, P_{CO_2})\) and pH in arterial blood distributed to body tissues. The \(O_2\) delivery to the body and the \(CO_2\) elimination from the body are the result of a combined action of the lungs and the heart: of the heart, by providing an adequate total blood flow (cardiac output); of the lungs, by insuring optimal arterialization of the blood which perfuses organs and tissues. Furthermore, since \(P_{CO_2}\) is a major determinant of the pH in blood and tissues, the lungs play an important role in the control of the acid-base equilibrium of the body (cf. Chap. 78). Evidently, the pulmonary gas exchange function must be adjusted to the changing metabolic demand (e.g., a large increase in exercise) and to varying environmental conditions (e.g., low \(O_2\) partial pressure at high altitude; cf. Chaps. 108, 109).

### 101.2 Physical Concepts and Quantities [10]

#### 101.2.1 Gas Volumes

The volume of an amount of gas is a function of pressure and temperature. The quantitative relationships follow from the general gas law (ideal gas law),

\[
P \times V = n \times R \times T,
\]

where \(P\) is pressure, \(V\) volume, \(T\) absolute temperature [in kelvins (K), equal to the temperature in °C + 273], \(n\) the amount of substance, usually expressed in moles but in respiratory physiology often in milliliters (STPD, see below), and \(R\) the gas constant \((\approx 8.33 \times 10^{-5} \text{ atm L mol}^{-1} \text{ K}^{-1})\). The equation is valid for pure gases and for gas mixtures. In addition to depending on pressure and temperature, gas volume depends on water vapor saturation (see below).

In respiratory physiology, the following three conditions of gas volume measurement are used:

- Gas volumes and flows (flow = volume/time) are usually measured at the ambient barometric pressure and at room temperature, saturated with water vapor ("spirometer conditions"). These are called *ATPS* conditions (ambient temperature, pressure, saturated).
- Lung volumes and ventilations are defined to denote volumes and volume changes within the airways. Therefore, they are expressed for "body conditions", called *BTPS* conditions (body temperature, pressure, saturated).
- \(O_2\) uptake and \(CO_2\) output designate amounts of gas transferred in unit time, and are, therefore, transformed to "standard physical conditions": 0°C, 760 mmHg, dry. These are termed *STPD* conditions (standard temperature, pressure, dry).

From the gas law, the conversion factors compiled in Table 101.1 are obtained. It is evident that the magnitude of the conversion factors is such that they cannot be disregarded. It is important to note that in equations all gas volumes (and flows) must be expressed in the same units and volume measurement conditions. An alternative, frequently
Table 101.1. Gas volume calculations. Derivation of formulae for transformation of volumes between various measuring conditions

| Temperature (absolute) | Pressure | Water vapor | Total | Typical value
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>V(BTPS) / V(ATPS)</td>
<td>310 / T</td>
<td>P_a - P_n,o</td>
<td>P_a - 47</td>
<td>310(P_a - P_n,o) / (T(P_a - 47)) = 1.09</td>
</tr>
<tr>
<td>V(STPD) / V(ATPS)</td>
<td>273 / T</td>
<td>P_a - P_n,o</td>
<td>2.78×T</td>
<td>P_a - P_n,o / 2.78×T = 0.98</td>
</tr>
<tr>
<td>V(STPD) / V(BTPS)</td>
<td>273 / T</td>
<td>P_a - 47c</td>
<td>P_a - 47c</td>
<td>P_a - 47c / 863 = 0.78</td>
</tr>
</tbody>
</table>

APTS, ambient temperature, pressure, saturated; BTPS, body temperature, pressure, saturated; STPD, standard temperature, pressure, dry; T, absolute room temperature (K); P_n,o, water vapor saturation pressure (mmHg) at T; P_b, barometric pressure (mmHg)

For P_b = 747 mmHg (corresponding to mean P_a at 140 m above sea level), T = 295 K (°C), P_n,o = 20 mmHg

\[ \frac{V(STPD)}{V(BTPS)} = f_{vol} \]

The ratio \( f_{vol} \) is used in many equations (101.4a,b; 101.6a,b; 101.11a,b; 101.12a,b; 101.14a,b; 101.19)

\[ 47 \text{ is the water vapor saturation pressure (in mmHg) at } 37^\circ \text{C} \]

used, is to include the STPD/BTPS volume conversion factor in certain equations (see Sect. 101.4). In this chapter, for sake of clarity, the volume conversion factors will be explicitly indicated in quantitative relationships.

### 101.2.2 Concentrations and Partial Pressures of Gases

Gas concentrations in gas phase are conventionally expressed in fractional (dimensionless) concentrations, \( F_x \), defined as volume of a gas species \( x \) in the total gas volume in dry conditions (i.e., excluding water vapor): \( F_x = V_x / V \). Concentrations (or content) of gases in blood (and other liquids), \( C_x \), are expressed as amount of gas \( (V_x) \) per unit volume of blood \( (Q) \): \( C_x = V_x / Q \). The traditional unit is volumes percent \( [\text{vol} \% = \text{ml gas (STPD)/100 ml blood}], \) but more recently molar units have been preferred: mmol/l = 2.24 vol%. Disregard of the different definitions of gas concentration in gas phase and in blood may lead to confusion and serious errors.

In a gas mixture, the total pressure is the sum of the partial pressures of the component gases (Dalton’s law). The partial pressures are proportional to the fractional concentrations, \( F \). Since \( F \) refers to dry gas mixture, the sum of partial pressures is equal to the difference between the total pressure (often atmospheric pressure, \( P_a \)) and the partial pressure of water vapor \( (P_{n,o}) \):

\[ P_a = F_x \times (P_a - P_{n,o}) \]  

By definition, in equilibrium, the partial pressure of a gas in a liquid (blood) is equal to that in the gas phase: \( P_{x(liquid)} = P_{x(gas)} \). Commonly used units of partial pressures (both for gas and liquid phase) are millimeters of mercury (mmHg, equivalent to torr), kilopascal (kPa), and physical atmosphere (atm): 1 kPa = 7.5 mmHg; 1 atm = 760 mmHg = 101.3 kPa.

### 101.2.3 Atmospheric Air

Dry atmospheric air has the following composition: 20.9% \( O_2 \), 0.03% \( CO_2 \), 78.1% \( N_2 \), 0.9% Ar, and traces of other inert gases. The concentration of \( CO_2 \) 0.03% \( (F_{co2} = 0.003) \), although of fundamental importance as essential to plant photosynthesis and thus to all animal life (and which nowadays is causing grave concern because of its tendency to rise), can often be neglected in respiratory physiology. Since the metabolic reactions in the human body are generally assumed to neither produce nor consume molecular \( N_2 \), it is justifiable to regard \( N_2 \) as a physically inert gas. Therefore, it is customary to regard \( N_2 \) and other inert gases together as one total inert gas termed “nitrogen”. Thus, the composition of atmospheric air as simplified for respiratory physiology, is: \( F_{o2} = 0.209; F_{co2} = 0.000; F_{n2} = 0.791 \).

In addition, atmospheric air contains a variable amount of water vapor (i.e., gaseous water). The water in air is usually expressed as relative humidity (fractional saturation). From this and the saturation pressure of water vapor for a given temperature, the partial pressure of water vapor can be derived. The saturation pressure of water vapor at body temperature (37°C) is 47 mmHg (6.3 kPa).

Atmospheric pressure (barometric pressure, \( P_b \)) depends on the altitude above sea level and the meteorological conditions. The average \( P_b \) at sea level \( (P_{b0}) \) is 760 mmHg (101.3 kPa). With increasing altitude \( (h, \text{ altitude in km}) \) the barometric pressure \( (P_{bh}) \) decreases exponentially:

\[ P_{bh} = P_{bo} \times 10^{-0.0055h} \]  

leading to halving of \( P_b \) at an altitude of 5.5 km (≈ log 0.5/0.055). Since the composition of atmospheric air is fairly independent of altitude, the above equation is also valid for \( P_{bo} \) in inspired dry air. For \( P_{bh} \) in the physiologically relevant water vapor-saturated air, \( P_b \) must be replaced by \( (P_a - P_{n,o}) \) in Eq. 101.3.
101.3 Overall Exchange [14]

101.3.1 Ventilation and Gas Transport

The amount of O₂ taken up and that of CO₂ eliminated with a breath is equal to the difference between the inspired and expired amounts of the gases. In terms of fractional concentrations (for the volume measurement conversion factor \(f_{vol}\), see Sect. 101.2.1 and Table 101.1):

\[
\begin{align*}
V_{O₂} &= f_{vol} \times (V_l \times F_{I_{O₂}} - V_l \times F_{E_{O₂}}) \quad (101.4a) \\
V_{CO₂} &= f_{vol} \times (V_l \times F_{E_{CO₂}} - V_l \times F_{I_{CO₂}}) \quad (101.4b)
\end{align*}
\]

Since in many conditions the expired and inspired amounts of the inert gas \(N₂\) may be considered as identical (\(V_l \times F_{E_{N₂}} = V_l \times F_{I_{N₂}}\), known as \(N₂\) equilibrium), the "\(N₂\) concentration ratio" is used for eliminating either \(VE\) or (usually) \(V_l\):

\[
r_{N₂} = F_{I_{N₂}}/F_{E_{N₂}} = V_l/V_l
\]  
(101.5)

The ratio \(r_{N₂}\) is usually only one or a few percent below unity. For \(CO₂\), \(F_l\) can be disregarded when ambient air is breathed.

Per unit time (e.g., minute) one thus obtains the relationship between \(O₂\) uptake, \(CO₂\) output, and (expired) ventilation, \(\dot{V}_E = V_l \times f_{resp}\) (respiratory frequency):

\[
\begin{align*}
\dot{V}_{O₂} &= f_{vol} \times \dot{V}_E \times (r_{N₂} \times F_{I_{N₂}} - F_{E_{N₂}}) \quad (101.6a) \\
\dot{V}_{CO₂} &= f_{vol} \times \dot{V}_E \times (F_{E_{CO₂}} - r_{N₂} \times F_{I_{CO₂}}) \quad (101.6b)
\end{align*}
\]

The ratio \(\dot{V}_{CO₂}/\dot{V}_{O₂}\) is the respiratory exchange ratio (respiratory quotient), \(R\):

\[
R = \dot{V}_{CO₂}/\dot{V}_{O₂}
\]  
(101.7)

In the steady state, \(R\) is equal to the metabolic respiratory quotient, \(R_{met}\), designating the ratio of \(CO₂\) production and \(O₂\) consumption in tissue metabolism. \(R_{met}\) is determined by the kind of substrate oxidized: \(R = 1.0\) for carbohydrates, \(R = 0.7\) for fat, \(R = 0.8\) for protein. Usually, \(R_{met} = R_E \approx 0.85\) is found in the steady state at rest.

101.3.2 Blood Flow and Gas Transport: The Fick Principle

The \(O₂\) taken up in the lungs is transported to the body by blood (only about 1% is consumed in the lungs), and the \(CO₂\) eliminated by the lungs is brought from the body to the lungs by blood flow. In mammals (and birds), with complete separation of arterial and venous blood in the heart, pulmonary blood flow is equal to the total systemic blood flow, designated as cardiac output. By analogy to the above equations for the relationship between \(\dot{V}_{O₂}\), \(\dot{V}_{CO₂}\), and \(\dot{V}_E\), the following relationship between \(O₂\) uptake, \(CO₂\) output, and the difference in concentration between arterial blood (\(C_a\)) and mixed venous blood (\(C_v\)) obtains:

\[
\begin{align*}
\dot{V}_{O₂} &= \dot{Q} \times (C_a - C_v) \quad (101.8a) \\
\dot{V}_{CO₂} &= \dot{Q} \times (C_v - C_a) \quad (101.8b)
\end{align*}
\]

This is the so-called Fick principle, and it is the basis of the classical method of determining the cardiac output from \(O₂\) uptake and the arteriovenous difference in \(O₂\) concentration. It is important to remember that venous blood from different organs has different \(O₂\) (and \(CO₂\)) contents, due to variations in the utilization of blood \(O₂\). The influence of all venous blood in the right atrium gives rise to mixed venous blood, which is the blood that enters the lungs and is therefore to be used in the Fick principle equation. Mixed venous blood is best obtained from the pulmonary artery (by cardiac catheter introduced via a peripheral vein). In contrast, arterial blood is the same everywhere in the arterial system (except in individuals with rare cardiovascular abnormalities) and may be obtained from any artery.

101.3.3 Methods

Inspired and expired volumes are measured as volume change by spirometers, which are gas-filled vessels with variable, calibrated volume. Ventilation is measured either by volume changes per unit time or by pneumotachometry, i.e., recording of the pressure drop across a (small) airflow resistance that is proportional to the gas flow rate. Expired and inspired volumes can be ascertained by integration of the gas flow.

Concentrations in gas are measured by volumetric analysis after consecutive absorption of \(CO₂\) (by alkali) and of \(O₂\) (by dithionite). The volume changes indicate fractional concentrations \(E\) (Haldane and Scholander apparatuses). Continuous gas analysis is achieved by mass spectrometers (all gases), infrared gas analyzers (\(CO₂\), \(CO\)), paramagnetic gas analyzers (\(O₂\)), and other devices (for measurements in blood, see Sect. 102.2.1).

\(O₂\) uptake (\(\dot{V}_{O₂}\)) and \(CO₂\) output (\(\dot{V}_{CO₂}\)) are usually measured from \(\dot{V}_E\), \(F_l\), and \(F_l\) (open system). \(O₂\) uptake may be directly measured as the volume decrease of an \(O₂\)-filled spirometer provided with a \(CO₂\) absorber (closed system).

101.3.4 Values at Rest and During Exercise

Typical values for a normal human being are shown in Table 101.2. At rest, the \(O₂\) consumption is about 0.3 l/min. This corresponds to a metabolic rate of 1.5 kcal/min (average energetic equivalent of \(O₂\), 4.85 kcal/l) or around 80 W (equivalent to a typical electric bulb). During heavy exercise the metabolic rate may rise by factor of 10, to 800 W (equivalent to an electric heater!). The rise in respiratory quotient (\(R\)) during short-term exercise is attributable to increased utilization of carbohydrates (glycogen) in mus-
cle energy metabolism, partly due to liberation of extra CO₂ from bicarbonate by lactic acid formed in anaerobic glycolysis. Ventilation increases nearly proportionately to O₂ consumption, due to an increase in both respiratory frequency and tidal volume. However, cardiac output increases less than proportionately to O₂ uptake. The arterial O₂ content changes little, whereas the O₂ content of mixed venous blood decreases, leading to an increased arterial-mixed-venous difference in blood O₂ content.

101.4 Dead Space and Alveolar Ventilation [1,14]

Before reaching the alveolar ducts and alveoli, inspired gas passes through nasal cavities, pharynx, larynx, trachea, and the bronchial tree. In these "conducting airways" inspired air is cleaned of particles (dust), heated (rarely cooled) to body temperature, and saturated with water vapor. This conditioning of inspired gas is an important function of the conducting airways. The airways are lined with a thin layer of mucus, secreted by bronchial glands and transported up the airways towards the esophageal ostium by the beat of the cilia of the respiratory epithelium, finally to be swallowed. Extraneous particles adhere to the mucous layer and are transported with it. Heating and humidification are effected by contact of inspired air with large-surface mucous membranes (particularly nasal conchae, small bronchi) and potentially high blood flow (in the bronchi via bronchial vessels, in part anastomosing with pulmonary blood vessels). For gas exchange, however, the conducting airways are considered as constituting dead space, because, compared with gas exchange in alveoli, their contribution to respiratory gas exchange is negligible: inspired gas remaining in dead space is expired essentially without any change in its composition except for water vapor.

For a quantitative evaluation of the effects of dead space on gas exchange, a simplified lung model consisting of a rigid tube, dead space, and an extensible bag, the alveolar space, is employed (Fig. 101.2). Upon expiration, first gas from the dead space (V₀) is expired, at the same gas concentrations as in inspired gas. Then follows gas from the alveolar space, in volume Vₐₑ = Vₑ - Vₐ, with the alveolar gas concentrations FA. The mixed expired gas arises from subsequent mixing (e.g., in a spirometer) of the functional components, dead space gas and alveolar gas. The following relationships obviously obtain (see also Chap. 100):

\[
V₀ + Vₐₑ = Vₑ \tag{101.9a}
\]

for amounts of gas:

\[
(V₀ × F₀) + (Vₐₑ × Fₐ) = Vₑ × Fₑ \tag{101.9b}
\]

Combination and rearrangement yields the Bohr formula:

\[
\frac{V₀}{Vₑ} = \frac{Fₐ - F₀}{Fₐ - Fₑ} \tag{101.9c}
\]

which allows calculation of V₀ (from Vₑ and F₀ values) or of FA (from V₀/Vₑ, F₀ and Fₑ). Note that for CO₂, FA > FE > Fₑ, for O₂, Fₑ > FE > FA.

For the normal, resting human being the following values are typical: Vₑ = 0.50 l; V₀ = 0.15 l; Vₐₑ/Vₑ = 0.3. V₀ is not

\[\text{Fig. 101.2. Relationships between dead space gas, alveolar gas, and expired gas. For explanation, see text.}\]

<table>
<thead>
<tr>
<th>Table 101.2. Typical values of respiratory and gas transport quantities in humans at rest and during heavy exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symbol</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>O₂ uptake</td>
</tr>
<tr>
<td>CO₂ output</td>
</tr>
<tr>
<td>Respiratory exchange ratio, R</td>
</tr>
<tr>
<td>Breathing frequency</td>
</tr>
<tr>
<td>Tidal volume</td>
</tr>
<tr>
<td>Total ventilation</td>
</tr>
<tr>
<td>Dead space</td>
</tr>
<tr>
<td>Alveolar ventilation</td>
</tr>
<tr>
<td>Cardiac output</td>
</tr>
<tr>
<td>Arterial P₀₂</td>
</tr>
<tr>
<td>Mixed venous P₀₂</td>
</tr>
<tr>
<td>Arterial PCO₂</td>
</tr>
<tr>
<td>Arterial-mixed venous O₂ content difference</td>
</tr>
</tbody>
</table>

*Values may decrease or increase during exercise
constant; it increases with tidal volume and breathing frequency. Such changes are due to mechanically or neurally induced changes in the diameter of the bronchi and to airflow-dependent (convective and diffusive) mixing between inspired and resident lung gas. The diameter of the bronchi is controlled by the autonomic nervous system, with sympathetic (adrenergic) dilatation and parasympathetic cholinergic (vagal) constriction.

In the same way as shown above for \( V_e \) (Eq. 101.9a), the total (expired) ventilation, \( V_e \), is composed of two parts, the **dead space ventilation**, \( V_d \), and the alveolar ventilation, \( V_A \):

\[
V_e = V_d + V_A
\]  
(101.10)

The relationship between \( V_d \), \( V_A \), and \( V_e \) is variable. It is evident that with shallow and frequent breathing \( V_d/V_e \) is higher and therefore \( V_A/V_e \) is lower than with slow and deep breathing. The quantitative relations may be complex due to the dependence of \( V_d \) upon tidal volume and frequency (see above).

Because no respiratory gas exchange occurs in dead space, the whole O\(_2\) uptake and CO\(_2\) output must be provided by the **alveolar ventilation**, \( V_A \). By analogy to the relationships between \( V_{co2} \), \( V_{o2} \), \( V_e \), and \( F_e \) (Eqs. 101.6a,b), one obtains:

\[
\dot{V}_{o2} = fvol \times V_A \times (F_{o2} - F_{A})_{o2} \quad \text{and} \quad \dot{V}_{co2} = fvol \times V_A \times (F_{co2} - F_{A})_{co2}
\]  
(101.11a, 101.11b)

Rearrangement and introduction of partial pressures (\( P_x = F_x(P_B - P_{H_2}O) \) yields:

\[
P_{o2} = r_{o2} \times P_{A} - \frac{\dot{V}_{o2}(P_{o2} - P_{atm})}{V_A \times f_{vol}} \quad \text{and} \quad P_{co2} = \frac{\dot{V}_{co2}(P_{co2} - P_{atm})}{V_A \times f_{vol}} - r_{o2} \times P_{co2},
\]  
(101.12a, 101.12b)

According to these relationships, the **alveolar partial pressures**, \( P_A \), are determined by the inspired gas (\( P_{A{o2}}, P_{A{co2}} \)) and by the ratio of metabolic rate (\( V_{o2}, V_{co2} \)) and alveolar ventilation (\( V_A \)). It should be noted that with \( P_{atm} = 47 \text{ mmHg} \), the factor \( (P_{o2} - P_{atm})/f_{vol} \) equals \( 863 \text{ mmHg} \) (see Table 101.1), which factor is frequently used in equations corresponding to Eqs. 101.12a,b.

For a normal resting human at an altitude of 140 m (\( V_o2 = 0.31 \text{ l/min}; \dot{V}_{o2} = 0.26 \text{ l/min}; V_A = 5.6 \text{ l/min}; r_{o2} = 0.99; P_{atm} = 47 \text{ mmHg}; P_B = 747 \text{ mmHg}; P_{A{o2}} = 146 \text{ mmHg}; f_{vol} = 0.81 \text{ l/min} \), Eqs. 101.12a,b yield:

\[
P_{A{o2}} = 40 \text{ mmHg} = 5.3 \text{ kPa}
\]
\[
P_{A{co2}} = 100 \text{ mmHg} = 13.3 \text{ kPa}
\]

Since arterialized blood reaches, more or less closely, equilibrium with alveolar gas (see below), these equations can be used to estimate arterial \( P_{co2} \) and, less accurately, arterial \( P_{o2} \), which are the prime output parameters of pulmonary gas exchange.

It is evident from Eqs. 101.12a,b that for a given metabolic rate (\( V_{o2}, V_{co2} \)) and inspired gas (\( P_{o2} \)), the alveolar (=arterial) \( P_{co2} \) and \( P_{o2} \) are determined by \( V_A \). An (imposed) increase of \( V_A \) (at constant metabolic rate and \( F_e \)) elevates \( P_{A{o2}} \) and diminishes \( P_{A{co2}} \) (hyperventilation); the reverse occurs with decreased \( V_A \) (hyperventilation). In light to medium exercise, \( P_{A{o2}} \) (and \( P_{A{co2}} \)) and \( P_{A{o2}} \) (and \( P_{A{co2}} \)) tend to remain fairly constant in the face of a large increase of \( V_{o2} \) and \( V_{co2} \). This is achieved by an increase of \( V_A \) in proportion to an increase of \( V_{o2} \) and \( V_{co2} \) (see Table 101.2). With inspiratory hypoxia, i.e., decrease of \( P_{A{o2}} \) (either by decreasing \( F_{A{o2}} \), constant \( P_{o2} \), or decreasing \( P_{o2} \) at constant \( P_{A{o2}} \) (altitude)), \( V_A \) increases, thus preventing part of the expected fall of \( P_{A{o2}} \). However, the increase of \( V_A \) produces an (undesirable) fall of \( P_{A{co2}} \) (hypocapnic alkalosis, see Sect. 102.4).

In testing of the efficiency of (chemical) respiratory control, subjects inspire gas with added CO\(_2\) (increased \( P_{A{co2}} \)). The regulatory increase in \( V_A \) reduces the rise in \( P_{A{co2}} \). The relationship between increase in \( V_A \) as a function of \( P_{A{co2}} \) (or \( P_{A{o2}} \)), with the slope \( \Delta V_A/\Delta P_{A{o2}} \), is the CO\(_2\) response curve, a steeper slope meaning more efficient control. In a similar manner, the \( O_2 \) response curve is established by progressive reduction of \( F_{A{o2}} \) (either with constant \( F_{A{co2}} \), or with \( P_{A{co2}} \) varied to achieve constant \( P_{A{o2}} \)).

### 101.5 Models of Alveolar Gas Exchange in Real Lungs [5,19,24]

In an assumed ideal lung model, complete gas exchange equilibrium is reached between alveolar gas and pulmonary capillary blood, and partial pressures for CO\(_2\) and O\(_2\) in arterial blood (\( Pa \)) are equal to those in alveolar gas (\( PA \)). In real lungs, partial pressure differences between alveolar gas and arterialized blood – an alveolar-to-arterial \( P_{o2} \) difference (\( aA_{o2} \)) and an arterial-to-alveolar \( P_{co2} \) difference (\( aA_{co2} \)) – are found. In the conventional model analysis of alveolar gas exchange, these differences are attributed to three mechanisms:

- Unequal distribution of alveolar ventilation (\( V_A \)) to pulmonary blood flow (\( Q \))
- Shunt
- Diffusion limitation.

### 101.6 Unequal Distribution of Ventilation to Perfusion (\( V_A/Q \) Inequality)

#### 101.6.1 Effects on Gas Exchange [4,30]

The effects of unequal distribution of alveolar ventilation (\( V_A \)) to pulmonary perfusion (\( Q \)) can be studied in a lung
model devoid of diffusion resistance, which consists of compartments having different ratios of alveolar ventilation to perfusion ($V_A/Q$). An alveolar-to-tissue $P_{ao}$ difference ($aA_{D_{ao}}$) and an arterial-to-alveolar $P_{co}$ difference ($aA_{D_{co}}$) can be shown to arise, although in each compartment full equilibration is assumed ($P_A = P_a$ for both CO$_2$ and O$_2$; Fig. 101.3). This is due to flow-weighted averaging: in the gas phase more gas from the high $V_A/Q$ compartment (with high $P_{ao}$ and low $P_{co}$) contributes to “mixed” alveolar gas, whereas in the blood, more blood from the low $V_A/Q$ compartment (with low $P_{ao}$ and high $P_{co}$) contributes to “mixed” arterial blood. It is evident that the ensuing $aA_{D_{ao}}$ and $aA_{D_{co}}$ increase with increasing inequality of distribution of $V_A$ to $Q$.

The $aA_{D_{co}}$ due to $V_A/Q$ inequality may amount to 10-15 mmHg in normal individuals, the $aA_{D_{ao}}$ to 2-4 mmHg. The extreme cases are of particular interest. $V_A/Q = 0$ means lack of ventilation and therefore absence of gas exchange, its perfusion constituting shunt or venous admixture (see below). $V_A/Q = \infty$, due to $Q = 0$, designates the presence of ventilated but unperfused alveoli. Again there is no gas exchange, and the ventilation of such a compartment is functionally a dead space ventilation. It is called parallel or alveolar dead space ventilation, as distinguished from conducting airway ventilation, which is series or anatomic dead space ventilation. The sum of both is equivalent to total ventilation not contributing to gas exchange. It is termed physiologic dead space ventilation. The physiologic dead space ventilation, $V_D_{phys}$, and its complement, the effective alveolar ventilation $V_{A_{eff}}$ ($= V_E - V_D_{phys}$), can be calculated from the Bohr formula (Eq. 101.9c) by introduction of arterial $P_{co}$, $P_a_{co}$, instead of the alveolar value:

$$V_{A_{eff}} = V_E (P_E - P_{co})_{co}/(P_a - P_{co})_{co}$$

(101.13)

Substitution of $V_{A_{eff}}$ into Eq. 101.12b allows calculation of $P_a_{co}$ in lungs with alveolar dead space ventilation.

### 101.6.2 Multiple Inert Gas Elimination Method [26,27]

In real (normal and diseased) lungs, a continuous distribution of $V_A$ and $Q$ is present. The pattern of $V_A/Q$ inequality could be estimated on the basis of the method involving continuous intravenous infusion of multiple inert gases with differing solubilities in blood.

For an ideal lung model (no diffusion limitation, no shunt, no $V_A/Q$ inequality, $P_A = P_a$), Eqs. 101.8b and 101.11b can be combined and applied to any intravenously infused foreign inert gas ($P_f = 0$):

$$Q \times (C_f - C_a) = f_{vol} \times V_A \times P_a/(P_B - P_{w_{vol}})$$

(101.14a)

The solubility of an inert gas in blood is expressed as the partition coefficient, $\lambda$, the ratio of gas concentrations in blood and gas phase in equilibrium, using the same units, e.g., ml (STPD)/100 ml, for both phases. With $f_{vol}$ (Table 101.1) one obtains for $\lambda$:

$$\lambda = C_f/(f_{vol} \times P_f) = C \times (P_B - P_{w_{vol}})/(f_{vol} \times P_f)$$

(101.14b)

Combination of Eqs. 101.14a and 101.14b, with $P_A = P_a$, yields:

$$Q \times \lambda \times (P_f - P_a) = V_A \times P_a$$

(101.14c)

Since in the ideal lung $P_A = P_a$, one obtains by rearrangement:

$$\frac{P_a}{P_f} = \frac{\lambda}{V_A/Q + \lambda}$$

(101.14d)

This equation predicts the dependence of $P_a/P_f$ upon $\lambda$ for an ideal lung ($V_A/Q$ constant). In a system with unequal $V_A/Q$, the relationship between $P_a/P_f$ and $\lambda$ is different (due to blood-flow-weighted averaging of $P_a$, see above). From the difference between the measured and the predicted relationship between $P_a/P_f$ and $\lambda$, the pattern of $V_A/Q$ inequality can be derived (Fig. 101.4).

In practice, a solution containing several (usually six) inert test gases with widely differing solubilities in blood ($\lambda$) is continuously infused intravenously. The concentrations (partial pressures) of the test gases are measured in mixed venous and arterial blood samples ($P_f$ and $P_a$) by gas chromatography or mass spectrometry. A very high precision of measurement is essential for this method.

### 101.6.3 Effects of Gravity [30]

At least a part of the $V_A/Q$ inequality in normal lungs is due to the effects of gravity on $Q$ and $V_A$. The marked effect of gravity on pulmonary circulation stems from the low pulmonary arterial pressure (about 2 kPa) and the very differ-
ent densities of blood and air. Because there is a hydrostatic gradient in blood (= 1 kPa/10 cm), but (practically) none in alveolar air, the transmural pressure in pulmonary vessels increases vertically from top to bottom, leading to distension of vessels and increased blood volume and blood flow in the lower (dependent) lung regions. According to West [30], three zones are distinguished (Fig. 101.5):

- In the uppermost lung regions of a resting human with the thorax upright, blood flow is close to zero because the pulmonary arterial pressure (Ppa) is lower than the intrapulmonary (alveolar) pressure (Pl), due to the vertical distance from the heart: Pl > Ppa (zone 1).
- In the lung areas beneath zone 1, Ppa is higher than Pl, but Ppv (pulmonary venous pressure) is lower than Pl. This results in collapse of the pulmonary veins, with increased resistance to flow. The effective perfusion pressure head may be considered to approximate Ppa – Pl instead of Ppa – Ppv (zone 2).
- In the areas beneath the zone 2, the transmural pressure of all vessels is positive and increases down the lung. Thus there is no vascular collapse, and the perfusion decreases down the lung because of increasing vessel distension (Ppv > Pl: zone 3).

With increasing Ppa, as in exercise, zone 1 is suppressed, and zone 2 is reduced, and the overall lung perfusion should be more homogeneously distributed. The effect of recumbency is similar, due to the decrease in the vertical height of the lungs. With increasing intrapulmonary pressure (Pl), as during artificial ventilation with positive pressure, zones 1 and 2 would be expected to increase, and blood flow distribution becomes more unequal. The gravity-dependent vertical gradient of Q is in part compensated in its effects on gas exchange by a (smaller) gradient of $\dot{V}_A$ in the same direction. The gradient of $\dot{V}_A$ is explained as follows. Because of gravity, the upper lung regions are relatively overexpanded and the lower ones compressed. Since the elastic distensibility (compliance) of the lungs decreases with increasing distension, the upper parts are less ventilated than the lower parts. According to recent experimental results, a substantial part of the $\dot{V}_A/Q$ inequality appears to be due not to gravity, but to anatomical heterogeneity of airways and blood vessels [6,7].

A mechanism contributing to reduce the $\dot{V}_A/Q$ inequality is based on hypoxic pulmonary vasoconstriction. In contrast to most systemic vessels, hypoxia elicits vasoconstriction in pulmonary vessels (amplified by hypercapnia). Thus local hypoxia, e.g., as produced by local hypoventilation, produces vasoconstriction with local reduction of blood flow, which leads to increase of the $\dot{V}_A/Q$ ratio towards normal. This reduces the spread of the $\dot{V}_A/Q$ ratios and the overall lung gas exchange efficiency is improved. This in called the von Euler-Liljestrand effect [22].

In pulmonary diseases, $\dot{V}_A/Q$ inequality is in many cases conspicuously increased, leading to low arterial $P_{O_2}$ and large $aaD_{O_2}$.

### 101.7 Shunt or Venous Admixture

A shunt, i.e., short-circuiting of blood past gas exchanging regions of the lungs, leads to admixture of venous blood to arterialized blood, and thus to decrease of $P_{O_2}$ in arterial blood. This decrease is dependent on the shape of the blood $P_{O_2}$ equilibrium curve (see Chap. 102). The same shunt produces the same reduction in arterial $O_2$ content, but a largely different $aaD_{O_2}$, depending on the slope of the $O_2$ equilibrium curve (Fig. 101.6). Since the largest $aaD_{O_2}$ is produced in hyperoxia (due to the flatness of the $O_2$ dissociation curve, representing physical solution of $O_2$ only), shunt is usually calculated from the $aaD_{O_2}$ measured in hyperoxia ($Fi_{O_2} = 0.3$ or higher).

In normal individuals breathing air, the shunt is about one to a few percent of the pulmonary blood flow, and gives
rise to an $\AAaDo_2$ of about 5–10 mmHg. The important sources of shunt are perfusion of hypoventilated alveoli (which, more correctly, is an effect of low $\bar{V}A/Q$) and of collapsed, atelectatic lung areas. In addition to these, admixture of bronchial venous blood to the arterialized pulmonary venous blood and myocardial venous outflow via the thalamic veins (leading to the left heart) also contribute to shunt. A massive extrapulmonary venous admixture resulting from the right-left shunt is observed in individuals with cardiac septal defects.

**Fig. 101.6.** Blood $O_2$ equilibrium curve to show the production of alveolar-to-arterial $P_{O_2}$ differences, $(PA - PA_0)_{O_2}$ by a shunt (relative shunt flow, $\dot{V}sh/\dot{Q}_{tot}$) in hypoxia, normoxia, and hyperoxia. $Cc'_{O_2}$ is the $O_2$ content of blood in equilibrium with $PA_0_{O_2}$. The shunt effect in terms of the $O_2$ content difference, $(Cc' - Ca)_{O_2}$, is in all cases the same, but the corresponding $P_{O_2}$ difference, $(PA - Pa)_{O_2}$, is large in hypoxia, medium in normoxia, and small in hyperoxia, resulting from the shape of the $O_2$ equilibrium curve of blood.

Fig. 101.5. Model to explain the effect of gravity on the vertical distribution of blood flow in lungs. See Sect. 101.6.3

**101.8 Alveolar-Capillary Diffusion and Pulmonary Diffusing Capacity**

[2,17,21,25,29]

**101.8.1 Oxygen**

In modeling alveolar-capillary diffusion of $O_2$, the diffusion flux of $O_2$, i.e., the pulmonary $O_2$ uptake ($\dot{V}_{O_2}$), is considered to be proportional to the mean effective $P_{O_2}$ difference between alveolar gas and blood $\Delta P_{O_2} = (PAO_2 - PC_{O_2})$, where $PC_{O_2}$ is the mean pulmonary capillary $P_{O_2}$. The ratio of $\dot{V}_{O_2}$ and $\Delta P_{O_2}$ is termed **pulmonary diffusing capacity**, $DL_{O_2}$, or transfer factor, $T_{O_2}$ (usually expressed in ml/min × mmHg):

$$DL_{O_2} = \frac{\dot{V}_{O_2}}{\Delta P_{O_2}} = \frac{\dot{V}_{O_2}}{PAO_2 - PC_{O_2}}$$

(101.15)

The $PC_{O_2}$ value is calculated from the $\AAaDo_2$ component due to diffusion limitation, alveolar and mixed venous $P_{O_2}$, and the blood $O_2$ equilibrium curve by a procedure called Bohr integration. In hypoxia, the gas/blood $P_{O_2}$ difference $(PAO_2 - PV_{O_2})$, which initially is very large, contracts rapidly as blood passes through the pulmonary capillary, and at the end of the capillary no $P_{O_2}$ difference (i.e., $\AAaDo_2$) is left (Fig. 101.7). In normoxia as well, in resting normal individuals, an $\AAaDo_2$ attributable to diffusion limitation is usually too small to measure.
In reality, the structure and function of the “diffusion barrier” in lungs is complex. The tissue barrier separating alveolar gas from capillary blood is composed of heterogeneous layers (alveolar epithelium, interstitium, endothelium) of nonuniform thickness. Part of the resistance to O₂ uptake is to be sought in the flowing plasma and within the red blood cells, whose shape depends on flow conditions (see Chap. 88). However, convective mixing in blood is assumed to assist O₂ equilibration. The finite reaction kinetics of O₂ with hemoglobin may also exert some retarding effect, but according to recent measurements O₂ uptake of red blood cells is more rapid than previously estimated [8]. Thus, neither intra-erythrocyte diffusion of O₂ nor its reaction with hemoglobin are assumed to limit pulmonary O₂ transfer significantly.

101.8.2 Carbon Dioxide

Because the Krogh diffusion constant (Eq. 101.17) for CO₂ is about 25 times higher than for O₂, CO₂ transport in lungs is usually considered not diffusion-limited. However, in CO₂ output in lungs, dehydration of H₂CO₃, and chloride/bicarbonate exchange between red blood cells and plasma are involved, and both processes may be rate-limiting (see Sect. 102.3.4). Experimental data suggest that with high CO₂ output (heavy exercise, effective transfer limitation is expected to occur, leading to positive arterial-to-alveolar CO₂ differences [11,23]. Remarkably, in some experimental conditions, Pₐco₂ lower in arterial blood than in alveolar gas has been reported, and special mechanisms involving intracapillary electrical fields have been proposed to explain this. However, these observations have remained controversial [16].

101.8.3 Carbon Monoxide

A convenient test gas for estimation of DL is carbon monoxide, CO. Due to the very high affinity of hemoglobin for CO, Pₐco₂ in blood during the passage through pulmonary capillaries stays practically constant and is close to zero if the subjects are not exposed to external CO (in smokers, blood Pₐco₂ should be estimated because of the presence of appreciable amounts of CO-Hb in blood). Thus, the pulmonary diffusing capacity (transfer factor) for CO, Dₗco₂, can be estimated from the uptake of externally administered CO, Vₜ, and from the difference between alveolar Pₐco₂ and Pₐco₂ and Pₐco₂ in blood, Pbco₂ (estimated from blood CO content or by rebreathing equilibration):

\[
D_{l_{CO}} = \frac{\dot{V}_{CO}}{P_{a_{CO}} - P_b_{CO}} \quad (101.18)
\]

The Krogh diffusion constant for CO in tissue is similar to that of O₂ (Kₒ/Kₒ = 1.2).

With the steady state method, about 0.1% CO is inspired for some minutes before measurements of Vₜ and Pₐco₂ are
performed. With the single-breath method, a deep inspired breath containing about 0.3% CO is held for 10 s, and \( DL_{co} \) is calculated from the exponential rate constant of CO absorption, \( k_{co} \), and the alveolar volume, \( VA \):

\[
DL_{co} = k_{co} \times \frac{VA \times f \text{ vol}}{P_{B} - P_{n,0}}
\]  

(101.19)

\( DL_{co} \) values found in resting normal individuals are about 30–50 ml min \(^{-1} \) mmHg \(^{-1} \). In pulmonary diseases, \( DL_{co} \) may be much reduced.

The problem in interpreting \( DL_{co} \) determined with CO is that its uptake is delayed by the slow reaction of hemoglobin with CO. However, this property can be exploited for further analysis [20]. The CO uptake rate of oxygenated red blood cells, \( \theta_{co} \), has been shown to be strongly dependent on \( P_{ao} \), due to competition between \( O_{2} \) and CO for hemoglobin. In the following equation, the total resistance to CO uptake (= \( DL_{co} \)) is broken into a resistance to CO diffusion across the air/blood barrier (= \( DM_{co} \)) and the resistance to CO uptake offered by red blood cells (= \( 1/(\theta_{co} \times Vc) \)). \( Vc \) is the pulmonary capillary volume, and \( \theta_{co} \) is the specific conductance of blood for CO uptake (i.e., including both diffusion and reaction kinetics), which decreases with increasing \( P_{ao} \):

\[
\frac{1}{DL_{co}} = \frac{1}{DM_{co}} + \frac{1}{\theta_{co} \times Vc}
\]  

(101.20)

Measurements of \( DL_{co} \) at two (or more) alveolar \( P_{ao} \) levels, and thus at different \( \theta_{co} \), allow calculation of \( DM_{co} \) and \( Vc \) (both of which have to be assumed to be independent of \( P_{ao} \)). In exercise, both \( DM_{co} \) and \( Vc \) are found to be increased, whereas in diseased lungs, both tend to be decreased.

A variable frequently considered as a limiting factor in diffusive pulmonary gas exchange is the mean transit time (contact time) \( t_{tr} \). It is related to blood flow (\( \dot{Q} \)) and capillary volume (\( Vc \)) by the relationship:

\[
t_{tr} = Vc/\dot{Q}
\]  

(101.21)

Evidently \( t_{tr} \) decreases with increase of \( \dot{Q} \) at constant \( Vc \). However, during exercise \( Vc \) increases, and thus \( t_{tr} \) decreases less than in proportion to the increase in \( \dot{Q} \).

101.9 Time Course of Expired Gas Concentrations: Expiograms

With the advent of rapid, continuously recording gas analyzers (infrared spectroscopy, mass spectrometry), the time course of gas concentrations in expired gas can now be recorded. For both \( O_{2} \) and \( CO_{2} \) (and foreign test gases), the following phases occur if recorded against time or expired volume (Fig. 101.8):

- First, unchanged inspired gas is expired from dead space: phase I.
- Next, a more or less rapid change to alveolar gas levels occurs. The slope in this phase, phase II, is attributed to mixing of alveolar and dead space gas, and to unequal expiration times of different regions of the lung.
- The alveolar plateau (phase III) is not flat but has a slope, moving away from the inspired value (\( P_{co2} \) rises, \( P_{o2} \) falls) and oscillating with cardiac frequency (cardiogenic oscillations).

The cardiogenic oscillations are explained by mechanical impact of the heart or of the pulsatile pulmonary arterial blood flow on expiratory gas flow from lung regions with differing gas compositions. The sloping plateau is attributed to the following factors:

- During expiration, exchange between alveolar gas and blood continues, whereas no fresh gas is admitted (functional breath-hold). High metabolic rate, slow breathing, and small lung volume would be expected to increase the slope.
- With regional \( V_{A}/Q \) inequality, a local variation of \( P_{A_{ao}} \) and \( P_{A_{co2}} \) is present. Relatively underventilated lung regions (with low \( P_{ao} \) and high \( P_{co2} \)) tend to expire later than relatively overventilated regions (with high \( P_{ao} \) and low \( P_{co2} \)). Thus \( V_{A}/Q \) inequality combined with sequential expiration produces sloping alveolar plateaus. The magnitude of the effect is expected to depend on the extent of \( V_{A}/Q \) inequality and of the time patterns of expiration. Due to this mechanism, the expirograms of diseased lungs may show steep alveolar slopes, up to apparent absence of an alveolar plateau (i.e., no clear distinction between phases II and III).
- The mixing of inspired and lung resident gas, particularly with rapid shallow breathing or in diseased lungs, is not completed during a respiratory cycle. This leads to

---

**Fig. 101.8.** General format of a CO₂ expirogram, i.e., recording of \( P_{co2} \) during an expiration, plotted against expired volume (\( V_e \)). Phases I, II, and III are marked. The cardiogenic oscillations and the slope of the alveolar plateau (phase III) are indicated. The location of the line delimiting the dead space (\( V_d \)) is established (dotted line), yielding equal (dotted) areas between the line, phase II of the expirogram, the (smoothed) extrapolated alveolar plateau, and the inspired value.
stratification of alveolar gas, with $P_a$ decreasing and $P_{co}$ increasing in the proximal-to-distal direction in peripheral airways. The extent of stratification due to incomplete intrapulmonary gas mixing has been a subject of recent research [3,12,13,15,18]. There is also evidence of unequal distribution of gas phase (and alveolar-capillary) diffusing conditions in lungs [9].

101.10 Ideal Alveolar $P_{co}$

In the face of the changing composition of gas exhaled from the alveolar space (see Sect. 101.9), the analysis of $\dot{V}A/Q$ inequality and shunt based on steady-state models becomes questionable. In normal individuals at rest, a meaningful alveolar gas sample can be obtained from the last part of expired gas. But in exercise, and particularly in patients with lung disease, no constant reproducible value is obtained as $P_{co}$ rises and $P_a$ falls continuously during expiration.

For this reason, an indirect procedure can be useful, in which “ideal” alveolar gas ($A_i$) is calculated on the assumption that $P_{co}$ is the same in arterial blood and alveolar gas: $P_{Ai_{co}} = P_{Aco}$. This assumption is reasonable for normal lungs and is an acceptable hypothesis in diseased lungs. Since expired gas may be considered as a mixture of expired alveolar gas and inspired gas reexpired from the dead space, the inspired, expired, and “ideal” alveolar $P_{co}$ and $P_a$ must lie on a straight line (the so-called gas R line) in a ($P_a - P_{co}$) diagram (Fig. 101.9). The “ideal” alveolar $P_{co}$, $P_{Ai_{co}}$, is obtained as:

$$P_{Ai_{co}} = P_{co} - \frac{(P - P_e)_{co}}{(P_e - P)_{co}} \times (P_a - P_{co})$$  \hspace{1cm} (101.22)

The difference $(P_{Ai} - P_a)$ may be taken to approximate the $\Delta A_{co}$ caused by $\dot{V}A/Q$ inequality, shunt, and/or diffusion as explained above.

The “gas R line” and its negative slope is close to the R value, which can be obtained by applying the $N_2$ correction (see Sect. 101.3.1, Eqs. 101.6 and 101.7).

General References


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Specific References


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