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Gas Exchange in Acute Respiratory Distress Syndrome

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Gas exchange in ARDS

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Abstract: The acute respiratory distress syndrome (ARDS) is characterized by severe impairment of gas exchange. Hypoxemia is mainly due to intrapulmonary shunt, while increased alveolar dead space explains the alteration of CO_2 clearance. Assessment of the severity of gas exchange impairment is a requisite for the characterization of the syndrome and the evaluation of its severity. Confounding factors linked to hemodynamic status can greatly influence the relationship between the severity of lung injury and the degree of hypoxemia and/or the effects of ventilator settings on gas exchange. Apart from situations of rescue treatment, targeting optimal gas exchange in ARDS has become less a priority nowadays compared to prevention of injury. A complex question for clinicians is to understand when improvement in oxygenation and alveolar ventilation is related to a lower degree or risk of injury for the lungs. In this regard, a full understanding of gas exchange mechanism in ARDS is imperative for individualized symptomatic support of patients with ARDS.

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Introduction

Hypoxemia and impaired CO_2 clearance are characteristics of the Acute Respiratory Distress Syndrome (ARDS) (1-3). A considerable literature has explored the mechanisms of gas exchange abnormalities in ARDS. Because gas exchange remains the main physiological abnormality assessed by the clinician, understanding the complexity of the factors at play remains of considerable importance in the modern area of ARDS management. This article will review the basic principles of pulmonary gas exchange, the pathophysiology of gas exchange alterations in ARDS (Table 1), the effects of various therapeutic measures (Tables 2 and 3), and how to use the assessment of gas exchange for individualized symptomatic support.

Pathophysiology of gas exchange in ARDS

The concept of ventilation to perfusion ratio

The concept of ventilation perfusion ratio ($\dot{V}_A/\dot{Q}$) implies that an optimal ratio is necessary to obtain normal gas exchange and that an imbalance in this global and/or regional ratio is one of the few fundamental reasons explaining abnormal gas exchange: low $\dot{V}_A/\dot{Q}$ ratios tend to induce hypoxemia and high $\dot{V}_A/\dot{Q}$ ratios tend to induce hypercapnia. Impaired diffusion is another possible mechanism at the blood-gas interface. However, eIn the ventilated areas in ARDS, because of the high diffusion coefficient of CO_2 and the increased O_2 diffusion gradient induced by the high inspired O_2 fractions (F_IO_2), equilibration of gas partial pressures between the blood and gas phases is complete in a functional gas exchange unit (i.e. alveolus and corresponding capillaries). Consequently impaired diffusion across the gas-blood barrier does not appear to play any role in gas exchange abnormalities in ARDS (4,5). Therefore, for a given F_IO_2, total cardiac output ($\dot{Q}_T$), hemoglobin (Hb) content, and Respiratory Exchange Ratio (the ratio of whole body CO_2 production to O_2

consumption, $\dot{V}CO_2/\dot{V}O_2$, usually of 0.8 at rest with a normal diet), impaired gas exchange is explained by an altered distribution of alveolar ventilation and perfusion ($\dot{V}_A/\dot{Q}$) (6-8).

$\dot{V}_A/\dot{Q}$ ratios can vary from 0 (perfused, but non-ventilated alveoli; gas partial pressures being those of the mixed-venous blood), also referred to as shunt, to infinity (∞) (ventilated, but non-perfused alveoli; gas partial pressure being those of the inspired gas), referred to as dead space (figure 1). In a homogenous lung, i.e. having an *ideal* (*i*) $\dot{V}_A/\dot{Q}$ ratio corresponding to the respiratory exchange ratio (RER), arterial (a) equal mean alveolar (A) gas partial pressures(figure 1). However, even a healthy lung comprises regions where perfusion exceeds ventilation (i.e. $0 \leq \dot{V}_A/\dot{Q} < i$), and where ventilation exceeds perfusion (i.e. $i < \dot{V}_A/\dot{Q} \leq \infty$). Since arterial blood is the sum of the blood from all gas exchange units, any $\dot{V}_A/\dot{Q}$ inhomogeneity will cause alveolar-arterial (A-a) gas partial pressure differences (Δ). The more perfusion exceeds ventilation, the more p_aO_2 will fall, creating a $\Delta_{A\text{-}a}pO_2$. To describe the ideal alveolar air and analyze ventilation-perfusion relationships in the lungs, Riley & Cournand described a simple model with three compartments (normal ratio, i.e. $\dot{V}_A/\dot{Q}$=RER, shunt, i.e. $\dot{V}_A/\dot{Q}=0$, and dead space, i.e. $\dot{V}_A/\dot{Q}=\infty$), which is displayed on figure 2(9). Increasing the $\dot{V}_A/\dot{Q}$ ratio by increasing minute ventilation ($\dot{V}_E$) cannot compensate for this effect, because of *i)* the relatively small contribution to $\dot{Q}_T$ of lung regions where ventilation markedly exceeds perfusion (i.e. $\dot{V}_A/\dot{Q}>10$), and *ii)* the virtually unchanged end-capillary blood O_2 content resulting from the sigmoid Hb-O_2-dissocation curve in these regions. Consequently, increasing F_IO_2 and/or re-aeration of non-ventilated lung regions are the cornerstones of the management of hypoxemia in ARDS. In contrast, a $\Delta_{a\text{-}A}pCO_2$ will only develop when alveoli with very high $\dot{V}_A/\dot{Q}$ ratios contribute to total ventilation. In other words, p_aCO_2 will only increase, when $\dot{V}_E$

in proportion to $\dot{V}CO_2$ can no longer compensate for inhomogeneity of intrapulmonary ventilation distribution.

In summary, in patients with ARDS, the pulmonary causes leading to impaired gas exchange are virtually solely related to disturbed matching of alveolar ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$) (6-8,10). While hypoxemia is the results of blood flow to non- and/or hypoventilated lung regions, impaired CO_2 elimination is mainly due to the contribution of non- and/or hypoperfused areas (7,8,10).

Dead space

A single tidal breath, V_T, and the expired volume per unit of time, $\dot{V}_E$, comprise a component that does not contribute to gas exchange, the dead space (V_D and $\dot{V}_D$, respectively), as well as the volume of gas delivered to the alveolus (V_A and $\dot{V}_A$, respectively):

$V_T = V_D + V_A$ [1A], and $\dot{V}_E = \dot{V}_D + \dot{V}_A$ [1B].

Dead space ventilation consists of an anatomical (the conducting airways) and an alveolar component (ventilated, but non-perfused alveoli and/or alveoli over-ventilated relative to perfusion). According to the above-mentioned model by Riley & Cournand (9), dead space can be referred to as “wasted” ventilation. Since CO_2 eliminated in the expired gas ($\dot{V}CO_2$) can only originate from gas-exchanging parts of the lung, $\dot{V}_E$ is the sum of the amount of inspiratory gas not participating in gas exchange ($\dot{V}_D$) added to the alveolar gas transporting CO_2 ($\dot{V}_A$). Since $F_ICO_2 \approx 0$ and $p_aCO_2 \approx p_ACO_2$,

$\dot{V}CO_2 = \dot{V}_E \cdot F_ECO_2 = \dot{V}_D \cdot F_ICO_2 + \dot{V}_A \cdot F_ACO_2$ [2],

where F_ECO_2, F_ICO_2, and F_ACO_2 are the mixed expiratory, inspiratory, and alveolar CO_2 fractions, respectively. Substituting $\dot{V}_A$ and re-writing equation 2 in terms of pCO_2 yields

$\dot{V}_D/\dot{V}_E = V_D/V_T = (p_aCO_2 - p_ECO_2)/p_aCO_2$ [3].

This equation represents the simplified quantification of the overall V_D/V_T according to Enghoff (11). If p_aCO_2 really equals p_ACO_2 – which is often not the case, particularly in ARDS –, V_D/V_T according to (11) equals the anatomical dead space. Based on the above-mentioned assumptions that $F_ICO_2 \approx 0$ and $p_aCO_2 \approx p_ACO_2$, equation 2 can be rewritten

$\dot{V}CO_2 = \dot{V}_A \cdot k \cdot p_aCO_2$ [4] (k=0.863 for mmHg and mL, 2.561 for SI units),

or, for a given $\dot{V}CO_2$,

$\dot{V}_A \sim 1/p_aCO_2$ [5],

i.e. $\dot{V}_A$ is inversely proportional to p_aCO_2. In other words, p_aCO_2 is a function of $\dot{V}_A$ in proportion to $\dot{V}CO_2$. Therefore, i) for a given $\dot{V}_A$, metabolic CO_2 production ($\dot{V}CO_2$) determines p_aCO_2, and ii) any rise in V_D/V_T requests increases in $\dot{V}_E$ to maintain p_aCO_2.

Dead space is classically divided in two components, the airway dead space and the alveolar dead space (12). Applying the method proposed by Fowler for N_2 (13) to CO_2, Fletcher & Jonson proposed a graphical analysis of the $p_ECO_2/\dot{V}_E$-curve named "*volumetric capnography*", which allows calculating V_D/V_T using the Enghoff equation and its partition between airway (anatomical) and alveolar dead space (figure 3) (14). In summary, in patients with ARDS, impaired CO_2 clearance is mainly due to increased V_D/V_T, i.e. "wasted" ventilation" in ventilated but non-perfused lung regions (9). Hence, increasing $\dot{V}_E$ and/or decreasing V_D (see below) can allow maintaining p_aCO_2; hypercapnia will occur when increasing $\dot{V}_E$ in proportion to metabolic $\dot{V}CO_2$ can no longer compensate for inhomogenous ventilation distribution(7-9).

The alveolar gas equation

As mentioned p_aCO_2 is often used as a surrogate for p_ACO_2, albeit this approximation is erroneous, particularly during severe ARDS, when $\Delta_{a\text{-}A}pCO_2$=10-15mmHg may develop. Under normal conditions, the $\Delta_{A\text{-}a}pO_2$ is of that magnitude but during ARDS,

this $\Delta_{A\text{-}a}pO_2$ can be several-fold higher and it reflects the ARDS definition requiring increased F_IO_2.

Theoretically, to quantify the $\Delta_{A\text{-}a}pO_2$, p_AO_2 can be calculated after substituting p_ACO_2 by p_aCO_2 and correction for RER≠1:

$p_AO_2 = p_IO_2 – p_aCO_2 \cdot (F_IO_2 + (1 – F_IO_2)/RER)$ [6]

This *calculated* P_AO_2 refers to the overall *ideal mean* alveolar pO_2 of a homogenous lung. In ARDS however, p_AO_2 may vary substantially within different lung regions due to inhomogeneity of the distribution of alveolar ventilation. Therefore, in clinical practice, this complicated correction for the p_AO_2 calculation is unnecessary, so that simply approximating the value is sufficient, in particular at high F_IO_2 (15):

$p_AO_2 \approx p_IO_2 – p_aCO_2/0.8$ [7].

Venous admixture and intrapulmonary shunt

Pulmonary blood flow ("*perfusion*") guarantees that CO_2 and O_2 are transported from the tissues to the lung and *vice versa*. The pulmonary circulation is unique since *i*) total cardiac output ($\dot{Q}_T$) passes through one organ, and *ii)* due to the low pressures, flow distribution, and consequently, pulmonary vascular resistance depend on the surrounding alveolar pressures.

Pulmonary blood flow ($=\dot{Q}_T$) consists of flow through normally ventilated lung regions, and a "shunted" component; the latter comprising the anatomical structures without contact with alveolar gas (Thebesian and bronchial veins), and an alveolar component originating from non-ventilated (right-to-left shunt, $\dot{Q}_S$) and/or hypo-ventilated alveoli. This alveolar component is called "*physiological shunt*" or "*venous admixture*" ($\dot{Q}_{VA}$). According to the model by Riley & Cournand (9) and in analogy to V_D/V_T, it can be referred to as "*wasted*" pulmonary blood flow: the blood gas partial pressures from these regions are equal to or only slightly higher than the mixed-

venous ones, and therefore are the cause of arterial hypoxemia. $\dot{Q}_{VA}$ can be quantified according to the assumption that total pulmonary blood flow ($\dot{Q}_T$) is the sum of $\dot{Q}_{VA}$ and capillary blood coming from alveoli with ideal $\dot{V}_A/\dot{Q}$ ratios ($\dot{Q}_C$) (9) (figure 2):

$\dot{Q}_T = \dot{Q}_{VA} + \dot{Q}_C$ [8A],

or, re-written as the amount of O_2 transported:

$\dot{Q}_T \cdot C_aO_2 = \dot{Q}_{VA} \cdot C_{\bar{v}}O_2 + \dot{Q}_C \cdot C_cO_2$ [8B]

with C_aO_2, $C_{\bar{v}}O_2$, and C_cO_2 being the arterial, mixed-venous and ideal capillary O_2 content values, respectively. For the calculation of C_cO_2, p_AO_2 is approximated using equation 6 or 7, and in patients with ARDS, ideal capillary Hb-O_2-saturation can be assumed as 100%, since usually F_IO_2>0.3-0.4. Merging equations 8A and 8B then yields the Berggren formula (16):

$\dot{Q}_{VA}/\dot{Q}_T = (C_cO_2 - C_aO_2)/(C_cO_2 - C_{\bar{v}}O_2)$ [9].

Quantification of $\dot{Q}_{VA}/\dot{Q}_T$ requires right-heart catheterization for pulmonary arterial blood sampling. Moreover, $\dot{Q}_{VA}/\dot{Q}_T$ cannot differentiate between $\dot{Q}_S$ in totally non-ventilated alveoli, and in hypo-ventilated lung regions with low $\dot{V}_A/\dot{Q}$ ratios (normally defined as $\dot{V}_A/\dot{Q}$<0.1). This differentiation is by no means academic: while blood gas partial pressures in non-ventilated alveoli are unresponsive to increases in F_IO_2, higher F_IO_2 will allow for at least partial correction of arterial hypoxemia in hypo-ventilated lung regions (figure 3). Theoretically, switching from maintenance F_IO_2 to pure O_2 ventilation allows separating these two main pulmonary causes of arterial hypoxemia: N_2 wash-out from ventilated alveoli should correct for any hypoxemia related to lung regions with low $\dot{V}_A/\dot{Q}$ ratios. However, the time required for complete de-nitrogenation is unknown in the presence of profound heterogeneity of the distribution of $\dot{V}_A$, e.g. especially in patients with ARDS. Moreover, this manoeuver

can *per se* increase $\dot{Q}_S$ (17,18): *i*) in "unstable" alveoli with very low $\dot{V}_A/\dot{Q}$ ratios, resorption atelectasis may develop (19), when gas inflow into the alveoli is lower than uptake into the blood (20), and *ii*) the hyperoxia-induced increase of both $p_{\bar{v}}O_2$ and p_AO_2 can inhibit hypoxic pulmonary vasoconstriction (21-24), and thereby deteriorate gas exchange. Theoretically, analyzing the arterial-alveolar N_2 partial pressure gradient ($\Delta_{aA}pN_2$) allows differentiating between $\dot{Q}_S/\dot{Q}_T$ and low $\dot{V}_A/\dot{Q}$ but its determination is technically impractical at the bedside (25).

It should be noted that high levels of $\dot{Q}_S/\dot{Q}_T$ will also increase $\Delta_{a\text{-}A}pCO_2$ and thereby V_D/V_T calculated using the Enghoff formula since the pCO_2 of the blood originating from these lung regions is the mixed venous pCO_2 ($p_{\bar{v}}CO_2$) (26). This effect is pronounced with low $\dot{Q}_T$, anemia and/or metabolic acidosis as a result of the increased difference $p_{\bar{v}}CO_2 – p_aCO_2$ (27).

In summary, in patients with ARDS, hypoxemia is due to increased $\dot{Q}_{VA}/\dot{Q}_T$, i.e. "wasted" perfusion originating from non- ($\dot{Q}_S/\dot{Q}_T$ or shunt) *and/or* hypoventilated (low $\dot{V}_A/\dot{Q}$ ratios) lung regions (10). Increasing the $\dot{V}_A/\dot{Q}$ ratio by increasing $\dot{V}_E$ cannot compensate for this effect, and, consequently, increasing F_IO_2 and/or re-aeration of non-ventilated lung regions are the cornerstones of the management of hypoxemia in ARDS. While $\dot{Q}_S/\dot{Q}_T$ is unresponsive to increased F_IO_2, higher F_IO_2 allows for at least partial correction of arterial hypoxemia resulting from low $\dot{V}_A/\dot{Q}$(6-8,10).

Assessment of ventilation/perfusion-distribution

As mentioned above, the 3-compartment model (9). represents all "wasted" ventilation as V_D/V_T, i.e. ventilated but non-perfused lung regions, and all "wasted" perfusion as $\dot{Q}_S/\dot{Q}_T$, i.e. blood flow through non-ventilated lung areas. Virtually continuous ventilation/perfusion distributions assuming a 50-compartment lung model covering the whole range of $\dot{V}_A/\dot{Q}$ ratios can be described with the "*multiple inert gas*

elimination technique" (MIGET) (28,29). The MIGET makes use of the solubility-related kinetics of physiologically inert, only physically dissolved gases at trace concentrations. During continuous infusion of a mixture of gases with blood–gas partition coefficients over a range of five orders of magnitude retention ($R=p_A/p_v$) and excretion ($E=p_e/p_{\bar{v}}$) are determined according to the principle of mass conservation:

$p_A/p_{\bar{v}}=\lambda/(\lambda+\dot{V}_A/\dot{Q})$ [13]

with p_A, $p_{\bar{v}}$, and p_e being the alveolar, mixed-venous, and mixed-expiratory inert gas tensions, λ being the substance-specific blood-gas partition coefficient (30). Typical examples of a healthy young volunteer and a patient with ARDS (before and during i.v. infusion of prostacyclin) are shown in figure 4. Pulmonary arterial sampling, and hence right-heart catheterization is not mandatory, since with cardiac output available, the inert gas p_v can be calculated from the p_e and p_a values using the Fick principle (28). The MIGET demonstrated that patients with ARDS present with bi-modal distributions of both pulmonary blood flow and alveolar ventilation (figure 4)(9): hypoxemia is due to a high proportion of blood flow to lung regions with true right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$) (e.g. collapsed and/or flooded alveoli) together with low $\dot{V}_A/\dot{Q}$ ($\dot{V}_A/\dot{Q}<0.1$) in some patients. Impairment of CO_2 elimination is caused by true dead space ventilation (V_D/V_T) with some additional "wasted" ventilation in hypo-perfused lung areas (9,31-41).

Imaging of ventilation/perfusion-distribution

MIGET can only yield quantitative analyses without topographic information of ventilation/perfusion ratios (42). Various imaging techniques have been proposed, i.e combining inhalation of ^{133}Xe or ^{81m}Kr and subsequent infusion of these gases dissolved in aqueous solutions (43,44), magnetic resonance using proton density, hyperpolarized ^{3}He, or ^{129}Xe imaging (45-47), positron emission tomography using $H_2{}^{15}O$-labeled water, $^{13}N_2$ dissolved in saline, or ^{18}F-fluoro-2-deoxy-glucose that

detects inflammatory cell metabolism (48-50), and electrical impedance tomography (51-54). These techniques provide information on spatial distribution and allow for independent assessment of absolute $\dot{V}$ and $\dot{Q}$ values, i.e. not only on the distribution of $\dot{V}/\dot{Q}$ ratios. Quantitative images of the respective $\dot{V}$ and $\dot{Q}$ distribution are difficult to obtain, in particular as a result of the mandatory high spatial resolution mapping of the same lung region. Moreover, these techniques are costly and require patient transport. Hence, with the exception of electrical impedance tomography, they are unlikely to gain the potential for bedside monitoring (55-57).

Effect of gravity

Gravitational force is a major determinant of the distribution of ventilation and perfusion: in the upright position there is a near-linear increase of blood flow from the lung apex to base due to gravitational force. Alveolar ventilation also follows this pattern, the slope being much flatter. This gravitation-related change in the distribution of $\dot{V}/\dot{Q}$ ratios can be visualized by using imaging techniques (55-57). Since this gravitation-dependent variation of pulmonary blood flow is more pronounced than that of alveolar ventilation, $\dot{V}_A/\dot{Q}$ ratios decrease from the apex to basis of the lung, or, in the supine position, from ventral to dorsal lung regions. In healthy volunteers in the semi-recumbent position $\dot{V}_A/\dot{Q}$ ratios can range from 0.3–2.1 from apex to base (58), while patients with ARDS present with much larger variability. Hence, the lowest $\dot{V}_A/\dot{Q}$ ratios and $\dot{Q}_S/\dot{Q}_T$ are typically present in the dependent lung areas. Data obtained in the prone position challenged the concept of the influence of gravity: this manoeuver indeed reduces $\dot{Q}_S/\dot{Q}_T$ in favor of increased blood flow to well-ventilated lung regions (32,59,60). In some patients, this effect was further enhanced by adding inhaled nitric oxide and/or almitrine infusion (60-65).

Several mechanisms have been identified to explain the beneficial effect of prone position on oxygenation. First, prone position reduces the pleural pressure gradient and homogenizes trans-pulmonary pressure across the lung (66-68). A number of factors can explain this effect of prone position, including the reversal of gravitational lung weight gradients (69,70), elimination of the compressive force of the heart on dorsal lung regions (71,72), and the release of the compression of abdominal contents on caudal regions of the dorsal lung (73,74). The net effect is an homogenization of regional lung inflation, which increases in dorsal lung regions and decreases in ventral regions (75). In addition, both animal and human studies showed that distribution of pulmonary blood flow, which is prevalent in the dorsal lung in the supine position, surprisingly does not change when turning patient prone (76-79). Thus, the improvement in oxygenation in the prone position is due to a reduction in $\dot{Q}_S/\dot{Q}_T$ resulting from the concomitant increase in the aeration in the dorsal lung regions, with dorsal recruitment being greater than ventral de-recruitment, and the persistence of better lung perfusion in these regions.

In sum, there is a pronounced, gravitation-related regional variability of $\dot{V}_A/\dot{Q}$ ratios with $\dot{Q}_S/\dot{Q}_T$ being particularly present in the dependent lung regions. The beneficial gas exchange effect of prone position is mainly due to the persistence of higher pulmonary blood flow in regions better aerated in prone position (32).

Pulmonary vascular tone

Pulmonary vascular tone may cause marked regional $\dot{V}_A/\dot{Q}$ differences, in particular as a result of hypoxic pulmonary vasoconstriction (80): local aveolar hypoxia induces regional vasoconstriction and thus reduces perfusion to hypo- and/or non-ventilated lung areas, thereby improving gas exchange (31). In patients with ARDS, increasing pulmonary vascular tone improved gas exchange (38,61), whereas reducing pulmonary artery pressure by hyperoxia and/or intravenous vasodilators further

aggravated hypoxemia (34-36). In contrast, selective pulmonary vasodilation using inhaled vasodilators improved gas exchange: short-acting inhaled vasodilators (e.g. nitric oxide (NO) or prostacyclin) are only effective in ventilated lung areas (figure 5). Consequently, they will redistribute pulmonary blood flow away from unventilated alveoli, and thereby attenuate $\dot{Q}_S/\dot{Q}_T$ (39-42,82). Combining i.v. pulmonary vasoconstrictors (e.g. almitrine) and inhaled vasodilators even further improved arterial oxygenation in some patients without aggravating right ventricular afterload (83-85).

In sum, augmenting pulmonary vascular tone generally improves $\dot{V}_A/\dot{Q}$ distribution. Selective pulmonary vasodilating using inhaled, short-acting compounds can improve $\dot{V}_A/\dot{Q}$ distributions, because they are only effective in ventilated lung regions (86).

Non-pulmonary factors

In addition to the degree of low $\dot{V}_A/\dot{Q}$ and $\dot{Q}_S/\dot{Q}_T$, non-pulmonary factors affect gas exchange, namely F_IO_2 (see below "High F_IO_2"), cardiac output ($\dot{Q}_T$) and $\dot{V}O_2$ (87). $\dot{Q}_T$ affects gas exchange both indirectly by its effect on O_2 extraction, and thus on p_vO_2, and directly by modifying $\dot{V}_A/\dot{Q}$ distributions. The complexity is that these factors may have various effects potentially influencing oxygenation in opposite directions. According to the Fick principle

$\dot{V}O_2=\dot{Q}_T\cdot(C_aO_2-C_{\bar{v}}O_2) \Leftrightarrow C_{\bar{v}}O_2=C_aO_2-\dot{V}O_2/\dot{Q}_T$ [13],

i.e. C_vO_2 and, due to the steep, near-linear shape of the Hb-O_2-dissociation curve, p_vO_2, are directly related to arterial O_2 content and $\dot{V}O_2$, and inversely related to $\dot{Q}_T$. Hence, variations of $\dot{Q}_T$ will directly affect p_aO_2 as a result of this interplay between $\dot{Q}_T$ and $\dot{V}O_2$ and $p_{\bar{v}}O_2$. Consequently, for a given $\dot{V}O_2$ and $\dot{Q}_S/\dot{Q}_T$, there is a linear relationship between p_aO_2 and the difference $C_aO_2-C_{\bar{v}}O_2$(figure 6) (88,89). In other words, any rise in $p_{\bar{v}}O_2$ should also increase p_aO_2. In patients treated with

extracorporeal CO_2 removal, increasing $p_{\bar{v}}O_2$ by increasing the F_IO_2 of the membrane lung was associated with a parallel rise of p_aO_2, while whole-body $\dot{V}O_2$, $\dot{Q}_T$, $\dot{Q}_S/\dot{Q}_T$, and the $\dot{V}_A/\dot{Q}$ distributions remained unchanged (90). However, under clinical conditions the magnitude of this effect may depend on the initial level of $p_{\bar{v}}O_2$ and of other factors. Indeed, pharmacological (e.g. inotropic and/or vasoactive drugs) or non-pharmacologic (PEEP maneuvers, patient positioning) approaches frequently influence $\dot{Q}_T$ and $\dot{V}O_2$ as well, and, hence, $p_{\bar{v}}O_2$. Moreover, another factor shown both in experimental models and in patients with ARDS, is the fact that changes in $\dot{Q}_T$ induce parallel changes in $\dot{Q}_S/\dot{Q}_T$ (91-93) including when induced by increasing PEEP or V_T (94). The most likely explanation seems to be an alteration of hypoxic pulmonary vasoconstriction induced by changes in $P_{\bar{v}}O_2$ (95,96). Variations in $p_{\bar{v}}O_2$ can also directly affect $\dot{Q}_S/\dot{Q}_T$ due to changes in pulmonary vascular tone: in patients with ARDS treated with ECMO, $\dot{Q}_S/\dot{Q}_T$ showed a direct, linear dependence on both pulmonary blood flow and calculated pulmonary vascular resistance (97). Consequently, any variation of $\dot{Q}_T$ can affect arterial oxygenation in different directions. Therefore, in an individual patient, the effect of $\dot{Q}_T$ variations on p_aO_2 are often unpredictable and will be a consequence of the interplay between effects on $\dot{Q}_S/\dot{Q}_T$, $\dot{V}_A/\dot{Q}$ distributions, $\dot{V}O_2$ and $p_{\bar{v}}O_2$ (figure 7) (86,87,97).

Albeit to a lesser degree due to the small difference between arterial and mixed-venous levels, the same is true for any effect of $\dot{Q}_T$ and $p_{\bar{v}}CO_2$, respectively, on p_aCO_2: theoretically, any increase in $\dot{Q}_T$ should result in fall of p_aCO_2. However, the effects of $\dot{Q}_T$ variations on p_aCO_2 can also work in different directions, e.g. the expected fall of p_aCO_2 resulting from a vasodilator-induced increase in $\dot{Q}_T$ may be offset by the simultaneous rise in $\dot{Q}_S/\dot{Q}_T$ and, in particular, $\dot{V}_D/\dot{V}_T$. The latter can be caused by the vasodilator-induced reduction in pulmonary arterial pressure, which

may result in “de-recruitment” of the pulmonary vasculature: as mentioned above, pulmonary vascular resistance and, consequently, the distribution of pulmonary blood flow, depend on the relation between intravascular, i.e. arterial (P_a) and venous (P_v), and alveolar (P_A) pressures (58). Any fall in intravascular pressure can transform “Zone II” regions of the lung (with $P_a>P_A>P_v$) into so-called “Zone I” regions of the lung, which are non-perfused because $P_A>P_a$ (58).

Non-pulmonary factors, namely F_IO_2, cardiac output ($\dot{Q}_T$), $\dot{V}O_2$, and, as a result of the $p_{\bar{v}}O_2$, will also directly affect p_aO_2.

Extra-pulmonary shunt

Intra-cardiac shunt *via* a *patent foramen ovale* (PFO) may also contribute to compromised gas exchange in ARDS. Under normal conditions, a PFO does not affect gas exchange, because the gradient between left and right atrial pressure precludes significant blood transfer from the venous to the arterial side. However, pulmonary artery hypertension is a common phenomenon in patients with ARDS and can lead to *acute cor pulmonale* (98-100). Prevalence of a PFO during ARDS has been reported between 15-19%, and is often associated with *acute cor pulmonale* (101,102). Frequently, in the presence of a moderate-to-large PFO shunting, there is a poor oxygenation response to PEEP. High PEEP may further increase the right atrial pressure, thereby increasing the occurrence and severity of right-to-left shunting due to PFO (60,101,103,104). Lowering PEEP and/or inhaled nitric oxide may reduce pulmonary hypertension, thus decreasing or abolishing right-sided shunting in some patients (≈14%), thereby improving oxygenation (103,104).

Clinical Applications

There is a real difficulty for the clinician at the bedside to accurately interpret gas exchange abnormalities in ARDS. In particular different maneuvers can influence gas exchange through various mechanism. It can be a pure redistribution of blood flow

(see vasodilators), a change in mixed venous blood oxygen content or it can reflect a reopening of previously no aerated lung units (see recruitment). Therefore the same effects on gas exchange may indicate a real change in lung function due to a specific maneuver or to the natural resolution of the disease, a simple “cosmetic” effect without alteration in lung function, or even a worsening of lung distension with a reduction in cardiac output and consequently of shunt. Therefore a careful interpretation merits a multimodal clinical approach and a careful reasoning.

Diagnosis and assessment of severity

Hypoxemia is a central component of the diagnosis of ARDS. Several indices have been proposed to characterize hypoxemia e.g. $\dot{Q}_{VA}/\dot{Q}_T$, $\Delta_{Aa}pO_2$, the oxygenation index and the p_aO_2/F_IO_2 ratio. These indices are influenced by many factors, e.g. ventilator settings (V_T, respiratory rate, PEEP) and hemodynamics ($\dot{Q}_T$ and $p_{\bar{v}}O_2$). Due to its simplicity, p_aO_2/F_IO_2 ratio has been adopted for routine practice and is used to characterize the severity of ARDS (1). The use of the p_aO_2/F_IO_2 ratio is underlined by the necessity to assess hypoxemia independently from F_IO_2. Unfortunately, due to the complex mathematical relationship between the Hb level, the Hb-O_2-dissocation curve, and the arterial – mixed venous O_2 content difference, the relationship between p_aO_2/F_IO_2 and F_IO_2 is non-linear and depends on the underlying $\dot{Q}_S/\dot{Q}_T$ (105,106) (figure 8).

Thus, no matter the possible effect of F_iO_2 on $\dot{Q}_S/\dot{Q}_T$ *per se* (de-nitrogenation atelectasis), any change in F_IO_2 may also modify p_aO_2/F_IO_2. This variability of p_aO_2/F_IO_2 suggests that its use be cautioned in an individual ARDS patient, when ventilator settings are modified. Despite these limitations, classification of patients with ARDS in three categories of severity according to p_aO_2/F_IO_2 (“mild” for $300 \leq p_aO_2/F_IO_2 < 200$, “moderate” for $200 \leq p_aO_2/F_IO_2 < 100$ and “severe” for $p_aO_2/F_IO_2 \leq 100$ mmHg) allows to identify patients with different duration of mechanical

ventilation and mortality (1,107). Furthermore, the p_aO_2 during pure O_2 ventilation was shown to be strongly correlated with the CT-quantified percentage of non-aerated lung (108). Finally, this simple index appears to be useful for identifying patients that could benefit from additional therapeutic interventions such as high PEEP, prone positioning, and/or neuromuscular blockade (109-111). As shown by Villar *et al*., the prognostic value of p_aO_2/F_IO_2 depends greatly on the time and conditions of its measurement, the better stratification of the risk of death being obtained with on PEEP≥10cmH_2O and F_IO_2≥0.5 after 24 hours of protective ventilation (112,113).

The ratio of transcutaneous arterial Hb-O_2-saturation (S_pO_2) to F_IO_2 (S_pO_2/F_IO_2) was suggested as a screening tool for ARDS, when arterial blood gases are not available (114). Unfortunately, due to its poor accuracy, this non-invasive method cannot be used to assess the effects of therapeutic interventions on oxygenation (115). Finally, it was recently suggested that a non-linear equation gave more reliable estimate of the p_aO_2/F_IO_2 ratio (116).

Impaired CO_2 elimination is also a hallmark of ARDS. In ARDS patients of variable severity, V_D/V_T measured on PEEP=5cmH_2O was highly correlated with CT scan-quantification of lung aeration inhomogeneity, suggesting that V_D/V_T could be useful for individual assessment of the risk of VILI (117). In line with this observation, V_D/V_T measured in standardized conditions at the early or the intermediate phase independently predicted mortality (3,118). Calculation of V_D/V_T with the Enghoff formula requires the determination of p_eCO_2 and/or F_ECO_2, which is not routine linical practice. Several methods have been proposed for V_D/V_T estimation without measuring F_ECO_2, or for the calculation of indices reflecting ventilatory efficiency: Minute ventilation standardized at a p_aCO_2 of 40 mmHg ($\dot{V}_Ecorr=\dot{V}_E\cdot p_aCO_2/40$) (119), ventilatory ratio=$(\dot{V}_E\cdot p_aCO_2)$/(predicted minute ventilation·37.5) with predicted $\dot{V}_E$=100

mL·kg^{-1}predicted body weight(PBW)·min^{-1} (120). Retrospective analysis of the ARDS network databases suggest that both V_D/V_T using the Harris-Benedict calculation of energy expenditure, and the ventilatory ratio are predictive of mortality (121-123). Although not mandatory for the diagnosis, assessment of the impaired CO_2 elimination using either V_D/V_T and/or calculation of a surrogate index should be part of the initial evaluation of ARDS severity.

Therapeutic targets

Arterial pO_2

Although prevention of death from hypoxemia is a major goal of mechanical ventilation in patients with ARDS, very few studies addressed the question of the optimal target for oxygenation. There is ample evidence from studies outside the field of ARDS suggesting that hyperoxemia (p_aO_2>120-150mmHg) should be avoided in critical illness (124,125). In most of the large randomized controlled trials on symptomatic support in ARDS, the recommended targets for oxygenation were a p_aO_2=55-80mmHg and/or a S_aO_2=88-95%. Interestingly, the data reported in these studies show that mean values for p_aO_2 were mostly close to or even higher than the upper target limits (111,126-130). This observation is well in line with data from observational studies showing that high p_aO_2 and/or S_aO_2 values are frequently observed in critically ill patients, and suggests that investigators do not feel comfortable with lower p_aO_2 and/or S_aO_2 values. This was probably due to much more concern about the risk of hypoxia than that of pulmonary O_2 toxicity and/or deleterious effects of hyperoxia (131). The safety of moderate levels of oxygenation has been questioned by the observation of an association between lower levels of oxygenation and long term neuropsychiatric impairment in a subgroup of survivors from ARDS (132). Nevertheless, in ARDS the “optimal” S_aO_2 and p_aO_2 level remains undetermined, because experimental data suggest that hyperoxia can worsen

ventilator-induced lung injury (VILI) (133). Moreover, a retrospective analysis demonstrated that the number of days with hyperoxemia as defined with a p_aO_2>120 mmHg was an independent risk factor of ventilator-associated pneumonia (134). More evidence for the toxicity of hyperoxemia was provided by the randomized controlled trials “Optimal Oxygenation in the Intensive Care Unit (O2-ICU)”, and “Hyperoxia and Hypertonic Saline in Septic Shock (HYPER2S)” (135,136). The “O2-ICU” trial compared PaO_2 targets of 120 (“conventional”) versus 75 (“conservative”) mmHg in 434 general ICU patients with an expected length-of stay >72hours: the conservative approach was associated with a 50% reduction of overall mortality (11.6 *vs*. 20.2%, p=0.01); the authors concluded that the findings must be considered preliminary because of the early trial termination due to difficult patient enrolment. Moreover, only 67% of the patients were mechanically ventilated at inclusion (135). The “Hyper2S” trial comparing target SaO_2 88–95% *vs.* pure O_2 ventilation during the first 24 hours in patients with septic shock was preliminary stopped for safety reasons after enrolment of 442 patients (136). In this study, 50% of the patients had ARDS with p_aO_2/F_IO_2<200mmHg at baseline. Mortality did not significantly differ at day 28 and 90, but hyperoxia was associated with a significantly higher incidence of serious adverse events with a clinically relevant higher number of patients with ICU-acquired weakness and atelectasis.

Arterial pCO_2

Experimental studies have shown that hypercapnia and/or respiratory acidosis may have numerous beneficial cellular and physiological effects, e.g. attenuated pulmonary inflammation, protection against VILI and oxidant-induced lung injury (137-139), improved $\dot{V}_A/\dot{Q}$ distribution through enhanced hypoxic pulmonary vasoconstriction (140), increased $\dot{Q}_T$ and O_2 delivery secondary to catecholamine release (141,142), improved microcirculation (143), and facilitation of peripheral O_2

release through the Bohr effect (rightward shift of the Hb-O_2-dissocation curve) (144). On the other hand, hypercapnia decreases alveolar fluid clearance (145), and its anti-inflammatory effect may be associated with impaired antimicrobial host defenses (146) and delayed cellular wound healing (147). Moreover, the hypercapnia-related increase in right ventricular afterload can contribute to acute *cor pulmonale* (148), which in turn increased mortality (149). In the clinical setting, it is virtually impossible to separate the effect hypercapnia *per se* from those of reduced biomechanical lung injury resulting from reduced V_E. A *post hoc* analysis of the results of the ARMA trial showed that in patients receiving the "conventional" tidal volume (12 $mL \cdot kg^{-1}$PBW), moderate respiratory acidosis was independently associated with a lower odds ratio of death on Day 28, suggesting a protective effect of hypercapnia against VILI (150). Finally, a secondary analysis of three cohort studies including 1889 patients with ARDS suggested that a p_aCO_2>50mmHg was independently associated with increased mortality (151). Thus, while normalization of p_aCO_2 and/or arterial pH should no longer be considered as an absolute priority, the safety of permissive hypercapnia appears questionable (147). Therefore, many randomized trials recommended to keep a p_aCO_2 resulting in a pH=7.30-7.40.

Therapeutic measures

Several therapeutic measures have been proposed to correct gas exchange in ARDS (tables 2 and 3). In the original description of ARDS, Ashbaugh *et al.* were the first to report on the use of increased F_IO_2 and of PEEP (152). For a long time, correcting hypoxemia was the main objective of mechanical ventilation. Other approaches proposed and/or used different strategies of artificial ventilation, pharmacologic manipulation of pulmonary vascular tone, and later, patient positioning. Because during extra-corporeal membrane oxygenation both arterial oxygenation and CO_2

elimination mainly depend on the extra-corporeal device, this technique will not be discussed in this review.

High F_IO_2

Although the pivotal mechanism of hypoxemia in ARDS is $\dot{Q}_S/\dot{Q}_T$, high F_IO_2 is common practice. As expected in the presence of high $\dot{Q}_S/\dot{Q}_T$, the effect of increasing F_iO_2 on p_aO_2 is often modest, especially in the severely hypoxemic patients (figure 9). In addition, as mentioned above, several authors have reported an increased $\dot{Q}_S/\dot{Q}_T$ while breathing 100%O_2 due to development of reabsorption atelectasis resulting from denitrogenation of units with low $\dot{V}_A/\dot{Q}$ ratios, which can be prevented by PEEP or recruitment maneuvers (19,20,153). In patients with ARDS ventilated with low V_T (6mL·kg^{-1}) and low PEEP (approximately 5cmH_2O), Aboab *et al*. reported that increasing F_iO_2 from 0.6 to 1.0 caused a decrease of p_aO_2/F_iO_2 and lung de-recruitment that could be prevented with a PEEP of approximately 15cmH_2O (19). On the other hand, pure O_2 breathing does not affect hypoxic pulmonary vasoconstriction in patients with ARDS (153), suggesting that hypoxic pulmonary vasoconstriction is attenuated.

Positive End-Expiratory Pressure

ARDS is characterized by a decrease in aerated lung volume caused by atelectasis, lung edema, small airway closure, and surfactant perturbation (154). Use of PEEP to correct gas exchange impairment in ARDS was initially proposed by Asbaugh *et al.* (152), and remains the cornerstone of ventilatory management of these patients. Extensive data supports the use of PEEP for improving oxygenation in hypoxemic respiratory failure, alone (during Continuous Positive Airway Pressure, CPAP) or combined with various ventilator modes (155-162). Several mechanisms may explain the effect of PEEP on gas exchange, the main one being an increased number of alveoli that remain aerated at end-expiration, i.e. alveolar recruitment, which, in turn,

decreases $\dot{Q}_S/\dot{Q}_T$ (37). Physics laws and data from animal studies suggest that PEEP may also balance the increased tendency to alveolar collapse due to increased surface forces related to surfactant perturbation. Although not definitively demonstrated in patients, it is likely that this phenomenon may play a role in explaining the effect of PEEP on lung recruitment (163). Albeit questioned (164), several studies reported a direct relation between the improvement in oxygenation and PEEP-induced lung recruitment (158,160,165,166). However, this correlation may be too weak to allow, in an individual patient, to assess PEEP-induced recruitment by its effect on oxygenation. The lack of a bedside method to quantify recruitment induced by PEEP has always limited the interpretation of oxygenation as a marker of recruitment. Some studies suggested that PEEP may protect against the development of pulmonary edema (167-169), partly because of a concomitant reduction in $\dot{Q}_T$ (170). Although an increase in lung volume is the main mechanism for PEEP-induced changes in oxygenation, a small decrease in $\dot{Q}_T$ also reduces $\dot{Q}_S/\dot{Q}_T$ and may thereby improve p_aO_2 (94). Many studies showed that PEEP in reality does not reduce extravascular lung water but mostly redistributes edema (171,172). By recruiting non-aerated alveoli and stabilizing airways, PEEP may also influence the regional distribution of tidal ventilation (173-175): when the predominant effect of PEEP is recruitment, alveolar ventilation is expected to become more homogeneous, particularly in the dependent zones and confer a protective effect against VILI. Patients subjected to increased PEEP while receiving dopamine to maintain the same cardiac output exhibited significant reductions in $\dot{Q}_S/\dot{Q}_T$, suggesting that alveolar recruitment, rather than reduced $\dot{Q}_T$ (94,176) was the predominant mechanism for improved oxygenation from increased PEEP (177).

The effects of PEEP on V_D/V_T and CO_2 elimination are complex. On the one hand, PEEP-induced alveolar recruitment may decrease physiological V_D/V_T due to a more

homogeneous distribution of V_T and thereby decreased $\dot{Q}_S/\dot{Q}_T$ (26,27,155). However, on the other hand, PEEP may favor over-distension of previously well-aerated alveoli resulting in increased physiological dead space (10,178). Overall, the impact of PEEP on V_D/V_T and p_aCO_2 is usually modest (179-182). Increases in p_aCO_2 may indicate predominant hyperinflation.

Recruitment maneuvers

Recruitment maneuvers can improve oxygenation in many patients with ARDS (183). These maneuvers are integral part of the “Open Lung Strategy” that aims at maximizing recruitment (184). However, the safety of these maneuvers is debated and, moreover, unless combined with increased PEEP levels, their effect is usually very transient, lasting 15-20 minutes (183). Some authors showed that most of the effect is obtained after 10 seconds, before side effects occur suggesting that these maneuvers could be aborted rapidly (185).

Ventilatory mode

It has been suggested that, due to a more homogeneous distribution of V_T, the decelerating flow characteristic of pressure-targeted ventilation could result in improved gas exchange compared to the square wave flow usually used in volume-targeted modes (186). However, several studies demonstrated that, when the main settings (VT, PEEP) are comparable, pressure- and volume-controlled ventilation have similar effects on gas exchange (187,188).

Lengthening inspiratory time in order to increase mean airway pressure without increasing peak alveolar pressure has been considered an attractive approach to improve oxygenation and lower the risk of barotrauma (189,190). Inverse ratio ventilation, i.e., an inspiratory-to-expiratory time ratio>1 was therefore proposed as an alternative to conventional ventilation in ARDS. Several uncontrolled studies reported improved oxygenation with inverse ratio ventilation (191,192). Controlled

studies, however, did not find advantages for inverse ratio over conventional ventilation in terms of oxygenation when total end-expiratory pressure was kept constant (187,188,193). Extending inspiratory time by lengthening the duration of inspiratory pause slightly decreases V_D/V_T and thereby p_aCO_2 due to improved end-inspiratory gas mixing between alveoli and airways (194-196). Although usually of small magnitude, this effect may allow to decrease V_T and thus plateau pressure with unchanged p_aCO_2 (196). A prolonged inspiratory time may also increase right ventricular afterload (193).

High frequency oscillation (HFO) has been proposed as an alternative to conventional ventilation in patients with severe ARDS (197). In this mode, oxygenation depends mainly on mean airway pressure and F_IO_2 while CO_2 elimination depends on the frequency, the amplitude of oscillations, and the inspiratory time on expiratory time ratio. The negative results of two large randomized controlled trials have led to a discontinuation of the use of this technique in adults with ARDS (198,199). Whether the hemodynamic effects of a high intrathoracic and mean airway pressure explain these negative results has been questioned (200).

Tidal volume and minute ventilation

Low tidal volume (V_T) is a key element of lung-protective ventilation to decrease mortality (126). In the ARMA trial the low V_T arm was associated with a lower level of oxygenation than the high V_T (126). When compared to “conventional” V_T at unchanged respiratory rate and PEEP, reducing V_T increases p_aCO_2 due to decreased $\dot{V}_E$ and increased $\dot{Q}_S/\dot{Q}_T$ resulting from increased $\dot{Q}_T$ and de-recruitment of poorly ventilated respiratory units (units with very low $\dot{V}_A/\dot{Q}$ ratios) (201). Due to the concomitant increase in p_vO_2 associated with increased $\dot{Q}_T$, the rise in $\dot{Q}_S/\dot{Q}_T$ associated with the reduced V_T results in an inconstant and small decrease in p_aO_2 (141,201). Reducing V_T is associated decreased V_D, usually resulting in unchanged

V_D/V_T (141,201). Due to the high V_D/V_T, the $\dot{V}_E$ required to obtain normocapnia is abnormally high (3). When using a VT=6 mL·kg^{-1}PBW, a respiratory rate of 25-35·min^{-1} is therefore usually necessary to achieve a p_aCO_2 with arterial pH=7.30-7.45 (126).

Reduction of dead space

In mechanically ventilated patients, instrumental dead space contributes to total V_D/V_T. Because $V_A = V_T - V_D$, the impact of instrumental dead space on p_aCO_2 or on the required $\dot{V}_E$ is especially significant when using low V_T. Several clinical studies have shown that in patients with ARDS ventilated with a low V_T, reducing the instrumental dead space by replacing the heat and moisture exchanger by an active humidifier significantly decreased p_aCO_2 (202,203).

Tracheal gas insufflation (TGI) consists of a continuous or an expiratory injection of fresh gas into the central airways *via* an endotracheal catheter, in order to flush CO_2 from airway dead space and thereby to decrease anatomical dead space (204). Several studies have shown that TGI significantly reduced p_aCO_2 and/or allowed reducing V_T at constant p_aCO_2 (205,206). Due to safety issues and technical difficulties (increased intrinsic PEEP, inaccurate or difficult measurements of V_T and airway pressure, humidification of the insufflated fresh gas, monitoring of the position of the catheter, tracheal lesions), this technique has been difficult to apply in daily practice, and has progressively lost interest. De Robertis and Jonson developed a technique of aspiration and flushing of airway dead space during expiration that allowed to significantly decrease ventilatory requirements without increasing intrinsic PEEP (207,208). This technique requires a specific device synchronized with the ventilator, and, hence, is not yet available for clinical use.

Spontaneous breathing vs muscle paralysis

While muscle paralysis and controlled mechanical ventilation have been classically used in patients with ARDS, allowing spontaneous breathing during mechanical ventilation gained increased interest during recent years. During assisted mechanical ventilation, the patient's inspiratory effort triggers the start of gas-flow delivery by the ventilator, which is maintained until a predefined termination criterion is met. Conversely, during non-assisted spontaneous breathing, the patient breathes freely in a continuous or demand-flow system without any specific assistance of inspiratory efforts (i.e., during CPAP or airway pressure release ventilation, APRV). Experimental (209-213) and clinical studies (214-217) demonstrated that spontaneous breathing during mechanical ventilation can improve oxygenation. Two mechanisms have been postulated for the possible beneficial effect of additional spontaneous breathing on gas exchange: *i)* alveolar recruitment of atelectatic regions, mainly in the dependent portions of the lung, eased by the preserved contraction of the diaphragm, and *ii)* shifting of pulmonary blood flow toward lung regions with higher $\dot{V}_A/\dot{Q}$ ratios (215,218). When spontaneous breathing is preserved during mechanical ventilation, the pressure generated by the respiratory muscles adds to the pressure delivered by the ventilator, thus magnifying trans-pulmonary pressure (219,220). In addition, local overstretch in dependent lung regions may occur, when a local rise in trans-pulmonary pressure causes alveolar air shift from non-dependent to dependent parts of the lung (i.e., pendelluft) (221). Through these mechanisms, spontaneous breathing may increase the risk of VILI. Thus, three points should be considered when allowing spontaneous breathing during mechanical ventilation: *i)* the severity of ARDS, ii) the evolution phase of the disease, and *iii)* the degree of synchronization between ventilator assistance and the patient's inspiratory effort. Most of the studies suggesting benefits of spontaneous breathing were performed in mild-to-moderate ARDS with only moderate ventilatory demands and/or

after the acute phase of the disease. In patients with severe ARDS, the use of a neuromuscular blocking agents during the first 48 hours improved oxygenation and, ultimately, survival (111). Finally, the synchronization between ventilator assistance and the patient's inspiratory effort also determines the gas exchange effects of spontaneous breathing. When comparing the effects of pressure support (fully synchronized, pressure-targeted, assisted ventilatory mode) and APRV (non-synchronized pressure-targeted ventilatory mode allowing unassisted spontaneous breathing) to pressure-controlled ventilation, Putensen *et al* showed in patients with ARDS, that APRV increased $\dot{Q}_T$ and improved oxygenation due to better $\dot{V}_A/\dot{Q}$ matching resulting from decreased $\dot{Q}_S/\dot{Q}_T$ and V_D/V_T. Pressure support did not have beneficial effects (215). Interestingly, these beneficial effects of unassisted spontaneous breaths during APRV were obtained despite a quite small spontaneous breathing activity.

In summary, spontaneous breathing can improve oxygenation in ARDS, but this approach should probably be limited to patients not exhibiting strong inspiratory efforts, after improvement of the acute phase or even in the early phase of mild or moderate ARDS (222). During pressure-targeted, assisted ventilator modes, monitoring of V_T is mandatory to estimate the inspiratory effort and, thereby indirectly, of trans-pulmonary pressure (220). The use of a non-synchronized mode may prove useful to limit V_T and trans-pulmonary pressure. Finally, excessive ventilator efforts leading to an increase in respiratory muscle metabolic rate and thus to an increase in ventilator requirements should be avoided.

Patient positioning

Prone positioning has been used to improve oxygenation in patients with ARDS since the 1970s (223,224). Several studies demonstrated that prone positioning improves oxygenation (defined as an increase in $p_aO_2 \geq 20\%$ or $p_aO_2/F_IO_2 \geq 20$mmHg, as

compared to supine) in approximately 75% of patients (110,225-227). By recruiting the lung and homogenizing alveolar ventilation, prone position should theoretically decrease p_aCO_2 and V_D/V_T as well (228,229). The effect of prone position on p_aCO_2, however, is less predictable, and has mostly been considered less important than the effect on oxygenation. Nevertheless, the decrease in p_aCO_2, rather than the increased p_aO_2/F_IO_2, is associated with improved recruitment and better outcome with prone position (230,231). Besides the effects on gas exchange, prone position decrease lung stress and strain and prevent VILI (232-234). Hence, it seems to improves outcome of the most severe ARDS patients (110,235-237).

Limited data suggested that vertical positioning can also improve oxygenation (237,238). Richard *et al.* showed that, as compared with supine position, upright positioning (trunk elevated at 45° and legs down at 45°) improved oxygenation in 11/16 patients with ARDS (237). The improved oxygenation was associated with an increased lung volume, suggesting an increase in lung recruitment. By relieving abdominal compression on lung bases, verticalization may, hence, allow caudal displacement of the diaphragm and thereby promote recruitment of dependent lung areas. These results were confirmed by Dellamonica *et al.*, who found that vertical position improved oxygenation, increased end-expiratory lung volume and decreased lung strain in 13/40 patients with ARDS (238). However, the individual oxygenation response to verticalization was unrelated to changes in lung volume, suggesting that mechanisms other than recruitment, for instance changes in cardiac output, also contributed to the improved oxygenation with vertical positioning.

Pharmacological manipulation of $\dot{V}_A/\dot{Q}$ distribution

Inhaled NO decreases $\dot{Q}_S/\dot{Q}_T$ of well-ventilated respiratory units due to regional vasodilatation (39). In most patients with ARDS, concentrations of 1-10ppm are sufficient to achieve an NO effect on oxygenation (240). These low concentrations of

inhaled NO allow avoiding formation of harmful NO_2 concentrations and the occurrence of met-hemoglobinemia. The inhaled NO-related improvement of oxygenation is usually transient (≤72 hours) (241), and the risk of rebound necessitates a progressive withdrawal (242). Finally, this transiently improved oxygenation was not associated with improved outcome (243). Aerosolized prostacyclin is an alternative to inhaled NO resulting in similar improvement in oxygenation (40,41,82,86). By enhancing hypoxic vasoconstriction, intravenous almitrine, a selective pulmonary vasoconstrictor, redistributes blood flow from shunt units to ventilated units and may thereby improve oxygenation (83,85). Low-dose intravenous almitrine ($4\mu g \cdot kg^{-1} \cdot min^{-1}$) comparably increased paO_2 as 5ppm inhaled NO, the combination of the two drugs eventually resulting in additive effects (83-85). Interestingly, the association of inhaled NO allows to offset the increase in pulmonary arterial pressure induced by almitrine (84).

Individualized adjustment of ventilator settings

Currently, strategies proposed for V_T adaptation are mainly based on PBW and/or indices of lung stress, such as plateau pressure, trans-pulmonary pressure or driving pressure. Reducing V_T is accompanied by a decreased V_D (201,244). The resultant effect on CO_2 elimination efficiency assessed by V_D/V_T is variable. A decreased V_D/V_T has been suggested to be indicative of attenuated over-inflation(140). However, changes in V_D/V_T secondary to changes in V_T are usually quite small (201,244), and the clinical impact of a strategy including measurement of V_D/V_T for individual setting of V_T has not been evaluated so far.

Reducing V_T at constant PEEP levels increases $\dot{Q}_S/\dot{Q}_T$ due to alveolar de-recruitment and increased $\dot{Q}_T$ (141,201,245,246). As mentioned-above the net effect on p_aO_2 depends on the respective magnitudes of the changes in $\dot{Q}_S/\dot{Q}_T$ and p_vO_2. Any

increase in $\dot{Q}_S/\dot{Q}_T$ induced by V_T reduction is easily counterbalanced by increasing PEEP (159).

Although the effect of PEEP on oxygenation cannot be considered an accurate estimate of its effect on alveolar recruitment (158,164), data from physiologic studies and from large randomized controlled trials suggest that oxygenation should be taken into account for individual PEEP titration (109). Studies from Gattinoni's group assessing the effect of PEEP using CT scan clearly demonstrate a relationship between p_aO_2/F_IO_2 measured on low PEEP (5cmH_2O), and the quantity of lung tissue that can be recruited and protected from tidal opening and closing with high PEEP, this quantity being much more important in patients with a p_aO_2/F_IO_2<150mmHg on PEEP 5cmH_2O, than in patients with less severe hypoxemia (180,247). In line with this finding, an individual meta-analysis of the three large randomized clinical trials comparing high PEEP to moderate PEEP in patients with ARDS ventilated with a low V_T (127-129)(, demonstrated that impact of high PEEP on mortality varies according to the p_aO_2/F_IO_2 (109). High PEEP was associated with decreased mortality in patients with a p_aO_2/F_IO_2<200mmHg (moderate or severe ARDS), while a tendency for an opposite effect was observed in the less severely hypoxemic patients (200<p_aO_2/F_IO_2<300mmHg). Another argument for taking into account oxygenation for PEEP setting was provided by Goligher *et al*, who retrospectively analyzed the results of the "LOVS" and "ExPress" trials (248): the effect of increasing PEEP on oxygenation was highly variable, and the magnitude of the PEEP-induced increase in p_aO_2/F_IO_2 was strongly associated with decreased adjusted odds ratio for death. Measurement of V_D/V_T has been proposed as a tool for determination of the optimal level of PEEP (155), but the magnitude of the changes of p_aCO_2 secondary to PEEP is usually too small to allow an easy identification of an optimal PEEP level (182,183). Finally, Gattinoni *et al*. reported that the best combination of physiological parameters

predicting more pronounced recruitment as measured by CT scan, was p_aO_2/F_IO_2 on PEEP 5cmH_2O <150mmHg together with increased compliance of the respiratory system and a decreased V_D/V_T when PEEP was increased from 5 to 15 cmH_2O (180).

Altogether, these findings strongly suggest that individual titration of PEEP in patients with ARDS should take into account effects on both oxygenation and CO_2 elimination.

Table 1. Main pathophysiologic mechanisms of impaired gas exchange in ARDS

Disturbance	**Main mechanisms**
Hypoxemia	• $\dot{Q}_S/\dot{Q}_T$ • low $\dot{V}_A/\dot{Q}$ • Low p_vO_2 • Intra-cardiac shunt (e.g., PFO)
Hypercapnia	• Increased V_D/V_T • Inhomogeneous distribution of ventilation (high $\dot{V}_A/\dot{Q}$) • Increased $\dot{V}CO_2$

ARDS: acute respiratory distress syndrome; PFO: patent foramen ovale; $p_{\bar{v}}O_2$: mixed venous O_2 partial pressure; $\dot{Q}_S/\dot{Q}_T$ intrapulmonary right-to-left shunt; $\dot{V}_A/\dot{Q}$: ventilation/perfusion ratio; $\dot{V}CO_2$: metabolic CO_2 production; V_D/V_T: dead space

Table 2. Therapeutic measures to correct hypoxemia

Treatment	**Beneficial effects**	**Risks**
High F_IO_2	Increases in p_AO_2, p_IO_2 and p_vO_2	Resorption atelectasis
PEEP	Alveolar recruitment with decrease in $\dot{Q}_S/\dot{Q}_T$	Lung over-distension Decreased $\dot{Q}_T$
Spontaneous breathing (mild-moderate ARDS, post-acute phase)	Alveolar recruitment Improved $\dot{V}_A/\dot{Q}$ matching (redirection of pulmonary blood flow to more aerated regions)	Lung over-distension VILI
Recruitment maneuver	Transient recruitment and decreased $\dot{Q}_S/\dot{Q}_T$	Transient decrease in $\dot{Q}_T$ Barotrauma
Prone position	Homogenization of ventilation distribution (improved aeration in the dorsal regions) Decrease in $\dot{Q}_S/\dot{Q}_T$ (unchanged perfusion, predominantly directed to dorsal regions)	
Vertical positioning	Alveolar recruitment	Unpredictable effect

	Increased lung volume	Decreased $\dot{Q}_T$
Inhaled NO	Decrease in $\dot{Q}_S/\dot{Q}_T$ (improved perfusion of aerated lung regions with normal $\dot{V}_A/\dot{Q}$ ratios)	Transient effect Rebound at withdrawal
Inhaled PGI_2	Decrease in $\dot{Q}_S/\dot{Q}_T$ (improved perfusion of aerated lung regions with normal $\dot{V}_A/\dot{Q}$ ratios)	Transient effect Rebound at withdrawal
Intravenous almitrine	Decrease in $\dot{Q}_S/\dot{Q}_T$ (increased pulmonary vascular tone)	Increase in PAP and RV afterload

ARDS: acute respiratory distress syndrome; F_IO_2: inspired fraction of oxygen; NO: nitric oxide; p_AO_2: alveolar O_2 partial pressure; PAP: pulmonary artery pressure; PEEP: positive end-expiratory pressure; PGI_2: prostacyclin; p_IO_2: inspired O_2 partial pressure; p_vO_2: mixed-venous O_2 partial pressure of oxygen; $\dot{Q}_S/\dot{Q}_T$ intrapulmonary right-to-left shunt; $\dot{Q}_T$: cardiac output; RV: right ventricular; $\dot{V}_A/\dot{Q}$: ventilation/perfusion ratio; VILI ventilator-induced lung injury

.

Table 3. Therapeutic measures to correct hypercapnia

Treatment	**Beneficial effects**	**Risks**
Sedation +/- paralysis	Reduced $\dot{V}CO_2$	Delayed weaning
Lengthening inspiratory pause	Improved homogeneity of ventilation distribution	Increase in $PEEP_i$ and $PEEP_{tot}$ (shortening of expiratory time)
Increasing respiratory rate	Increase in minute ventilation	Increase in $PEEP_i$ and $PEEP_{tot}$ (shortening of expiratory time)
Decrease of instrumental dead space	Decrease of V_D/V_T	-
TGI	Decrease of V_D/V_T due to reduced airway dead space	Increase in $PEEP_i$ and $PEEP_{tot}$ Inaccurate V_T measurement Tracheal lesions
Prone position	Homogenization of ventilation distribution	Unpredictable effect

Abbreviations. PEEP: positive end-expiratory pressure; PEEP: positive end-expiratory pressure; $PEEP_i$: intrinsic PEEP; $PEEP_{tot}$: total PEEP; TGI: tracheal gas insufflation; V_D/V_T: dead space; V_T: tidal volume.

Figure legends

Figure 1: The pO_2/pCO_2 diagram for single gas exchange unit at F_IO_2=0.21 and an CO_2/O_2 exchange ratio, i.e. respiratory exchange ratio RER=$\dot{V}CO_2/\dot{V}O_2$ =0.8. For any given F_IO_2, hemoglobin (Hb) content, and RER, each $\dot{V}_A/\dot{Q}$ ratio in a gas exchange unit is associated with a single pair of pO_2 and pCO_2 values. V_A/Q ratios can vary from 0 (perfused but non-ventilated alveoli; their gas partial pressures being those of the mixed-venous blood) to ∞ (ventilated, but non-perfused alveoli; their gas partial pressures being those of the inspired gas); a single line connecting these extreme values can be drawn through all possible pO_2/pCO_2 pairs. In a lung without inhomogeneity, arterial (a) and mean alveolar (A) gas partial pressures would be super-imposed at the "*ideal*" $\dot{V}_A/\dot{Q}$ ratio that corresponds to the RER. Arterial blood is the sum of the blood from all individual gas exchange units, i.e. those where perfusion exceeds ventilation or where there is no perfusion at all (i.e. $0 \leq \dot{V}_A/\dot{Q} < i$), as well as those where ventilation exceeds perfusion or where there is no ventilation at all (i.e. $i < \dot{V}_A/\dot{Q} < \infty$). Consequently, the real value pairs of arterial and mean alveolar gas partial pressures move away from this line, giving rise to the development of arterial-alveolar (a-A) partial pressure differences (Δ). Adapted from (6) with kind permission from Springer Science and Business Media.

Figure 2: The 3-compartment model by Riley & Cournand (9). Dead space (V_D/V_T) and right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$) are represented as shunted ("wasted"; see text) ventilation and perfusion, respectively. Adapted from (42) with kind permission from Springer Science and Business Media.

Figure 3: Expired pCO_2 as a function of expired volume. "*Phase I"* refers to the CO_2-free gas from the conducting airways. "*Phase II*" refers to the *S*-shaped steep part of the expired pCO_2-curve, i.e. the transition between gas from the airways and alveolar gas, whereas "*Phase III*" refers to the near-plateau alveolar phase until end-tidal pCO_2 ($p_{et}CO_2$) is reached, which allows for calculating V_D/V_T using the Enghoff equation (11), and partitioning of dead space between the airway (anatomical) and the alveolar component according to Fletcher *et al* (14). Adapted from (249) with kind permission from Springer Science and Business Media.

Figure 4: Exemplary mixed venous (blue), alveolar (black), and arterial (red) pO_2 and pCO_2 values in lung regions without ventilation (right-to-left shunt, $\dot{Q}_S/\dot{Q}_T$), where perfusion exceeds ventilation (i.e. $0<\dot{V}_A/\dot{Q}<$normal $\dot{V}_A/\dot{Q}$, i.e. "*low*" $\dot{V}_A/\dot{Q}$ ratios), where ventilation exceeds perfusion (i.e. normal $\dot{V}_A/\dot{Q}$ ratio$<\dot{V}_A/\dot{Q}<\infty$, i.e. "*high*" $\dot{V}_A/\dot{Q}$ ratios), or where there is no ventilation at all (dead space, V_D/V_T) at an inspired O_2 concentration $F_iO_2=0.5$, a hemoglobin (Hb) content=150g·L^{-1}, and a respiratory exchange ratio RER=0.8.

Figure 5: Continuous distributions of alveolar ventilation (open symbols) and pulmonary blood flow (closed symbols) as assessed using the MIGET technique in a young, healthy volunteer breathing air (left panel) and a patient with severe ARDS before (middle panel) and during (right panel) continuous i.v. prostacyclin (PGI_2). In this individual patient, there was a substantial fraction of pulmonary blood flow to lung regions with low $\dot{V}_A/\dot{Q}$ ratios ($0<\dot{V}_A/\dot{Q}<$normal$\dot{V}_A/\dot{Q}$) under baseline conditions, which was markedly reduced due to increased $\dot{Q}_S/\dot{Q}_T$ during vasodilator infusion. Note that despite the marked increase in $\dot{Q}_S/\dot{Q}_T$ (from 37 to 51% of cardiac output), p_aO_2 even

increased during the PGI_2 infusion due to the increase in $\dot{Q}_T$ and the subsequent rise in $p_{\bar{v}}O_2$ (see also figures 8 and 9). Middle and right panel: Adapted from (36) with kind permission from Wolters Kluwer Health.

Figure 6: Effects of intravenous (left panel) and inhaled (right panel) prostacyclin on systemic and pulmonary hemodynamics and gas exchange in patients with ARDS. PAP pulmonary artery pressure, PVR pulmonary vascular resistance, RVEF right ventricular ejection fraction, CO cardiac output, DO_2 systemic O_2 delivery, MAP mean blood pressure, SVR systemic vascular resistance. Adapted from (71) with kind permission from Springer Science and Business Media.

Figure 7: Arterial pO_2 during pure O_2 breathing, plotted as a function of the arterial – mixed venous O_2 content difference (in $mL \cdot dL^{-1}$) for incremental $\dot{Q}_S/\dot{Q}_T$ (in % of total pulmonary blood flow) levels. Note that for any given $\dot{Q}_S/\dot{Q}_T$ level, the higher the arterial–mixed venous O_2 content difference, the lower the mixed venous pO_2 and, consequently the lower the p_aO_2. Adapted from Radermacher P, Falke KJ: Pulmonary ventilation and gas exchange; in: Care of the Critically Ill Patient 2nd edition (Tinker J, Zapol WM, editors), Springer Heidelberg NewYork, 1992, pp. 59 – 67, with kind permission from Springer Science and Business Media.

Figure 8: Effect of a rise in cardiac output on arterial pO_2 (p_aO_2). Note that increasing cardiac output may lead to a rise of p_aO_2 due to the increased in mixed venous pO_2 ($p_{\bar{v}}O_2$) (see also figure 6). On the other hand, any increase may even cause a fall of p_aO_2 as a result of an increase in right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$), either directly (93) and/or due to the fall in pulmonary vascular tone (34-41).

Figure 9: The ratio p_aO_2/F_IO_2 plotted as function of F_IO_2 ranging from 0.21(air)-1.0(pure O_2) for $\dot{Q}_S/\dot{Q}_T$ values ranging from 1-50% at a constant hemoglobin (Hb) content=100g·L^{-1} and an arterial–mixed venous O_2 content difference=3.5 mL·dL^{-1}. Adapted from (106) with kind permission from Wolters Kluwer Health.

Figure 10: Iso-shunt diagram showing the effect of increasing F_IO_2 (x-axis) on p_aO_2 (y-axis) for various levels of intrapulmonary shunt. Adapted from (250) with kind permission from Oxford University Press.

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Gas Exchange in ARDS

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Abstract:

~~The acute respiratory distress syndrome (ARDS) is characterized by severe impairment of gas exchange. Hypoxemia is mainly due to intrapulmonary shunt, while increased alveolar dead space explains the alteration of CO_2 clearance. Assessment of the severity of gas exchange impairment is a requisite for the characterization of the syndrome and the evaluation of its severity. Confounding factors linked to hemodynamic status can greatly influence the relationship between the severity of lung injury and the degree of hypoxemia and the effects of ventilator settings on gas exchange. Apart from situations of rescue treatment, targeting optimal gas exchange in ARDS has become less a priority nowadays compared to prevention of injury. A complex question for clinicians is to understand when improvement in oxygenation and alveolar ventilation is related to a lower degree or risk of injury for the lungs. In this regard, a full understanding of gas exchange mechanism in ARDS is imperative for individualized symptomatic support of patients with ARDS.~~

The acute respiratory distress syndrome (ARDS) is characterized by severe impairment of gas exchange. Hypoxemia is mainly due to intrapulmonary shunt, while increased alveolar dead space explains the alteration of CO_2 clearance. Assessment of the severity of gas exchange impairment is a requisite for the characterization of the syndrome and the evaluation of its severity. Confounding factors linked to hemodynamic status can greatly influence the relationship between the severity of lung injury and the degree of hypoxemia and/or the effects of ventilator settings on gas exchange. Apart from situations of rescue treatment, targeting optimal gas exchange in ARDS has become less a priority nowadays compared to prevention of injury. A complex question for clinicians is to understand when improvement in oxygenation and alveolar ventilation is related to a lower degree or risk of injury for

the lungs. In this regard, a full understanding of gas exchange mechanism in ARDS is imperative for individualized symptomatic support of patients with ARDS.

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Introduction

Hypoxemia and impaired CO_2 clearance are characteristics of the Acute Respiratory Distress Syndrome (ARDS)(1)(2)(3). A considerable literature has explored the mechanisms of gas exchange abnormalities in ARDS. Because gas exchange remains the main physiological abnormality assessed by the clinician, understanding the complexity of the factors at play remains of considerable importance in the modern area of ARDS management. This article will review the basic principles of pulmonary gas exchange, the pathophysiology of gas exchange alterations in ARDS (Table 1), the effects of various therapeutic measures (Tables 2 and 3), and how to use the assessment of gas exchange for individualized symptomatic support.

Pathophysiology of gas exchange in ARDS

The concept of ventilation to perfusion ratio

The concept of ventilation perfusion ratio ($\dot{V}_A/\dot{Q}$) implies that an optimal ratio is necessary to obtain normal gas exchange and that an imbalance in this global and/or regional ratio is one of the few fundamental reasons explaining abnormal gas exchange: low $\dot{V}_A/\dot{Q}$ ratios tend to induce hypoxemia and high $\dot{V}_A/\dot{Q}$ ratios tend to induce hypercapnia. Impaired diffusion is another possible mechanism at the blood-gas interface. ~~Impaired diffusion is another mechanism at the blood-gas interface. In the ventilated areas in ARDS, because of the high diffusion coefficient of CO_2 and the increased O_2 diffusion gradient induced by the high inspired O_2 fractions (F_IO_2), equilibration of gas partial pressures between the blood and gas phases is complete in a functional gas exchange unit (i.e. alveolus and corresponding capillaries).~~ However, eIn the ventilated areas in ARDS, because of the high diffusion coefficient of CO_2 and the increased O_2 diffusion gradient induced by the high inspired O_2 fractions (F_IO_2), equilibration of gas partial pressures between the blood and gas phases is complete in a functional gas exchange unit (i.e. alveolus and

corresponding capillaries). Consequently impaired diffusion across the gas-blood barrier does not appear to play any role in gas exchange abnormalities in ARDS (4)(5). Therefore, for a given F_IO_2, total cardiac output ($\dot{Q}_T$), hemoglobin (Hb) content, and Respiratory Exchange Ratio (the ratio of whole body CO_2 production to O_2 consumption, $\dot{V}CO_2/\dot{V}O_2$, usually of 0.8 at rest with a normal diet), impaired gas exchange ~~is~~ explained by an altered distribution of alveolar ventilation and perfusion ($\dot{V}_A/\dot{Q}$)(6)(7)(8).

$\dot{V}_A/\dot{Q}$ ratios can vary from 0 (perfused, but non-ventilated alveoli; gas partial pressures being those of the mixed-venous blood), ~~also referred to as shunt,~~ to infinity (∞) (ventilated, but non-perfused alveoli; gas partial pressure being those of the inspired gas), referred to as dead space (figure 1). In a homogenous lung, i.e. having an *ideal* (*i*) $\dot{V}_A/\dot{Q}$ ratio corresponding to the respiratory exchange ratio (RER), arterial (a) equal mean alveolar (A) gas partial pressures(figure 1). However, even a healthy lung comprises regions where perfusion exceeds ventilation (i.e. $0 \leq \dot{V}_A/\dot{Q} < i$), and where ventilation exceeds perfusion (i.e. $i < \dot{V}_A/\dot{Q} \leq \infty$). Since arterial blood is the sum of the blood from all gas exchange units, any $\dot{V}_A/\dot{Q}$ inhomogeneity will cause alveolar-arterial (A-a) gas partial pressure differences (Δ). The more perfusion exceeds ventilation, the more p_aO_2 will fall, creating a $\Delta_{A\text{-}a}pO_2$. To describe the ideal alveolar air and analyze ventilation-perfusion relationships in the lungs, Riley & Cournand described a simple model with three compartments (normal ratio, i.e. $\dot{V}_A/\dot{Q}$=RER, shunt, i.e. $\dot{V}_A/\dot{Q}=0$, and dead space, i.e. $\dot{V}_A/\dot{Q}=\infty$), which is displayed on figure 2 (9). Increasing the $\dot{V}_A/\dot{Q}$ ratio by increasing minute ventilation ($\dot{V}_E$) cannot compensate for this effect, because of *i)* the relatively small contribution to $\dot{Q}_T$ of lung regions where ventilation markedly exceeds perfusion (i.e. $\dot{V}_A/\dot{Q}>10$), and *ii)* the virtually unchanged end-capillary blood O_2 content resulting from the sigmoid Hb-O_2-

dissocation curve in these regions. Consequently, increasing F_IO_2 and/or re-aeration of non-ventilated lung regions are the cornerstones of the management of hypoxemia in ARDS. In contrast, a $\Delta_{a-A}pCO_2$ will only develop when alveoli with very high $\dot{V}_A/\dot{Q}$ ratios contribute to total ventilation. In other words, p_aCO_2 will only increase, when $\dot{V}_E$ in proportion to $\dot{V}CO_2$ can no longer compensate for inhomogeneity of intrapulmonary ventilation distribution.

In summary, in patients with ARDS, the pulmonary causes leading to impaired gas exchange are virtually solely related to disturbed matching of alveolar ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$)(6)(7)(10). While hypoxemia is the results of blood flow to non- and/or hypoventilated lung regions, impaired CO_2 elimination is mainly due to the contribution of non- and/or hypoperfused areas(7) (10).

Dead space

A single tidal breath, V_T, and the expired volume per unit of time, $\dot{V}_E$, comprise a component that does not contribute to gas exchange, the dead space (V_D and $\dot{V}_D$, respectively), as well as the volume of gas delivered to the alveolus (V_A and $\dot{V}_A$, respectively):

$V_T = V_D + V_A$ [1A], and $\dot{V}_E = \dot{V}_D + \dot{V}_A$ [1B].

Dead space ventilation consists of an anatomical (the conducting airways) and an alveolar component (ventilated, but non-perfused alveoli and/or alveoli over-ventilated relative to perfusion). According to the above-mentioned model by Riley & Cournand (9), dead space can be referred to as “wasted” ventilation. Since CO_2 eliminated in the expired gas ($\dot{V}CO_2$) can only originate from gas-exchanging parts of the lung, $\dot{V}_E$ is the sum of the amount of inspiratory gas not participating in gas exchange ($\dot{V}_D$) added to the alveolar gas transporting CO_2 ($\dot{V}_A$). Since $F_ICO_2 \approx 0$ and $p_aCO_2 \approx p_ACO_2$,

$\dot{V}CO_2 = \dot{V}_E \cdot F_ECO_2 = \dot{V}_D \cdot F_ICO_2 + \dot{V}_A \cdot F_ACO_2$ [2],

where F_ECO_2, F_ICO_2, and F_ACO_2 are the mixed expiratory, inspiratory, and alveolar CO_2 fractions, respectively. Substituting $\dot{V}_A$ and re-writing equation 2 in terms of pCO_2 yields

$\dot{V}_D/\dot{V}_E=V_D/V_T= (p_aCO_2–p_ECO_2)/p_aCO_2$ [3].

This equation represents the simplified quantification of the overall V_D/V_T according to Enghoff (11). If p_aCO_2 really equals p_ACO_2 – which is often not the case, particularly in ARDS –, V_D/V_T according to (11) equals the anatomical dead space. Based on the above-mentioned assumptions that $F_ICO_2\approx0$ and $p_aCO_2\approx p_ACO_2$, equation 2 can be rewritten

$\dot{V}CO_2=\dot{V}_A\cdot k\cdot p_aCO_2$ [4] (k=0.863 for mmHg and mL, 2.561 for SI units),

or, for a given $\dot{V}CO_2$,

$\dot{V}_A\sim1/p_aCO_2$ [5],

i.e. $\dot{V}_A$ is inversely proportional to p_aCO_2. In other words, p_aCO_2 is a function of $\dot{V}_A$ in proportion to $\dot{V}CO_2$. Therefore, i) for a given $\dot{V}_A$, metabolic CO_2 production ($\dot{V}CO_2$) determines p_aCO_2, and ii) any rise in V_D/V_T requests increases in $\dot{V}_E$ to maintain p_aCO_2.

Dead space is classically divided in two components, the airway dead space and the alveolar dead space (12). Applying the method proposed by Fowler for N_2 (13) to CO_2, Fletcher & Jonson proposed a graphical analysis of the $p_ECO_2/\dot{V}_E$-curve named "*volumetric capnography*", which allows calculating V_D/V_T using the Enghoff equation and its partition between airway (anatomical) and alveolar dead space (figure3) (14).

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In summary, in patients with ARDS, impaired CO_2 clearance is mainly due to increased V_D/V_T, i.e. "wasted" ventilation" in ventilated but non-perfused lung regions(9). Hence, increasing $\dot{V}_E$ and/or decreasing V_D (see below) can allow maintaining p_aCO_2; hypercapnia will occur when increasing $\dot{V}_E$ in proportion to metabolic $\dot{V}CO_2$ can no longer compensate for inhomogenous ventilation distribution(7)(9).

The alveolar gas equation

As mentioned p_aCO_2 is often used as a surrogate for p_ACO_2, albeit this approximation is erroneous, particularly during severe ARDS, when $\Delta_{a\text{-}A}pCO_2$=10-15mmHg may develop. Under normal conditions, the $\Delta_{A\text{-}a}pO_2$ is of that magnitude but during ARDS, this $\Delta_{A\text{-}a}pO_2$ can be several-fold higher and it reflects the ARDS definition requiring increased F_IO_2.

Theoretically, to quantify the $\Delta_{A\text{-}a}pO_2$, p_AO_2 can be calculated after substituting p_ACO_2 by p_aCO_2 and correction for RER≠1:

$$p_AO_2 = p_IO_2 - p_aCO_2 \cdot (F_IO_2 + (1 - F_IO_2)/RER) \quad [6]$$

This *calculated* P_AO_2 refers to the overall *ideal mean* alveolar pO_2 of a homogenous lung. In ARDS however, p_AO_2 may vary substantially within different lung regions due to inhomogeneity of the distribution of alveolar ventilation. Therefore, in clinical practice, this complicated correction for the p_AO_2 calculation is unnecessary, so that simply approximating the value is sufficient, in particular at high F_IO_2(15):

$$p_AO_2 \approx p_IO_2 - p_aCO_2/0.8 \quad [7].$$

Venous admixture and intrapulmonary shunt

Pulmonary blood flow ("*perfusion*") guarantees that CO_2 and O_2 are transported from the tissues to the lung and *vice versa*. The pulmonary circulation is unique since *i*) total cardiac output ($\dot{Q}_T$) passes through one organ, and *ii)* due to the low pressures, flow distribution, and consequently, pulmonary vascular resistance depend on the surrounding alveolar pressures.

Pulmonary blood flow (=$\dot{Q}_T$) consists of flow through normally ventilated lung regions, and a "shunted" component; the latter comprising the anatomical structures without contact with alveolar gas (Thebesian and bronchial veins), and an alveolar component originating from non-ventilated (right-to-left shunt, $\dot{Q}_S$) and/or hypo-ventilated alveoli. This alveolar component is called "*physiological shunt*" or "*venous admixture*" ($\dot{Q}_{VA}$). According to the model by Riley & Cournand(9) and in analogy to V_D/V_T, it can be referred to as "*wasted*" pulmonary blood flow: the blood gas partial pressures from these regions are equal to or only slightly higher than the mixed-venous ones, and therefore are the cause of arterial hypoxemia. $\dot{Q}_{VA}$ can be quantified according to the assumption that total pulmonary blood flow ($\dot{Q}_T$) is the sum of $\dot{Q}_{VA}$ and capillary blood coming from alveoli with ideal $\dot{V}_A/\dot{Q}$ ratios ($\dot{Q}_C$)(9) (figure 2):

$\dot{Q}_T = \dot{Q}_{VA} + \dot{Q}_C$ [8A],

or, re-written as the amount of O_2 transported:

$\dot{Q}_T \cdot C_aO_2 = \dot{Q}_{VA} \cdot C_{\bar{v}}O_2 + \dot{Q}_C \cdot C_cO_2$ [8B]

with C_aO_2, $C_{\bar{v}}O_2$, and C_cO_2 being the arterial, mixed-venous and ideal capillary O_2 content values, respectively. For the calculation of C_cO_2, p_AO_2 is approximated using equation 6 or 7, and in patients with ARDS, ideal capillary Hb-O_2-saturation can be

assumed as 100%, since usually F_IO_2>0.3-0.4. Merging equations 8A and 8B then yields the Berggren formula(16):

$\dot{Q}_{VA}/\dot{Q}_T = (C_cO_2 - C_aO_2)/(C_cO_2 - C_{\bar{v}}O_2)$ [9].

Quantification of $\dot{Q}_{VA}/\dot{Q}_T$ requires right-heart catheterization for pulmonary arterial blood sampling. Moreover, $\dot{Q}_{VA}/\dot{Q}_T$ cannot differentiate between $\dot{Q}_S$ in totally non-ventilated alveoli, and in hypo-ventilated lung regions with low $\dot{V}_A/\dot{Q}$ ratios (normally defined as $\dot{V}_A/\dot{Q}$<0.1). This differentiation is by no means academic: while blood gas partial pressures in non-ventilated alveoli are unresponsive to increases in F_IO_2, higher F_IO_2 will allow for at least partial correction of arterial hypoxemia in hypo-ventilated lung regions (figure 3). Theoretically, switching from maintenance F_IO_2 to pure O_2 ventilation allows separating these two main pulmonary causes of arterial hypoxemia: N_2 wash-out from ventilated alveoli should correct for any hypoxemia related to lung regions with low $\dot{V}_A/\dot{Q}$ ratios. However, the time required for complete de-nitrogenation is unknown in the presence of profound heterogeneity of the distribution of $\dot{V}_A$, e.g. especially in patients with ARDS. Moreover, this manoeuver can *per se* increase $\dot{Q}_S$(17)(18): *i*) in “unstable” alveoli with very low $\dot{V}_A/\dot{Q}$ ratios, resorption atelectasis may develop (19), when gas inflow into the alveoli is lower than uptake into the blood(20), and *ii*) the hyperoxia-induced increase of both $p_{\bar{v}}O_2$ and p_AO_2 can inhibit hypoxic pulmonary vasoconstriction(21)(22)(23)(24), and thereby deteriorate gas exchange. Theoretically, analyzing the arterial-alveolar N_2 partial pressure gradient ($\Delta_{aA}pN_2$) allows differentiating between $\dot{Q}_S/\dot{Q}_T$ and low $\dot{V}_A/\dot{Q}$ but its determination is technically impractical at the bedside

It should be noted that high levels of $\dot{Q}_S/\dot{Q}_T$ will also increase $\Delta_{a\text{-}A}pCO_2$ and thereby V_D/V_T calculated using the Enghoff formula since the pCO_2 of the blood originating from these lung regions is the mixed venous pCO_2 ($p_{\bar{v}}CO_2$)(25). This effect is

pronounced with low $\dot{Q}_T$, anemia and/or metabolic acidosis as a result of the increased difference $p_{\bar{v}}CO_2 - p_aCO_2$(26).

In summary, in patients with ARDS, hypoxemia is due to increased $\dot{Q}_{VA}/\dot{Q}_T$, i.e. "wasted" perfusion originating from non- ($\dot{Q}_S/\dot{Q}_T$ or shunt) *and/or* hypoventilated (low $\dot{V}_A/\dot{Q}$ ratios) lung regions(10). Increasing the $\dot{V}_A/\dot{Q}$ ratio by increasing $\dot{V}_E$ cannot compensate for this effect, and, consequently, increasing F_IO_2 and/or re-aeration of non-ventilated lung regions are the cornerstones of the management of hypoxemia in ARDS. While $\dot{Q}_S/\dot{Q}_T$ is unresponsive to increased F_IO_2, higher F_IO_2 allows for at least partial correction of arterial hypoxemia resulting from low $\dot{V}_A/\dot{Q}$ (6)(7)(9)(10)

Assessment of ventilation/perfusion-distribution

As mentioned above, the 3-compartment model (9). represents all "wasted" ventilation as V_D/V_T, i.e. ventilated but non-perfused lung regions, and all "wasted" perfusion as $\dot{Q}_S/\dot{Q}_T$, i.e. blood flow through non-ventilated lung areas. Virtually continuous ventilation/perfusion distributions assuming a 50-compartment lung model covering the whole range of $\dot{V}_A/\dot{Q}$ ratios can be described with the "*multiple inert gas elimination technique*" (MIGET)(27)(28). The MIGET makes use of the solubility-related kinetics of physiologically inert, only physically dissolved gases at trace concentrations. During continuous infusion of a mixture of gases with blood–gas partition coefficients over a range of five orders of magnitude retention ($R=p_A/p_v$) and excretion ($E=p_e/p_{\bar{v}}$) are determined according to the principle of mass conservation:

$p_A/p_{\bar{v}} = \lambda/(\lambda+\dot{V}_A/\dot{Q})$ [13]

with p_A, $p_{\bar{v}}$, and p_e being the alveolar, mixed-venous, and mixed-expiratory inert gas tensions, λ being the substance-specific blood-gas partition coefficient(29). Typical examples of a healthy young volunteer and a patient with ARDS (before and during i.v. infusion of prostacyclin) are shown in figure 4. Pulmonary arterial sampling, and

hence right-heart catheterization is not mandatory, since with cardiac output available, the inert gas p_v can be calculated from the p_e and p_a values using the Fick principle(27). The MIGET demonstrated that patients with ARDS present with bi-modal distributions of both pulmonary blood flow and alveolar ventilation (figure 4)(9): hypoxemia is due to a high proportion of blood flow to lung regions with true right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$) (e.g. collapsed and/or flooded alveoli) together with low $\dot{V}_A/\dot{Q}$ ($\dot{V}_A/\dot{Q}<0.1$) in some patients. Impairment of CO_2 elimination is caused by true dead space ventilation (V_D/V_T) with some additional "wasted" ventilation in hypo-perfused lung areas(9)(30)(31)(32)(33)(34)(35)(36)(37)(38)(39)(40).

Imaging of ventilation/perfusion-distribution

MIGET can only yield quantitative analyses without topographic information of ventilation/perfusion ratios(41). Various imaging techniques have been proposed, i.e combining inhalation of ^{133}Xe or ^{81m}Kr and subsequent infusion of these gases dissolved in aqueous solutions(42)(43), magnetic resonance using proton density, hyperpolarized ^{3}He, or ^{129}Xe imaging(44)(45)(46), positron emission tomography using $H_2{}^{15}O$-labeled water, $^{13}N_2$ dissolved in saline, or ^{18}F-fluoro-2-deoxy-glucose that detects inflammatory cell metabolism(47)(48)(49), and electrical impedance tomography(50)(51)(52)(53). These techniques provide information on spatial distribution and allow for independent assessment of absolute $\dot{V}$ and $\dot{Q}$ values, i.e. not only on the distribution of $\dot{V}/\dot{Q}$ ratios. Quantitative images of the respective $\dot{V}$ and $\dot{Q}$ distribution are difficult to obtain, in particular as a result of the mandatory high spatial resolution mapping of the same lung region. Moreover, these techniques are costly and require patient transport. Hence, with the exception of electrical impedance tomography, they are unlikely to gain the potential for bedside monitoring(54)(55)(56).

Effect of gravity

Gravitational force is a major determinant of the distribution of ventilation and perfusion: in the upright position there is a near-linear increase of blood flow from the lung apex to base due to gravitational force. Alveolar ventilation also follows this pattern, the slope being much flatter. This gravitation-related change in the distribution of $\dot{V}/\dot{Q}$ ratios can be visualized by using imaging techniques(54)(55)(56). Since this gravitation-dependent variation of pulmonary blood flow is more pronounced than that of alveolar ventilation, $\dot{V}_A/\dot{Q}$ ratios decrease from the apex to basis of the lung, or, in the supine position, from ventral to dorsal lung regions. In healthy volunteers in the semi-recumbent position $\dot{V}_A/\dot{Q}$ ratios can range from 0.3–2.1 from apex to base(57), while patients with ARDS present with much larger variability. Hence, the lowest $\dot{V}_A/\dot{Q}$ ratios and $\dot{Q}_S/\dot{Q}_T$ are typically present in the dependent lung areas. ~~This is the basis for the gas exchange effects of mechanical ventilation in the prone position: this manoeuver reduced $\dot{Q}_S/\dot{Q}_T$ in favor of increased blood flow to well-ventilated lung regions(31)(58)(59).~~ Data obtained in the prone position challenged the concept of the influence of gravity: this manoeuver indeed reduces $\dot{Q}_S/\dot{Q}_T$ in favor of increased blood flow to well-ventilated lung regions(31)(58)(59). In some patients, this effect was further enhanced by adding inhaled nitric oxide and/or almitrine infusion(60)(61)(62)(63)(64).

Several mechanisms have been identified to explain the beneficial effect of prone position on oxygenation. First, prone position reduces the pleural pressure gradient and homogenizes trans-pulmonary pressure across the lung(211)(212)(213). A number of factors can explain this effect of prone position, including the reversal of gravitational lung weight gradients(214)(215), elimination of the compressive force of the heart on dorsal lung regions(216)(217), and the release of the compression of abdominal contents on caudal regions of the dorsal lung(218)(219). The net effect is

an homogenization of regional lung inflation, which increases in dorsal lung regions and decreases in ventral regions (220). In addition, both animal and human studies showed that distribution of pulmonary blood flow, which is prevalent in the dorsal lung in the supine position, surprisingly does not change when turning patient prone(221)(222)(223)(224)(177). Thus, the improvement in oxygenation in the prone position is due to a reduction in $\dot{Q}_S/\dot{Q}_T$ resulting from the concomitant increase in the aeration in the dorsal lung regions, with dorsal recruitment being greater than ventral de-recruitment, and the persistence of better lung perfusion in these regions.

In sum, there is a pronounced, gravitation-related regional variability of $\dot{V}_A/\dot{Q}$ ratios with $\dot{Q}_S/\dot{Q}_T$ being particularly present in the dependent lung regions. The beneficial gas exchange effect of prone position is mainly due to the persistence of higher pulmonary blood flow in regions better aerated in prone position(31).

Pulmonary vascular tone

Pulmonary vascular tone may cause marked regional $\dot{V}_A/\dot{Q}$ differences, in particular as a result of hypoxic pulmonary vasoconstriction (65): local aveolar hypoxia induces regional vasoconstriction and thus reduces perfusion to hypo- and/or non-ventilated lung areas, thereby improving gas exchange(30). In patients with ARDS, increasing pulmonary vascular tone improved gas exchange(37)(66), whereas reducing pulmonary artery pressure by hyperoxia and/or intravenous vasodilators further aggravated hypoxemia(33)(34)(35). In contrast, selective pulmonary vasodilation using inhaled vasodilators improved gas exchange: short-acting inhaled vasodilators (e.g. nitric oxide (NO) or prostacyclin) are only effective in ventilated lung areas (figure 5). Consequently, they will redistribute pulmonary blood flow away from unventilated alveoli, and thereby attenuate $\dot{Q}_S/\dot{Q}_T$(38)(39)(40)(67). Combining i.v. pulmonary vasoconstrictors (e.g. almitrine) and inhaled vasodilators even further

improved arterial oxygenation in some patients without aggravating right ventricular afterload(68)(69)(70).

In sum, augmenting pulmonary vascular tone generally improves $\dot{V}_A/\dot{Q}$ distribution. Selective pulmonary vasodilating using inhaled, short-acting compounds can improve $\dot{V}_A/\dot{Q}$ distributions, because they are only effective in ventilated lung regions(71).

Non-pulmonary factors

In addition to the degree of low $\dot{V}_A/\dot{Q}$ and $\dot{Q}_S/\dot{Q}_T$, non-pulmonary factors affect gas exchange, namely F_IO_2 (see below "High F_IO_2"), cardiac output ($\dot{Q}_T$) and $\dot{V}O_2$(72). $\dot{Q}_T$ affects gas exchange both indirectly by its effect on O_2 extraction, and thus on p_vO_2, and directly by modifying $\dot{V}_A/\dot{Q}$ distributions. The complexity is that these factors may have various effects potentially influencing oxygenation in opposite directions. According to the Fick principle

$\dot{V}O_2=\dot{Q}_T\cdot(C_aO_2-C_{\bar{v}}O_2) \Leftrightarrow C_{\bar{v}}O_2=C_aO_2-\dot{V}O_2/\dot{Q}_T$ [13],

i.e. C_vO_2 and, due to the steep, near-linear shape of the Hb-O_2-dissociation curve, p_vO_2, are directly related to arterial O_2 content and $\dot{V}O_2$, and inversely related to $\dot{Q}_T$. Hence, variations of $\dot{Q}_T$ will directly affect p_aO_2 as a result of this interplay between $\dot{Q}_T$ and $\dot{V}O_2$ and $p_{\bar{v}}O_2$. Consequently, for a given $\dot{V}O_2$ and $\dot{Q}_S/\dot{Q}_T$, there is a linear relationship between p_aO_2 and the difference $C_aO_2-C_{\bar{v}}O_2$(figure 6)(73)(74). In other words, any rise in $p_{\bar{v}}O_2$ should also increase p_aO_2. In patients treated with extracorporeal CO_2 removal, increasing $p_{\bar{v}}O_2$ by increasing the F_IO_2 of the membrane lung was associated with a parallel rise of p_aO_2, while whole-body $\dot{V}O_2$, $\dot{Q}_T$, $\dot{Q}_S/\dot{Q}_T$, and the $\dot{V}_A/\dot{Q}$ distributions remained unchanged(75). However, under clinical conditions the magnitude of this effect may depend on the initial level of $p_{\bar{v}}O_2$ and of other factors. Indeed, pharmacological (e.g. inotropic and/or vasoactive drugs) or non-pharmacologic (PEEP maneuvers, patient positioning) approaches frequently

influence $\dot{Q}_T$ ~~and~~ $\dot{V}O_2$ as well, and, hence, $p_{\bar{v}}O_2$. Moreover, another factor shown both in experimental models and in patients with ARDS, is the fact that changes in $\dot{Q}_T$ induce parallel changes in $\dot{Q}_S/\dot{Q}_T$(76)(77)(78) including when induced by increasing PEEP or V_T(79). The most likely explanation seems to be an alteration of hypoxic pulmonary vasoconstriction induced by changes in $P_{v\bar{v}}O_2$(80)(81). Variations in $p_{\bar{v}}O_2$ can also directly affect $\dot{Q}_S/\dot{Q}_T$ due to changes in pulmonary vascular tone: in patients with ARDS treated with ECMO, $\dot{Q}_S/\dot{Q}_T$ showed a direct, linear dependence on both pulmonary blood flow and calculated pulmonary vascular resistance(77). Consequently, any variation of $\dot{Q}_T$ can affect arterial oxygenation in different directions. Therefore, in an individual patient, the effect of $\dot{Q}_T$ variations on p_aO_2 are often unpredictable and will be a consequence of the interplay between effects on $\dot{Q}_S/\dot{Q}_T$, $\dot{V}_A/\dot{Q}$ distributions, $\dot{V}O_2$ and $p_{\bar{v}}O_2$(71)(figure 7)(72)(82).

Albeit to a lesser degree due to the small difference between arterial and mixed-venous levels, the same is true for any effect of $\dot{Q}_T$ and $p_{\bar{v}}CO_2$, respectively, on p_aCO_2: theoretically, any increase in $\dot{Q}_T$ should result in fall of p_aCO_2. However, the effects of $\dot{Q}_T$ variations on p_aCO_2 can also work in different directions, e.g. the expected fall of p_aCO_2 resulting from a vasodilator-induced increase in $\dot{Q}_T$ may be offset by the simultaneous rise in $\dot{Q}_S/\dot{Q}_T$ and, in particular, $\dot{V}_D/\dot{V}_T$. The latter can be caused by the vasodilator-induced reduction in pulmonary arterial pressure, which may result in “de-recruitment” of the pulmonary vasculature: as mentioned above, pulmonary vascular resistance and, consequently, the distribution of pulmonary blood flow, depend on the relation between intravascular, i.e. arterial (P_a) and venous (P_v), and alveolar (P_A) pressures(57). Any fall in intravascular pressure can transform “Zone II” regions of the lung (with $P_a>P_A>P_v$) into so-called “Zone I” regions of the lung, which are non-perfused because $P_A>P_a$ (57).

Non-pulmonary factors, namely F_IO_2, cardiac output ($\dot{Q}_T$), $\dot{V}O_2$, and, as a result of the $p_{\bar{v}}O_2$, will also directly affect p_aO_2.

Extra-pulmonary shunt

Intra-cardiac shunt *via* a *patent foramen ovale* (PFO) may also contribute to compromised gas exchange in ARDS. Under normal conditions, a PFO does not affect gas exchange, because the gradient between left and right atrial pressure precludes significant blood transfer from the venous to the arterial side. However, pulmonary artery hypertension is a common phenomenon in patients with ARDS and can lead to *acute cor pulmonale*(83)(84)(85). Prevalence of a PFO during ARDS has been reported between 15-19%, and is often associated with *acute cor pulmonale*(86)(87). Frequently, in the presence of a moderate-to-large PFO shunting, there is a poor oxygenation response to PEEP. High PEEP may further increase the right atrial pressure, thereby increasing the occurrence and severity of right-to-left shunting due to PFO(59)(86)(88)(89). Lowering PEEP and/or inhaled nitric oxide may reduce pulmonary hypertension, thus decreasing or abolishing right-sided shunting in some patients (≈14%), thereby improving oxygenation(88)(89).

Clinical Applications

There is a real difficulty for the clinician at the bedside to accurately interpret gas exchange abnormalities in ARDS. In particular different maneuvers can influence gas exchange through various mechanism. It can be a pure redistribution of blood flow (see vasodilators), a change in mixed venous blood oxygen content or it can reflect a reopening of previously no aerated lung units (see recruitment). Therefore the same effects on gas exchange may indicate a real change in lung function due to a specific maneuver or to the natural resolution of the disease, a simple “cosmetic” effect without alteration in lung function, or even a worsening of lung distension with a

reduction in cardiac output and consequently of shunt. Therefore a careful interpretation merits a multimodal clinical approach and a careful reasoning.

Diagnosis and assessment of severity

Hypoxemia is a central component of the diagnosis of ARDS. Several indices have been proposed to characterize hypoxemia e.g. $\dot{Q}_{VA}/\dot{Q}_T$, $\Delta_{Aa}pO_2$, the oxygenation index and the p_aO_2/F_IO_2 ratio. These indices are influenced by many factors, e.g. ventilator settings (V_T, respiratory rate, PEEP) and hemodynamics ($\dot{Q}_T$ and $p_{\bar{v}}O_2$). Due to its simplicity, p_aO_2/F_IO_2 ratio has been adopted for routine practice and is used to characterize the severity of ARDS(1). The use of the p_aO_2/F_IO_2 ratio is underlined by the necessity to assess hypoxemia independently from F_IO_2. Unfortunately, due to the complex mathematical relationship between the Hb level, the Hb-O_2-dissocation curve, and the arterial – mixed venous O_2 content difference, the relationship between p_aO_2/F_IO_2 and F_IO_2 is non-linear and depends on the underlying $\dot{Q}_S/\dot{Q}_T$(90)(91)(figure 8).

Thus, no matter the possible effect of F_iO_2 on $\dot{Q}_S/\dot{Q}_T$ *per se* (de-nitrogenation atelectasis), any change in F_IO_2 may also modify p_aO_2/F_IO_2. This variability of p_aO_2/F_IO_2 suggests that its use be cautioned in an individual ARDS patient, when ventilator settings are modified. Despite these limitations, classification of patients with ARDS in three categories of severity according to p_aO_2/F_IO_2 (“mild” for $300 \leq p_aO_2/F_IO_2 < 200$, “moderate” for $200 \leq p_aO_2/F_IO_2 < 100$ and “severe” for $p_aO_2/F_IO_2 \leq 100$ mmHg) allows to identify patients with different duration of mechanical ventilation and mortality(1)(92). Furthermore, the p_aO_2 during pure O_2 ventilation was shown to be strongly correlated with the CT-quantified percentage of non-aerated lung(93). Finally, this simple index appears to be useful for identifying patients that could benefit from additional therapeutic interventions such as high PEEP, prone positioning, and/or neuromuscular blockade(94)(95)(96). As shown by Villar *et al*., the

prognostic value of p_aO_2/F_IO_2 depends greatly on the time and conditions of its measurement, the better stratification of the risk of death being obtained with on PEEP≥10cmH_2O and F_IO_2≥0.5 after 24 hours of protective ventilation(97)(98).

The ratio of transcutaneous arterial Hb-O_2-saturation (S_pO_2) to F_IO_2 (S_pO_2/F_IO_2) was suggested as a screening tool for ARDS, when arterial blood gases are not available(99). Unfortunately, due to its poor accuracy, this non-invasive method cannot be used to assess the effects of therapeutic interventions on oxygenation(100). Finally, it was recently suggested that a non-linear equation gave more reliable estimate of the p_aO_2/F_IO_2 ratio(101).

Impaired CO_2 elimination is also a hallmark of ARDS. In ARDS patients of variable severity, V_D/V_T measured on PEEP=5cmH_2O was highly correlated with CT scan-quantification of lung aeration inhomogeneity, suggesting that V_D/V_T could be useful for individual assessment of the risk of VILI(102). In line with this observation, V_D/V_T measured in standardized conditions at the early or the intermediate phase independently predicted mortality(3)(103). Calculation of V_D/V_T with the Enghoff formula requires the determination of p_eCO_2 and/or F_ECO_2, which is not routine linical practice. Several methods have been proposed for V_D/V_T estimation without measuring F_ECO_2, or for the calculation of indices reflecting ventilatory efficiency: Minute ventilation standardized at a p_aCO_2 of 40 mmHg ($\dot{V}_Ecorr=\dot{V}_E\cdot p_aCO_2/40$)(104), ventilatory ratio=$(\dot{V}_E\cdot p_aCO_2)/$(predicted minute ventilation$\cdot$37.5) with predicted $\dot{V}_E$=100 mL$\cdot kg^{-1}$predicted body weight(PBW)$\cdot min^{-1}$(105). Retrospective analysis of the ARDS network databases suggest that both V_D/V_T using the Harris-Benedict calculation of energy expenditure, and the ventilatory ratio are predictive of mortality(106)(107)(108). Although not mandatory for the diagnosis, assessment of the impaired CO_2 elimination using either V_D/V_T and/or calculation of a surrogate index should be part of the initial evaluation of ARDS severity.

Therapeutic targets

Arterial pO_2

Although prevention of death from hypoxemia is a major goal of mechanical ventilation in patients with ARDS, very few studies addressed the question of the optimal target for oxygenation. There is ample evidence from studies outside the field of ARDS suggesting that hyperoxemia (p_aO_2>120-150mmHg) should be avoided in critical illness(109)(110). In most of the large randomized controlled trials on symptomatic support in ARDS, the recommended targets for oxygenation were a p_aO_2=55-80mmHg and/or a S_aO_2=88-95%. Interestingly, the data reported in these studies show that mean values for p_aO_2 were mostly close to or even higher than the upper target limits(96)(111)(112)(113)(114) (115). This observation is well in line with data from observational studies showing that high p_aO_2 and/or S_aO_2 values are frequently observed in critically ill patients, and suggests that investigators do not feel comfortable with lower p_aO_2 and/or S_aO_2 values. This was probably due to much more concern about the risk of hypoxia than that of pulmonary O_2 toxicity and/or deleterious effects of hyperoxia(116). The safety of moderate levels of oxygenation has been questioned by the observation of an association between lower levels of oxygenation and long term neuropsychiatric impairment in a subgroup of survivors from ARDS(117). Nevertheless, in ARDS the “optimal” S_aO_2 and p_aO_2 level remains undetermined, because experimental data suggest that hyperoxia can worsen ventilator-induced lung injury (VILI)(118). Moreover, a retrospective analysis demonstrated that the number of days with hyperoxemia as defined with a p_aO_2>120 mmHg was an independent risk factor of ventilator-associated pneumonia(119). More evidence for the toxicity of hyperoxemia was provided by the randomized controlled trials “Optimal Oxygenation in the Intensive Care Unit (O2-ICU)”, and “Hyperoxia and Hypertonic Saline in Septic Shock (HYPER2S)”(120)(121). The “O2-ICU” trial

compared PaO_2 targets of 120 (“conventional”) versus 75 (“conservative”) mmHg in 434 general ICU patients with an expected length-of stay >72hours: the conservative approach was associated with a 50% reduction of overall mortality (11.6 *vs*. 20.2%, p=0.01); the authors concluded that the findings must be considered preliminary because of the early trial termination due to difficult patient enrolment. Moreover, only 67% of the patients were mechanically ventilated at inclusion(120). The “Hyper2S” trial comparing target SaO_2 88–95% *vs.* pure O_2 ventilation during the first 24 hours in patients with septic shock was preliminary stopped for safety reasons after enrolment of 442 patients(121). In this study, 50% of the patients had ARDS with p_aO_2/F_IO_2<200mmHg at baseline. Mortality did not significantly differ at day 28 and 90, but hyperoxia was associated with a significantly higher incidence of serious adverse events with a clinically relevant higher number of patients with ICU-acquired weakness and atelectasis.

Arterial pCO_2

Experimental studies have shown that hypercapnia and/or respiratory acidosis may have numerous beneficial cellular and physiological effects, e.g. attenuated pulmonary inflammation, protection against VILI and oxidant-induced lung injury(122)(123)(124), improved $\dot{V}_A/\dot{Q}$ distribution through enhanced hypoxic pulmonary vasoconstriction (125), increased $\dot{Q}_T$ and O_2 delivery secondary to catecholamine release(126)(127), improved microcirculation(128), and facilitation of peripheral O_2 release through the Bohr effect (rightward shift of the Hb-O_2-dissocation curve)(129). On the other hand, hypercapnia decreases alveolar fluid clearance(130), and its anti-inflammatory effect may be associated with impaired antimicrobial host defenses(131) and delayed cellular wound healing(132). Moreover, the hypercapnia-related increase in right ventricular afterload can contribute to acute *cor pulmonale*(133), which in turn increased mortality(134). In the clinical setting, it is

virtually impossible to separate the effect hypercapnia *per se* from those of reduced biomechanical lung injury resulting from reduced V_E. A *post hoc* analysis of the results of the ARMA trial showed that in patients receiving the “conventional” tidal volume (12 mL·kg^{-1}PBW), moderate respiratory acidosis was independently associated with a lower odds ratio of death on Day 28, suggesting a protective effect of hypercapnia against VILI(135). Finally, a secondary analysis of three cohort studies including 1889 patients with ARDS suggested that a p_aCO_2>50mmHg was independently associated with increased mortality(136). Thus, while normalization of p_aCO_2 and/or arterial pH should no longer be considered as an absolute priority, the safety of permissive hypercapnia appears questionable (132). Therefore, many randomized trials recommended to keep a p_aCO_2 resulting in a pH=7.30-7.40.

Therapeutic measures

Several therapeutic measures have been proposed to correct gas exchange in ARDS (tables 2 and 3). In the original description of ARDS, Ashbaugh *et al.* were the first to report on the use of increased F_IO_2 and of PEEP(137). For a long time, correcting hypoxemia was the main objective of mechanical ventilation. Other approaches proposed and/or used different strategies of artificial ventilation, pharmacologic manipulation of pulmonary vascular tone, and later, patient positioning. Because during extra-corporeal membrane oxygenation both arterial oxygenation and CO_2 elimination mainly depend on the extra-corporeal device, this technique will not be discussed in this review.

High F_IO_2

Although the pivotal mechanism of hypoxemia in ARDS is $\dot{Q}_S/\dot{Q}_T$, high F_IO_2 is common practice. As expected in the presence of high $\dot{Q}_S/\dot{Q}_T$, the effect of increasing F_iO_2 on p_aO_2 is often modest, especially in the severely hypoxemic patients (figure 9). In addition, as mentioned above, several authors have reported an increased $\dot{Q}_S/\dot{Q}_T$

while breathing 100%O_2 due to development of reabsorption atelectasis resulting from denitrogenation of units with low $\dot{V}_A/\dot{Q}$ ratios, which can be prevented by PEEP or recruitment maneuvers (19)(20)(138). In patients with ARDS ventilated with low V_T (6mL·kg^{-1}) and low PEEP (approximately 5cmH_2O), Aboab *et al*. reported that increasing F_iO_2 from 0.6 to 1.0 caused a decrease of p_aO_2/F_iO_2 and lung de-recruitment that could be prevented with a PEEP of approximately 15cmH_2O(19). On the other hand, pure O_2 breathing does not affect hypoxic pulmonary vasoconstriction in patients with ARDS(138), suggesting that hypoxic pulmonary vasoconstriction is attenuated.

Positive End-Expiratory Pressure

ARDS is characterized by a decrease in aerated lung volume caused by atelectasis, lung edema, small airway closure, and surfactant perturbation(139). Use of PEEP to correct gas exchange impairment in ARDS was initially proposed by Asbaugh *et al.*(137), and remains the cornerstone of ventilatory management of these patients. Extensive data supports the use of PEEP for improving oxygenation in hypoxemic respiratory failure, alone (during Continuous Positive Airway Pressure, CPAP) or combined with various ventilator modes(140)(141)(142)(143)(144)(145)(146)(147). Several mechanisms may explain the effect of PEEP on gas exchange, the main one being an increased number of alveoli that remain aerated at end-expiration, i.e. alveolar recruitment, which, in turn, decreases $\dot{Q}_S/\dot{Q}_T$(36). Physics laws and data from animal studies suggest that PEEP may also balance the increased tendency to alveolar collapse due to increased surface forces related to surfactant perturbation. Although not definitively demonstrated in patients, it is likely that this phenomenon may play a role in explaining the effect of PEEP on lung recruitment(148). Albeit questioned(149), several studies reported a direct relation between the improvement in oxygenation and PEEP-induced lung recruitment(143)(145)(150)(151). However,

this correlation may be too weak to allow, in an individual patient, to assess PEEP-induced recruitment by its effect on oxygenation. The lack of a bedside method to quantify recruitment induced by PEEP has always limited the interpretation of oxygenation as a marker of recruitment. Some studies suggested that PEEP may protect against the development of pulmonary edema(152)(153)(154), partly because of a concomitant reduction in $\dot{Q}_T$(155). Although an increase in lung volume is the main mechanism for PEEP-induced changes in oxygenation, a small decrease in $\dot{Q}_T$ also reduces $\dot{Q}_S/\dot{Q}_T$ and may thereby improve p_aO_2(79). Many studies showed that PEEP in reality does not reduce extravascular lung water but mostly redistributes edema(156)(157). By recruiting non-aerated alveoli and stabilizing airways, PEEP may also influence the regional distribution of tidal ventilation(158)(165)(160): when the predominant effect of PEEP is recruitment, alveolar ventilation is expected to become more homogeneous, particularly in the dependent zones and confer a protective effect against VILI. Patients subjected to increased PEEP while receiving dopamine to maintain the same cardiac output exhibited significant reductions in $\dot{Q}_S/\dot{Q}_T$, suggesting that alveolar recruitment, rather than reduced $\dot{Q}_T$, was the predominant mechanism for improved oxygenation from increased PEEP(162).

The effects of PEEP on V_D/V_T and CO_2 elimination are complex. On the one hand, PEEP-induced alveolar recruitment may decrease physiological V_D/V_T due to a more homogeneous distribution of V_T and thereby decreased $\dot{Q}_S/\dot{Q}_T$(140). However, on the other hand, PEEP may favor over-distension of previously well-aerated alveoli resulting in increased physiological dead space(163). Overall, the impact of PEEP on V_D/V_T and p_aCO_2 is usually modest(164)(165)(166)(167). Increases in p_aCO_2 may indicate predominant hyperinflation.

Recruitment maneuvers

Recruitment maneuvers can improve oxygenation in many patients with ARDS(168). These maneuvers are integral part of the “Open Lung Strategy” that aims at maximizing recruitment(169). However, the safety of these maneuvers is debated and, moreover, unless combined with increased PEEP levels, their effect is usually very transient, lasting 15-20 minutes(168). Some authors showed that most of the effect is obtained after 10 seconds, before side effects occur suggesting that these maneuvers could be aborted rapidly.

Ventilatory mode

It has been suggested that, due to a more homogeneous distribution of V_T, the decelerating flow characteristic of pressure-targeted ventilation could result in improved gas exchange compared to the square wave flow usually used in volume-targeted modes(170). However, several studies demonstrated that, when the main settings (VT, PEEP) are comparable, pressure- and volume-controlled ventilation have similar effects on gas exchange(171)(172).

Lengthening inspiratory time in order to increase mean airway pressure without increasing peak alveolar pressure has been considered an attractive approach to improve oxygenation and lower the risk of barotrauma(173)(174). Inverse ratio ventilation, i.e., an inspiratory-to-expiratory time ratio>1 was therefore proposed as an alternative to conventional ventilation in ARDS. Several uncontrolled studies reported improved oxygenation with inverse ratio ventilation (175)(176). Controlled studies, however, did not find advantages for inverse ratio over conventional ventilation in terms of oxygenation when total end-expiratory pressure was kept constant(177)(171)(172). Extending inspiratory time by lengthening the duration of inspiratory pause slightly decreases V_D/V_T and thereby p_aCO_2 due to improved end-inspiratory gas mixing between alveoli and airways(178)(179)(180). Although usually of small magnitude, this effect may allow to decrease V_T and thus plateau pressure

with unchanged p_aCO_2(180). A prolonged inspiratory time may also increase right ventricular afterload(177).

High frequency oscillation (HFO) has been proposed as an alternative to conventional ventilation in patients with severe ARDS(181). In this mode, oxygenation depends mainly on mean airway pressure and F_IO_2 while CO_2 elimination depends on the frequency, the amplitude of oscillations, and the inspiratory time on expiratory time ratio. The negative results of two large randomized controlled trials have led to a discontinuation of the use of this technique in adults with ARDS(182)(183). Whether the hemodynamic effects of a high intrathoracic and mean airway pressure explain these negative results has been questioned.

Tidal volume and minute ventilation

Low tidal volume (V_T) is a key element of lung-protective ventilation to decrease mortality(111). In the ARMA trial the low V_T arm was associated with a lower level of oxygenation than the high V_T(111). When compared to “conventional” V_T at unchanged respiratory rate and PEEP, reducing V_T increases p_aCO_2 due to decreased $\dot{V}_E$ and increased $\dot{Q}_S/\dot{Q}_T$ resulting from increased $\dot{Q}_T$ and de-recruitment of poorly ventilated respiratory units (units with very low $\dot{V}_A/\dot{Q}$ ratios)(184). Due to the concomitant increase in p_vO_2 associated with increased $\dot{Q}_T$, the rise in $\dot{Q}_S/\dot{Q}_T$ associated with the reduced V_T results in an inconstant and small decrease in p_aO_2(184)(126). Reducing V_T is associated decreased V_D, usually resulting in unchanged V_D/V_T(184)(126). Due to the high V_D/V_T, the $\dot{V}_E$ required to obtain normocapnia is abnormally high(3). When using a VT=6 mL·kg^{-1}PBW, a respiratory rate of 25-35·min^{-1} is therefore usually necessary to achieve a p_aCO_2 with arterial pH=7.30-7.45(111).

Reduction of dead space

In mechanically ventilated patients, instrumental dead space contributes to total V_D/V_T. Because $V_A = V_T - V_D$, the impact of instrumental dead space on p_aCO_2 or on the required $\dot{V}_E$ is especially significant when using low V_T. Several clinical studies have shown that in patients with ARDS ventilated with a low V_T, reducing the instrumental dead space by replacing the heat and moisture exchanger by an active humidifier significantly decreased p_aCO_2(185)(186).

Tracheal gas insufflation (TGI) consists of a continuous or an expiratory injection of fresh gas into the central airways *via* an endotracheal catheter, in order to flush CO_2 from airway dead space and thereby to decrease anatomical dead space(187). Several studies have shown that TGI significantly reduced p_aCO_2 and/or allowed reducing V_T at constant p_aCO_2(188)(189). Due to safety issues and technical difficulties (increased intrinsic PEEP, inaccurate or difficult measurements of V_T and airway pressure, humidification of the insufflated fresh gas, monitoring of the position of the catheter, tracheal lesions), this technique has been difficult to apply in daily practice, and has progressively lost interest. De Robertis and Jonson developed a technique of aspiration and flushing of airway dead space during expiration that allowed to significantly decrease ventilatory requirements without increasing intrinsic PEEP(190)(191). This technique requires a specific device synchronized with the ventilator, and, hence, is not yet available for clinical use.

Spontaneous breathing vs muscle paralysis

While muscle paralysis and controlled mechanical ventilation have been classically used in patients with ARDS, allowing spontaneous breathing during mechanical ventilation gained increased interest during recent years. During assisted mechanical ventilation, the patient's inspiratory effort triggers the start of gas-flow delivery by the ventilator, which is maintained until a predefined termination criterion is met. Conversely, during non-assisted spontaneous breathing, the patient breathes freely

in a continuous or demand-flow system without any specific assistance of inspiratory efforts (i.e., during CPAP or airway pressure release ventilation, APRV). Experimental (192)(193)(194)(195)(196) and clinical studies(197)(198)(199)(200) demonstrated that spontaneous breathing during mechanical ventilation can improve oxygenation. Two mechanisms have been postulated for the possible beneficial effect of additional spontaneous breathing on gas exchange: *i)* alveolar recruitment of atelectatic regions, mainly in the dependent portions of the lung, eased by the preserved contraction of the diaphragm, and *ii)* shifting of pulmonary blood flow toward lung regions with higher $\dot{V}_A/\dot{Q}$ ratios(198)(201). When spontaneous breathing is preserved during mechanical ventilation, the pressure generated by the respiratory muscles adds to the pressure delivered by the ventilator, thus magnifying trans-pulmonary pressure(202)(203). In addition, local overstretch in dependent lung regions may occur, when a local rise in trans-pulmonary pressure causes alveolar air shift from non-dependent to dependent parts of the lung (i.e., pendelluft)(204). Through these mechanisms, spontaneous breathing may increase the risk of VILI. Thus, three points should be considered when allowing spontaneous breathing during mechanical ventilation: *i)* the severity of ARDS, ii) the evolution phase of the disease, and *iii)* the degree of synchronization between ventilator assistance and the patient's inspiratory effort. Most of the studies suggesting benefits of spontaneous breathing were performed in mild-to-moderate ARDS with only moderate ventilatory demands and/or after the acute phase of the disease. In patients with severe ARDS, the use of a neuromuscular blocking agents during the first 48 hours improved oxygenation and, ultimately, survival(96). Finally, the synchronization between ventilator assistance and the patient's inspiratory effort also determines the gas exchange effects of spontaneous breathing. When comparing the effects of pressure support (fully synchronized, pressure-targeted, assisted ventilatory mode) and APRV

(non-synchronized pressure-targeted ventilatory mode allowing unassisted spontaneous breathing) to pressure-controlled ventilation, Putensen *et al* showed in patients with ARDS, that APRV increased $\dot{Q}_T$ and improved oxygenation due to better $\dot{V}_A/\dot{Q}$ matching resulting from decreased $\dot{Q}_S/\dot{Q}_T$ and V_D/V_T. Pressure support did not have beneficial effects(198). Interestingly, these beneficial effects of unassisted spontaneous breaths during APRV were obtained despite a quite small spontaneous breathing activity.

In summary, spontaneous breathing can improve oxygenation in ARDS, but this approach should probably be limited to patients not exhibiting strong inspiratory efforts, after improvement of the acute phase or even in the early phase of mild or moderate ARDS(205). During pressure-targeted, assisted ventilator modes, monitoring of V_T is mandatory to estimate the inspiratory effort and, thereby indirectly, of trans-pulmonary pressure(203). The use of a non-synchronized mode may prove useful to limit V_T and trans-pulmonary pressure. Finally, excessive ventilator efforts leading to an increase in respiratory muscle metabolic rate and thus to an increase in ventilator requirements should be avoided.

Patient positioning

Prone positioning has been used to improve oxygenation in patients with ARDS since the 1970s(206)(207). Several studies demonstrated that prone positioning improves oxygenation (defined as an increase in $p_aO_2 \geq 20\%$ or $p_aO_2/F_IO_2 \geq 20$mmHg, as compared to supine) in approximately 75% of patients(95)(208)(209)(210). ~~Several mechanisms have been identified to explain the beneficial effect of prone position on oxygenation. First, prone position homogenizes pleural pressure and trans-pulmonary pressure across the lung(211). In fact, the ventral-to-dorsal gradient of pleural pressure becomes less negative in non-dependent lung regions and less positive in dependent areas(212)(213). A number of factors can explain this effect of~~

~~prone position, including the reversal of gravitational lung weight gradients(214)(215), elimination of the compressive force of the heart on dorsal lung regions(216)(217), and the release of the compression of abdominal contents on caudal regions of the dorsal lung(218)(219). The net effect is the homogenization of regional lung inflation, which increases in dorsal lung regions and decreases in ventral regions, and can be more evident when lung injury is more heterogeneous as in lobar ARDS(220). In addition, both animal and human studies showed that distribution of pulmonary blood flow, which is prevalent in the dorsal lung in the supine position, does not change when turning patient prone(221)(222)(223)(224)(177). Thus, the improvement in oxygenation in the prone position is due to a reduction in $\dot{Q}_S/\dot{Q}_T$ resulting from the concomitant increase in the aeration in the dorsal lung regions, with dorsal recruitment being greater than ventral de-recruitment, and the persistence of better lung perfusion in these regions.~~By recruiting the lung and homogenizing alveolar ventilation, prone position should theoretically decrease p_aCO_2 and V_D/V_T as well(226)(227). The effect of prone position on p_aCO_2, however, is less predictable, and has mostly been considered less important than the effect on oxygenation. Nevertheless, the decrease in p_aCO_2, rather than the increased p_aO_2/F_IO_2, is associated with improved recruitment and better outcome with prone position(228)(229). ~~Besides the effects on gas exchange, prone position decrease lung stress and strain and prevent VILI(230)(231)(232). Hence, it seems to improves outcome of the most severe ARDS patients(95)(233)(234).~~

Limited data suggested that vertical positioning can also improve oxygenation(235)(236). Richard *et al.* showed that, as compared with supine position, upright positioning (trunk elevated at 45° and legs down at 45°) improved oxygenation in 11/16 patients with ARDS(195). The improved oxygenation was associated with an increased lung volume, suggesting an increase in lung

recruitment. By relieving abdominal compression on lung bases, verticalization may, hence, allow caudal displacement of the diaphragm and thereby promote recruitment of dependent lung areas. These results were confirmed by Dellamonica *et al.*, who found that vertical position improved oxygenation, increased end-expiratory lung volume and decreased lung strain in 13/40 patients with ARDS(236). However, the individual oxygenation response to verticalization was unrelated to changes in lung volume, suggesting that mechanisms other than recruitment, for instance changes in cardiac output, also contributed to the improved oxygenation with vertical positioning.

Pharmacological manipulation of $\dot{V}_A/\dot{Q}$ distribution

Inhaled NO decreases $\dot{Q}_S/\dot{Q}_T$ of well-ventilated respiratory units due to regional vasodilatation(38). In most patients with ARDS, concentrations of 1-10ppm are sufficient to achieve an NO effect on oxygenation(237). These low concentrations of inhaled NO allow avoiding formation of harmful NO_2 concentrations and the occurrence of met-hemoglobinemia. The inhaled NO-related improvement of oxygenation is usually transient (≤72 hours)(238), and the risk of rebound necessitates a progressive withdrawal(239). Finally, this transiently improved oxygenation was not associated with improved outcome(240). Aerosolized prostacyclin is an alternative to inhaled NO resulting in similar improvement in oxygenation(39)(40)67)(71). By enhancing hypoxic vasoconstriction, intravenous almitrine, a selective pulmonary vasoconstrictor, redistributes blood flow from shunt units to ventilated units and may thereby improve oxygenation(68)(70). Low-dose intravenous almitrine ($4\mu g \cdot kg^{-1} \cdot min^{-1}$) comparably increased paO_2 as 5ppm inhaled NO, the combination of the two drugs eventually resulting in additive effects(68)(69)(70). Interestingly, the association of inhaled NO allows to offset the increase in pulmonary arterial pressure induced by almitrine(69).

Individualized adjustment of ventilator settings

Currently, strategies proposed for V_T adaptation are mainly based on PBW and/or indices of lung stress, such as plateau pressure, trans-pulmonary pressure or driving pressure. Reducing V_T is accompanied by a decreased V_D(184)(241). The resultant effect on CO_2 elimination efficiency assessed by V_D/V_T is variable. A decreased V_D/V_T has been suggested to be indicative of attenuated over-inflation(140). However, changes in V_D/V_T secondary to changes in V_T are usually quite small(184)(241), and the clinical impact of a strategy including measurement of V_D/V_T for individual setting of V_T has not been evaluated so far.

Reducing V_T at constant PEEP levels increases $\dot{Q}_S/\dot{Q}_T$ due to alveolar de-recruitment and increased $\dot{Q}_T$(184)(242)(126)(243). As mentioned-above the net effect on p_aO_2 depends on the respective magnitudes of the changes in $\dot{Q}_S/\dot{Q}_T$ and p_vO_2. Any increase in $\dot{Q}_S/\dot{Q}_T$ induced by V_T reduction is easily counterbalanced by increasing PEEP(144).

Although the effect of PEEP on oxygenation cannot be considered an accurate estimate of its effect on alveolar recruitment(143)(149), data from physiologic studies and from large randomized controlled trials suggest that oxygenation should be taken into account for individual PEEP titration(94). Studies from Gattinoni's group assessing the effect of PEEP using CT scan clearly demonstrate a relationship between p_aO_2/F_IO_2 measured on low PEEP (5cmH_2O), and the quantity of lung tissue that can be recruited and protected from tidal opening and closing with high PEEP, this quantity being much more important in patients with a p_aO_2/F_IO_2<150mmHg on PEEP 5cmH_2O, than in patients with less severe hypoxemia(165)(244). In line with this finding, an individual meta-analysis of the three large randomized clinical trials comparing high PEEP to moderate PEEP in patients with ARDS ventilated with a low V_T(112)(113)(114), demonstrated that impact of high PEEP on mortality varies according to the p_aO_2/F_IO_2 (94). High PEEP was associated with decreased mortality

in patients with a p_aO_2/F_IO_2<200mmHg (moderate or severe ARDS), while a tendency for an opposite effect was observed in the less severely hypoxemic patients (200<p_aO_2/F_IO_2<300mmHg). Another argument for taking into account oxygenation for PEEP setting was provided by Goligher *et al*, who retrospectively analyzed the results of the “LOVS” and “ExPress” trials(245): the effect of increasing PEEP on oxygenation was highly variable, and the magnitude of the PEEP-induced increase in p_aO_2/F_IO_2 was strongly associated with decreased adjusted odds ratio for death. Measurement of V_D/V_T has been proposed as a tool for determination of the optimal level of PEEP(140), but the magnitude of the changes of p_aCO_2 secondary to PEEP is usually too small to allow an easy identification of an optimal PEEP level(166)(167). Finally, Gattinoni *et al*. reported that the best combination of physiological parameters predicting more pronounced recruitment as measured by CT scan, was p_aO_2/F_IO_2 on PEEP 5cmH_2O <150mmHg together with increased compliance of the respiratory system and a decreased V_D/V_T when PEEP was increased from 5 to 15 cmH_2O(165).

Altogether, these findings strongly suggest that individual titration of PEEP in patients with ARDS should take into account effects on both oxygenation and CO_2 elimination.

Table 1. Main pathophysiologic mechanisms of impaired gas exchange in ARDS

Disturbance	**Main mechanisms**
Hypoxemia	• $\dot{Q}_S/\dot{Q}_T$ • low $\dot{V}_A/\dot{Q}$ • Low p_vO_2 • Intra-cardiac shunt (e.g., PFO)
Hypercapnia	• Increased V_D/V_T • Inhomogeneous distribution of ventilation (high $\dot{V}_A/\dot{Q}$) • Increased $\dot{V}CO_2$

ARDS: acute respiratory distress syndrome; PFO: patent foramen ovale; $p_{\bar{v}}O_2$: mixed venous O_2 partial pressure; $\dot{Q}_S/\dot{Q}_T$ intrapulmonary right-to-left shunt; $\dot{V}_A/\dot{Q}$: ventilation/perfusion ratio; $\dot{V}CO_2$: metabolic CO_2 production; V_D/V_T: dead space

Table 2. Therapeutic measures to correct hypoxemia

Treatment	**Beneficial effects**	**Risks**
High F_IO_2	Increases in p_AO_2, p_IO_2 and p_vO_2	Resorption atelectasis
PEEP	Alveolar recruitment with decrease in $\dot{Q}_S/\dot{Q}_T$	Lung over-distension Decreased $\dot{Q}_T$
Spontaneous breathing (mild-moderate ARDS, post-acute phase)	Alveolar recruitment Improved $\dot{V}_A/\dot{Q}$ matching (redirection of pulmonary blood flow to more aerated regions)	Lung over-distension VILI
Recruitment maneuver	Transient recruitment and decreased $\dot{Q}_S/\dot{Q}_T$	Transient decrease in $\dot{Q}_T$ Barotrauma
Prone position	Homogenization of ventilation distribution (improved aeration in the dorsal regions) Decrease in $\dot{Q}_S/\dot{Q}_T$ (unchanged perfusion, predominantly directed to dorsal regions)	
Vertical positioning	Alveolar recruitment	Unpredictable effect

	Increased lung volume	Decreased $\dot{Q}_T$
Inhaled NO	Decrease in $\dot{Q}_S/\dot{Q}_T$ (improved perfusion of aerated lung regions with normal $\dot{V}_A/\dot{Q}$ ratios)	Transient effect Rebound at withdrawal
Inhaled PGI_2	Decrease in $\dot{Q}_S/\dot{Q}_T$ (improved perfusion of aerated lung regions with normal $\dot{V}_A/\dot{Q}$ ratios)	Transient effect Rebound at withdrawal
Intravenous almitrine	Decrease in $\dot{Q}_S/\dot{Q}_T$ (increased pulmonary vascular tone)	Increase in PAP and RV afterload

ARDS: acute respiratory distress syndrome; F_IO_2: inspired fraction of oxygen; NO: nitric oxide; p_AO_2: alveolar O_2 partial pressure; PAP: pulmonary artery pressure; PEEP: positive end-expiratory pressure; PGI_2: prostacyclin; p_IO_2: inspired O_2 partial pressure; p_vO_2: mixed-venous O_2 partial pressure of oxygen; $\dot{Q}_S/\dot{Q}_T$ intrapulmonary right-to-left shunt; $\dot{Q}_T$: cardiac output; RV: right ventricular; $\dot{V}_A/\dot{Q}$: ventilation/perfusion ratio; VILI ventilator-induced lung injury

.

Table 3. Therapeutic measures to correct hypercapnia

Treatment	**Beneficial effects**	**Risks**
Sedation +/- paralysis	Reduced $\dot{V}CO_2$	Delayed weaning
Lengthening inspiratory pause	Improved homogeneity of ventilation distribution	Increase in $PEEP_i$ and $PEEP_{tot}$ (shortening of expiratory time)
Increasing respiratory rate	Increase in minute ventilation	Increase in $PEEP_i$ and $PEEP_{tot}$ (shortening of expiratory time)
Decrease of instrumental dead space	Decrease of V_D/V_T	-
TGI	Decrease of V_D/V_T due to reduced airway dead space	Increase in $PEEP_i$ and $PEEP_{tot}$ Inaccurate V_T measurement Tracheal lesions
Prone position	Homogenization of ventilation distribution	Unpredictable effect

Abbreviations. PEEP: positive end-expiratory pressure; PEEP: positive end-expiratory pressure; $PEEP_i$: intrinsic PEEP; $PEEP_{tot}$: total PEEP; TGI: tracheal gas insufflation; V_D/V_T: dead space; V_T: tidal volume.

Table 4. Practical approach for individualizing ventilator settings in moderate-severe ARDS (p_aO_2/F_IO_2 < 200 mmHg).

Step	What to do	Notes
1. Assess ARDS severity	Measure p_aO_2/F_IO_2 Measure V_D/V_T Lung imaging	Highest severity if p_aO_2/F_IO_2 <150 mmHg at PEEP 5 cm H_2O, together with a high V_D/V_T and diffuse lung injury
2. PEEP test	Increase PEEP from 5 to 15 cm H_2O	High recruitability if p_aO_2/F_IO_2 increases, while V_D/V_T and/or p_aCO_2 decrease and compliance of respiratory system increases
3. Optimize PEEP	High severity and high recruitability: set the highest PEEP for P_{plat} < 30 cm H_2O and driving pressure < 15 cm H_2O. Low severity (p_aO_2/F_IO_2 ≥ 150 mmHg) or low recruitability: set the minimal PEEP to obtain acceptable oxygenation (i.e., S_pO_2 > 88%) with lowest F_IO_2 (with P_{plat} < 30 cm H_2O and driving pressure < 15 cm H_2O)	Target oxygenation = p_aO_2 55-80 mmHg and/or S_pO_2 88-95 % Target p_aCO_2 = ≤ 50 mmHg
4. Control hypercapnia	Increase RR (up to 30-35/min)	Check PEEPi

	Lengthen end-inspiratory pause (up to 0.7 s) Decrease instrumental deadspace (i.e. replace HME with a heated humidifier)	
5. Change position	Prone position	
6. Rescue strategies	Inhaled NO or PGI_2 ECMO ECCO2R	

ARDS: acute respiratory distress syndrome; ECCO2R: extracorporeal carbon dioxide removal; ECMO: extracorporeal membrane oxygenation; F_IO_2: inspired fraction of oxygen; HME: heat and moisture exchanger; NO: nitric oxide; p_aCO_2: arterial CO_2 partial pressure of carbon dioxide; p_aO_2: arterial O_2 partial pressure of oxygen; PEEP: positive end-expiratory pressure; PGI_2: prostacyclin; P_{plat}: end-inspiratory plateau pressure; RR: respiratory rate; V_D/V_T: physiologic deadspace; S_pO_2: percutaneous hemoglobin O_2 saturation;

Figure legends

Figure 1: The pO_2/pCO_2 diagram for single gas exchange unit at F_IO_2=0.21 and an CO_2/O_2 exchange ratio, i.e. respiratory exchange ratio RER=$\dot{V}CO_2/\dot{V}O_2$ =0.8. For any given F_IO_2, hemoglobin (Hb) content, and RER, each $\dot{V}_A/\dot{Q}$ ratio in a gas exchange unit is associated with a single pair of pO_2 and pCO_2 values. V_A/Q ratios can vary from 0 (perfused but non-ventilated alveoli; their gas partial pressures being those of the mixed-venous blood) to ∞ (ventilated, but non-perfused alveoli; their gas partial pressures being those of the inspired gas); a single line connecting these extreme values can be drawn through all possible pO_2/pCO_2 pairs. In a lung without inhomogeneity, arterial (a) and mean alveolar (A) gas partial pressures would be super-imposed at the "*ideal*" $\dot{V}_A/\dot{Q}$ ratio that corresponds to the RER. Arterial blood is the sum of the blood from all individual gas exchange units, i.e. those where perfusion exceeds ventilation or where there is no perfusion at all (i.e. $0 \leq \dot{V}_A/\dot{Q} < i$), as well as those where ventilation exceeds perfusion or where there is no ventilation at all (i.e. $i < \dot{V}_A/\dot{Q} < \infty$). Consequently, the real value pairs of arterial and mean alveolar gas partial pressures move away from this line, giving rise to the development of arterial-alveolar (a-A) partial pressure differences (Δ). Adapted from (8) with kind permission from Springer Science and Business Media.

Figure 2: The 3-compartment model by Riley & Cournand(10). Dead space (V_D/V_T) and right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$) are represented as shunted ("wasted"; see text) ventilation and perfusion, respectively. Adapted from (41) with kind permission from Springer Science and Business Media.

Figure 3: Expired pCO_2 as a function of expired volume. "*Phase I"* refers to the CO_2-free gas from the conducting airways. "*Phase II*" refers to the *S*-shaped steep part of the expired pCO_2-curve, i.e. the transition between gas from the airways and alveolar gas, whereas "*Phase III*" refers to the near-plateau alveolar phase until end-tidal pCO_2 ($p_{et}CO_2$) is reached, which allows for calculating V_D/V_T using the Enghoff equation(11), and partitioning of dead space between the airway (anatomical) and the alveolar component according to Fletcher *et al*(14). Adapted from (250) with kind permission from Springer Science and Business Media.

Figure 4: Exemplary mixed venous (blue), alveolar (black), and arterial (red) pO_2 and pCO_2 values in lung regions without ventilation (right-to-left shunt, $\dot{Q}_S/\dot{Q}_T$), where perfusion exceeds ventilation (i.e. $0<\dot{V}_A/\dot{Q}<$normal $\dot{V}_A/\dot{Q}$, i.e. "*low*" $\dot{V}_A/\dot{Q}$ ratios), where ventilation exceeds perfusion (i.e. normal $\dot{V}_A/\dot{Q}$ ratio$<\dot{V}_A/\dot{Q}<\infty$, i.e. "*high*" $\dot{V}_A/\dot{Q}$ ratios), or where there is no ventilation at all (dead space, V_D/V_T) at an inspired O_2 concentration $F_iO_2=0.5$, a hemoglobin (Hb) content=150g·L^{-1}, and a respiratory exchange ratio RER=0.8.

Figure 5: Continuous distributions of alveolar ventilation (open symbols) and pulmonary blood flow (closed symbols) as assessed using the MIGET technique in a young, healthy volunteer breathing air (left panel) and a patient with severe ARDS before (middle panel) and during (right panel) continuous i.v. prostacyclin (PGI_2). In this individual patient, there was a substantial fraction of pulmonary blood flow to lung regions with low $\dot{V}_A/\dot{Q}$ ratios ($0<\dot{V}_A/\dot{Q}<$normal$\dot{V}_A/\dot{Q}$) under baseline conditions, which was markedly reduced due to increased $\dot{Q}_S/\dot{Q}_T$ during vasodilator infusion. Note that despite the marked increase in $\dot{Q}_S/\dot{Q}_T$ (from 37 to 51% of cardiac output), p_aO_2 even

increased during the PGI_2 infusion due to the increase in $\dot{Q}_T$ and the subsequent rise in $p_{\bar{v}}O_2$ (see also figures 8 and 9). Middle and right panel: Adapted from (35) with kind permission from Wolters Kluwer Health.

Figure 6: Effects of intravenous (left panel) and inhaled (right panel) prostacyclin on systemic and pulmonary hemodynamics and gas exchange in patients with ARDS. PAP pulmonary artery pressure, PVR pulmonary vascular resistance, RVEF right ventricular ejection fraction, CO cardiac output, DO_2 systemic O_2 delivery, MAP mean blood pressure, SVR systemic vascular resistance. Adapted from (71) with kind permission from Springer Science and Business Media.

Figure 7: Arterial pO_2 during pure O_2 breathing, plotted as a function of the arterial – mixed venous O_2 content difference (in $mL \cdot dL^{-1}$) for incremental $\dot{Q}_S/\dot{Q}_T$ (in % of total pulmonary blood flow) levels. Note that for any given $\dot{Q}_S/\dot{Q}_T$ level, the higher the arterial–mixed venous O_2 content difference, the lower the mixed venous pO_2 and, consequently the lower the p_aO_2. Adapted from Radermacher P, Falke KJ: Pulmonary ventilation and gas exchange; in: Care of the Critically Ill Patient 2nd edition (Tinker J, Zapol WM, editors), Springer Heidelberg NewYork, 1992, pp. 59 – 67, with kind permission from Springer Science and Business Media.

Figure 8: Effect of a rise in cardiac output on arterial pO_2 (p_aO_2). Note that increasing cardiac output may lead to a rise of p_aO_2 due to the increased in mixed venous pO_2 ($p_{\bar{v}}O_2$) (see also figure 6). On the other hand, any increase may even cause a fall of p_aO_2 as a result of an increase in right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$), either directly (78) and/or due to the fall in pulmonary vascular tone(33)(34)(35)(37)(38)(39)(40).

Figure 9: The ratio p_aO_2/F_IO_2 plotted as function of F_IO_2 ranging from 0.21(air)-1.0(pure O_2) for $\dot{Q}_S/\dot{Q}_T$ values ranging from 1-50% at a constant hemoglobin (Hb) content=100g·L^{-1} and an arterial–mixed venous O_2 content difference=3.5 mL·dL^{-1}. Adapted from (91) with kind permission from Wolters Kluwer Health.

Figure 10: Iso-shunt diagram showing the effect of increasing F_IO_2 (x-axis) on p_aO_2 (y-axis) for various levels of intrapulmonary shunt. Adapted from (246) with kind permission from Oxford University Press.

Figure 1

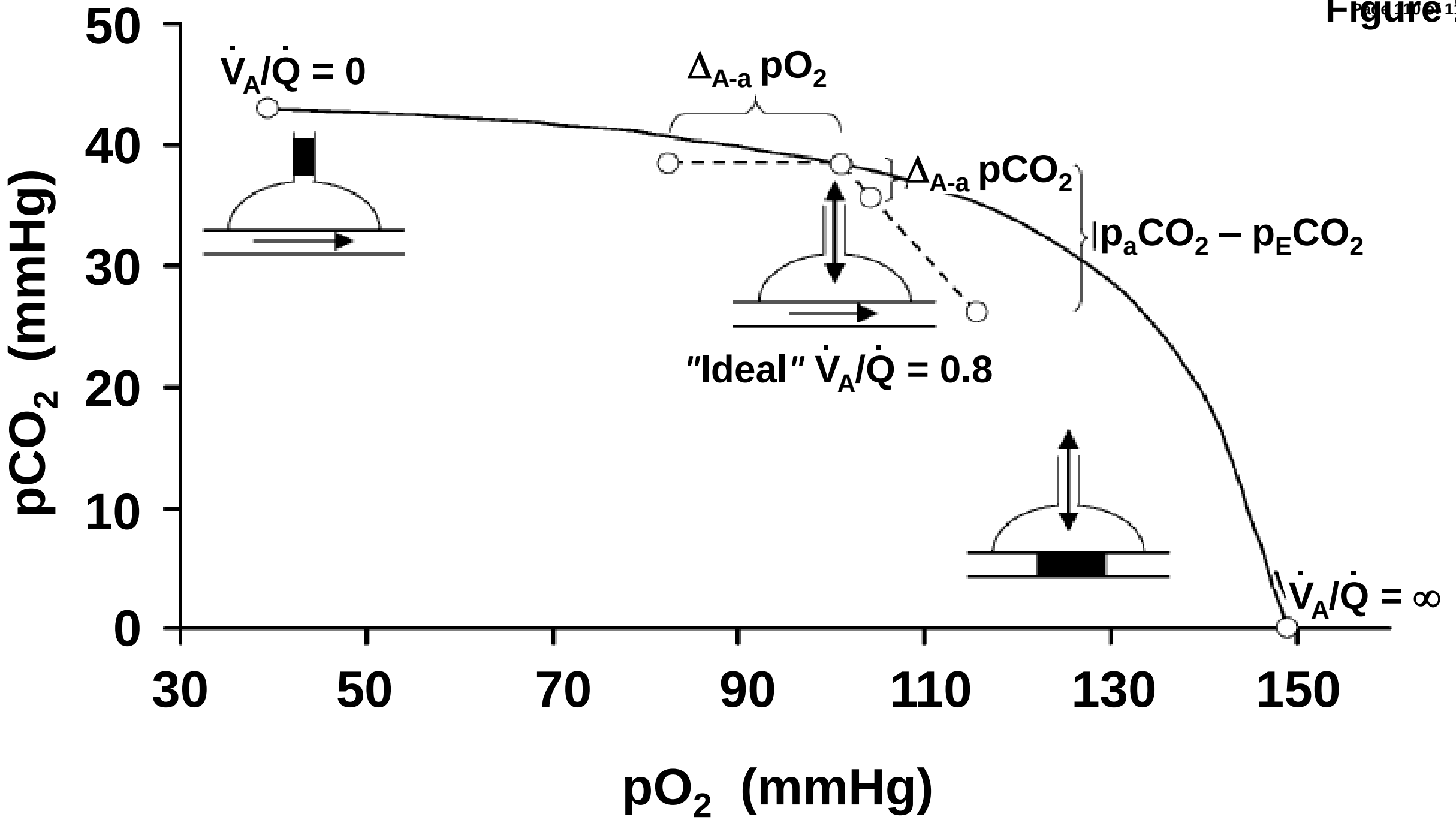

50
40
30
20
10
0
pCO_2 (mmHg)
30
50
70
90
110
130
150
pO_2 (mmHg)
$\dot{V}_A/\dot{Q} = 0$
$\Delta_{A-a}\,pO_2$
$\Delta_{A-a}\,pCO_2$
$|p_aCO_2 - p_ECO_2$
"Ideal" $\dot{V}_A/\dot{Q} = 0.8$
$\dot{V}_A/\dot{Q} = \infty$

Figure 2

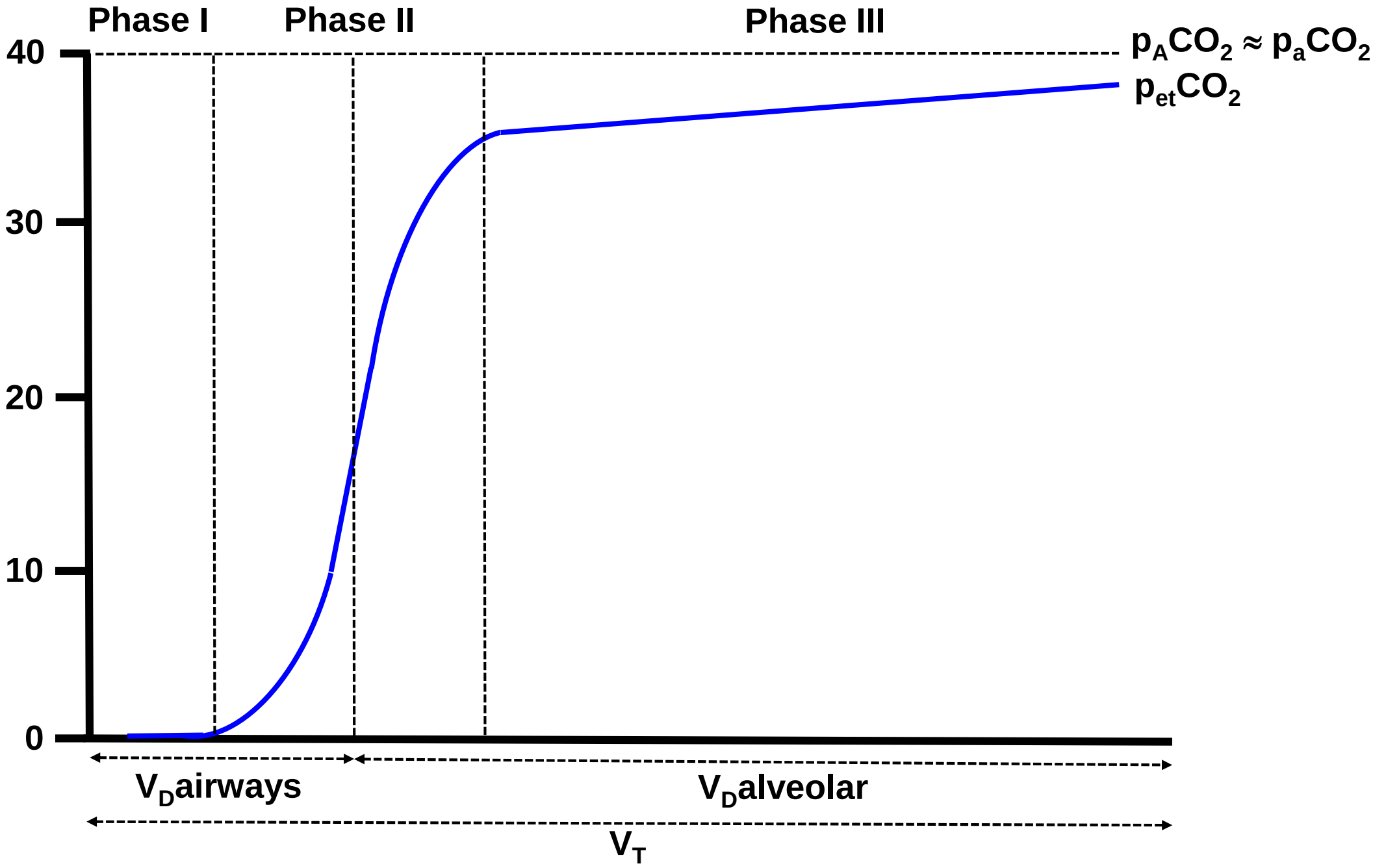

Phase I
Phase II
Phase III
40
30
20
10
0
$p_ACO_2 \approx p_aCO_2$
$p_{et}CO_2$
$V_D$airways
$V_D$alveolar
V_T

Figure 3

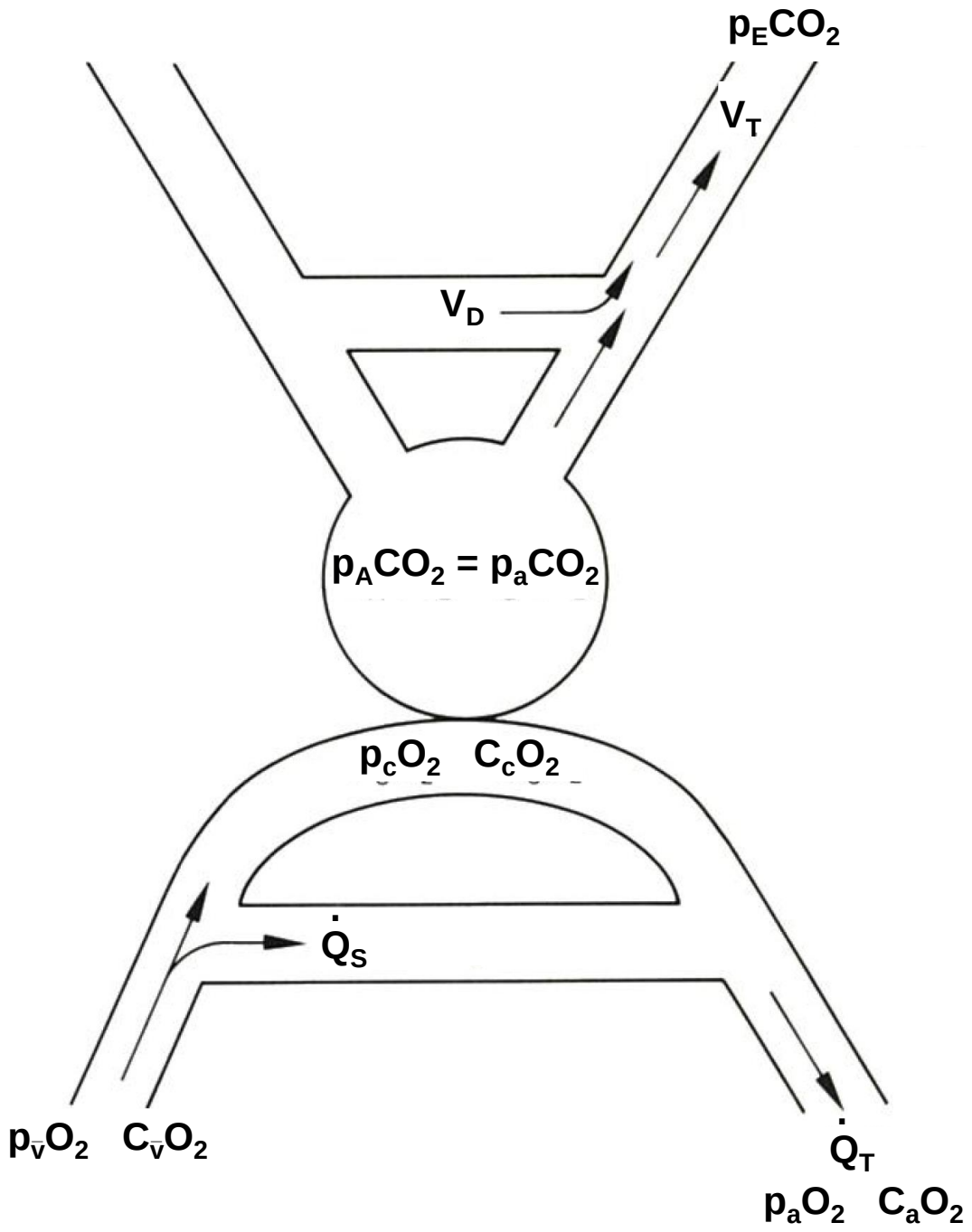

p_ECO_2
V_T
V_D
$p_ACO_2 = p_aCO_2$
p_cO_2 C_cO_2
$\dot{Q}_S$
$p_{\bar{v}}O_2$ $C_{\bar{v}}O_2$
$\dot{Q}_T$
p_aO_2 C_aO_2

Figure 4

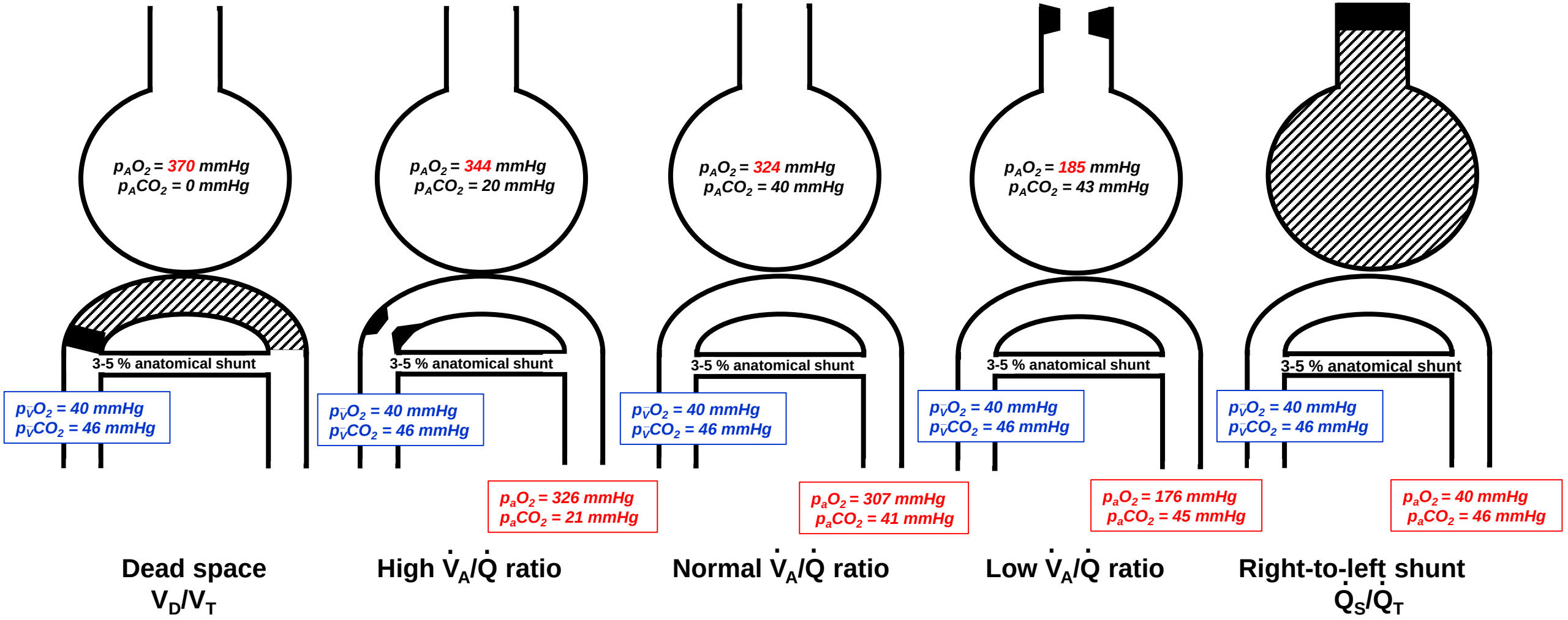

p_AO_2 = 370 mmHg
p_ACO_2 = 0 mmHg
3-5 % anatomical shunt
$p_{\bar{V}}O_2$ = 40 mmHg
$p_{\bar{V}}CO_2$ = 46 mmHg
Dead space
V_D/V_T
p_AO_2 = 344 mmHg
p_ACO_2 = 20 mmHg
3-5 % anatomical shunt
$p_{\bar{V}}O_2$ = 40 mmHg
$p_{\bar{V}}CO_2$ = 46 mmHg
p_aO_2 = 326 mmHg
p_aCO_2 = 21 mmHg
High $\dot{V}_A/\dot{Q}$ ratio
p_AO_2 = 324 mmHg
p_ACO_2 = 40 mmHg
3-5 % anatomical shunt
$p_{\bar{V}}O_2$ = 40 mmHg
$p_{\bar{V}}CO_2$ = 46 mmHg
p_aO_2 = 307 mmHg
p_aCO_2 = 41 mmHg
Normal $\dot{V}_A/\dot{Q}$ ratio
p_AO_2 = 185 mmHg
p_ACO_2 = 43 mmHg
3-5 % anatomical shunt
$p_{\bar{V}}O_2$ = 40 mmHg
$p_{\bar{V}}CO_2$ = 46 mmHg
p_aO_2 = 176 mmHg
p_aCO_2 = 45 mmHg
Low $\dot{V}_A/\dot{Q}$ ratio
3-5 % anatomical shunt
$p_{\bar{V}}O_2$ = 40 mmHg
$p_{\bar{V}}CO_2$ = 46 mmHg
p_aO_2 = 40 mmHg
p_aCO_2 = 46 mmHg
Right-to-left shunt
$\dot{Q}_S/\dot{Q}_T$

Figure 5

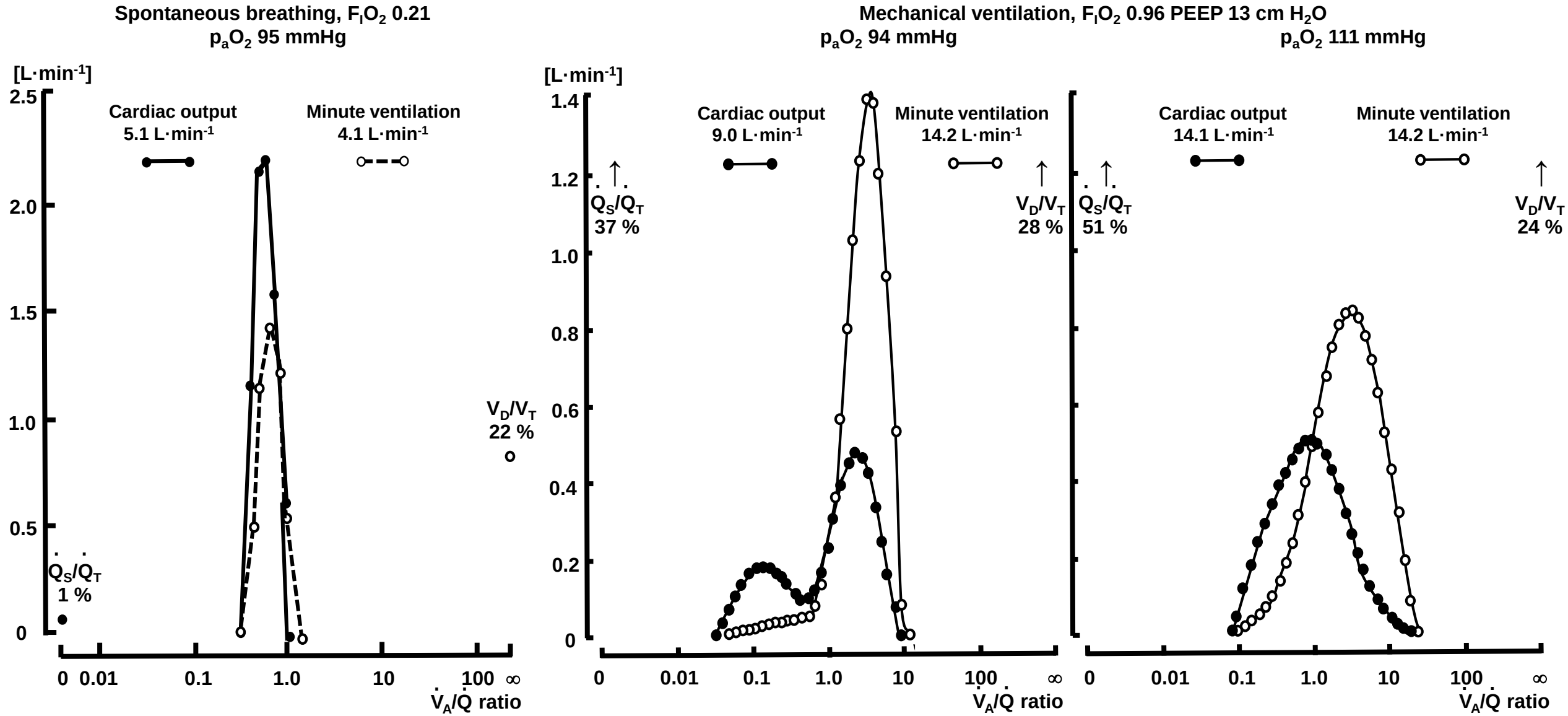
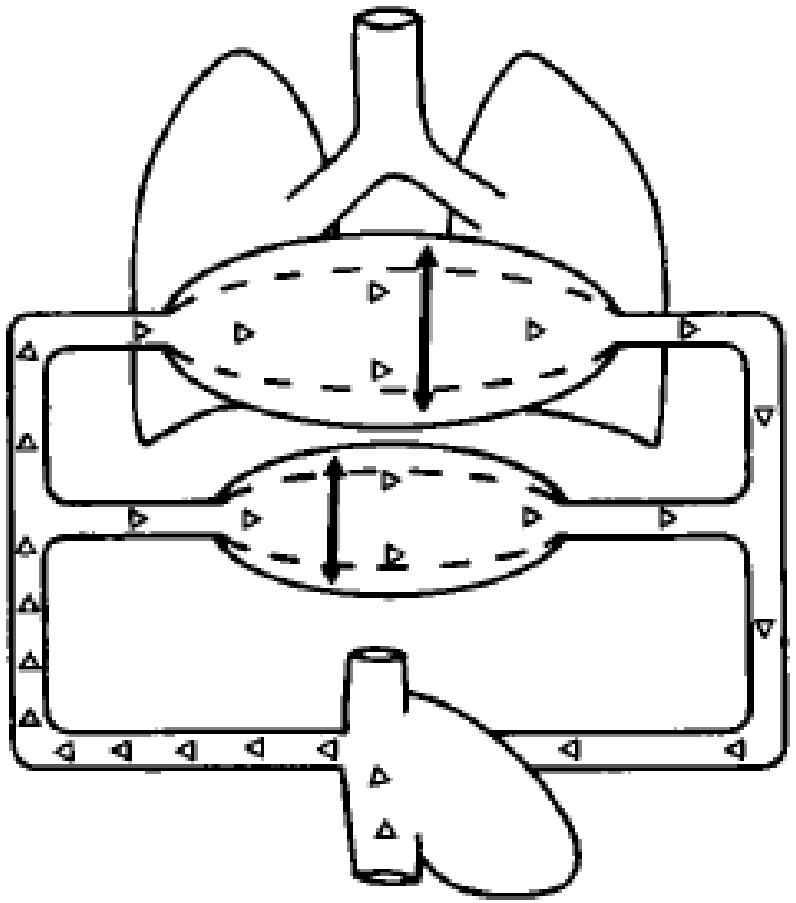

Spontaneous breathing, F_IO_2 0.21
p_aO_2 95 mmHg
[L·min-1]
Cardiac output
5.1 L·min-1
Minute ventilation
4.1 L·min-1
V_D/V_T
22 %
$\dot{Q}_S/\dot{Q}_T$
1 %
2.5
2.0
1.5
1.0
0.5
0
0 0.01 0.1 1.0 10 100 ∞
$\dot{V}_A/\dot{Q}$ ratio
Mechanical ventilation, F_IO_2 0.96 PEEP 13 cm H_2O
p_aO_2 94 mmHg
[L·min-1]
Cardiac output
9.0 L·min-1
Minute ventilation
14.2 L·min-1
$\dot{Q}_S/\dot{Q}_T$
37 %
V_D/V_T
28 %
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
0 0.01 0.1 1.0 10 100 ∞
$\dot{V}_A/\dot{Q}$ ratio
p_aO_2 111 mmHg
Cardiac output
14.1 L·min-1
Minute ventilation
14.2 L·min-1
$\dot{Q}_S/\dot{Q}_T$
51 %
V_D/V_T
24 %
0 0.01 0.1 1.0 10 100 ∞
$\dot{V}_A/\dot{Q}$ ratio

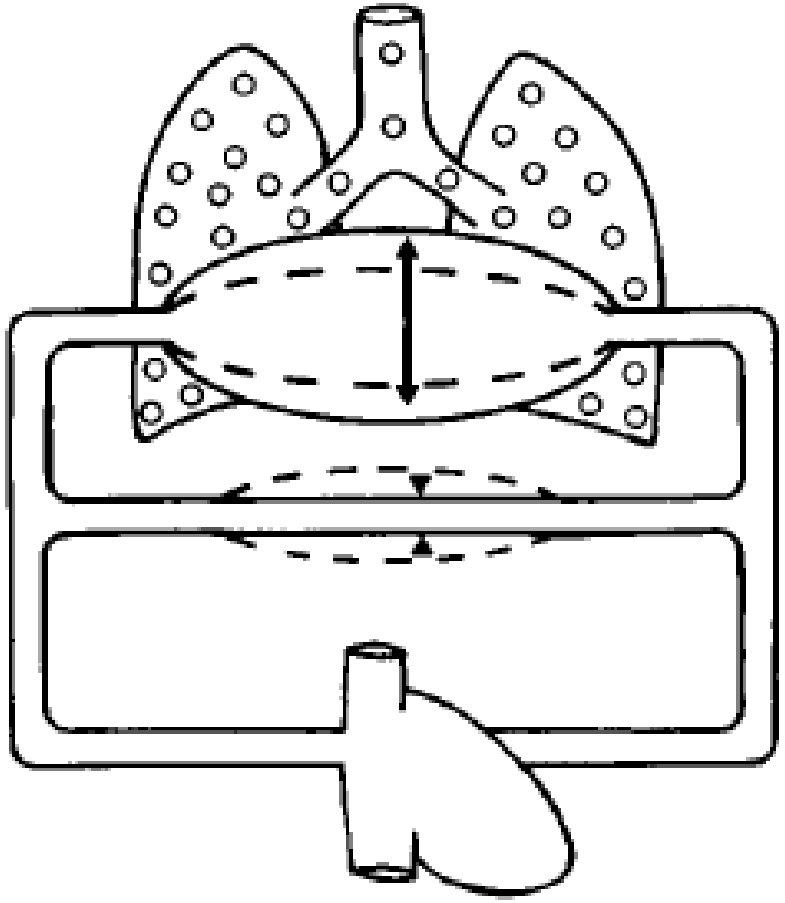
Figure 6



Vasodilator i.v.

- PAP ⇓
- PVR ⇓
- RVEF ⇑
- CO ⇑
- Shunt ⇑
- P_aO_2 ⇓
- DO_2 ⇑
- MAP ⇓
- SVR ⇓

Vasodilator inhaled



- PAP ⇓
- PVR ⇓
- RVEF ⇑
- CO ±0/⇑
- Shunt ⇓
- P_aO_2 ⇑
- DO_2 (⇑)
- MAP ±0/⇑
- SVR ±0

Figure 7

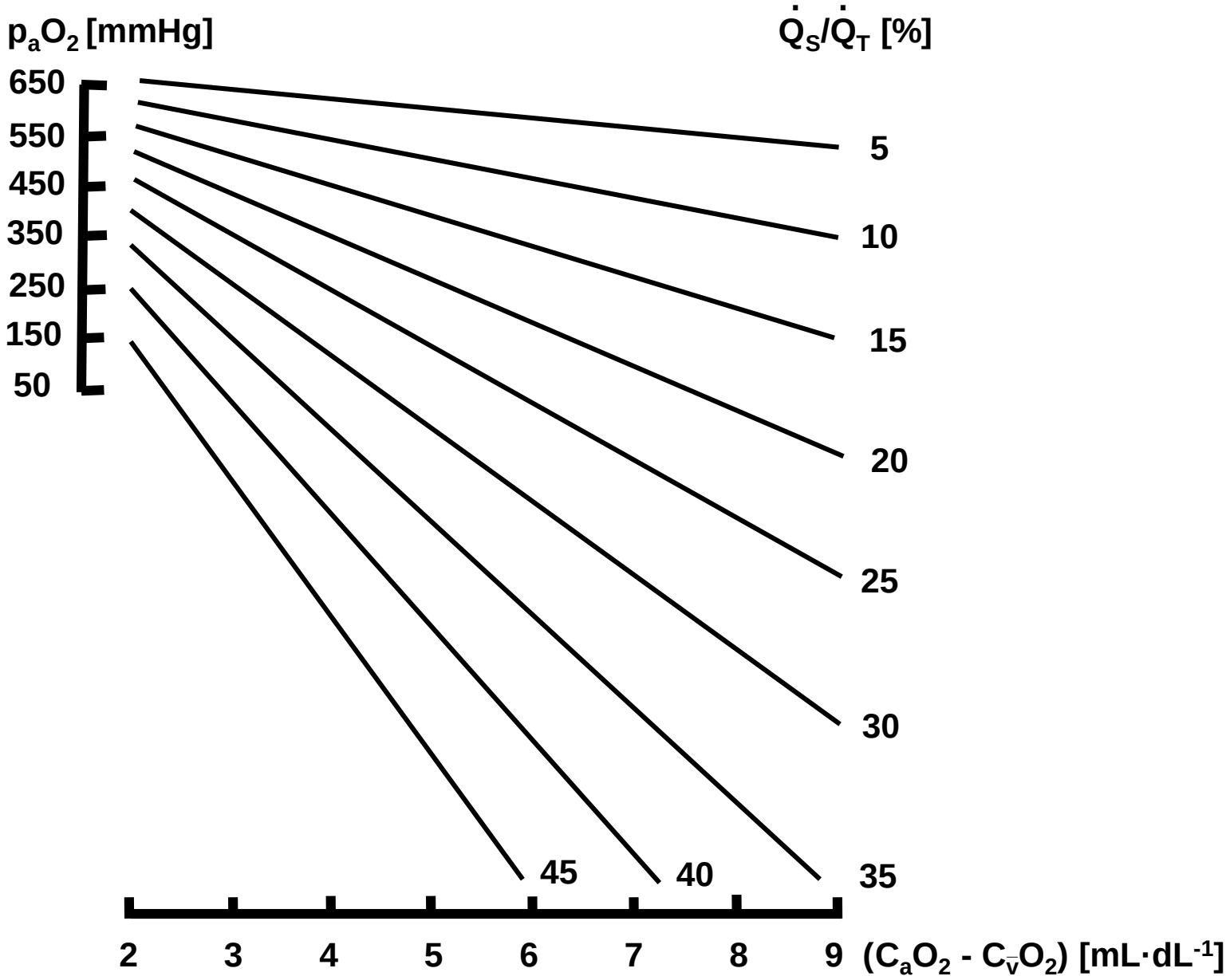

p_aO_2 [mmHg]
650
550
450
350
250
150
50
$\dot{Q}_S/\dot{Q}_T$ [%]
5
10
15
20
25
30
35
40
45
2
3
4
5
6
7
8
9
$(C_aO_2 - C_{\bar{v}}O_2)$ [mL·dL^{-1}]

Figure 8

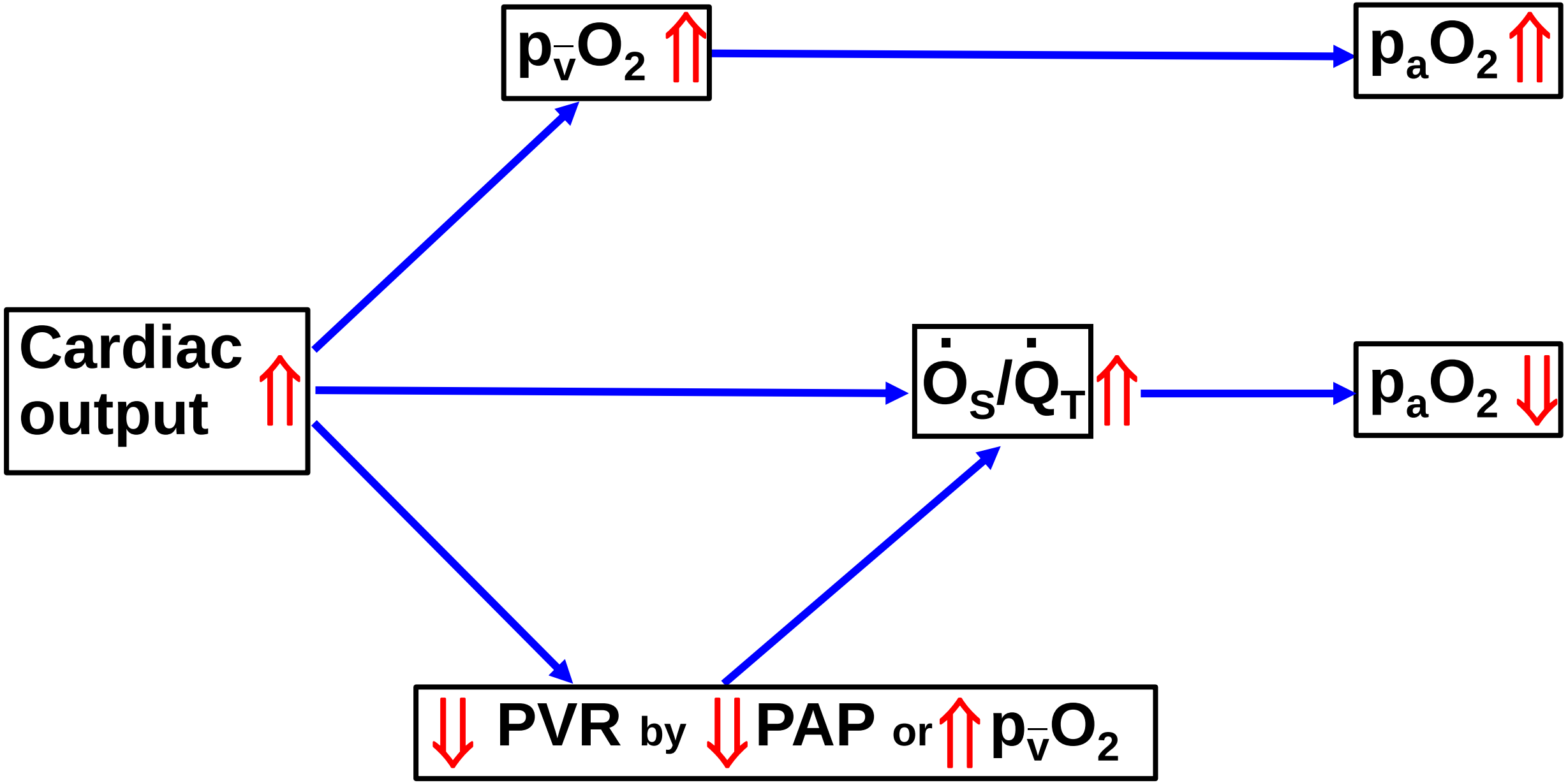

$p_{\bar{v}}O_2$ ⇑
p_aO_2 ⇑
Cardiac output ⇑
$\dot{O}_S/\dot{Q}_T$ ⇑
p_aO_2 ⇓
⇓ PVR by ⇓ PAP or ⇑ $p_{\bar{v}}O_2$

Figure 9

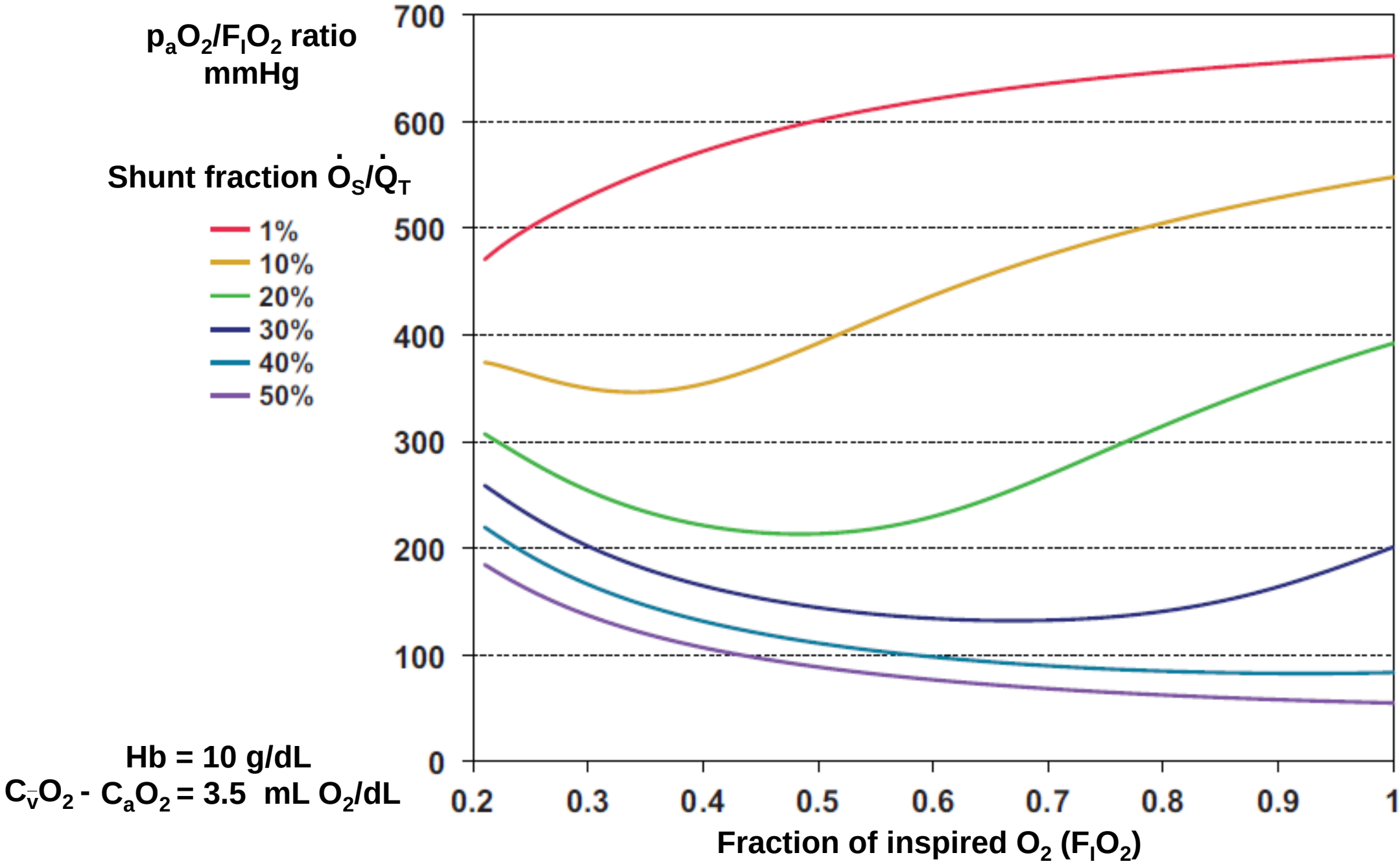
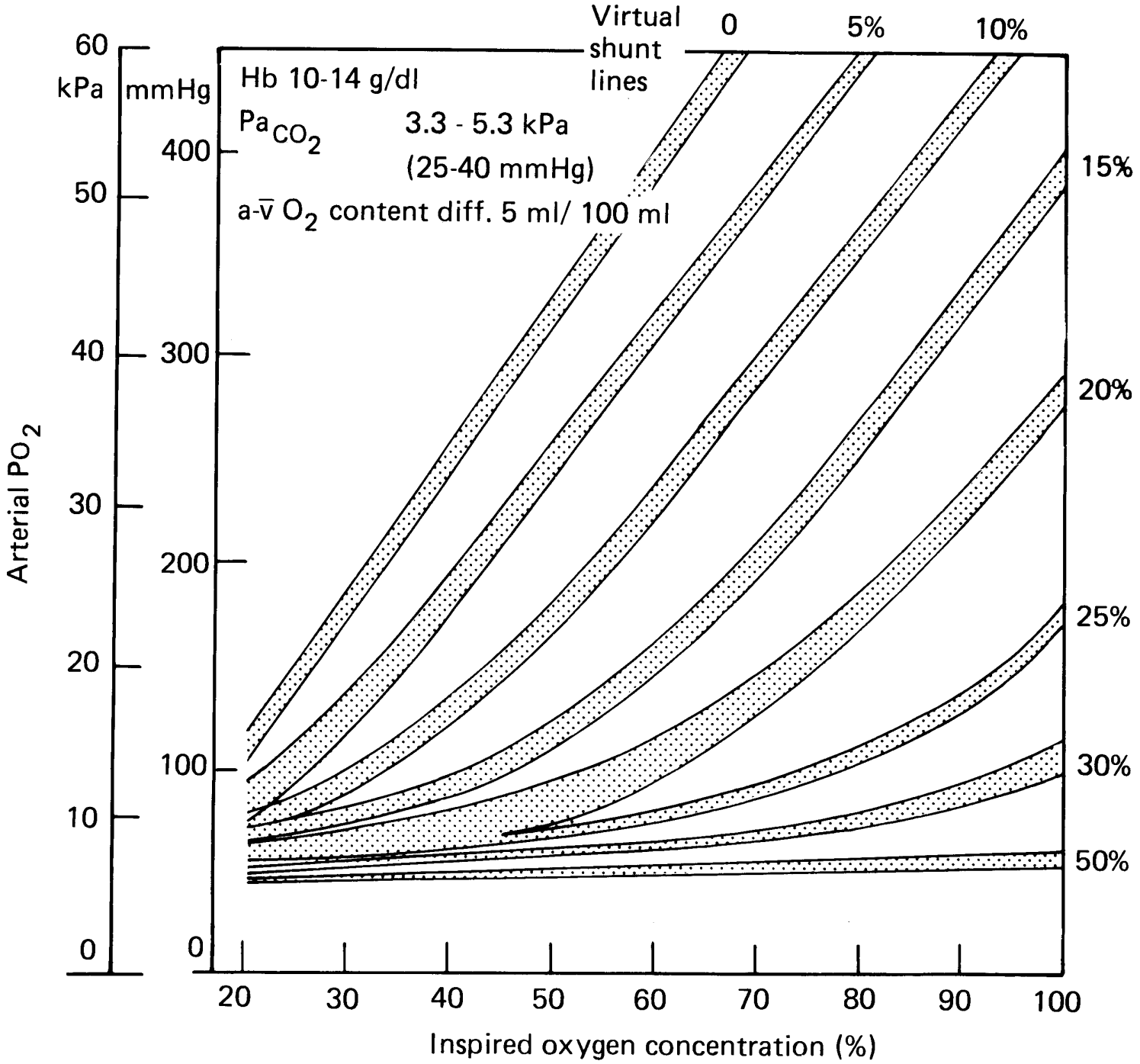

p_aO_2/F_IO_2 ratio
mmHg
Shunt fraction $\dot{O}_S/\dot{Q}_T$
1%
10%
20%
30%
40%
50%
700
600
500
400
300
200
100
0
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Fraction of inspired O_2 (F_IO_2)
Hb = 10 g/dL
$C_{\bar{v}}O_2 - C_aO_2 = 3.5$ mL O_2/dL

Figure 10


Virtual shunt lines
0
5%
10%
15%
20%
25%
30%
50%
Hb 10-14 g/dl
Pa_{CO_2} 3.3 - 5.3 kPa
(25-40 mmHg)
a-$\bar{v}$ O_2 content diff. 5 ml/ 100 ml
kPa
mmHg
Arterial PO_2
60
50
40
30
20
10
0
400
300
200
100
0
20
30
40
50
60
70
80
90
100
Inspired oxygen concentration (%)