Normal respiration is controlled by complex physiological pathways in the body. A respiratory failure can prove fatal and can cause death if untreated. In this article, normal physiology of respiration, types, pathophysiology, and treatment of respiratory failure will be discussed in detail.

Definition of Respiratory Failure

Respiratory dysfunction resulting in failure of gas exchange i.e. decrease in arterial oxygen tension, PaO₂, lower than 60 mm Hg (hypoxemia). It may or may not accompany with hypercapnia, a PaCO₂ higher than 50 mm Hg (decreased CO₂ elimination).

Normal Physiology of Respiration

In normal individuals, the "alveolar" oxygen tension PAO₂ is maintained close to 100 mmHg, while alveolar carbon-dioxide tension PACO₂ is maintained close to 40 mmHg.

There is a small difference of 5-10 mmHg between "Alveolar (A)" and "arterial (a)" oxygen tension because around 2 % of the systemic cardiac output bypasses the pulmonary circulation (physiologic shunt) and is not oxygenated.

The resulting mixing of a small amount of deoxygenated blood makes the PO₂ of arterial blood (PaO₂) slightly lower than that of alveolar air (PAO₂). Normal A-a gradient is about <
10 mmHg. If A-a gradient is normal, it means there is no defect in the diffusion of gases. The A-a gradient helps to outline the different causes of respiratory failure.

At steady state, the rate of carbon dioxide production within the body is constant. The PACO₂ depends on and is ‘inversely proportional’ to the ventilation, so the increased ventilation will lead to decreased PACO₂ and decreased ventilation will cause increased PACO₂.

The alveolar oxygen tension, PAO₂, depends on the concentration of inhaled oxygen (FIO₂), and alveolar carbon-dioxide tension (PACO₂), as in the following equation:

\[
PAO_2 = FIO_2 \times (PB - PH_2O) - PACO_2/R
\]

- PAO₂: Alveolar PO₂
- FIO₂: Fractional concentration of oxygen in inspired gas
- PB: Barometric pressure
- PH₂O: water vapor pressure at 37°C
- PACO₂: Alveolar PCO₂
- R: Respiratory exchange ratio.

Types of Respiratory Failure

There are two types of respiratory failure that are classified using arterial blood gases (ABG) analysis:

**Type I:** It is characterized by:
- **Hypoxemia** (PaO₂ less than 60 mmHg)
- Without hypercapnia. **Normal or low** PaCO₂ (PaCO₂ less than 50 mmHg)
- It usually occurs due to significant ventilation-perfusion mismatch

**Type II:** It is characterized by:
- **Hypoxemia** (PaO₂ less than 60 mmHg) and
- **Hypercapnia. Increased** PaCO₂ (PaCO₂ more than 50 mmHg)
- It usually occurs due to hypoventilation.

Respiratory failure may be further classified as either acute or chronic onset.

**Acute respiratory failure** occurs within minutes and hours and is usually an emergency. It is characterized by life-threatening changes in arterial blood gases and the acid base status of the body. E.g. tension pneumothorax, pulmonary embolism, acute respiratory distress syndrome, anaphylactic reactions.
Chronic respiratory failure occurs gradually over weeks and months. It is less dramatic and not always readily apparent. The kidneys usually compensate and normalize the acid-base status of the body by altering bicarbonate and acid excretion. Polycythemia may also occur. E.g. chronic obstructive pulmonary disease, pneumoconiosis.

Pathophysiology of Hypoxemia

Hypoxemia is a decrease in arterial PO$_2$, while hypoxia is decreased oxygen delivery to the tissues. Patient may develop hypoxia in the presence of normal PaO$_2$, as in cases of carbon-monoxide poisoning or decreased hemoglobin (anemia).

There are five important pathophysiological causes of hypoxemia and respiratory failure, which are as follows:

1. Hypoventilation

The minute ventilation depends on the respiratory rate and the tidal volume, which is the amount of inspired air during each normal breath at rest.
Minute ventilation = Respiratory rate × Tidal volume

The normal respiratory rate is about 12 breaths per minute and the normal tidal volume is about 500 mL. Therefore, the minute respiratory volume normally averages about 6 L/min.

**Hypoventilation** occurs when there is decrease in the respiratory rate and/or tidal volume, so that decreased amount of air is exchanged per minute. There will be decreased oxygen entry within the alveoli and the arteries leading to decreased PaO₂. As already described, the PaCO₂ is inversely proportional to the ventilation. Hence, the hypoventilation will lead to increased PaCO₂.

The **alveolar-arterial gradient** will be normal and less than 10 mmHg as there is no defect in diffusion of gases. In these cases, increasing the ventilation and/or increasing the oxygen concentration will correct the deranged blood gases.

### 2. Diffusion Impairment

In diffusion impairment, there is a structural problem within the lung. There may be decreased surface area (as in **emphysema**), or increased thickness of alveolar membranes (as in **fibrosis** and **restrictive lung diseases**) that impairs the diffusion of gases across the alveoli leading to increased alveolar-arterial gradient. In increased A-a gradient, the alveolar PO₂ will be normal or increased, but arterial PO₂ will be decreased. The greater the structural problem is present, the greater the alveolar-arterial gradient will be.

Since diffusion of gases is directly proportional to the concentration of gases, therefore increasing the concentration of inhaled oxygen will correct PaO₂ but the increased A-a gradient will be present as long as the structural problem is present.

### 3. Pulmonary Shunt

In pulmonary shunt, also known as **right-to-left shunt**, the venous deoxygenated blood from the right side enters the left side of the heart and systemic circulation without getting oxygenated within the alveoli. In simple words, shunt refers to “normal perfusion, poor ventilation.” The lungs are having normal blood supply, but ventilation is decreased or absent that fails to exchange gases with the incoming deoxygenated blood. The ventilation/perfusion ratio is or near to zero.

For example, **atelectasis** and **cyanotic heart diseases**. In atelectasis, the collapsed lung is not ventilated and blood within that segment fails to oxygenate. In cyanotic heart diseases, the blood from right side bypasses (shunts) the lungs and enter the left side, causing **hypoxemia** and **cyanosis**.

The A – a gradient is increased as deoxygenated blood enters the arterial (systemic) circulation decreasing the arterial oxygen tension, PaO₂.

Since venous blood does not oxygenate in the pulmonary shunt, therefore increasing the oxygen concentration does not correct the hypoxemia. The blood will bypass the lungs, no matter how much increased oxygen concentration is used. **This failure to increase PaO₂ after oxygen administration** is a very important point and helps to differentiate from the impaired diffusion and other causes of hypoxemia that correct with the supplemental oxygen.
4. Ventilation – Perfusion (V/Q) Mismatch

It is the ratio of alveolar ventilation (V) to pulmonary blood flow (Q). The matching of ventilation and perfusion is essential to achieve the adequate exchange of oxygen and carbon-dioxide within the alveoli. The V/Q ratio in normal individuals is around 0.8, but this ratio alters in the presence of significant ventilation or perfusion defects.

Within lung, all the alveoli do not have uniform ventilation and perfusion. They tend to vary due to the effects of gravity. At the apex of lung, alveoli are large and completely inflated, while they are small at the bases. Similarly, the blood supply is more at the base of the lung than at the apex. This creates physiological ventilation (V) – perfusion (Q) mismatch between different alveoli.

The decreased V/Q ratio (< 0.8) may occur either from decreased ventilation (airway or interstitial lung disease) or from over-perfusion. The blood is wasted in these cases and fails to properly oxygenate. In extreme conditions, when ventilation is significantly decreased and V/Q approaches to zero, it will behave as a pulmonary shunt.

The increased V/Q ratio (> 0.8) usually occurs when perfusion is decreased (pulmonary embolism preventing the blood flow distal to obstruction) or over-ventilation. The air is wasted in these cases and is unable to diffuse within the blood. In extreme conditions, when perfusion is significantly decreased and V/Q approaches to 1, the alveoli will act as dead space and no diffusion of gases occur.

Therefore the increased mismatch in ventilation and perfusion within the lung impairs the gas exchange processes and ultimately will lead to hypoxemia and respiratory failure.

5. High Altitude

At high altitudes, the barometric pressure (PB) is decreased, which will lead to decreased alveolar PO$_2$ as in the equation:

$$\text{PAO}_2 = \text{FIQ}_2 \times (\text{PB} - \text{PH}_2\text{O}) - \text{PACO}_2/R$$

The decreased alveolar PAO$_2$ will lead to decreased arterial PaO$_2$ and hypoxemia but the A - a gradient remains normal as there is no defect within the gas exchange processes. In these conditions, supplementing with additional oxygen (increasing the FIO$_2$) increases the PAO$_2$ and corrects the hypoxemia.

When a person suddenly ascends to the high altitude, the body responds to the hypoxemia by hyperventilation causing respiratory alkalosis. The concentrations of 2, 3-diphosphoglycerate (DPG) are increased, shifting the oxygen – hemoglobin dissociation curve to the right.

Chronically, the acclimatization takes place and body responds by increasing the oxygen carrying capacity of the blood (polycythemia). The kidneys excrete bicarbonates and maintain the pH within normal limits.

<table>
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<tr>
<th>Causes of Hypoxemia</th>
<th>PaO$_2$</th>
<th>A - a gradient</th>
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<tr>
<td>Hypoventilation</td>
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<td>Increases</td>
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Pathophysiology of Hypercapnia

**Hypercapnia** occurs when carbon-dioxide tension (PCO₂) increases to more than 50 mmHg. As explained above, at steady state, the rate of carbon dioxide production within the body is constant. The PACO₂ depends on and is inversely proportional to the ventilation, so decreased ventilation will cause increased PACO₂ and vice versa. Therefore, hypercapnia (along with hypoxemia, Type II respiratory failure) occurs usually due to conditions that decrease the ventilation.

- Reduced central respiratory drive, e.g. opioid overdose, head injury.
- Upper airway obstruction (foreign body, edema, infection).
- Late severe acute asthma, COPD.
- Peripheral neuromuscular diseases, e.g. Guillain-Barre syndrome, myasthenia gravis, botulism.
- Respiratory muscle fatigue.

For example:

**Main symptoms of Carbon dioxide toxicity**

- Visual
  - Dimmed sight

- Auditory
  - Reduced hearing

- Respiratory
  - Shortness of breath

- Muscular
  - Tremor

- Central
  - Drowsiness
  - Mild narcosis
  - Dizziness
  - Confusion
  - Headache
  - Unconsciousness

- Skin
  - Sweating

- Heart
  - Increased heart rate and blood pressure

For example:

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- Upper airway obstruction (foreign body, edema, infection).
- Late severe acute asthma, COPD.
- Peripheral neuromuscular diseases, e.g. Guillain-Barre syndrome, myasthenia gravis, botulism.
- Respiratory muscle fatigue.

**Treatment of Respiratory Failure**

The patients with acute respiratory failure have an increased risk of hypoxic tissue damage and should be admitted to a respiratory/intensive care unit. The airway, breathing, and circulation (ABCs) are to be assessed and managed first, similar to all
emergencies.

The first goal in the management is to correct hypoxemia and/or prevent tissue hypoxia by maintaining an arterial oxygen tension (PaO$_2$) of 60 mm Hg or arterial oxygen saturation (SaO$_2$) greater than 90 %. It is usually achieved initially by providing supplemental oxygen and mechanical ventilation, which is provided by facial mask (non-invasive) or by tracheal intubation.

The specific treatment of the respiratory failure depends on the underlying cause. Therefore, we should try to identify the underlying pathophysiologic disturbances that led to respiratory failure and correct it by providing the specific treatment. For example, **steroids** and **bronchodilators** for COPD and asthma, **antibiotics** for pneumonia, **heparin** for **pulmonary embolism**, etc.

**Principles of Mechanical Ventilation**

There are two principal goals for mechanical ventilation:

1. Increase PaO$_2$: It is achieved by increasing the concentration of inhaled oxygen (FIO$_2$) and positive end-expiratory pressure (PEEP).
2. Decrease PaCO$_2$. It is achieved by increasing the ventilation by adjusting the tidal volume and respiratory rate of the mechanical ventilators.

**Mechanical ventilation** is also an appropriate therapy for **respiratory muscle fatigue** as it rests the respiratory muscles.

**Review Questions**

The answers are below the references.

1. A 6-day-old neonate presents with severe shortness of breath and cyanosis. Vitals are RR 56, Pulse 158, BP 60/40, Temp 98°F.
   Arterial blood gases reveal PaO$_2$ 55 mmHg, PaCO$_2$ 35 mmHg, pH 7.48. The A-a gradient is 47 mmHg. After giving 100 % of oxygen, the arterial blood gases are PaO$_2$ 58 mm Hg, PaCO$_2$ 35 mmHg, pH 7.47.
   **What is the underlying pathophysiology of the hypoxemia?**
   A. Decreased surfactant
   B. Decreased alveolar surface area
   C. Left to Right shunt
   D. Right to Left shunt
   E. Hypoventilation

2. A 32-year-old male has developed acute respiratory distress syndrome secondary to acute pancreatitis. He has been mechanically ventilated with the following preset values:
   - Inhaled O$_2$ concentration FIO$_2$ = 0.6 (60 %)
   - Positive End Expiratory Pressure = 5 cm H2O
   - Tidal volume = 350 ml
   - Respiratory rate = 12 breaths/min
   **The patient’s current arterial blood gases are as follows:**
Which of the following should be done to increase the PCO₂ and normalize the pH?

A. Increase FiO₂  
B. Increase Tidal volume  
C. Decrease respiratory rate  
D. Increase positive end expiratory pressure  
E. Increase the respiratory rate

3. A 45-year-old male is admitted for severe shortness of breath. PaO₂ is 59 mmHg. A ventilation-perfusion ratio has been ordered. Which of the following V/Q ratios indicate that the presence of pulmonary shunt?

A. 0.05  
B. 0.4  
C. 0.6  
D. 0.8  
E. 1.0

References

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Kaynar AM. Respiratory Failure. [Date assessed: 10th March, 2016].

Feller-Kopman DJ. The Evaluation, Diagnosis, and Treatment of the Adult Patient with Acute Hypercapnic Respiratory Failure. [Date assessed: 10th March, 2016].


Correct answers: 1D, 2C, 3A

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Notes