Review Article

Mechanisms of hypoxemia

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ABSTRACT

Oxygen is an essential element for life and without oxygen humans can survive for few minutes only. There should be a balance between oxygen demand and delivery in order to maintain homeostasis within the body. The two main organ systems responsible for oxygen delivery in the body and maintaining homeostasis are respiratory and cardiovascular system. Abnormal function of any of these two would lead to the development of hypoxemia and its detrimental consequences. There are various mechanisms of hypoxemia but ventilation/perfusion mismatch is the most common underlying mechanism of hypoxemia. The present review will focus on definition, various causes, mechanisms, and approach of hypoxemia in human.

KEY WORDS: Diffusion limitation, hypoxemia, shunt, ventilation-perfusion mismatch

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INTRODUCTION

The term hypoxia and hypoxemia are not synonymous. Hypoxemia is defined as a decrease in the partial pressure of oxygen in the blood whereas hypoxia is defined by reduced level of tissue oxygenation. It can be due to either defective delivery or defective utilization of oxygen by the tissues. Hypoxemia and hypoxia do not always coexist. Patients can develop hypoxemia without hypoxia if there is a compensatory increase in hemoglobin level and cardiac output (CO). Similarly, there can be hypoxia without hypoxemia. In cyanide poisoning, cells are unable to utilize oxygen despite having normal blood and tissue oxygen level.

MECHANISMS OF HYPOXEMIA

There are various mechanisms of hypoxemia. These are V/Q mismatch, right-to-left shunt, diffusion impairment, hypoventilation, and low inspired PO_2.

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Alveolar-arterial oxygen gradient

It is the difference between alveolar oxygen level (PAO_2) and arterial oxygen level (PaO_2) and is represented by the following equation: Alveolar to arterial (A-a) oxygen gradient = PAO_2 - PaO_2. The A-a oxygen gradient indicates the integrity of the alveolocapillary membrane and effectiveness of gas exchange. Pathology of the alveolocapillary unit widens the gradient. Therefore, hypoxemia due to V/Q mismatch, diffusion limitation, and shunt will have widened gradient, whereas hypoxemia due to hypoventilation would have normal gradient. The word gradient is a misnomer, and ideally, it should be referred to as A-a oxygen difference as the difference between alveolar and arterial oxygen is not due to any diffusion gradient. The difference between alveolar and arterial oxygen tensions is due to other factors: (1) V/Q imbalance in various parts of the lungs, (2) small right to left shunt (bronchial vein, thebesian vein, and small pulmonary arteriovenous anastomosis), and (3) resistance to the diffusion of oxygen across the alveolar membrane.[1,2]

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Unlike PaO_2, PAO_2 is not measured but calculated by using the alveolar gas equation:

$PAO_2 = FiO_2 \times (Pb - PH_2O) - (PACO_2/R)$.

PAO_2 is the mean alveolar oxygen pressure.

FiO_2 is the fractional concentration of inspired oxygen. It is 0.21 at room air.

Pb is the barometric pressure (760 mmHg at sea level).

PH_2O is the water vapor pressure (47 mmHg at 37°C).

$PaCO_2$ is the alveolar carbon dioxide tension. It is assumed to be equal to arterial PCO_2.

R is the respiratory quotient and is approximately 0.8 at steady state on standard diet.

Normal PAO_2 is:

$PAO_2 = FiO_2 \times (Pb - PH_2O) - (PACO_2/R)$.

$= 0.21 \times (760 - 47) - (40/0.8)$.

$= 100$ mmHg.

In young person, the A-a oxygen difference is <10 mmHg. The A-a oxygen difference increases with age. It is primarily due to age-induced decrease in the PaO_2 level because of the rise in V/Q mismatch. The drop in PaO_2 after 70 years is about 0.43 mmHg per year.[3] High FiO_2 by increasing both the alveolar and arterial oxygen level widens the gradient. The rise in gradient is due to disproportionate increase in alveolar oxygen level. The arterial blood oxygen level does not rise to the same proportion as the alveolar oxygen level due to its admixing with unoxygenated blood coming from bronchial veins, mediastinal veins, and thebesian veins.[1]

Ventilation/perfusion mismatch

V/Q mismatch is the most common cause of hypoxemia.[4] Normal V/Q level is 0.8. Ventilation, perfusion and V/Q ratio are not uniform in the human lungs. There is regional heterogeneity of V/Q ratio caused by variable subatmospheric intrapleural pressure and gravity. Ventilation and perfusion is higher at the base and lower at the apex of the lungs. However, V/Q ratio is higher at the apex and lower at the base. The ratio is low at the base as the rise in perfusion is much more than the rise in ventilation. The V/Q ratio is higher at apex because the fall in perfusion is higher than the fall in ventilation at the apex. Since ventilation is responsible for gas exchange, apical region with high ratio has low alveolar CO_2 content and high oxygen content and the basal region, on the other hand, has low alveolar oxygen content and high CO_2 content. Only low V/Q ratio produces hypoxemia by decreasing the alveolar oxygen level (PAO_2) and subsequently arterial oxygen level [Figure 1].[5] There is an important compensatory mechanism due to hypoxemia, particularly when chronic. The human body will try to restrict perfusion in areas of the lungs with reduce ventilation. This is done by hypoxic pulmonary vasoconstriction (HPV) which is unique to pulmonary vasculature. By reducing perfusion to areas of the lungs with reduce ventilation, blood is diverted to the well-ventilated lung regions.[6,7] The basic goal is to maintain matching between ventilation and perfusion. The pulmonary selectivity of hypoxia can be explained by the presence of an oxygen-sensitive channel in the pulmonary circulation. The vessels mainly involved in HPV are the small pulmonary arteries.[8] Arteries with an internal diameter of 200–400 μm are most commonly involved in the animal study.[9] HPV also possesses negative consequences when chronic. Chronic HPV causes vascular structural remodeling and subsequent development of sustained pulmonary hypertension.[10] The inhibition of oxygen-sensitive potassium channel initiates the process of HPV. Patel *et al*. subsequently revealed that the K^+ channels involved are voltage-gated K^+ channels (K_V), particularly K_V 1.5.[11] Hypoxia inhibits the voltage-gated K^+ channels present in the pulmonary artery leading to accumulation of intracellular K^+ and depolarization of the cells. Depolarization opens up the voltage-gated L-Type Ca^{2+} channels resulting in Ca^{2+} influx and vasoconstriction [Figure 2].[12,13]

### High ventilation/perfusion ratio

High V/Q ratios develop when ventilation is excess in proportion to perfusion. Figure 3 is showing an example of high V/Q ratio in pulmonary embolism (PE). It can produce a dead space like effect.[14] Since perfusion is less; removal of CO_2 by high V/Q unit is low. Although the impact of high V/Q unit on blood oxygenation is minimal, it can cause hypoxemia if the compensatory rise in total ventilation is absent. Since the high V/Q unit receiving less perfusion, blood from this area is diverted to other areas leading to the development of low V/Q in other areas of the lungs. It results in the development of hypoxemia unless the compensatory rise in total ventilation is impaired. The compensatory rise in ventilation can lead to normalization of V/Q ratio of the low V/Q areas.

Effects of beta-2 agonist on ventilation/perfusion ratio

Beta-2 agonist can produce mild hypoxemia by causing V/Q mismatch. Wagner *et al*.[15] in a multiple inert gas elimination
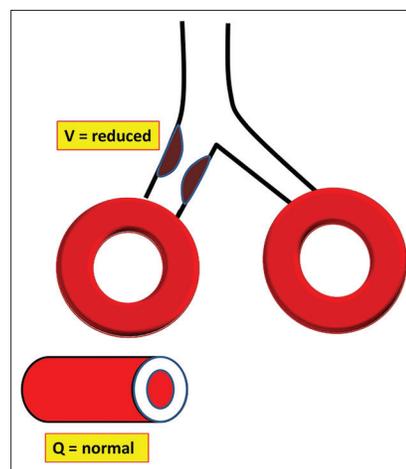
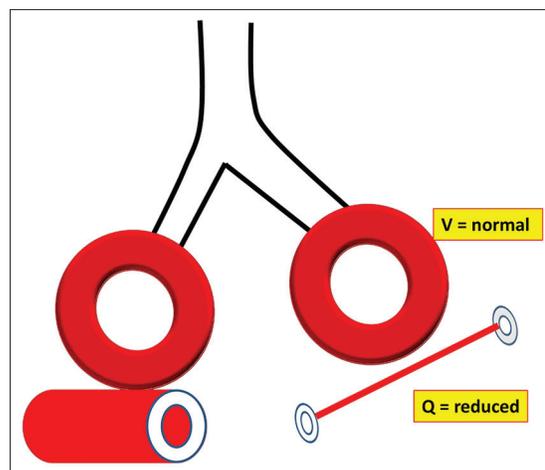**Figure 1:** The low ventilation/perfusion ratio. Ventilation is reduced but perfusion is normal
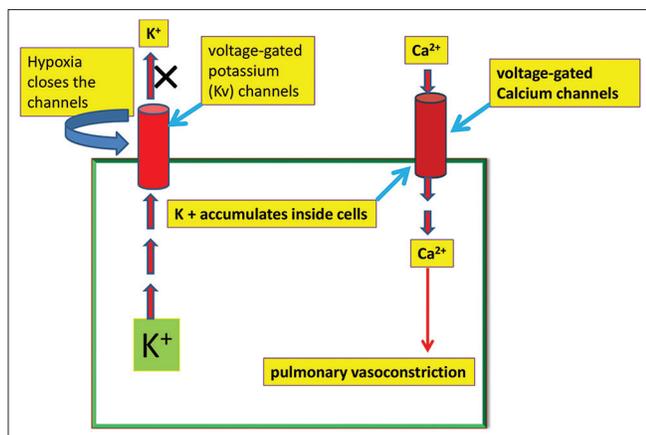
Figure 2: The mechanism of hypoxic pulmonary vasoconstriction. Hypoxia causes closure of voltage-gated potassium channel, leading to K+ accumulation intracellularly. It leads to depolarization of the cells, opening of voltage-gated calcium channel and calcium-mediated pulmonary vasoconstriction

technique (MIGET)-based study in asymptomatic asthma patients reported transient deterioration in V/Q ratio and PaO_2 after nebulized isoproterenol therapy. These changes happen despite the forced expiratory volume in one second (FEV_1) and forced expiratory flow between 25% and 75% returning to normal. Polverino *et al*.[16] could not find any gas exchange abnormality after salbutamol therapy in chronic obstructive pulmonary disease (COPD) patients with severe exacerbations requiring hospitalization but detected small decrement in PaO_2 during convalescence period only. The worsening V/Q ratio is due to increase perfusion of poorly ventilated areas due to salbutamol-induced release of HPV. Moreover, diversion of perfusion from adjacent well-ventilated areas creates new areas with low V/Q ratio.[17] Ballester *et al*.[18] reported different effects of intravenous and inhaled bronchodilator on cardiopulmonary parameters. Intravenous salbutamol, but not inhaled salbutamol, caused a significant increase in heart rate, CO, and V/Q inequality. However, PaO_2 remained unchanged during salbutamol administration by both the routes. Normal PaO_2 along with worsened V/Q ratio may be explained by the elevated CO in the intravenous salbutamol group. However, all these studies should not be a deterrent for its use in acute bronchospasm as the benefits of reversing bronchospasm far outweighs its small detrimental effect on arterial oxygenation and V/Q ratio.

Characteristic features of ventilation/perfusion mismatch
1. Hypoxemia due to V/Q mismatch can be easily corrected by supplemental oxygen therapy
2. Widened A-a oxygen gradient is another feature of V/Q mismatch.

Some common causes of hypoxemia due to V/Q mismatch include asthma, COPD, bronchiectasis, cystic fibrosis, interstitial lung diseases (ILDs), and pulmonary hypertension.

Figure 3: High ventilation/perfusion ratio in a patient with pulmonary embolism

Shunt
The shunt is a condition whereby blood from the right side of the heart enters the left side without taking part in any gas exchange. Figure 4 is showing an example of shunt. Normally, we have a small fraction of the shunt (2–3% of CO). It occurs when bronchial veins drain into pulmonary veins. Some of the coronary veins may also drain directly into the left ventricle and is called the thebesian veins. Shunt is the extreme degree of V/Q mismatch where there is no ventilation. Poor response to oxygen therapy is the feature that differentiates shunt from other mechanisms of hypoxemia. Failure to improve PaO_2 by oxygen therapy is due to the inability of oxygen to improve PAO_2 in unventilated lung units.[11] Hypercapnia is uncommon in shunt until the shunt fraction reaches 50%.[1] Lack of hypercapnia is due to stimulation of the respiratory center by chemoreceptor as the PCO_2 in the arterial blood leaving the shunt unit is high. PaO_2/FiO_2 is a rough estimate of shunt fraction. If PaO_2/FiO_2 is <200, shunt fraction is more than 20%, whereas a PaO_2/FiO_2 of more than 200 indicates a shunt fraction of <20%.[19]

Characteristics of pulmonary shunt
1. P (A-a) O_2 is elevated
2. Poor response to oxygen therapy
3. PCO_2 is normal.

Causes of shunt include pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS), alveolar collapse, and pulmonary arteriovenous communication.
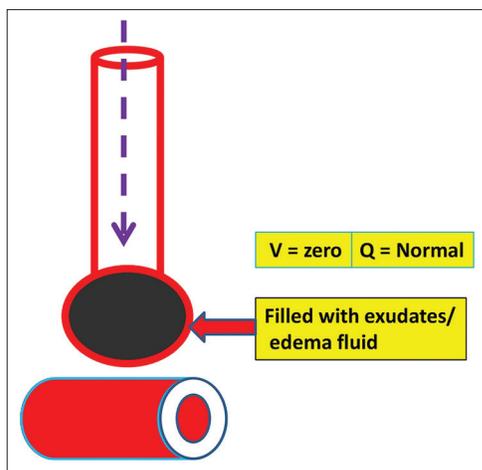
Pulmonary shunt can be calculated by the following equation [Figure 5].

Q'_T is the total pulmonary blood flow.

Q'_S is the blood flow to the nonventilated or shunt area.

CaO_2 is the oxygen content of the arterial blood.

$CecO_2$ is the end-capillary oxygen content of the effective gas exchanging unit.

Figure 4: Shunt where ventilation is zero but perfusion normal

$Cec'O_2$ is the end-capillary oxygen content of the shunt area.

$C\overline{v}O_2$ is the mixed venous blood oxygen content.

The total amount of oxygen leaving this unit is equal to the sum of oxygen content of shunted blood and effective gas exchanging unit.

$$CaO_2 \times Q'_T = C\overline{v}O_2 \times Q'_S + CecO_2 \times (Q'_T - Q'_S).$$

Rearranging the equation, amount of shunt fraction (Q'_S / Q'_T)

$$\frac{Q'_s}{Q'_T} = \frac{CecO_2 - CaO_2}{CecO_2 - C\overline{v}O_2}$$

Diffusion limitation

It occurs when the oxygen transport across the alveolocapillary membrane is impaired. Diffusion limitation may be due to decrease in lung surface area for diffusion, inflammation, and fibrosis of the alveolocapillary membrane, low alveolar oxygen, and extremely short capillary transit time. Since both oxygen and carbon dioxide transport occur through the alveolar-capillary membrane, theoretically it should cause both hypoxemia and hypercapnia. However, hypercapnia is uncommon due to diffusion limitation. Since CO_2 is 20 times more soluble in water than O_2, it is less likely to be affected by diffusion limitation.[20] Another reason could be hypoxemia-mediated stimulation of ventilation, leading to CO_2 washout. Normal pulmonary capillary transit time is 0.75 s, and the time required to complete gas exchange is 0.25 s. One important characteristics of diffusion limitation is the development or worsening of hypoxemia during exercise. During exercise, the capillary transit time is shortened due to rise in CO. Moreover, mixed venous oxygen level also falls due to increase oxygen extraction by the tissues. However, hypoxemia usually does not develop due to the following reasons: Recruitment of capillaries,
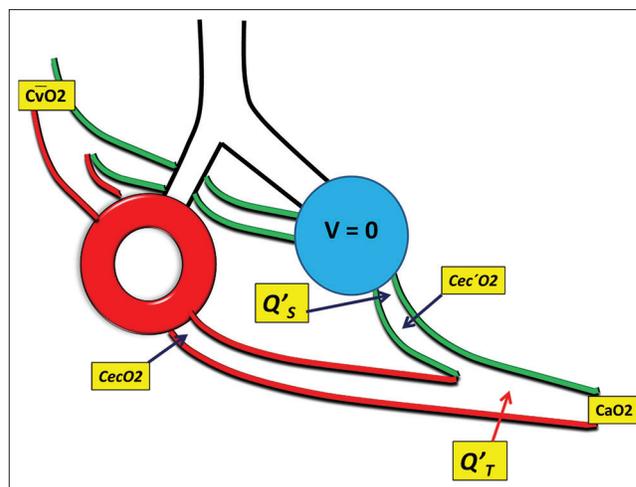
Figure 5: The calculation of shunt

distension of capillaries, and rise in alveolar oxygen. Patients with pulmonary fibrosis fail to recruit additional capillaries and develop exercise-induced/exaggerated hypoxemia. Important causes of diffusion limitation are emphysema and ILDs.

Characteristics
1. Hypoxemia shows good response to oxygen therapy
2. P (A-a) O_2 is elevated
3. $PaCO_2$ is usually normal.

Hypoventilation

The hallmark of hypoventilation is a high $PaCO_2$ level as adequate ventilation is necessary for the removal of CO_2. Ventilation is also required for oxygenation, and hypoventilation leads to low PAO_2 and subsequent low PaO_2. Another unique feature of hypoventilation is normal $P(A-a)O_2$ gradient as the alveolar – capillary membrane is intact in this condition. Prolonged hypoventilation, however, may lead to atelectasis of some parts of the lungs and widening of $P(A-a)O_2$ gradient.[21] Hypoventilation does not produce significant hypoxemia in healthy lung, but in the presence of lung diseases, hypoxemia can be severe. One characteristic feature of hypoventilation induced hypoxemia is that it is easily correctible by supplemental oxygen. Oxygen therapy corrects hypoxemia even when hypoventilation and hypercapnia persists. Normal pulse oximetry in a patient breathing room air indicates adequacy of ventilation (normal $PaCO_2$). However, it cannot be used to judge the adequacy of ventilation in patients on supplemental oxygen if hypoventilation persists.[14] Patients of COPD, asthma, ILD, and other lung diseases initially cause Type-1 respiratory failure but after certain period of time may develop Type-2 respiratory failure due to alveolar hypoventilation.

Alveolar gas equation describes the relationship between $PACO_2$ level and alveolar ventilation (V_A). Reduced V_A increases the PCO_2 level and increase in V_A decreases the PCO_2 level.

Alveolar gas equation
Equation-1:

$$PaCO_2 = K \frac{V'CO_2}{V'_A}$$

$V'CO_2$ is the CO_2 production in the body.

V'_A is alveolar ventilation.

Factor k (0.863) is constant.

We can also rearrange the equation in the following ways.

$$V'_A = V'_E - V'_D.$$

V'_E is the minute ventilation and V'_D is the dead space ventilation. V'_E is the amount of air inhaled per minute and is derived by multiplying respiratory frequency and with tidal volume (V_T). V_A can be decreased either by a reduction in V_T or an increase in V_D.

Equation-2:

$$PaCo_2 = K \frac{V'CO_2}{V'_E - V'_D}$$

Rearranging the equation-2

Equation-3:

$$PaCO_2 = K \frac{V'CO_2}{V_T \times RR \left(1 - \frac{V'_D}{V_T}\right)}$$

There are several causes of high CO_2 level. It can be due to high VCO_2 production without compensatory rise in V_A, rise in V_D and fall in V_T and/or RR. A-a oxygen gradient can help differentiating whether the high $PaCO_2$ is due to reduction in V_T or increase in V_D. Gradient will be normal in the former and high in the latter. Increase VCO_2 normally does not contribute to raise $PaCO_2$ level if the ventilatory compensating mechanism is functioning normally.[22] In certain conditions, CO_2 production is increased in the body, for example, burns, sepsis, exercise, hyperthermia, intake of carbohydrate rich diet, tetanus, seizures, and tremor. Various causes of rise in V_D/V_T leading to high CO_2 level are PE, acute reduction in CO, COPD, ARDS, and bronchiectasis.

Hypoventilation occurs due to dysfunction of the respiratory pump at various levels: Respiratory center in the brainstem, spinal cord, nerves supplying the respiratory muscles, neuromuscular junction, respiratory muscles, and chest wall bellows. One characteristic feature of hypoventilation is the fact that both PaO_2 and $PaCO_2$

moves in opposite direction to same extent. If they do not move to same extent, rule out other causes of hypoxemia.[1]

Various causes of hypoventilations are given below:
1. Impaired central drive
   • Drug overdose: Opioids, benzodiazepines, alcohol
   • Brainstem hemorrhage, infarction
   • Primary alveolar hypoventilation
2. Spinal cord level: Amyotrophic lateral sclerosis, cervical spinal cord injury
3. Nerve supplying respiratory muscle: Guillain–Barre syndrome
4. Neuromuscular junction: Myasthenia gravis, Lambert–Eaton syndrome
5. Respiratory muscles: Myopathy
6. Defects in chest wall: Kyphoscoliosis, thoracoplasty, fibrothorax.

Characteristics
1. Hypoxemia shows good response to oxygen therapy
2. $P(A-a)O_2$ is usually normal
3. $PaCO_2$ is high
4. PaO_2 and $PaCO_2$ move in opposite direction to the same extent.

Various mechanisms and differentiating features of hypoxemia are given in Figure 6.

ASTHMA

The most common gas exchange abnormality in asthma is respiratory alkalosis. Carbon dioxide retention may occur with worsening asthma and development of respiratory muscle fatigue. V/Q mismatch is the main mechanism of gas exchange abnormality in asthma. Wagner *et al*. reported a bimodal pattern of V/Q distribution in patients of asthma: Majority of V/Q ratio lies within the normal range, and about 25% of the CO confines to a low V/Q ratio of ≤0.1.[15] Other characteristics features of Wagner's series were the absence of high V/Q ratio and shunt. There is also a poor correlation between V/Q mismatch and spirometric parameters. Wagner *et al*.[23] in another paper studied the relationship between V/Q mismatch and indices of airflow obstruction across the various clinical spectrum of asthma. They noted abnormal V/Q ratio despite the spirometric indices being well preserved. At this stage, PaO_2 may also remain normal despite the presence of V/Q mismatch and high $P(A-a)O_2$ gradient. The V/Q ratio remains stable till FEV_1 falls to 40% of predicted. Below this level of FEV_1, PaO_2 falls significantly. The presence of normal PaO_2 despite the clear evidence of gas exchange abnormality is due to the buffering action of high CO. This study clearly questions the utility of spirometry alone in the management of asthma. This dissociation between indices airflow obstruction and gas exchange abnormality is due to the following reasons. FEV_1 reflects the function of more central airways, and peripheral airway obstruction has a greater influence on the degree of V/Q mismatch. Second, lung units with low V/Q
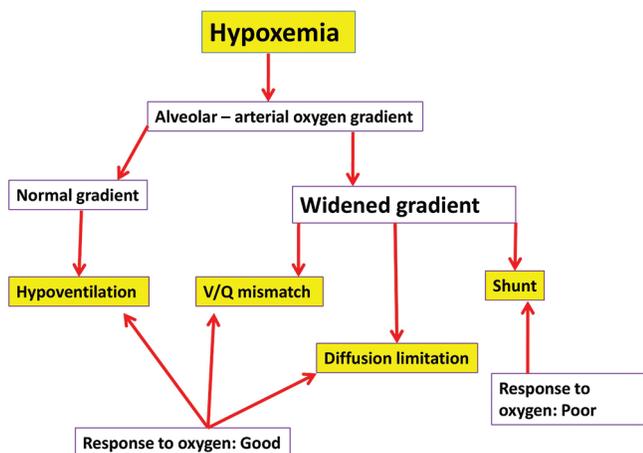
Figure 6: Various mechanisms and differentiating features of hypoxemia

ratio contribute little to the lung function measured at the mouth. Contribution to FEV_1 is mainly from lung units with good ventilation. Despite the presence of moderately severe V/Q mismatch, PaO_2 level can be normal. Large amount of CO and/or ventilation can explain this phenomenon. Shunt is also uncommon in stable asthma due to the presence of collateral ventilation between normal alveoli and the region distal to the obstruction.

Roca *et al.*[24] studied the V/Q distribution in 10 patients with acute severe asthma requiring hospitalization and the following recovery. All patients had a severe airflow obstruction and moderate to severe hypoxemia at the time of admission. The majority of their patients showed bimodal blood flow distributions. They also reported a lack of correlation between V/Q mismatch and spirometric criteria. Moreover, the improvement in V/Q mismatch lags behind spirometric and clinical criteria. Clinical and spirometric improvement occurred at the time of discharge, whereas maximum improvement in V/Q mismatch occurs at the end of 4 weeks. The lack of correlation between the two variables indicates that different pathophysiologic processes are involved. Spirometric abnormalities reflect a narrowing of large- and middle-sized bronchi, and V/Q mismatch reflects abnormalities involving peripheral small airways. The role of peripheral airways in V/Q mismatch is further strengthened by the fact that administration of beta-2 agonist was associated with transient worsening of V/Q mismatch despite relief of airway obstruction.[15] In future, there is a need to evaluate the role of gas exchange abnormalities in the follow-up of patients with asthma along with conventional parameters of clinical and spirometric criteria.[25] High V/Q and shunt are uncommon in all these studies except in children following an exercise challenge and in patients with acute severe asthma. Freyschuss *et al.*[26] evaluated the mechanisms of hypoxemia in children with exercise-induced asthma (EIA). The majority of children with EIA developed bimodal distribution: Normal V/Q ratio and high V/Q ratios. Shunt or a low V/Q ratio (V/Q

<0.1) was not detected. High V/Q developed due to hyperinflated lungs impeding local blood flow.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a lifestyle related lung diseases characterized by progressive loss of lung function and gas exchange abnormality. The major sites of airflow obstruction in COPD is the small airways (<2 mm in internal diameter).[27] Alveolar walls maintain patency of the small airway by exerting radial traction by the elastic fibers. Alveolar wall destruction leads to loss of these elastic fibers, resulting in airflow obstruction. Alveolar wall destruction also causes loss of the alveolar surface area and pulmonary capillaries, resulting in gas exchange abnormalities. Other mechanisms of airflow obstruction include bronchial mucosal inflammation, edema or fibrosis, and mucus hypersecretion.[28] The most common gas exchange abnormalities in COPD patients include arterial hypoxemia, with or without hypercapnia. The major mechanism of hypoxemia in COPD is V/Q mismatch.[29] Gas exchange abnormality depends on the phenotype of COPD. Phenotyping in COPD is not new as Burrows distinguished the two phenotypes of COPD as early as 1963.[30] He proposed the following classification of COPD based on clinical, roentgenologic, and physiologic characteristics: Type A (predominant emphysema/pink puffer), Type B (predominant chronic bronchitis/blue bloater), or type X (indeterminate type). Type A patients show hyperinflation decreased elastic recoil of the lung, mild hypoxemia and rarely hypercapnia, whereas, Type B patients develop worse hypoxemia and hypercapnia. They also develop cor pulmonale more frequently.

Ventilation/perfusion mismatch in advanced chronic obstructive pulmonary disease
Wagner *et al.* evaluated the V/Q distribution in 23 patients with stable but advanced COPD and showed the following three patterns of V/Q mismatch.[31]
1. Predominantly high V/Q ratio (H-type)
2. Predominantly low V/Q ratio (L-type)
3. Mixture of both low and high V/Q ratio (HL-type).

Shunt is characteristically absent. Most of the Type A emphysematous patients had high V/Q ratio, but it was also noted in Type B patients. High V/Q ratio is characterized by significant ventilation in the poorly perfused area. High V/Q ratio develops in emphysematous patients due to high compliance and reduced blood flow. Low V/Q ratio develops predominantly in bronchitis phenotype due to bronchial obstruction leading to reduced ventilation. Diffusion impairment is not important factor for hypoxemia development in COPD as exercise or breathing 100% oxygen produces only minimal changes in V/Q distributions.

Ventilation/perfusion mismatch in mild chronic obstructive pulmonary disease

V/Q mismatch can be present even in patients with mild COPD. Barbera *et al*.[32] reported V/Q mismatch in 23 mild COPD patients with mean predicted FEV_1 of $76 \pm 3\%$. Since the correlation between FEV_1 and V/Q mismatch is poor, the authors also studied the structural basis of V/Q mismatch in mild COPD and found both pulmonary emphysema and small airways abnormalities as a contributor to V/Q mismatch. However, the major correlate of the increase in P (A-a) O_2 is the morphological severity of emphysema. The V/Q mismatch in mild COPD may even produce pulmonary vascular remodeling.[33] Morphological changes in pulmonary vessels are greater in patients with airflow obstruction and poor response to oxygen therapy. Intimal changes are seen mainly in arteries of <500 μm in diameter. The intimal thickening may reduce the response to oxygen therapy. Barberà *et al*.[33] also reported positive correlation between degrees of V/Q mismatch with mean intimal area thickening. Dead space or wasted ventilation develops quite early in the natural history of COPD. Elbehairy *et al*.[34] evaluated 11 stable patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 1B COPD and 11 age-matched healthy control subjects by physiological testing and a symptom-limited incremental cycle exercise test. The $P(A\text{-}a)O_2$ gradient and dead space to the tidal volume ratio (V_D/V_T) are seen significantly higher level in COPD both at rest and exercise than in healthy control. Dead space or wasted ventilation represents almost 40% of total V_E at rest in mild COPD compared with 28% in control subjects. The mechanism of dead space development is overventilation of alveolar units relative to perfusion. Reduced perfusion may be due to reduced pulmonary capillary density or blood flow, impaired vessel recruitment and distension and smoking associated pulmonary vascular inflammation.[35-37]

The V/Q mismatch worsens along with the progression of COPD. Rodríguez-Roisin *et al*.[29] evaluated the V/Q mismatch in 150 patients with COPD of various severities and reported a steady worsening of both V/Q mismatch and arterial blood gas disturbances with the progression of COPD. However, in GOLD Stage IV, the V/Q mismatch was only modestly worse compared to Stage 1 despite the FEV_1 value fallen to 20% of predicted. One factor could be that V/Q mismatch is already at its worst in Stage 1, so there is less scope for further deterioration. Patients with GOLD Stage 1 COPD with minimum spirometric abnormalities developed substantial V/Q mismatch. It indicates that pulmonary gas exchange abnormalities occur quite early in the natural history of COPD even before lung function abnormalities develop. The second factor could be simultaneous decrease in both V_A and pulmonary blood flow producing a buffering effect. Airway obstruction causes reduced ventilation and alveolar dilatation and HPV causes reduced perfusion.

There is also no correlation between the radiological extent of emphysema and degree of V/Q mismatch. Sandek *et al*.[38] studied the relationship between V/Q ratios and extent of emphysema by high-resolution computed tomography (HRCT) in twenty patients of moderate to severe COPD. Similar to Wagner *et al*.[31] study, main V/Q defect in emphysema patients in this study was high V/Q ratio due to preferential ventilation to lung areas with poor perfusion. Shunt and low V/Q ratio were minimal. There was no correlation between V/Q ratios and the radiological extent of emphysema, diffusing capacity, and arterial blood gas levels. Severe V/Q mismatch does not develop in COPD patients as the destruction of the alveolar surface is associated with a reduction in perfusion also. Brudin *et al*.[39] measured blood volume on the basis of positron emission tomography scan and found lower tissue density and peripheral vascular volume within lungs in emphysematous patients. Morrison *et al*.[40] also reported reduced pulmonary capillary blood volume across all spectrum of emphysema. The reduced perfusion causes modest V/Q mismatch and explains the lack of correlation with extent of emphysema. Blood flow is also reduced due to compression by the overinflated alveolar walls.[40] Another characteristic of Sandek *et al*.[38] study is the presence of normal or near normal PaO_2 in 80% of patients despite having moderate to severe emphysema on HRCT in 75% of patients. It may be due to the lesser involvement of small airway as small airway obstruction may cause atelectasis resulting in the perfusion of poorly ventilated lung areas and development of hypoxemia. In the COPD gene study, female sex, higher body mass index, lower FEV_1 were independent risk factors for hypoxemia development in patients with moderate to very severe COPD. However, emphysema severity on quantitative chest computed tomography scan did not predict hypoxemia.[41] The shunt is an uncommon mechanism of hypoxemia in COPD patients. The factor that prevents the development of shunt is collateral ventilation. Collateral ventilation in the obstructed segments prevents absorption atelectasis and subsequent shunt formation by keeping the alveoli ventilated.[42]

Ventilation/perfusion mismatch in acute exacerbation of chronic obstructive pulmonary disease

Mechanisms responsible for the development of low V/Q ratio in patients with AE-COPD include airway narrowing due to bronchial inflammation, bronchospasm, or mucous accumulation. Shunt fraction is not increased during acute exacerbation probably due to the absence of complete airway occlusion or the presence of collateral ventilation.

Barberà *et al*.[43] evaluated the mechanism of hypoxemia in 13 male patients admitted to hospital with acute exacerbations COPD (AE-COPD). Both V/Q mismatch and reduced PvO_2 are responsible for hypoxemia development in AE-COPD. PvO_2 is an important contributor to hypoxemia and for a given level of V/Q mismatch; reduced PvO_2 is associated with reduced level of PaO_2.[44] PvO_2 is reduced

due to greater consumption of oxygen by the overactive respiratory muscles. CO is one extrapulmonary factor that can modulate the impact of low PvO_2 on resulting hypoxemia by improving the PvO_2 value. Therefore, we should be cautious in using drugs that can reduce CO in COPD patients during AE.[39]

PULMONARY EMBOLISM

Hypoxemia, hypocapnia, and an increase in the A-a oxygen tension gradient are the classical gas exchange abnormalities in patients with PE.[45,46] Patients with PE may also present with hypocapnia alone.[47] Hypocapnia develops due to hyperventilation. The exact mechanism of hyperventilation is not known but hypoxemia is probably not the only mechanism as correction of hypoxemia with supplemental oxygen does not always correct hyperventilation mediated respiratory alkalosis.[48] Proprioceptors and other receptors such as irritant and juxtacapillary sensors may be responsible for stimulation of ventilation.[48]

The main mechanisms of hypoxemia in PE are V/Q mismatch and low level of mixed venous blood oxygen (PvO_2).[49] V/Q mismatch occurs due to redistribution of blood from occluded pulmonary arteries to the nonoccluded vessels. This results in extremely high or infinite V/Q units in the embolized areas and low V/Q units in the nonembolized regions due to over perfusion.[50] Overperfusion of nonembolized regions leads to the development of hypoxemia. The second important mechanism causing hypoxemia is fall in PvO_2 due to reduction in CO.[51] Itti *et al*.[52] reported the following bimodal distribution of V/Q ratios in 99 consecutive patients with suspected PE. There was 15.5% increase in high V/Q ratios (>1.2) and 34.5% increase in low V/Q ratios (<0.8).

Patients of PE may also develop diffusion limitation due to a reduction in pulmonary blood flow by vascular obstruction and reduced CO. Normal PaO_2 and normal A-a oxygen gradient does not rule out acute PE. Stein *et al*. reported a PaO_2 >80 mmHg in 25% of patients with PE and no prior cardiopulmonary disease and 15% of patients with PE and prior cardiopulmonary disease. In the same series, 12% of 280 patients with acute PE had an A-a gradient <20 mm.[53] Dantzker *et al*.[51] reported a PaO_2 ≥90 mmHg in 6% of the patients and a PaO_2 ≥80 mmHg in 14%. Normal PaO_2 can be explained by hyperventilation mediated hypocapnia leading to increase in PaO_2 level according to the alveolar gas equation. High PAO_2 results in maintenance of PaO_2 level.

BRONCHOCONSTRICTION AND DEAD SPACE VENTILATION

Another physiological change in patients with PE is bronchoconstriction. Stein *et al*. in an animal model first reported bronchoconstriction and increased pulmonary resistance due to PE.[54] Gurewich *et al*. subsequently reported bronchoconstriction in a group of seven patients with PE.[55] Bronchoconstriction may be due to the release of substances with bronchoconstriction properties at the sites of thromboemboli, such as acetylcholine, histamine, serotonin, platelet-activating factor, prostaglandins and the plasma kinins leading to reflex bronchoconstriction.[56-59] Pulmonary artery obstruction by thromboemboli also reduces the elimination of CO_2, leading to reduced alveolar CO_2 tension and hypocapnia-induced bronchoconstriction.[60] Patients with PE may develop surfactant deficiency leading to development of alveolar collapse. Various factors are responsible for surfactant deficiency: Pulmonary gas exchange abnormalities, inflammation, ischemia and reperfusion and alteration in lung mechanics.[61,62] Patients of PE may also develop shunt, and it is particularly common in the presence of large emboli.[63] It may occur due to perfusion of unventilated areas due to surfactant deficiency, pulmonary edema, and pulmonary arteriovenous anastomosis or patent foramen ovale.[64,65] Preexisting pulmonary arterial-venous anastomosis may open up by the elevated pulmonary artery pressure.[66] PE may lead to the development of right ventricular failure and elevated right atrial pressure and when the right atrial pressure exceeds left atrial pressure, shunting occurs through the foramen ovale which remains patent in approximately 15% of patients. Recanalization of thrombi occurs earlier than the clearance red blood cells and debris from the infracted alveolar area and improved perfusion to this underventilated area may cause shunt formation.[49,65] Although PE reduces the elimination of CO_2, hypercapnia is rare except in large emboli. Hyperventilation of normally functioning alveoli eliminates CO_2. Dantzker and Bower in the animal study had shown that the development of hypoxemia depends on the size of the V/Q units. Embolization of smaller units leads to diversion of blood to larger unit with little impact, but embolization of the larger unit leads to significant reduction of V/Q ratio of smaller unit and development of significant hypoxemia.[67] Another factor that may lead to hypoxemia development in PE is reduced mixed venous oxygen level (PvO_2). PVO_2 may be reduced in PE due to a decrease in CO. The impact of PvO_2 has been noted in both V/Q mismatch and shunt.[68] Diffusion impairment is not a common mechanism of hypoxemia in PE.[69]

Mechanisms:
1. V/Q mismatching:
   a. Development of high V/Q ratio in areas with occluded pulmonary vessels
   b. Development of low V/Q areas caused by redistribution of pulmonary blood flow from obstructed vascular areas to adjacent normal areas
   c. Development of low V/Q areas following restoration of perfusion in areas with reduced ventilation due to pulmonary infarction

d. Development of bronchoconstriction by various mediators locally released and alveolar hypocapnia
e. Development of alveolar collapse due to surfactant loss
f. Decrease PvO_2 due to reduced CO

2. Shunt: Surfactant deficiency or opening of pulmonary arteriovenous anastomosis or patent foramen ovale or delayed clearance of alveolar exudates
3. Decreased diffusion capacity: Decrease in pulmonary blood flow.

IDIOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia. Most common gas exchange abnormality in IPF is hypoxemia without hypercapnia.[70] Hypoxemia is usually mild at rest until disease progresses to advanced stages. Another hallmark of IPF is the exercise-induced worsening of hypoxemia.[71] Hypercapnia may develop if FEV_1 falls below 1.0 L/s. Patients of IPF often adopt rapid shallow breathing pattern due to low V_T and stimulation of mechanoceptors. The increase ventilation is responsible for maintaining eucapnia even in the presence of severe restriction.[72] The mechanisms of hypoxemia in IPF may be a combination of V/Q mismatch, shunt, and diffusion limitation; however, V/Q mismatch is the most common cause of hypoxemia both at rest and during exercise.[73] Diffusion limitation contributes to 19% of hypoxemia at rest but plays a major role during exercise-induced hypoxemia. During exercise, Agustí *et al*.[73] did not notice any increase in V/Q mismatch, explaining a greater role of diffusion limitation during exercise. Diffusion limitation worsens during exercise due to reduced PvO_2 and short capillary transit time and contributes to 40% of hypoxemia at exercise. They also studied the role of pulmonary vascular tone in hypoxemia. There are basically two types of vascular involvement: Functional and fixed. Patients with functional vascular obstruction show better vascular response to oxygen therapy, less pulmonary hypertension during exercise, less V/Q mismatch and higher PaO_2 during exercise than patients with fixed vascular obstruction. Shunting is not very common in IPF patients.

ACUTE RESPIRATORY DISTRESS SYNDROME

The ARDS is a noncardiogenic pulmonary edema characterized by respiratory failure, development of new bilateral pulmonary infiltrates and severe hypoxemia and low lung compliance. It is associated with significant mortality. The main mechanism of hypoxemia in ARDS is the development of intrapulmonary shunting. The mechanism of shunting is due to alveolar flooding with exudates or alveolar collapse. Lamy *et al*.[74] in an elegant study of 45 consecutive patients of ARDS correlated gas exchange abnormalities with pathological changes. They divided the patients into three distinct groups. Group 1 developed most severe hypoxia and fixed shunt as PaO_2

changes is minimal despite a 10 mmHg increase in positive end-expiratory pressure (PEEP). Pathologically, they show consolidation. Group 2 patients had less severe hypoxemia and a moderate and slowly increased PaO_2 response to a 10 mmHg increase in PEEP. Pathologically, they show extensive fibrosis. The Group 3 patients had less severe hypoxemia and rapid response to PEEP therapy. They also show consolidation but less severe than those in Group 1. The V/Q mismatch and DL is responsible for hypoxemia in Group 2 and 3. Dantzker *et al*.[75] also reported predominant presence of shunt along with low V/Q units. Many ARDS patients develop increase shunting after high FiO_2 administration. Santos *et al*.[76] reviewed the response to 100% oxygen therapy in eight patients with acute lung injury (ALI) and four patients with COPD. In ALI patients there was a moderate increase in intrapulmonary shunt. The oxygen induced increment in shunt is due to reabsorbsion atelectasis. It usually involves the low unstable V/Q units. No increment in intrapulmonary shunt occurred in COPD patients and the main mechanism of gas exchange abnormalities in COPD is the release of HPV leading to increase perfusion to areas with low ventilation creating a dead space effects. The gas exchange abnormalities may persist long after resolution of ARDS. Elliott *et al*.[77] evaluated the lung function and exercise gas exchange in 13 survivors of ARDS. The FVC, and total lung capacity returned to normal by 4–6 months but pulmonary gas exchange abnormalities persisted longer, particularly after exercise. ARDS patients with very high percentage of shunting (~50%) show poor response to oxygen therapy due to extensive lung damage.[78] Matamis *et al*.[79] evaluated the effects on PEEP therapy in eight patients with acute respiratory failure (ARF). One prevailing mechanism of improvement in hypoxemia is the PEEP-induced fall in CO leading to reduced perfusion to shunt areas. However, reduction in CO is not the only mechanism. To negate the effect of low CO, Matamis et al. maintained the CO at control level by dopamine infusion. PEEP therapy reduced the shunt fraction significantly. There was also a redistribution of pulmonary blood flow from shunt area to areas with normal V/Q ratio.

Pleural effusion

Pleural effusion is a common clinical entity in pulmonary medicine and often causes symptoms and abnormal gas exchange. Agustí *et al*.[80] evaluated the mechanism of hypoxemia and the impact of thoracocentesis in nine patients with recent onset pleural effusion. The main mechanism of hypoxemia was the presence of intrapulmonary shunt. After thoracocentesis of significant amount of fluid (693 ± 424 ml), the PaO_2, $P(A-a)O_2$ and shunt remained unchanged. Intrapulmonary shunt develops due to continued perfusion in collapse lungs. The lack of improvement in gas exchange parameters after thoracocentesis can be explained by various factors. First, re-expansion of collapsed lungs does not occur immediately after aspiration of pleural fluid.[81] Second, patients may develop mild *ex-vacuo* pulmonary edema.

Sonnenblick *et al.*[82] studied the effect of body position on oxygenation status of patients with unilateral pleural effusion. The mean PaO_2 was better when the affected side was superior compared to PaO_2 when the affected side was positioned dependent. The mean PaO_2 when the affected side superior was 71.9 ± 9.3 mmHg compared with 66.7 ± 8.7 mmHg when the affected side dependent with the mean difference in PaO_2 between the two positions of 5.1 ± 1 mmHg ($P < 0.005$). When the affected side up, there is less perfusion going to the collapsed lung, thereby reducing the amount of shunt. Pneumothorax is also associated with arterial hypoxemia. Norris *et al.*[83] studied the pulmonary gas exchange in a series of 12 patients with spontaneous pneumothorax. Nine patients developed a PaO_2 below 80 mmHg and 10 patients developed widened A-a oxygen tension difference. With 100% oxygen, the majority of patients developed anatomical shunt. There is a negative correlation between the degree of shunt and Pneumothorax volume. When the pneumothorax volume is <25%, it is not associated with increased shunts. The minimal pneumothorax volume at which anatomical shunt appears is 35%. The effect of pleural aspiration on PaO_2, $PaCO_2$, P (A-a) O_2, dead space and an anatomical shunt was variable.

Liver disease

Arterial hypoxemia is a common clinical feature in patients with chronic liver disease. Fluckiger[84] in 1884 first reported the presence of cyanosis, and digital clubbing in a female with cirrhosis of liver. Hoffbauer and Rydell *et al.*[85] in a lung necropsy based study demonstrated intrapulmonary vascular dilatations and distinct anatomic arteriovenous communications that resulted in the development of severe hypoxemia in chronic liver disease patients. Eriksson *et al.*[86] in 1988 first coined the term "hepatopulmonary syndrome" (HPS) characterized by the triad of liver disease, arterial hypoxemia, and intrapulmonary vascular dilatation. The intrapulmonary vascular dilatation is responsible for the development of arterial hypoxemia. The mechanisms of hypoxemia include diffusion limitation, V/Q mismatch, and right to left intrapulmonary shunt. However, the main mechanism is V/Q mismatch. The V/Q mismatch occurs due to increase perfusion in the presence of normal ventilation.[87] Increased perfusion is due to intrapulmonary vascular dilatation and hyperdynamic circulation often seen in cirrhotic patients. The normal diameter of pulmonary capillaries at the alveolar level is 7–15 microns[88] and capillary diameters as large as 500 microns have been detected.[89] Dilatation of capillary produces diffusion defects. Erythrocytes carrying hemoglobin usually travels through the center of the capillaries and oxygen from adjacent alveoli fail to reach to the center of the dilated vessel in time leading to inadequate oxygenation and development of hypoxemia. High CO further reduces the capillary transit time. Diffusion limitation occurs in the advanced stages of HPS.[87] $P(A-a)O_2$ gradient is helpful in early diagnosis of disease. Patients of HPS often develop platypnoea characterized by increase dyspnea on standing position. The objective feature of platypnoea is orthodeoxia defined by a decrease in PaO_2 of ≥ 4 mmHg or $\geq 5\%$ from the supine position to the upright position.[90] On standing position, preferential perfusion occurs to the basal area of the lungs due to gravity. It leads to further dilatation of vasculature and worsening of V/Q mismatch. Krowka and Cortese discussed two patterns of intrapulmonary vascular dilatations. Type 1 lesions include diffuse pulmonary vascular dilatations at the precapillary level close to the gas exchange units and Type 2 lesions consist of localized dilatations away from the gas exchange units. Type 2 category show a poor response to oxygen.[91]

Oxygen induced hypercapnia

Uncontrolled oxygen therapy to correct hypoxemia in patients of COPD with ARF may lead to development or worsening of existing hypercapnia. This phenomenon has been observed since long time in the field of medicine.[92,93] However, there is controversy regarding the exact mechanism leading to the development of oxygen induced hypercapnia in COPD patients. The mechanism proposed initially and still being taught in the medical school is the hypoxic drive theory. According to this theory, COPD patients depend on hypoxic ventilatory drive as the hypercapnic drive is blunted in chronically hypercapnic COPD patients.

Rudolf proposed that prolonged hypoxemia in patients with COPD in ARF leads to lactate accumulation in the brain and establishes the hypoxic drive of breathing.[94]

Therefore, uncontrolled oxygen therapy may abolish the hypoxic drive resulting in fall in V_E and development of hypercapnia. However, there is an upper limit to the effect of oxygen therapy on V_E as any rise in PaO_2 above 100 mmHg have no impact on V_E. It occurs due to attenuation of carotid sinus discharge above 100 mmHg.[95] However, Aubier *et al.* did not find any correlation between oxygen therapy induced hypercapnia and changes in ventilation.[96] They administered oxygen to 22 patients with ARF due to COPD and studied the time course of changes in arterial blood gases, V_E, and respiratory rate. Oxygen therapy initially decreases V_E in all patients, and the nadir occurred 71 ± 9 s after initiation of oxygen therapy. The mean decrease in V_E was $18 \pm 2\%$. However, with continued oxygen therapy there is a significant improvement in V_E reaching a plateau after about 12 min of oxygen therapy. Surprisingly $PaCO_2$ showed a rising trend despite the recovery in V_E. At the end of 15 min of oxygen therapy, average fall in V_E was 7% compared to patients breathing room air and this can explain a $PaCO_2$ increase of 5 mmHg of the total 23 mmHg only. In another study, Aubier *et al.*[97] measured the respiratory drive by mouth occlusion pressure in the first 100 ms of inspiratory effort (P0.1) in twenty COPD patients with ARF. The P0.1 after oxygen therapy reduced to 4.9 ± 0.7 cm H_2O from a value of 8.3 ± 0.8 cm H_2O seen in patients on room air. However, this value is still greater than that of normal subjects, thereby clearly indicating that reduction

in V_E alone cannot explain the rise in $PaCO_2$. $PaCO_2$ level is influenced by V_T, RR, VCO_2, and V_D. Since V_E cannot explain the rise, it must be either rise in VCO_2 or V_D responsible for the rise in PCO_2. The V_D/V_T ratio increased from 77 ± 2 while breathing room air to 82 ± 2 after 15 min of O_2 inhalation ($P < 0.01$). Therefore, the oxygen-induced hypercapnia is due to V/Q mismatch. Oxygen therapy can lead to further worsening of V/Q mismatch by relieving HPV, thereby increasing perfusion to low ventilated areas. Since the alveolar-capillary unit remains poorly ventilated, CO_2 removal would be poor leading to rise in $PaCO_2$. On the other hand, blood from the adjacent better-ventilated unit would be diverted to the poorly ventilated unit due to the abolition of HPV, the former unit would become a high V/Q units. Another detrimental effect of uncontrolled oxygen therapy is the development of absorption atelectasis. It may happen with FiO_2 as low as 30–50%.[98] The increase in FiO_2 can cause nitrogen washout of the alveoli thereby leading to alveolar collapse as oxygen is absorbed rapidly distal to the obstruction in the airways. Another mechanism of oxygen-induced hypercapnia is Haldane effect. Haldane effect says that increasing FiO_2 displaces the CO_2 molecules from hemoglobin and can also explain the rise in $PaCO_2$ level.[99] Robinson *et al*.[100] evaluated the V/Q mismatch by MIGET in 22 patients during an acute exacerbation of COPD and studied the underlying mechanism of hypercapnia. They grouped the patients into CO2 retainer and non-retainer group. The features that differentiate the two groups are depression of ventilation and increase in alveolar dead space in the retainer groups. V/Q mismatch was equally distributed in both the groups. They proposed hypercapnia induced bronchodilatation as the mechanism for the increase in dead space. Therefore, the mechanism of oxygen-induced hypercapnia in COPD is still controversial. However, COPD patients should be treated with controlled oxygen therapy with a SaO_2 goal from 88% to 92% to avoid the risk of hypercapnia.[95]

The risk of hypercapnia following oxygen therapy has also been observed with other conditions: Morbid obesity, asthma, pneumonia, chest wall deformities and neuromuscular disorders.[95,100] Perrin *et al*.[101] in a randomized controlled trial of high versus controlled oxygen therapy in patients with severe exacerbations of asthma reported an increase in the transcutaneous partial pressure of carbon dioxide ($PtCO_2$) in patients on high concentration oxygen therapy. Similar to COPD patients, a controlled oxygen regime should be used in the treatment of severe asthma. The mechanism is the release of HPV by high concentration of oxygen therapy leading to dead space effect.[18,102] Hutchison *et al*.[103] proposed an interesting hypothesis that the response to hypoxia may be mediated in part by familial factor and those with this risk are at risk of developing respiratory failure after an asthma attack. Hollier *et al*.[104] reported hypoventilation and acidemia development after using moderate concentration of supplemental oxygen (FiO_2) in patients with obesity hypoventilation syndrome (OHS). The risk is higher in patients with a high baseline level of $PaCO_2$ and HCO_3. Both high $PaCO_2$ and HCO_3 level may blunt the hypercapnic ventilatory responses in OHS patients.[105,106]

Measurement of hypoxemia
Arterial oxygen tension (PaO₂)
The PaO_2 is the partial pressure of oxygen that indicates the dissolved oxygen in the plasma and not the oxygen bound to hemoglobin. It is measured by arterial blood gas analyzer. Mixed venous blood partial pressure of oxygen (PVO_2) is 40 mmHg and it is 75% saturated. The PaO_2 in the systemic artery after gas exchange at the alveolar level is 97%. It does not become 100% due to the presence of an anatomical shunt. The goal in oxygen therapy is to raise the PaO_2 above 60 mmHg as the oxygen-hemoglobin curve is flattened after a PaO_2 of 60 mmHg. The normal PaO_2 level varies from 80 to 100 mmHg.

Arterial oxygen content (CaO₂)
It is the combination of hemoglobin bound oxygen plus the dissolved oxygen in the arterial blood. It is calculated by the following equation:

$$CaO_2 = (Hgb \times 1.34 \times SaO_2) + (0.0031 \times PaO_2).$$

PaO_2 and the SaO_2 do not provide information on the number of oxygen molecules in the blood. CaO_2 quantifies the amount of oxygen in the blood-both bound and unbound fraction to hemoglobin. The contribution of the dissolved oxygen to CaO_2 is normally minimal. Since PaO_2 depends on dissolved oxygen, PaO_2 may remain normal in the presence of anemia.

Arterial oxygen saturation (SaO₂)
It is defined as the percentage of hemoglobin saturated with oxygen. It can be measured by both pulse oximetry and arterial blood gas analysis (SaO_2). Pulse oximetry is widely used in the assessment of patients and should be regarded as the fifth vital sign.[107] Measurement of oxygen saturation by pulse oximetry (SpO_2) is based on the Beer–Lambert–Bouguer law which states that the attenuation of light depends on the properties of the materials through which the light is traveling. Pulse oximeter contains light-emitting diodes that transmit light energies at two wavelengths of 660 nm (red light) and 940 nm (infrared) respectively. Oxy-hemoglobin (O2Hb) and deoxy-hemoglobin (HHb) differentially absorb red and near-infrared (IR) light.[108]

PaO₂/FiO₂ ratio
It is the ratio of partial pressure of oxygen to fractional inspired oxygen and is also known as Carrico index. The PaO_2/FiO_2 ratio assesses the hypoxemia at a different level of FiO_2. The normal ratio varies from 300 to 500 mmHg. It is a commonly used index because of the ease of measurement and its prognostic value in ARDS patients. According to Berlin definition, ARDS is differentiated into three subcategories based on the degree of hypoxemia measured by PaO_2/FiO_2 ratio: Mild (200 mmHg $< PaO_2/FiO_2 \leq 300$ mmHg), moderate (100 mmHg $< PaO_2/$

$FiO_2 \leq 200$ mmHg), and severe ($PaO_2/FIO_2 \leq 100$ mmHg). In all the subcategories, PEEP or continuous positive airway pressure ≥ 5 cm H_2O was used.[109] It can also be used for rough estimation of shunt fraction.[19] A PaO_2/FiO_2 ratio of <200 indicates a shunt fraction is more than 20%. In a healthy person who is breathing room air, the PaO_2 is 100 mmHg and FiO_2 is 0.21%. Therefore, the PaO_2/FiO_2 ratio is 100/0.21 or 500.

There are limitations of PaO_2/FiO_2 ratio also. A-a gradient can differentiate whether hypoxemia is due to alveolar hypoventilation or V/Q mismatch but PaO_2/FiO_2 ratio is unable to determine the underlying mechanism of hypoxemia. Gowda *et al*.[110] in a modeling study assessed the variability of PaO_2/FiO_2 ratio in ARDS patients. They observed that in ARDS patients, all the indices of hypoxemia are influenced by changes in extra-pulmonary factor like FiO_2. In ARDS patients with moderate shunts (<30%), PaO_2/FiO_2 ratio is better at extremes of FiO_2 than at intermediate FiO_2. In patients with large shunts (>30%) PaO_2/FiO_2 ratio is greater at low FiO_2. A stable PaO_2/FiO_2 ratio is seen with a FiO_2 of ≥ 0.5 and a PaO_2 of ≤ 100 mmHg. Karbing *et al*.[111] showed that PaO_2/FiO_2 ratio varied with FiO_2 in both mechanically ventilated and spontaneously breathing patients and proposed that the FiO_2 level at which the PaO_2/FiO_2 ratio is measured should be specified. They also advocated the replacement of the conventional single-parameter variable like PaO_2/FiO_2 ratio with two parameters model of hypoxemia development due to V/Q mismatch and shunt.

The arterial/alveolar oxygen tension ratio (a-A oxygen tension ratio)

The arterial to alveolar oxygen ratio is measured by dividing PaO_2 by the PaO_2. The a-A oxygen ratio is less dependence on FiO_2 unlike the alveolar/arterial oxygen tension difference.[112] Normal ratio varies between 0.75 and 1.0. The a-A oxygen ratio may be used to calculate the FiO_2 required to raise PaO_2 to certain levels. The formula for estimating the required FiO_2 can be done by the following formula:

$$\frac{PaO_2}{PAO_2} = \frac{New\ PaO_2}{New\ PAO_2}$$

A 65-year-old patients of COPD presented in the emergency with acute exacerbation. His ABGs is showing a PaO_2 of 40 mmHg and a $PaCO_2$ of 55 mmHg on FiO_2 28%. What should be the FiO_2 to raise PaO_2 to 60 mmHg?

$PaO_2 = FiO_2\ (PB - PH_2O) - PaCO_2/R$.

$= 0.28\ (760 - 47) - 55/0.8$.

$= 131$.

$PaO_2/PaO_2 = 40/131 = 0.30$.

$60/New\ PaO_2 = PaO_2/PaO_2 = 0.30$.

Required $FiO_2 = 0.37$ or 37%.

R is respiratory quotient.

Oxygenation index

The OI is calculated as mean airway pressure (MAP) times FiO_2 and whole divided by arterial PO_2. The advantage of OI is that it assesses both the gas exchange and compliance of the lung.[113]

$$Oxygenation\ Index\,(OI) = \frac{Mean\ airway\ pressure \times FiO_2}{PaO_2}$$

Dechert *et al*. reported that age-adjusted OI is equivalent to or better than other mortality prediction system used for ARDS.[114]

Mixed and central venous oxygen saturation

Mixed venous oxygen saturation (SvO_2) is the percentage of oxygen bound to hemoglobin in the mixed venous blood. It gives us idea about the oxygen extraction by the tissues. Normal SvO_2 is 60–80%. Central venous oxygen saturation ($ScVO_2$) is a surrogate of SvO_2 and is easier to measure unlike SvO_2. The goal of $ScVO_2$ of more than 70% has been incorporated in the surviving sepsis guidelines.[115] There are other advantages of $ScVO_2$ measurement. It can be used in estimating CO, shunt fraction. It gives better idea about adequacy of patient's oxygen delivery.[116]

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REFERENCES

1. Greene KE, Peters JI. Pathophysiology of acute respiratory failure. Clin Chest Med 1994;15:1-12.
2. Aviado DM, Daly MD, Lee CY, Schmidt CF. The contribution of the bronchial circulation to the venous admixture in pulmonary venous blood. J Physiol 1961;155:602-22.
3. Sorbini CA, Grassi V, Solinas E, Muiesan G. Arterial oxygen tension in relation to age in healthy subjects. Respiration 1968;25:3-13.
4. Belda JF, Soro M, Ferrando C. Pathophysiology of respiratory failure. Trends Anaesth Crit Care 2013;3:265-9.
5. Glenny RW. Teaching ventilation/perfusion relationships in the lung. Adv Physiol Educ 2008;32:192-5.
6. West JB, Dollery CT, Naimark A. Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. J Appl Physiol 1964;19:713-24.
7. Orchard CH, Sanchez de Leon R, Sykes MK. The relationship between hypoxic pulmonary vasoconstriction and arterial oxygen tension in the intact dog. J Physiol 1983;338:61-74.
8. Fishman AP. Hypoxia on the pulmonary circulation. How and where it acts. Circ Res 1976;38:221-31.
9. Shirai M, Sada K, Ninomiya I. Effects of regional alveolar hypoxia and hypercapnia on small pulmonary vessels in cats. J Appl Physiol (1985) 1986;61:440-8.
10. Leach RM, Treacher DF. Clinical aspects of hypoxic pulmonary vasoconstriction. Exp Physiol 1995;80:865-75.
11. Patel AJ, Lazdunski M, Honoré E. Kv2.1/Kv9.3, a novel ATP-dependent delayed-rectifier K+ channel in oxygen-sensitive pulmonary artery myocytes. EMBO J 1997;16:6615-25.
12. Ward JP, Aaronson PI. Mechanisms of hypoxic pulmonary vasoconstriction: Can anyone be right? Respir Physiol 1999;115:261-71.
13. Aaronson PI, Robertson TP, Knock GA, Becker S, Lewis TH, Snetkov V, *et al*. Hypoxic pulmonary vasoconstriction: Mechanisms and

controversies. J Physiol 2006;570(Pt 1):53-8.

14. Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. Eur Respir J 2014;44:1023-41.

15. Wagner PD, Dantzker DR, Iacovoni VE, Tomlin WC, West JB. Ventilation-perfusion inequality in asymptomatic asthma. Am Rev Respir Dis 1978;118:511-24.

16. Polverino E, Gómez FP, Manrique H, Soler N, Roca J, Barberà JA, *et al*. Gas exchange response to short-acting beta2-agonists in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med 2007;176:350-5.

17. Rodriguez-Roisin R, Wagner PD. Clinical relevance of ventilation-perfusion inequality determined by inert gas elimination. Eur Respir J 1990;3:469-82.

18. Ballester E, Reyes A, Roca J, Guitart R, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in acute severe asthma: Effects of salbutamol and 100% oxygen. Thorax 1989;44:258-67.

19. Covelli HD, Nessan VJ, Tuttle WK 3rd. Oxygen derived variables in acute respiratory failure. Crit Care Med 1983;11:646-9.

20. Gunning JE. Pathophysiology of respiratory failure and indications for respiratory support. Surgery (Oxf) 2003;21:72-6.

21. Williams AJ. ABC of oxygen: Assessing and interpreting arterial blood gases and acid-base balance. BMJ 1998;317:1213-6.

22. Roussos C, Koutsoukou A. Respiratory failure. Eur Respir J Suppl 2003;47:3s-14s.

23. Wagner PD, Hedenstierna G, Rodriguez-Roisin R. Gas exchange, expiratory flow obstruction and the clinical spectrum of asthma. Eur Respir J 1996;9:1278-82.

24. Roca J, Ramis L, Rodriguez-Roisin R, Ballester E, Montserrat JM, Wagner PD. Serial relationships between ventilation-perfusion inequality and spirometry in acute severe asthma requiring hospitalization. Am Rev Respir Dis 1988;137:1055-61.

25. Rodriguez-Roisin R. Acute severe asthma: Pathophysiology and pathobiology of gas exchange abnormalities. Eur Respir J 1997;10:1359-71.

26. Freyschuss U, Hedlin G, Hedenstierna G. Ventilation-perfusion relationships during exercise-induced asthma in children. Am Rev Respir Dis 1984;130:888-94.

27. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med 1968;278:1355-60.

28. Talag AA, Wilcox P. Clinical physiology of chronic obstructive pulmonary disease. BCMJ 2008;50:97-102.

29. Rodríguez-Roisin R, Drakulovic M, Rodríguez DA, Roca J, Barberà JA, Wagner PD. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. J Appl Physiol (1985) 2009;106:1902-8.

30. Burrows B, Niden AH, Fletcher CM, Jones NL. Clinical types of chronic obstructive lung disease in London and in Chicago. A study of one hundred patients. Am Rev Respir Dis 1964;90:14-27.

31. Wagner PD, Dantzker DR, Dueck R, Clausen JL, West JB. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest 1977;59:203-16.

32. Barbera JA, Ramirez J, Roca J, Wagner PD, Sanchez-Lloret J, Rodriguez-Roisin R. Lung structure and gas exchange in mild chronic obstructive pulmonary disease. Am Rev Respir Dis 1990;141(4 Pt 1):895-901.

33. Barberà JA, Riverola A, Roca J, Ramirez J, Wagner PD, Ros D, *et al*. Pulmonary vascular abnormalities and ventilation-perfusion relationships in mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;149(2 Pt 1):423-9.

34. Elbehairy AF, Ciavaglia CE, Webb KA, Guenette JA, Jensen D, Mourad SM, *et al*. Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance. Am J Respir Crit Care Med 2015;191:1384-94.

35. Wright JL, Lawson L, Paré PD, Hooper RO, Peretz DI, Nelems JM, *et al*. The structure and function of the pulmonary vasculature in mild chronic obstructive pulmonary disease. The effect of oxygen and exercise. Am Rev Respir Dis 1983;128:702-7.

36. Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. Eur Respir J 1999;13:197-205.

37. Santos S, Peinado VI, Ramírez J, Melgosa T, Roca J, Rodriguez-Roisin R, *et al*. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. Eur Respir J 2002;19:632-8.

38. Sandek K, Bratel T, Lagerstrand L, Rosell H. Relationship between lung function, ventilation-perfusion inequality and extent of emphysema as assessed by high-resolution computed tomography. Respir Med 2002;96:934-43.

39. Brudin LH, Rhodes CG, Valind SO, Buckingham PD, Jones T, Hughes JM. Regional structure-function correlations in chronic obstructive lung disease measured with positron emission tomography. Thorax 1992;47:914-21.

40. Morrison NJ, Abboud RT, Müller NL, Miller RR, Gibson NN, Nelems B, *et al*. Pulmonary capillary blood volume in emphysema. Am Rev Respir Dis 1990;141:53-61.

41. Kim DK, Jacobson FL, Washko GR, Casaburi R, Make BJ, Crapo JD, *et al*. Clinical and radiographic correlates of hypoxemia and oxygen therapy in the COPDGene study. Respir Med 2011;105:1211-21.

42. Morrell NW, Wignall BK, Biggs T, Seed WA. Collateral ventilation and gas exchange in emphysema. Am J Respir Crit Care Med 1994;150:635-41.

43. Barberà JA, Roca J, Ferrer A, Félez MA, Díaz O, Roger N, *et al*. Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. Eur Respir J 1997;10:1285-91.

44. West JB. State of the art: Ventilation-perfusion relationships. Am Rev Respir Dis 1977;116:919-43.

45. Wilson JE 3rd, Pierce AK, Johnson RL Jr., Winga ER, Harrell WR, Curry GC, *et al*. Hypoxemia in pulmonary embolism, a clinical study. J Clin Invest 1971;50:481-91.

46. Goldhaber SZ, Elliott CG. Acute pulmonary embolism: Part I: Epidemiology, pathophysiology, and diagnosis. Circulation 2003;108:2726-9.

47. Ayari A, Chaouch N, Bacha S, Kortas N, Racil H, Rouhou CS, *et al*. Isolated hypocapnia: A sign not to be neglected. European Respiratory Journal 2014;44(Suppl 58):P2308.

48. Elliott CG. Pulmonary physiology during pulmonary embolism. Chest 1992;101 4 Suppl: 163S-71S.

49. Santolicandro A, Prediletto R, Fornai E, Formichi B, Begliomini E, Giannella-Neto A, *et al*. Mechanisms of hypoxemia and hypocapnia in pulmonary embolism. Am J Respir Crit Care Med 1995;152:336-47.

50. D'Alonzo GE, Dantzker DR. Gas exchange alterations following pulmonary thromboembolism. Clin Chest Med 1984;5:411-9.

51. Dantzker DR, Bower JS. Alterations in gas exchange following pulmonary thromboembolism. Chest 1982;81:495-501.

52. Itti E, Nguyen S, Robin F, Desarnaud S, Rosso J, Harf A, *et al*. Distribution of ventilation/perfusion ratios in pulmonary embolism: An adjunct to the interpretation of ventilation/perfusion lung scans. J Nucl Med 2002;43:1596-602.

53. Stein PD, Goldhaber SZ, Henry JW. Alveolar-arterial oxygen gradient in the assessment of acute pulmonary embolism. Chest 1995;107:139-43.

54. Stein RM, Alkalay I, Bruderman I. Pulmonary function after experimental autologous pulmonary emboli. J Clin Invest 1962;41:1402.

55. Gurewich V, Thomas D, Stein M, Wessler S. Bronchoconstriction in the presence of pulmonary embolism. Circulation 1963;27:339-45.

56. Page IH. Serotonin (5-hydroxytryptamine); the last four years. Physiol Rev 1958;38:277-335.

57. Lewis GP. Active polypeptides derived from plasma proteins. Physiol Rev 1960;40:647-76.

58. Ruiz J, Monreal M, Sala H, Roncalés J, Fiz JA, Monsó E, *et al*. Effects of inhaled platelet activating factor on bronchial responsiveness in patients with symptomatic and asymptomatic pulmonary embolism. Chest 1992;102:819-23.

59. Clay TP, Hughes JM. The role of prostaglandins in the bronchoconstriction induced by pulmonary micro-embolism in the guinea-pig. J Physiol 1980;308:427-37.

60. Swenson EW, Finley TN, Guzman SV. Unilateral hypoventilation in man during temporary occlusion of one pulmonary artery. J Clin Invest 1961;40:828-35.

61. Nakos G, Kitsiouli EI, Lekka ME. Bronchoalveolar lavage alterations in pulmonary embolism. Am J Respir Crit Care Med 1998;158(5 Pt 1):1504-10.

62. Calkovska A, Mokra D, Calkovsky V. Lung surfactant alterations in pulmonary thromboembolism. Eur J Med Res 2009;14 Suppl 4:38-41.

63. D'Alonzo GE, Bower JS, DeHart P, Dantzker DR. The mechanisms of abnormal gas exchange in acute massive pulmonary embolism. Am Rev Respir Dis 1983;128:170-2.

64. Panoutsopoulos G, Ilias L, Christakopoulou I. Transient right-to-left shunt in massive pulmonary embolism. Ann Nucl Med 2000;14:217-21.

65. Said SI, Longacher JW Jr., Davis RK, Banerjee CM, Davis WM, Wooddell WJ. Pulmonary gas exchange during induction of pulmonary edema in anesthetized dogs. J Appl Physiol 1964;19:403-7.

66. Niden AH, Aviado DM Jr. Effects of pulmonary embolism on the

pulmonary circulation with special reference to arteriovenous shunts in the lung. Circ Res 1956;4:67-73.

67. Dantzker DR, Bower JS. Mechanisms of gas exchange abnormality in patients with chronic obliterative pulmonary vascular disease. J Clin Invest 1979;64:1050-5.

68. Manier G, Castaing Y, Guenard H. Determinants of hypoxemia during the acute phase of pulmonary embolism in humans. Am Rev Respir Dis 1985;132:332-8.

69. Sharma GV, Burleson VA, Sasahara AA. Effect of thrombolytic therapy on pulmonary-capillary blood volume in patients with pulmonary embolism. N Engl J Med 1980;303:842-5.

70. Agustí AG, Barberà JA. Contribution of multiple inert gas elimination technique to pulmonary medicine 2. Chronic pulmonary diseases: Chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. Thorax 1994;49:924-32.

71. Crystal RG, Fulmer JD, Roberts WC, Moss ML, Line BR, Reynolds HY. Idiopathic pulmonary fibrosis. Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. Ann Intern Med 1976;85:769-88.

72. Javaheri S, Sicilian L. Lung function, breathing pattern, and gas exchange in interstitial lung disease. Thorax 1992;47:93-7.

73. Agustí AG, Roca J, Gea J, Wagner PD, Xaubet A, Rodriguez-Roisin R. Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. Am Rev Respir Dis 1991;143:219-25.

74. Lamy M, Fallat RJ, Koeniger E, Dietrich HP, Ratliff JL, Eberhart RC, *et al*. Pathologic features and mechanisms of hypoxemia in adult respiratory distress syndrome. Am Rev Respir Dis 1976;114:267-84.

75. Dantzker DR, Brook CJ, Dehart P, Lynch JP, Weg JG. Ventilation-perfusion distributions in the adult respiratory distress syndrome. Am Rev Respir Dis 1979;120:1039-52.

76. Santos C, Ferrer M, Roca J, Torres A, Hernández C, Rodriguez-Roisin R. Pulmonary gas exchange response to oxygen breathing in acute lung injury. Am J Respir Crit Care Med 2000;161:26-31.

77. Elliott CG, Morris AH, Cengiz M. Pulmonary function and exercise gas exchange in survivors of adult respiratory distress syndrome. Am Rev Respir Dis 1981;123:492-5.

78. Rodriquez-Roisin R. Response to oxygen breathing in ALI/ARDS patients. Correspondence. Am J Respir Crit Care Med 2001;163:793-4.

79. Matamis D, Lemaire F, Harf A, Teisseire B, Brun-Buisson C. Redistribution of pulmonary blood flow induced by positive end-expiratory pressure and dopamine infusion in acute respiratory failure. Am Rev Respir Dis 1984;129:39-44.

80. Agustí AG, Cardús J, Roca J, Grau JM, Xaubet A, Rodriguez-Roisin R. Ventilation-perfusion mismatch in patients with pleural effusion: Effects of thoracentesis. Am J Respir Crit Care Med 1997;156(4 Pt 1):1205-9.

81. Brown NE, Zamel N, Aberman A. Changes in pulmonary mechanics and gas exchange following thoracocentesis. Chest 1978;74:540-2.

82. Sonnenblick M, Melzer E, Rosin AJ. Body positional effect on gas exchange in unilateral pleural effusion. Chest 1983;83:784-6.

83. Norris RM, Jones JG, Bishop JM. Respiratory gas exchange in patients with spontaneous pneumothorax. Thorax 1968;23:427-33.

84. Fluckiger M. Vorkommen von trommelschlagel-formigen fingerend phalangen ohne chronische veranderungen an der lungen order am herzen. Wien Med Wochenschr 1884;34:1457. [German].

85. Hoffbauer FW, Rydell R. Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. Am J Med 1956;21:450-60.

86. Eriksson LS, Söderman C, Wahren J, Ericzon BG, Eleborg L, Hedenstierna G. Is hypoxemia in cirrhotic patients due to a functional "hepatopulmonary syndrome"? [abstract]. J Hepatol 1988;1 Suppl 1:S29.

87. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome – A liver-induced lung vascular disorder. N Engl J Med 2008;358:2378-87.

88. Davis HH 2nd, Schwartz DJ, Lefrak SS, Susman N, Schainker BA. Alveolar-capillary oxygen disequilibrium in hepatic cirrhosis. Chest 1978;73:507-11.

89. Williams A, Trewby P, Williams R, Reid L. Structural alterations to the pulmonary circulation in fulminant hepatic failure. Thorax 1979;34:447-53.

90. Gómez FP, Martínez-Pallí G, Barberà JA, Roca J, Navasa M, Rodríguez-Roisin R. Gas exchange mechanism of orthodeoxia in hepatopulmonary syndrome. Hepatology 2004;40:660-6.

91. Krowka MJ, Cortese DA. Hepatopulmonary syndrome: An evolving perspective in the era of liver transplantation. Hepatology 1990;11:138-42.

92. Davies CE, Mackinnon J. Neurological effects of oxygen in chronic cor pulmonale. Lancet 1949;2:883-5.

93. Campbell EJ. The J. Burns Amberson Lecture. The management of acute respiratory failure in chronic bronchitis and emphysema. Am Rev Respir Dis 1967;96:626-39.

94. Rudolf M, Banks RA, Semple SJ. Hypercapnia during oxygen therapy in acute exacerbations of chronic respiratory failure. Hypothesis revisited. Lancet 1977;2:483-6.

95. O'Driscoll BR, Howard LS, Davison AG; British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. Thorax 2008;63 Suppl 6:vi1-68.

96. Aubier M, Murciano D, Milic-Emili J, Touaty E, Daghfous J, Pariente R, *et al*. Effects of the administration of O2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis 1980;122:747-54.

97. Aubier M, Murciano D, Fournier M, Milic-Emili J, Pariente R, Derenne JP. Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1980;122:191-9.

98. Downs JB. Has oxygen administration delayed appropriate respiratory care? Fallacies regarding oxygen therapy. Respir Care 2003;48:611-20.

99. Tyuma I. The Bohr effect and the Haldane effect in human hemoglobin. Jpn J Physiol 1984;34:205-16.

100. Robinson TD, Freiberg DB, Regnis JA, Young IH. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;16:1524-9.

101. Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, *et al*. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. Thorax 2011;66:937-41.

102. Rodriguez-Roisin R, Ballester E, Roca J, Torres A, Wagner PD. Mechanisms of hypoxemia in patients with status asthmaticus requiring mechanical ventilation. Am Rev Respir Dis 1989;139:732-9.

103. Hutchison AA, Olinsky A. Hypoxic and hypercapnic response in asthmatic subjects with previous respiratory failure. Thorax 1981;36:759-63.

104. Hollier CA, Harmer AR, Maxwell LJ, Menadue C, Willson GN, Unger G, *et al*. Moderate concentrations of supplemental oxygen worsen hypercapnia in obesity hypoventilation syndrome: A randomised crossover study. Thorax 2014;69:346-53.

105. Zwillich CW, Sutton FD, Pierson DJ, Greagh EM, Weil JV. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. Am J Med 1975;59:343-8.

106. Goldring RM, Turino GM, Heinemann HO. Respiratory-renal adjustments in chronic hypercapnia in man. Extracellular bicarbonate concentration and the regulation of ventilation. Am J Med 1971;51:772-84.

107. Neff TA. Routine oximetry. A fifth vital sign? Chest 1988;94:227.

108. Chan ED, Chan MM, Chan MM. Pulse oximetry: Understanding its basic principles facilitates appreciation of its limitations. Respir Med 2013;107:789-99.

109. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, *et al*. Acute respiratory distress syndrome: The Berlin definition. JAMA 2012;307:2526-33.

110. Gowda MS, Klocke RA. Variability of indices of hypoxemia in adult respiratory distress syndrome. Crit Care Med 1997;25:41-5.

111. Karbing DS, Kjaergaard S, Smith BW, Espersen K, Allerød C, Andreassen S, *et al*. Variation in the PaO_2/FiO_2 ratio with FiO_2: Mathematical and experimental description, and clinical relevance. Crit Care 2007;11:R118.

112. Doyle DJ. Arterial/alveolar oxygen tension ratio: A critical appraisal. Can Anaesth Soc J 1986;33:471-4.

113. Go L, Budinger GR, Kwasny MJ, Peng J, Forel JM, Papazian L, *et al*. Failure to improve the oxygenation index is a useful predictor of therapy failure in acute respiratory distress syndrome clinical trials. Crit Care Med 2016;44:e40-4.

114. Dechert RE, Park PK, Bartlett RH. Evaluation of the oxygenation index in adult respiratory failure. J Trauma Acute Care Surg 2014;76:469-73.

115. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al*. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.

116. Walley KR. Use of central venous oxygen saturation to guide therapy. Am J Respir Crit Care Med 2011;184:514-20.