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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

Beyond Respiratory Failure: A Panoptic Perspective of Ventilation and Ventilatory Failure

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Received: December 21, 2018; **Published:** January 22, 2019

Abstract

Respiratory Failures are comprised of similar, overlapping syndromes caused by many diseases and infirmities. Nevertheless, they are frequently diagnosed as if they were a single disease. In addition, marked variations in severity received this same diagnosis without differentiation.

This perspective presents a high level review of Ventilation and it components. It then discusses the two major types of ventilatory failure: 1) Hypoxemic Ventilatory Failure (HVF) and 2) Hypercapenic Ventilatory Failure (HCVF), how to distinguish between them and broadly lists their causes. It also describes how HVF can be further differentiated by its responsiveness to oxygen supplementation and appearance of the lungs on chest radiograph. It then discusses how ventilatory muscle fatigue is the most common causes of HCVF and how oxygen supplementation must be used cautiously.

In general, this panoptic perspective allows for an improved delineations of Ventilatory Failures syndromes that should help in their clinical diagnosis and management.

Keywords: *Respiratory Failure; Ventilation; Ventilatory Failure*

The human respiratory system's responses to diseases and infirmities are manifested by only a limited number of nonspecific symptoms, signs and findings. These include: 1) symptoms: productive and non-productive cough, shortness of breath, chest discomfort/pain, chest congestion; 2) physical findings: tachypnea, adventitious breath sounds such as crackles/rales, rhonchi, wheezing, pleural rubs; and 3) results on testing - hypoxemia and/or hypercapnia and, on chest radiograph - nodules/masses, infiltrates and effusions.

These limited responses cause diseases and infirmities adversely effecting respiration to present as nonspecific similar and overlapping syndromes [1]. When these syndromes include hypoxemia or hypercapnia, a diagnosis of Respiratory Failure is commonly made as if it was a disease rather than syndromes caused by myriads of dissimilar diseases. This misguided diagnosis then leads to markedly dissimilar diseases such as Interstitial Lung Diseases (ILD) and Persistent Airflow Limiting Diseases (PALDS) [2], a.k.a., 'COPD', to receive similar and frequently suboptimal clinical management.

In addition, the misguided diagnosis of Respiratory Failure is also given to markedly disparate syndrome severities such as mild pulse oximetry desaturation from Lower Respiratory Infections to marked hypoxemia from Adult Respiratory Distress Syndrome (ARDS) and PALDS exacerbations with and without hypercapnia requiring mechanical ventilation.

These practices make the diagnosis of Respiratory Failure clinically uninformative and not useful in differentiating and managing patients. A better clinical understanding and differentiations of syndromes causing Respiratory Failure are required to improve the clinical management of patients.

This high-level clinical overview re-identifies Respiration as Ventilation, lists its components and subcomponents and proposes a clinical classification of Ventilatory Failure Syndromes (VFS). This panoptic perspective along with its differentiating classification should improved clinical understanding of VFS and lead to more specific diagnoses and management of the diseases and infirmities causing them.

Respiration/respiratory failure vs. ventilation/ventilatory failure

The clinical misunderstandings start with terminology. Respiratory Failure is the current universal clinical term used for all types of failures of respiration. Yet, Respiratory Failure interventions at times require mechanical ventilation using a ventilator. Why doesn't Respiratory Failure require mechanical respiration using a respirator? They are two major reasons:

- First, the term 'Respirator' has been usurped and broadly applied to apparatuses worn over the mouth and nose to prevent the inhalation of airborne substances [3]. Confusion would result if ventilators were called 'respirators' and it would still not differentiate between the two types of respiration noted below.
- Second, the current incongruous terminology arose from the two definitions of respiration. Respiration is: 1) convection with the surrounding environment, i.e. ventilation, and 2) the intracellular biochemical transfer of electrons from organic fuel molecules to molecular oxygen, i.e. cellular respiration [4]. The interchange of terms respiration and ventilation leads to the current incongruity of clinical terminology.

For congruity, the terms Ventilation, Ventilatory Failure and Ventilator should be used when addressing clinical conditions involving ventilation and ventilatory failures. Respiration and Respiratory Failure should be reserved for cellular respiration and clinical conditions that impair or compromise cellular respiration and its energy production in animals. Cellular respiratory failure, i.e. Shock, is addressed in a different perspective [5].

Ventilation: Its definition, purpose and components

Biologically, ventilation is for gas exchange [6] with the surrounding environment. In single cell organisms, ventilation is through their cell membranes and depending on species - oxygen, hydrogen, carbon dioxide, sulfur or sulfide may be needed for metabolism [7]. In animals, ventilation occurs when oxygen is taken up from and carbon dioxide is excreted to the surrounding environment. Plants ventilate when carbon dioxide is taken up from and oxygen excreted to the surrounding environment.

It is critical to note that the purpose of ventilation in animals is to support cellular respiration [4]. Since dissolved oxygen in plasma is negligible and clinically insignificant, the vast majority of oxygen delivered to cells in tissues is in the form of oxyhemoglobin. Oxygen needs to diffuse and combined with deoxyhemoglobin to form oxyhemoglobin in capillaries while carbon dioxide is off loaded and excreted. The circulation then delivers the oxyhemoglobin to the cells in tissues where the oxygen is off loaded and carbon dioxide loaded. Hence, the delivery of oxygen to cells in the tissues for cellular respiration involves intact, adequately functioning ventilation and circulation systems and functioning and sufficient hemoglobin [8].

Different animals ventilate differently. For example, frogs have three ventilatory surfaces: the skin, in the lungs and on the lining of the mouth [9]. Fish ventilate in water using gills [10]. There are major differences between avian and mammalian ventilation. Birds have no diaphragms and continuously ventilate using unidirectional airflow through dual bronchi and a combination of air sacs and lungs that do not inflate and deflate [11].

In human beings, ventilation involves breathing [12]. Specifically, breathing refers to the inhalation of fresh air for delivery to the lungs' gas exchange airways (GEA) and exhalation for the removal of eliminated gases from the lungs' GEA to the external environment. The human lung's GEA start with the 16th of 23 order bronchioles [13]. At rest, gas exchange occurs in these bronchioles instead of the subsequent alveolar ducts, alveolar sacs and alveoli. The latter are recruited only when there are increased ventilatory demands.

Breathing in human beings has three major components and each has several subcomponents (Table 1). These are: 1) Central and Peripheral Neurologic Control, 2) Boney Thorax and Ventilatory Muscles and 3) Lungs with Airways, Circulation and Interstitium.

Normal human breathing has alternating active inhalation and passive exhalation phases. Inhalation is initiated by a neurologic signal starting automatically in the brain stem or voluntarily in the cerebrum. This signal passes out the spinal cord through the phrenic nerves innervating the diaphragms (the predominate ventilatory muscle) and the intercostal nerves innervating the intercostal muscles causing them to contract. These contractions cause the ribs to swing up and out and the diaphragm to descend like a piston decreasing intrathoracic pressure. This decreased pressure pulls on the thin film [14] layer interface between the diaphragms/thorax and lungs resulting in stretching/expansion of the lungs and the inhalation of atmospheric gases. Neurologic and mechanical feedback mechanisms through baro-, chemo- and mechanical-receptors stop the inhalation signal and results in passive exhalation through the elastic recoil of the lungs and thorax.

1) Neurologic Controls: Provides voluntary and automatic control with feedback to Ventilatory Muscles

A. Central Nervous System
   1) Voluntary Control of breathing through the Cerebrum
   2) Automatic Control of breathing through the Brain Stem

B. Peripheral Nervous System
   1) Efferent Nervous System
   2) Neuromuscular Junctions

C. Central and Peripheral Chemoreceptors and Mechanoreceptors for feedback

2) Thorax: Provides rigid skeleton and ventilatory muscles for lung expansion

A. Boney Thorax

B. Ventilatory Muscles
   1. Diaphragm
   2. Intercostal Muscles (internal and external)
   3. Cervical Accessory Muscles (scalenus, sternocleidomastoids)
   4. Abdominal Wall
   5. Pectoral Muscles

C. Thin Film Layer Interface of Thorax and Lungs

3) Lungs: Conveys environmental gases to the GEA and channels waste carbon dioxide into the environment

1. Conducting Airways: Conduits for cleaning, heating and humidifying and directing gases to GEA
   i. Upper: Nares; Mouth, Larynx, Extra-thoracic trachea
   ii. Lower: Intra-thoracic trachea, bronchi down to 15th order bronchioles
2. Gas Exchange Airways (GEA) start
   i. 16th Order Ventilatory ('Respiratory') Bronchioles
   ii. Alveolar Ducts
   iii. Alveoli/Alveoli Lining Cells
3. Interstitium
   i. Fibroskeleton
   ii. Lymphatics System
4. Pulmonary Circulation
   i. Pulmonary Artery
   ii. Pulmonary Capillaries
   iii. Pulmonary Veins

Table 1: *Ventilation components and subcomponents.*

When physiologic or pathophysiologic processes increase demand for oxygen uptake and carbon dioxide elimination, neurologic drive increases. This leads to increased ventilatory rates and more forceful ventilatory muscle contractions resulting in faster breathing and larger inhaled volumes. As ventilatory rates further increase, active exhalation using expiratory ventilatory muscles to decrease expiratory time may be needed to achieve the increased ventilatory rates.

Critical to note is that approximately 50% of ventilatory muscles are smooth, i.e. fatigue resistant and the rest are striated, i.e. fatigue prone. Thus, increased ventilatory demands that utilized the fatigue prone striated ventilatory muscles are endurance limited. This becomes clinically important when increased ventilatory demands continue beyond their endurance limit.

Ventilatory failure syndrome (VFS) types

There are myriads of diseases and infirmities that adversely affect ventilation. Yet, based on its functions, there are only two general types of VFS in humans: 1) the failure of oxygen uptake leading to hypoxemia and hemoglobin desaturation and 2) the failure of carbon dioxide elimination leading to hypercapnia. Both can be present at the same time.

The first type of VFS is Hypoxemic without Hypercapnia Ventilatory Failure or just Hypoxemic Ventilatory Failure (HVF). It is caused by a failure to completely oxygenate blood resulting in hypoxemia and hemoglobin desaturations. With uncommon and notable exceptions, HVF is almost always due to intrinsic lung pathophysiologies (See table 1 and 4).

Failures of oxygen uptake are diagnosed by: 1) arterial blood gases (ABG) showing low partial pressures of arterial (a) oxygen (P_aO_2) and low calculated oxyhemoglobin levels (S_aO_2) [15]; 2) CO-oximetry showing low measured oxyhemoglobin levels (S_aO_2); and/or 3) pulse (p) oximetry showing low oxyhemoglobin levels (S_pO_2) [16].

The second type of VFS is Hypoxemic with Hypercapnic Ventilatory Failure or just Hypercapnic Ventilatory Failure (HCVF). It involves the failure to eliminate carbon dioxide out to the external fresh environment. The HCVF are primarily due to intrinsic neurologic and/or thorax pathophysiologies (See table 1 and 2). The vast majority of HCVF is due to ventilatory muscle fatigue due to lung pathophysiologies that require continued use of the fatigue prone striated muscles.

Failure of carbon dioxide elimination is diagnosed by ABG showing high partial pressures of arterial carbon dioxide (P_aCO_2). It is critical to note that CO-oximetry and pulse oximetry do not assess carbon dioxide levels and therefore cannot differentiate between hypoxemia with or without hypercapnia.

As can be inferred from the alveolar gas equation (Figure 1) [8], on room air hypercapnia leads to hypoxemia through reduction of the alveolar partial pressure of oxygen (P_AO_2). Essentially, as the carbon dioxide tension increases in the GEA, the oxygen tension drops leading to hypoxemia.

Thus, in order to determine if there is an element of HVF in patients with HCVF, the Alveolar (A) to arterial (a) partial pressure of oxygen differences ($P_{A\text{-}a}O_2$) or 'A-a gradient' must be calculated (Figure 1). In patients with hypercapnia, if the $P_{A\text{-}a}O_2$ is normal or near normal, then only HCVF is present and if the $P_{A\text{-}a}O_2$ is abnormally widened, then HVF is concurrent with HCVF.

$P_AO_2 = (F_iO_2 * (P_B - P_{H2O})) - (P_aCO_2 / RQ)$
P_B = barometric pressure; clinically assumed 760 mm Hg; P_{H2O} = water vapor pressure; clinically assumed 47 mm Hg; RQ = respiratory quotient; clinically assumed to be 0.8
$P_AO_2 = (F_iO_2 * (760 - 47)) - (P_aCO_2 / 0.8)$
$P_AO_2 = [(100/100) * (F_iO_2 * 713)] - (1.25 * P_aCO_2)$
$P_AO_2 = [(100 * F_iO_2) * (713/100)] - (P_aCO_2 + ¼ P_aCO_2)$
$P_AO_2 = (\%O_2 * 7.\cancel{13}^{\#}) - (P_aCO_2 + ¼ P_aCO_2)$
$P_AO_2 = (\%O_2 * 7) - (P_aCO_2 + ¼ P_aCO_2)$
(The '.13' drop takes into account that on average the P_B is closer to 740 mm Hg in densely populated US areas and leads to a clinically acceptable maximum variance of < 2%. Also for each 50 mmHg drop in PB below 725 mmHg, this value is reduced by 0.5)
$P_{A\text{-}a}O_2 = P_AO_2 - P_aO_2$
P_aO_2 = Partial pressure of oxygen in arterial blood
Approximate Normal $P_{A\text{-}a}O_2$ is max (¼ age + 4) or
< 10 mmHg for age < 30 and < ⅓ age for age > 30

Figure 1: *Simplified alveolar to arterial oxygen pressure gradient ($P_{A\text{-}a}O_2$) calculation.*

Hypoxemic ventilatory failure (HVF)

As noted, HVF is due to failure to fully oxygenate blood resulting in hypoxemia and, more importantly, hemoglobin desaturation [8]. This results: 1) commonly from the failure of delivery of oxygen to the GEA to match its perfusion, i.e. Ventilation to Perfusion ($\dot{V}/\dot{Q}$) Mismatches; 2) less commonly from the inability to deliver any oxygen to still perfused GEA, i.e. pulmonary shunts; 3) very occasionally from venous blood anomalously bypassing the lungs' GEA leading to abnormal quantities of venous blood admixing with arterial blood, e.g. vascular or cardiac 'Right to Left' shunts; and 4) rarely from failure of the external environment such as very high altitudes, unventilated enclosures and smoke or gas filled spaces.

Cardiac output and oxygen consumption/extraction effects on HVF

For any $\dot{V}/\dot{Q}$ mismatches and shunt, the hypoxemias are worse in the presence of low cardiac outputs and/or increased oxygen consumptions. They're worse because these conditions increase the de-oxyhemoglobin levels of venous blood returning to the heart and worsens venous admixture. These circumstances should be kept in mind when assessing HVF.

HVF/OR subtype: Oxygen responsive (OR) $\dot{V}/\dot{Q}$ mismatches

As noted, in $\dot{V}/\dot{Q}$ mismatch situations the GEA ventilation does not match perfusion. One extreme is ventilation of GEA that have no perfusion, i.e. dead space ventilation. The other extreme is no ventilation of GEA that are still perfused, i.e. shunts. In between these extremes, depending on the degree of mismatch, the GEA ventilation may be sufficient or insufficient to completely oxygenate the blood in the perfused capillaries. Hypoxemia and hemoglobin desaturations result from insufficient GEA ventilation.

Oxygen supplementation increases the oxygen partial pressure in the low $\dot{V}/\dot{Q}$ mismatched GEA and allows for improved oxygenation of pulmonary capillary blood (Table 2) even when the GEA ventilation remains low. As a rule, $\dot{V}/\dot{Q}$ mismatched induced HVF requires less than 40% oxygen supplementation to maintain acceptable oxyhemoglobin saturation levels of $S_{a/p}O_2$ > 88 - 92%. Conversely, this oxygen responsiveness (OR) identifies the HVF/OR as due to $\dot{V}/\dot{Q}$ mismatches.

% Oxygen	21%	30%	40%	60%
Oxygen - P_AO_2	100	163	235	378
Nitrogen - P_AN_2	573	510	438	295
Carbon Dioxide - P_ACO_2	40	40	40	40
Water Vapor - P_{H2O}	47	47	47	47
Barometric Pressure - P_B	760	760	760	760

Table 2: *Alveolar gases partial pressures at different F_iO_2's.*

Paradoxically, on occasions, increasing oxygen supplementation can lead to worsening HVF. This happens when the oxygen in a higher P_AO_2's (Table 2) is totally depleted in very low $\dot{V}/\dot{Q}$ match GEA. Since the oxygen displaces significant amounts of alveolar nitrogen, this oxygen depletion results in large reductions in GEA sizes (Table 3). Some size reductions are below a critical airway opening volume resulting in airway collapse. These airway collapses in turn worsens hypoxemia through shunting. This leads to the institution of higher concentrations of oxygen supplementations and recurrence of this cycle over and over until the patient is on 100% oxygen from the development of pulmonary shunting due to oxygen supplementation! Fortunately, these situations are easily reverse through mobilization of the patient, pulmonary toilet and deep breathing exercises. These maneuvers rapidly reverses oxygen supplementation induced 'resorption atelectasis' type of HVF.

% Oxygen	21%	30%	40%	60%
Oxygen P_AO_2 as % of P_B	13%	21%	31%	50%

Table 3: *Alveolar oxygen partial pressure percent at different F_iO_2's.*

HVF/ONR subtype: Oxygen non-responsive (ONR) shunts

In contrast to $\dot{V}/\dot{Q}$ mismatches, shunts do not provide the possibility of oxygen reaching the venous blood. The pulmonary and/or cardiovascular shunt fraction (Q_s/Q_t) is that quantity of venous blood that bypasses oxygenation as a ratio of total perfusion (Q_t) [17].

In the lungs, this may result from the GEA being collapsed and/or filled with combinations of transudates or exudates such as edema, pus, protein, blood, cells, aspirated material and the like. Outside the lungs, shunts results from anomalous venous to arterial connections that bypass the pulmonary capillaries entirely. These anomalous shunts include right to left cardiac shunts [18], pulmonary and peripheral vascular malformations and abnormal vascular dilatations like seen in Hepatopulmonary Syndrome [19].

The normal anatomic/physiologic shunt fraction of the lungs is 5%. As shunts get larger, oxygen responsiveness drops precipitously. Shunts between 15 to 20% are minimally responsive to high concentrations of oxygen supplementation while shunts of 25% and greater are basically unresponsive to any concentration of oxygen supplementation (Figure 2) [20].

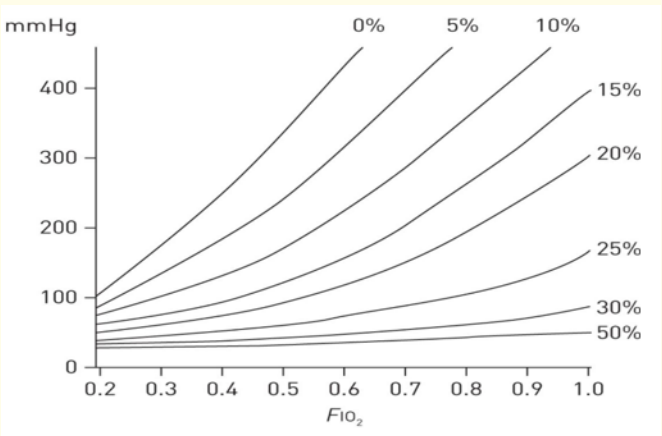

Figure 2: *The lung iso-shunt curves*

Clinical approach to HVF oxygen responsiveness and chest radiographs ('Chest X-rays')

The appearance of the lungs on a chest radiographs ('Chest X-ray' or CXR) is also a key clinical finding in delineating underlying disease pathophysiologies. The lung can be predominately 'black' with or without localized infiltrate on the radiograph or predominately 'white', i.e. there is essentially complete involvement of both lungs (or the lung when there is only one).

Thus, one can develop a clinical paradigm of classifying HVF by their clinical response to oxygen and the lung appearance on chest radiograph. This helps delineate the underlying pathophysiologies (Table 4).

VFS Type	Response to < 40% Oxygen	Lungs Fields on CXR	Ventilation Components	Examples
HVF	Positive: HVF/OR	Black	Conducting Airways, GEA	Asthmas, PALDS/COPD exacerbation, Localized Pneumonias, LRI, Pulmonary Emboli
		White	GEA, Interstitium	CHF, Interstitial Pulmonary Edemas
	Negative: HVF/ONR	Black	Vascular/Cardiac Shunts	Right to Left Heart Shunt, AV Malformations, Hepato-pulmonary Syndrome
		White	GEA, Interstitium	Diffuse Alveolar Damage Syndromes, Interstitial Lung Diseases

Table 4: *HVF, response to oxygen and lung fields on CXR categories.*

The treatment and management of the different causes of HVF is well addressed in medical literature and beyond the scope of this panoptic.

HCVF: Hypercapnic ventilatory failure

The most common cause of HCVF is ventilatory muscle fatigue. Specifically, pathophysiologic processes that increase ventilatory demands requiring the use the fatigue prone ventilatory striated muscles lead to hypercapnia when these muscles fatigue and the work of breathing cannot be sustained. This pathophysiology becomes readily apparent with the initiation of mechanical ventilation and the elimination of the accumulated carbon dioxide. If the lungs were primarily causing the hypercapnia it would be expected that mechanical ventilation would not be able to easily eliminate the carbon dioxide [21].

Acute ventilatory muscle fatigue occurs in patients with acute exacerbations of airway diseases such as PALDS and Asthma exacerbtions. Chronic venitlatory muscle fatigue and HCVF occurs in conditions such as Chronic Bronchitis, Severe Persistent Asthma and the like where the work of breathing would require the continued use of the fatigue prone ventilatory muscles.

Besides ventilatory muscle fatigue, neurologic (including neuromuscular) and boney/thorax diseases and infirmities may lead to hypercapnia (Table 1).

Of note, hypercapnia is rarely due to the failure of carbon dioxide diffusion in the lungs. This is because the total diffusion rate for carbon dioxide is 20 times faster than oxygen and it reaches an equilibrium between pulmonary capillaries and GEA more quickly than oxygen. Thus, carbon dioxide elimination is not impacted by GEA thickness as much as oxygen uptake [22].

Clinical approach to HCVF: Concurrent HVF and the worse hypercapnia with oxygen

As noted, whenever hypoxemia or hemoglobin desaturation is determined by any means, the question of hypercapnia must be addressed since hypercapnia causes hypoxemia. A normal calculated $P_{(A-a)}O_2$ (Figure 1) would indicated only HCVF present and an abnormally widened $P_{(A-a)}O_2$ would indicate concurrent HVF.

It is well known that HCVF worsens with oxygen supplementation [23]. Thus, it is recommended that oxygen supplementation be titrated to keep S_aO_2 between 88% and 92% in HCVF. In addition, the clinical management of HCVF requires detailed understanding of acid-base disorders as delineated by the ABG and serum electrolytes.

The causes of HCVF should be determined to properly treat it. Neurologic causes require reversal when possible. Boney skeleton abnormalities may need correction. Most frequently, the causes leading to ventilatory fatigue-prone muscle use and subsequent fatigue must be treated to prevent and treat their fatigue. Non-invasive and invasive mechanical ventitation are frequently necessary as support until the underlying causes are mitigated.

The treatment and management of the different causes of HCVF is well addressed in medical literature and beyond the scope of this panoptic. In addition, there are countless books addressing fluid, electrolyte and acid-base issues critical to understanding and managing HCVF [24].

Severity of ventilatory disorders and ventilatory failures

There is a general severity hierarchy of acute and chronic ventilatory symptoms/findings and ventilatory failures. These can be staged as:

- Stage 1: Symptoms/Findings Only (No HVF or HCV).
- Stage 2: HVF/OR
- Stage 3: HVF/NOR or HCVF
- Stage 4: HVF/NOR and HCVF.

Generally, both acute and chronic Stage 1 Ventilatory Disorders are managed on an outpatient basis. Acute Stage 2 disorders usually require brief hospitalizations and chronic Stage 2 disorders require continuous outpatient oxygen supplementation.

Stage 3 HVF/NOR disorders are almost always acute and required hospitalization until resolved. The unusual chronic HVF/NOR signify advanced lung diseases that may require lung transplantation for eligible patients or shunts that require treatment.

If uncompensated, acute Stage 3 HCVF may require non-invasive or invasive ventilatory support. Chronic and compensated Stage 3 HCVF when advanced may require home intermittent non-invasive ventilatory support.

Finally, acute Stage 4 Disorders are rare and universally fatal. There are no chronic Stage 4 patients.

Summary

When a patient presents with ventilatory symptoms and signs, testing for hypoxemia should be undertaken. This is commonly with pulse oximetry or ABG. Yet, if the presentation suggests the possible inhalation of abnormal gases or development of abnormal hemoglobins, then CO-oximetry should be ordered.

If hypoxemia is documented, an assessment for hypercapnia is mandatory. This requires ABG. If hypercapnia is present, then a $P_{(A-a)}O_2$ gradient must be calculated to see if there is concurrent HVF and HCVF. When both present both require treatment.

When HVF is present, oxygen responsiveness (HVF/OR vs HVF/NOR) and the appearance of the lung on chest radiographs should lead to further delineating its causes (Table 1).

Conclusion

In conclusion, understanding ventilation and ventilatory failure syndromes as describe should help direct the clinical diagnosis and management of the disease causing them.

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15. The calculated hemoglobin saturation is NOT accurate when abnormal hemoglobins are present. Thus, when abnormal hemoglobins such as carboxyhemoglobin, sulfhemoglobin, methemoglobin are suspected, CO-oximetry is required.

16. Pulse oximetry measure the percent oxyhemoglobin in relation to deoxyhemoglobin. It is NOT accurate when abnormal hemoglobins are present. Thus, when abnormal hemoglobins such as carboxyhemoglobin, sulfhemoglobin, methemoglobin are suspected, CO-oximetry is required.

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Volume 8 Issue 2 February 2019
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