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## LIST OF ABBREVIATIONS

<b>aA.Dco<sub>2</sub></b>	Arterial alveolar difference for CO <sub>2</sub>	<b>PAo<sub>2</sub></b>	Alveolar oxygen tension
<b>BPD</b>	Bronchopulmonary dysplasia	<b>PAco<sub>2</sub></b>	Alveolar carbon dioxide tension
<b>C</b>	Compliance	<b>Pi<sub>o<sub>2</sub></sub></b>	inspired oxygen tension
<b>CPAP</b>	Continuous Positive Airway Pressure	<b>PEEP</b>	Positive End Expiratory Pressure
<b>Fio<sub>2</sub></b>	Fraction of inspired oxygen	<b>PIP</b>	Peak Inspiratory Pressure
<b>FRC</b>	Functional Residual Capacity	<b>PPHN</b>	Persistent pulmonary hypertension
<b>HMD</b>	Hyaline membrane disease	<b>r</b>	radius of the curvature
<b>I/E ratio</b>	Inspiratory / Expiratory ratio	<b>R</b>	Respiratory quotient
<b>MAP</b>	Mean airway pressure	<b>RDS</b>	Respiratory distress syndrome
<b>OI</b>	Oxygenation index	<b>T</b>	Surface tension
<b>P</b>	pressure	<b>T<sub>I</sub></b>	Inspiratory Time
<b>Paw</b>	Mean airway pressure	<b>T<sub>E</sub></b>	Expiratory Time
<b>P(a/A)o<sub>2</sub></b>	Arterial - alveolar oxygen tension ratio	<b>TLC</b>	Total Lung Capacity
<b>P(A-a)o<sub>2</sub></b>	Arterial - alveolar oxygen tension gradient	<b>VC</b>	Vital Capacity
<b>Pa<sub>o<sub>2</sub></sub></b>	Arterial oxygen tension	<b>V / Q</b>	Ventilation / Perfusion ratio
<b>Paco<sub>2</sub></b>	Arterial carbon dioxide tension	<b>V<sub>T</sub></b>	Tidal Volume
<b>PAL</b>	Pulmonary air leak		

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## LUNG VOLUMES

The total volume of gas in the lungs and airways can be measured and subdivided into different volumes. The size of the lung compartments is related to the height, weight, and surface area of the subjects.

**Functional Residual Capacity (FRC) :** is the volume of gas that is in direct communication with the airways at the end of expiration. The volume of gas in the FRC serves as a buffer so that large changes in alveolar gas tension are reduced. As lung elasticity depends on lung volume, changes in FRC may alter lung compliance.<sup>1</sup>

**Tidal Volume ( $V_T$ ) :** Tidal volume is the volume of gas that is moved in and out of the lungs per breath i.e. the volume of gas exchanged during a single breath.<sup>2</sup> The normal tidal volume is 6 to 8 ml/kg, regardless of age.

**Total Lung Capacity (TLC):** is the volume of gas present in the lung with maximal inflation. The normal range for total lung capacity is 60 to 80 ml/kg.

**Vital Capacity :** is the volume of gas that can be maximally expired from TLC. The normal vital capacity is about 30 to 40 ml/kg in infants and 45 to 55 ml/kg in adults.

**Residual Volume :** is the volume of gas present in the lung at the end of a maximal expiratory effort that cannot be expelled from the lung.

## PULMONARY MECHANICS DURING ASSISTED VENTILATION

The elastic forces of the respiratory system may be estimated from simultaneous changes in volume and pressure . Compliance is a measure of elasticity or distensibility (e.g.,of the lung , chest wall, or respiratory system )and is calculated from the change in volume per unit change in pressure.<sup>1</sup> Compliance is the term used to describe the elastic properties of a system and is calculated as follows :

$$\text{Compliance} = \frac{\Delta \text{ Volume}}{\Delta \text{ Pressure}}$$

Therefore, the higher the compliance, the larger is the delivered volume per unit of pressure . Compliance decreases in :

- 1- surfactant deficiency .
- 2- Excess lung water .
- 3-lung fibrosis .
- 4- hyperexpansion .<sup>3</sup>

Compliance of the respiratory system includes the lungs and chest wall . the lung compliance is a measure of the intrinsic elasticity of pulmonary tissue . **In neonates** lung compliance is the most important component ,as in neonates the chest wall is very distensible and does not contribute a substantial elastic load when compared with the lungs . Respiratory system compliance in infants with normal lungs ranges from 0.003 to 0.006 L/cm H<sub>2</sub>O . The most striking abnormality of pulmonary mechanics in neonates with RDS is decreased lung compliance ,which ranges from 0.0005 to 0.001 L/cm H<sub>2</sub>O . Therefore,for the same pressure gradient ,the delivered V<sub>T</sub> will be reduced in infants with RDS , or , conversely , the pressure gradient would have to be increased to maintain a normal V<sub>T</sub>. The degree of elasticity corrected for lung volume or patient size is called specific compliance .<sup>1</sup>

Pulmonary resistance is a measure of the friction encountered by gas flowing through the nasopharynx ,trachea, and bronchi and by tissue moving against tissue and is calculated as the change in pressure per change in flow at midvolume . Resistance depends on the airway caliber,tissue properties,and flow rate .A major site of airway resistance in the neonate is the upper airway , particularly the nares. Conductance is the inverse of resistance.<sup>4</sup>

Resistance is the term used to describe the inherent capacity of the lungs to resist airflow .In addition to the pressure required to overcome the elasticity of the respiratory system , pressure is needed to force gas through the airways ( airway resistance) and exceed the viscous resistance of the lung tissue (tissue resistance). Resistance may be expressed as the change in pressure per unit change in flow as follow :

$$\text{Resistance} = \frac{\Delta \text{ Pressure}}{\Delta \text{ Flow}}$$

Resistance increases in diseases characterized by airway obstruction as meconium aspiration syndrome . It changes rapidly if for example secretions occlude the endotracheal tube.<sup>5</sup>

The pressure needed to open a lung unit is related to the radius of curvature and surface tension of the meniscus of fluid at the mouth of each collapsed lung unit.<sup>4</sup> According to LaPlace formula, the pressure at the surface of an alveolus is 2 times the surface tension divided by the radius of the bubble.<sup>6</sup>

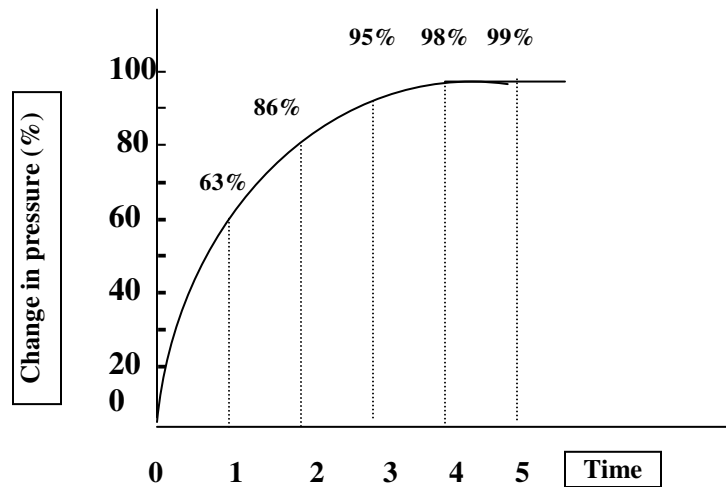
**LaPlace equation**                       $P = \frac{2T}{r}$

where P is pressure, T is surface tension,and r is radius of the curvature .Because the alveolus is open to atmospheric pressure , the pressure outside must be balanced by the pressure on the inner surface or the alveolus will collapse . The forces acting on the alveolus are chest wall elasticity, lung tissue elasticity,and surface tensions of the surface . All alveoli will not be the same size ; therefore, the LaPlace relationship predicts that the retractive force of surface tension will be greater on the small than on the large alveoli with the result being collapse of the small alveoli with enlargement of the large alveoli.<sup>6</sup>

The mathematical product of these two mechanical characteristics, compliance x resistance, is called the time constant of respiratory system.<sup>7</sup> Thus the time constant (expressed in seconds) of the total respiratory system may be calculated as follow :

$$\text{Time constant} = \text{Compliance} \times \text{Resistance}$$

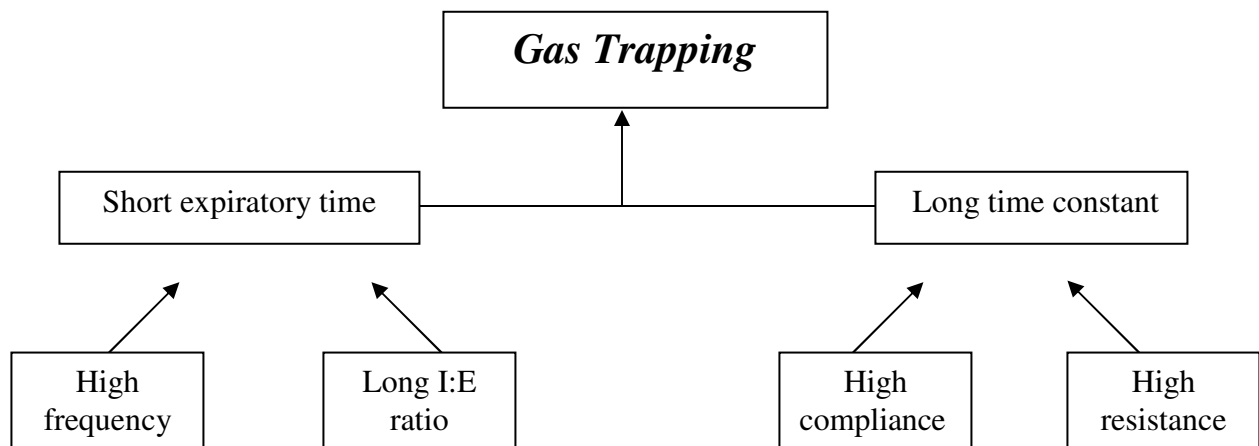
A time period equal to 1 time constant will allow a 63% equilibration of pressure (and volume) throughout the lungs . If a longer duration is allowed following a step change in pressure at the proximal airway , a higher percentage of the pressure will be equilibrated and a proportionally larger  $V_T$  will be delivered ( Fig. -1). As can be seen from the shape of the curve in Fig. -1, little further equilibration of pressure (and volume) occurs beyond 3 to 5 time constants .The time necessary for the lungs to inflate and deflate will depend on the inspiratory and expiratory time constants ,respectively.



**Fig. -1** Percentage change in pressure in relation to the time (in time constants )allowed for equilibration . As a longer time is allowed for equilibration ,a higher percentage change in pressure will occur .The same rules govern the equilibration for step changes in volume .( Modified from Carlo WA, et al:Pediatr Clin North Am 33 : 221,1986.)

The stiff lungs of an infant with RDS will complete inflation and deflation in a shorter time than normal lungs . The application of the concept of time constant becomes particularly important when a high ventilator frequency , short inspiratory time ( $T_I$ ),or short expiratory time ( $T_E$ ) lead to incomplete inspiration and / or expiration .If  $T_E$  is insufficient , expiration may not be complete ,leading to an increase in functional residual capacity and inadvertent positive end expiratory pressure (PEEP).<sup>8</sup> Because infants with RDS have a decreased time constant , short inspiratory and expiratory times may be appropriate during the period of peak severity of their disease but insufficient after recovery from RDS ,when compliance is much higher and the time constant becomes longer . It is important to note that the mechanical properties of the ventilator and delivery system have to be considered when determining the times necessary for complete inspiration and expiration .For example, since resistance increases as the radius of the lumen decreases, infants intubated with small endotracheal tubes will have prolonged inspiratory and expiratory time constants .<sup>9</sup>

A short expiratory time together with a long time constant will prediepose to gas trapping ( or inadvertent PEEP ) during mechanical ventilation ( Fig .- 2 ).<sup>10</sup>



( Fig . - 2 )

## GAS EXCHANGE DURING ASSISTED VENTILATION

### CARBON DIOXIDE

Carbon dioxide (CO<sub>2</sub>) diffuses rapidly from blood into the alveoli, and its elimination largely depends on the total amount of gas that goes through the alveoli (alveolar ventilation). Because some of the V<sub>T</sub> is distributed to parts of the lungs that are not involved in gas exchange (dead space) such as the airways, alveolar ventilation per minute is calculated as follows:

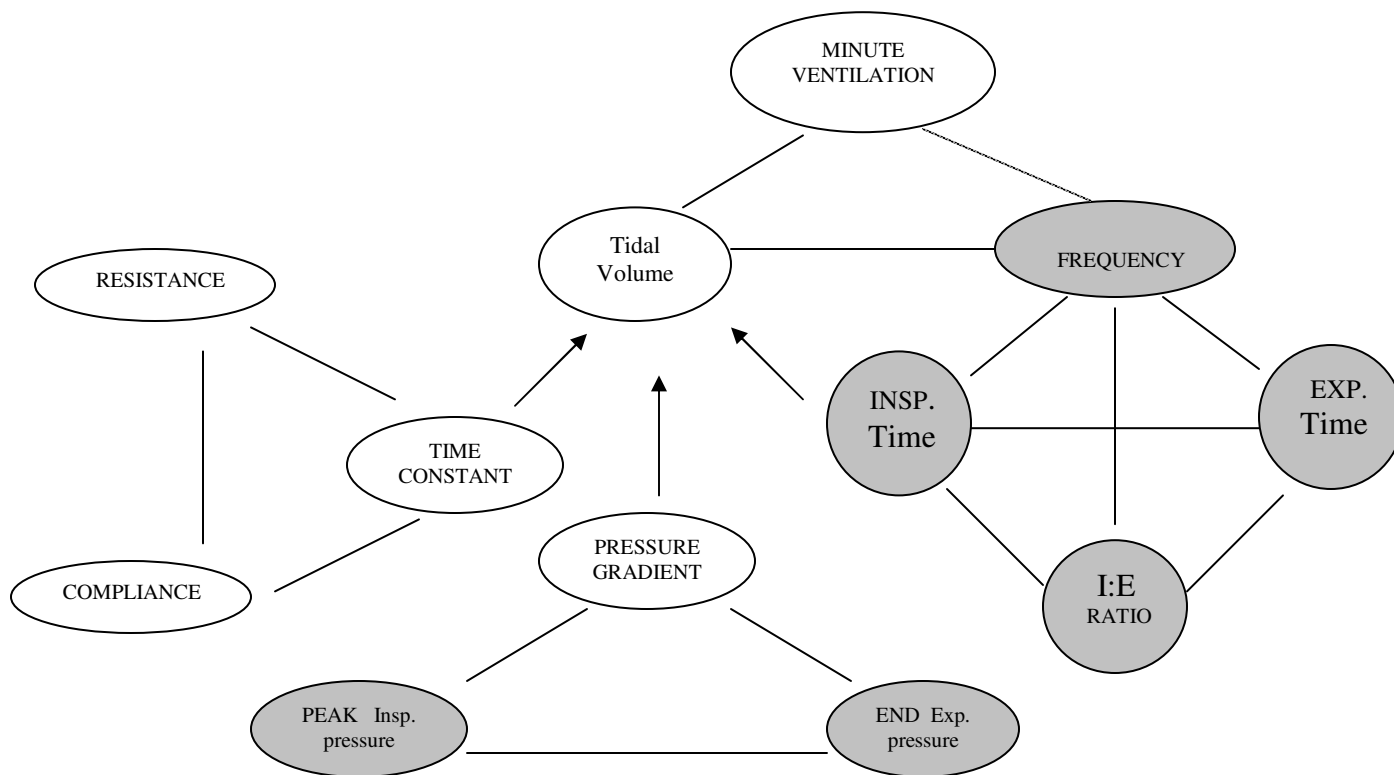
$$\text{Minute alveolar ventilation} = (\text{Tidal volume} - \text{Dead space}) \times \text{Frequency}$$

where frequency is the number of breaths per minute. Because dead space remains relatively constant at different ventilator settings, changes in V<sub>T</sub> or frequency largely determine alveolar ventilation. Increases in alveolar ventilation enhance the elimination of CO<sub>2</sub> and reduce PaCO<sub>2</sub>.<sup>11,12,13,14</sup>

Dead space is that portion of the tidal volume not involved in gas exchange, and thus it will vary with the presence or absence of areas of high V/Q. The dead space is divided into several compartments. **Anatomic dead space** is the airway volume not involved in gas exchange and is made up of the air passage from nares to terminal bronchioles. **Alveolar dead space** is the volumes of gas in alveoli that are well ventilated but underperfused. **Physiologic dead space** is the sum of anatomic and alveolar dead space. In the normal newborn, physiologic dead space is 6 to 8 cc; smaller values are obtained in premature infants. The relationship of dead space to V<sub>T</sub> is physiologically significant and normally about 0.3. It is of practical importance to minimize the dead space added by apparatus for assisted ventilation or measurement of lung function to prevent rebreathing and accumulation of carbon dioxide.

For a given compliance, V<sub>T</sub> is largely determined by the pressure gradient between inspiration and expiration, that is, peak inspiration pressure (PIP) minus PEEP. Changes in either PIP or PEEP may affect V<sub>T</sub> markedly. Under special circumstances the inspiratory duration may partially determine V<sub>T</sub>.<sup>15,16</sup>

For example, a very short  $T_I$  may not allow pressure to be equilibrated throughout the respiratory system in an infant with normal lungs (relatively long time constant), resulting in decrease  $V_T$ . Thus, despite an apparent constant pressure gradient and compliance,  $V_T$  could be reduced by shortening  $T_I$ . Frequency is the other major determinant of alveolar ventilation, and changes in ventilator frequency have a strong effect on  $CO_2$  elimination. Fig. - 3 illustrates the interrelationship between the ventilator settings (on a pressure ventilator) and the mechanical properties of the respiratory system in determining minute ventilation and thus  $CO_2$  elimination.<sup>17</sup>



**FIG. - 3**

Relationship between ventilator- controlled variables ( shaded circles ) and pulmonary mechanics in determining minute ventilation during pressure -limited ,time - cycled ventilation . The relation between the circles that are joined by solid lines is described by simple mathematical equations .Thus simple mathematical equations determine the time constant of the lungs, the pressure gradient , and the inspiratory time .These in turn determine the delivered tidal volume ,which when multiplied by respiratory frequency gives minute ventilation. Alveolar ventilation may be calculated from the product of tidal volume and frequency when dead space is subtracted from the former .(Adapted and reproduced with permission from Chatburn RL, et al.In Lough MD, et al ,editors:Pediatric respiratory therapy ,ed 3 ,Chicago,1985,Year Book Medical Publishers,Inc.)

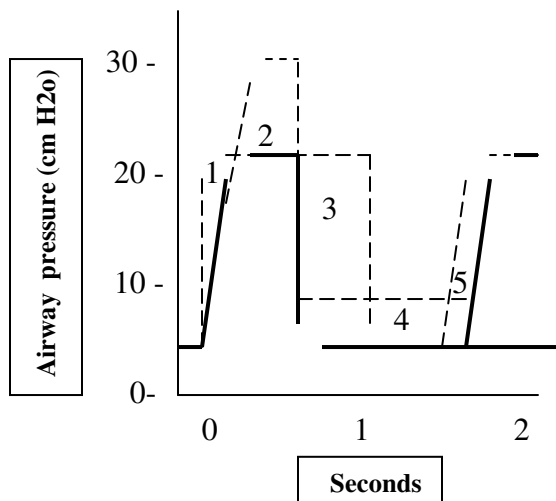
## Oxygen

Oxygen exchange depends largely on matching of perfusion with ventilation. Several studies in infants, mostly neonate, with RDS, have concluded that during assisted ventilation, oxygenation is largely determined by the mean airway pressure (Paw) applied (Fig.- 4).<sup>11,14</sup> Mean airway pressure is a measure of the average pressure to which the lungs are exposed during the respiratory cycle and may be calculated from the following equation:

$$Paw = K ( PIP - PEEP ) \{ T_I / ( T_I + T_E ) \} + PEEP$$

Where Paw is the mean airway pressure, K is a constant that depends on the rise of the airway pressure curve (in clinical situations, K is always less than 1), PIP is peak inspiratory pressure, PEEP is positive end expiratory pressure, T<sub>I</sub> is inspiratory time, and T<sub>E</sub> is expiratory time. Therefore Paw will be augmented by increasing any of the following ( Fig. - 4 )

1. inspiratory flow (will increase K)
2. PIP
3. Ratio of T<sub>I</sub> to T<sub>E</sub> (I / E ratio)
4. PEEP
5. Frequency (or rate) by shortening T<sub>E</sub>.<sup>18</sup>



**Fig. - 4. Five different ventilator setting increases that augment mean airway pressure :** (1) inspiratory flow, (2) peak inspiratory pressure, (3) I/E ratio, (4) positive end expiratory pressure, (5) frequency (or rate) by shortening expiratory time. Any of these five increases results in a larger area under the curve.

Frequency is the other major determinant of alveolar ventilation and may include both the frequency set on the ventilator and the spontaneous breaths the patient may initiate.<sup>19</sup>

The effect of  $P_{aw}$  on oxygenation is probably related to optimization of lung volume and prevention of atelectasis, thus improving ventilation - perfusion relationship. Although a direct relationship between  $P_{aw}$  and oxygenation may exist, there are several exceptions:

(1) for the same change in  $P_{aw}$ , increases in PIP and PEEP enhance oxygenation more than increases in I/E ratio;<sup>20</sup>

(2) very high  $P_{aw}$  may cause overdistension of airways and alveoli, leading to an increase in dead space and right-to-left shunting of blood in the lungs; and

(3) if a very high  $P_{aw}$  is transmitted to the intrathoracic structures, cardiac output may decrease secondary to decreased venous return and increased pulmonary vascular resistance, and thus despite an adequate  $P_{aO_2}$  and oxygen content, oxygen transport (arterial oxygen content x cardiac output) may decrease.<sup>21, 22</sup>

Hypoxemia can be due to ventilation - perfusion mismatch, shunt, diffusion abnormalities, and hypoventilation.<sup>23</sup> Ventilation - perfusion mismatch is a major cause of hypoxemia in infants with RDS and in neonates with other etiologies of respiratory failure.<sup>24</sup>

## BLOOD GASES

Blood gas measurement is the most widely used clinical method for assessing pulmonary function in neonates and forms the basis for diagnosis and management of infants with cardiorespiratory disease .

$P_{aO_2}$  and  $P_{aCO_2}$  values are dependent on the composition and volume of alveolar gas, the composition and volume of mixed venous blood ,and the mechanisms of pulmonary gas exchange impairment . Alveolar gas composition can be obtained from the equation :

$$P_{A_{O_2}} = P_{i_{O_2}} - P_{A_{CO_2}} \left\{ F_{i_{O_2}} + \left( \frac{1 - F_{i_{O_2}}}{R} \right) \right\}$$

where  $P_{A_{O_2}}$  is alveolar oxygen tension and  $P_{i_{O_2}}$  is inspired oxygen tension (  $P_{i_{O_2}} = F_{i_{O_2}} \times \{ \text{barometric pressure} - \text{water vapor pressure} \}$  ). At sea level barometric pressure is 760 mmHg, and with 100% humidity water vapor pressure is 47 mmHg .  $P_{A_{CO_2}}$  is the alveolar carbon dioxide tension , and R is the respiratory quotient ( usually 0.8 ).

Mixed venous blood composition and volumes are determined by the arterial oxygen content , cardiac output ,and oxygen consumption . The mechanisms of pulmonary gas exchange impairment include V/Q mismatch, shunt, hypoventilation , and diffusion limitation. Appropriate matching of the alveolar gas with the mixed venous blood yields optimal gas exchange.<sup>4</sup>

The partial pressure of oxygen in arterial blood not only depends on the ability of the lungs to transfer oxygen as determined by alveolar ventilation but also is largely influenced by the V/Q ratio .For normal gas exchange the ventilation and perfusion should be proportional . The ratio should be very close to 1:1 , that is , for every milliliter of gas that passes the alveoli there should be a proportional volume of blood in the pulmonary capillary bed .If the V/Q ratio is decreased as in RDS, only partial oxygenation and  $CO_2$  removal from the mixed venous blood will occur . Oxygen supplementation can largely overcome the hypoxemia when the V/Q ratio is decreased.<sup>4</sup>

**Three indexes can be used to estimate the degree of oxygenation derangement**

1-The arterial / alveolar oxygen tension ratio [P(a/A)o<sub>2</sub> or a/Ao<sub>2</sub> ratio ] has no units ,decreases with worsening oxygenation , and can be obtained from the equation :

$$P(a/A)o_2 = \frac{Pao_2}{Pio_2 - \frac{Paco_2}{R} \left[ Fio_2 + \left( \frac{1 - Fio_2}{R} \right) \right]}$$

where R is the respiratory quotient .Because Fio<sub>2</sub> + (1 - Fio<sub>2</sub>) / R approximates 1.0 and PAcO<sub>2</sub> approximates Paco<sub>2</sub>, the equation can be simplified as follows :

$$P(a/A)o_2 \sim \frac{Pao_2}{Pio_2 - \frac{Paco_2}{R}}$$

2 - The alveolar - arterial oxygen tension gradient [P (A-a)o<sub>2</sub> or A-a Do<sub>2</sub>] is expressed in mmHg , **increases** with worsening oxygenation , and can be obtained from the equation :

$$P(A - a) o_2 = Pio_2 - Paco_2 \left[ Fio_2 + \left( \frac{1 - Fio_2}{R} \right) \right] - Pao_2$$

OR

$$P(A - a)_{O_2} \sim P_{iO_2} - \frac{P_{aCO_2}}{R} - P_{aO_2}$$

3- The oxygenation ratio is expressed in mmHg ,**decreases** with worsening oxygenation , and can be obtained from the equation :

$$\text{The oxygenation ratio} = \frac{P_{aO_2}}{F_{iO_2}}$$

The oxygenation ratio is less frequently used as it is subject to inaccurate assessment of the oxygenation derangement when  $P_{aCO_2}$  varies markedly. Often it is necessary to correct the index of oxygenation for the ventilatory support because oxygenation is strongly influenced by mean airway pressure ( $P_{aw}$ ) during assisted ventilation. The oxygenation index ( OI ) is useful under these circumstances.<sup>4</sup> The OI, which increases with worsening oxygenation or increasing  $P_{aw}$ , has units of cm H<sub>2</sub>O / mm Hg as described by the equation<sup>4</sup> :

$$OI = \frac{P_{aw} \times F_{iO_2}}{P_{aO_2}} \times 100$$

## ***Ventilator setting and its effects on ventilation***

### **1- Fraction Of Inspired Oxygen Concentration ( $F_{iO_2}$ ):-**

When one is initiating mechanical ventilation for the patient in respiratory failure, it is best to use a high  $F_{iO_2}$  ( 0.7 to 1.0 ) to ensure adequate tissue oxygenation . After an initial blood gas value is obtained , the  $F_{iO_2}$  may be decreased to achieve The goal of a clinically acceptable  $PaO_2$  (>60 mmHg )with an  $F_{iO_2}$  of 0.5 or less .

$PaO_2$  of 60 mmHg or greater achieves an arterial oxygen saturation of 90 % or greater under conditions of normal body temperature and pH .An  $F_{iO_2}$  of 0.5 or less minimized oxygen toxicity . If an  $F_{iO_2}$  of > 0.6 is necessary to maintain , the addition of PEEP should be considered .<sup>25</sup>

Pulse oximetry should be considered for continuous monitoring of oxygenation and titration of the  $F_{iO_2}$  . If blood gas values are used , it is common practice to wait 20 minutes after a ventilator change before obtaining the blood sample.<sup>26</sup>

### **2- Peak Inspiratory Pressure ( PIP ) :-**

PIP is the major factor in determining tidal volume , PIP depends on patient weight , lung resistance , compliance and disease process , from ( Table - 1 ) it appears important to use the lowest PIP necessary to ventilate the patient adequately.<sup>27</sup>

**Table - 1 Peak Inspiratory Pressure ( PIP )**

<p><b><u>Low Peak Inspiratory Pressure ( PIP ) :-</u></b></p> <p><b>Advantages</b></p> <ul style="list-style-type: none"><li>* Fewer side effects especially BPD, PAL .</li></ul> <p><b>Side effects</b></p> <ul style="list-style-type: none"><li>* Insufficient ventilation ,may not control PaCO<sub>2</sub></li><li>* May have ↓ PaO<sub>2</sub> if it is too low .</li><li>* Generalized atelectasis may occur.</li></ul> <p><b><u>High Peak Inspiratory Pressure ( PIP ) :-</u></b></p> <p><b>Advantages</b></p> <ul style="list-style-type: none"><li>** May reexpand atelectasis .</li><li>** ↑ PaO<sub>2</sub> .</li><li>** ↓ PaCO<sub>2</sub> .</li><li>** ↓ pulmonary Hypertension .</li></ul> <p><b>Side effects :-</b></p> <ul style="list-style-type: none"><li>** Associated with PAL ,BPD .</li><li>** May impede venous return .</li></ul>
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**Abbreviations :PAL=** pulmonary air leak ,**BPD =** bronchopulmonary dysplasia  
The smoother increase of PIP may be advantageous for patient with maldistribution of ventilation .<sup>28</sup>

**3- Positive End Expiratory Pressure ( PEEP ) :-**

***The goals of PEEP are :-***

- (1) Increasing functional residual capacity above closing volume to prevent collapse .
- (2) Maintaining stability of alveolar segment .
- (3) Improvement in oxygenation .
- (4) Reduction in work of breathing.<sup>29</sup>

**The optimum PEEP** is the level at which there is an acceptable balance between the desired goals and undesired adverse effects such as air leak and barotrauma.<sup>30,31</sup>

Table - 2

**Advantages and disadvantages of Positive End Expiratory Pressure(PEEP).<sup>25</sup>**

**Low Positive End Expiratory Pressure ( PEEP ) :-**

**Advantages**

- \* Used for weaning .
- \* Used for premature infants .

**Side effects**

- \* May be too low to maintain adequate lung volume .

**High Positive End Expiratory Pressure ( PEEP ) :-**

**Advantages**

- \*\* Prevents alveolar collapse in surfactant deficiency with ↓ compliance and lung volume .
- \*\* Improves distribution of ventilation .

**Side effects :-**

- \*\* Pulmonary air leak ( PAL ) .
- \*\* ↓ compliance if lung volume increases too much (over distention) .
- \*\* May impede venous return .
- \*\* May increase pulmonary vascular resistance .
- \*\* CO<sub>2</sub> retention .

**4 - Inspiratory & Expiratory ratio ( I:E ratio ) :-**

The major effects of changes in I:E is on main airway pressure (MAP) and thus oxygenation .

Generally the I:E ratio is set at 1:2 ,so , 33% of the respiratory cycle is spent in inspiration and 66% in the expiration ,this setting mimics spontaneous respiration when lung function is normal .It is generally used because :

- 1- Shorter inspiratory time helps dead space ventilation by over expanding the more compliant alveoli .
- 2- Longer inspiratory times increases mean airway pressure leading to hemodynamic instability.<sup>32</sup>

### 5 - Rate :-

It determines minute ventilation ,so mechanical ventilatory rate is adjusted to normalize PH and / or PaCO<sub>2</sub> , clinician must be aware of side effects of high rates.<sup>33</sup>

**Table - 3 Mechanical Ventilatory Rate**

#### **Low Mechanical Ventilatory Rate:-**

##### **Advantages**

- \* Used for weaning .
- \* May ↑ oxygenation if used with long inspiratory time due to ↑ MAP.

##### **Side effects**

- \* With slow rate,to maintain ventilation ,must use high PIP .
- \* PIP could cause BPD or barotrauma .
- \* Patient may require paralysis .

#### **High Mechanical Ventilatory Rate:-**

##### **Advantages**

- \*\* Rapid rate ↓TV will allow ↓ PIP .
- \*\* Hyperventilation is useful in PPHN .
- \*\* Prevent atelectasis .

##### **Side effects :-**

- \*\* May have insufficient emptying time (inadvertent PEEP).
- \*\* May produce iatrogenic respiratory alkalosis .
- \*\* May result in inadequate TV or minute volume .

TV = tidal volume ,PPHN = persistent pulmonary hypertension , MAP =mean airway pressure .<sup>25</sup>

### 6 - Flow rate :-

It is an important determinant of the ability of the ventilator to attain desired level of PIP, wave form, I:E ratio and respiratory rate.<sup>34</sup>

### **Table - 4 Flow adjustment in mechanical ventilation .<sup>25</sup>**

**Definition :-** Speed with which the tidal volume is delivered .

**Average setting :-** 8-12 L / min .

#### **Low flow rates :-**

- \* ↑ inspiratory time .
- \* ↓ PIP ( more laminar flow ) .
- \* May improve distribution of gases .

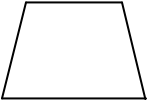
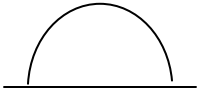
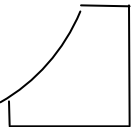
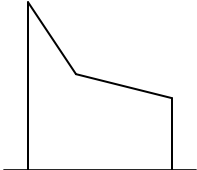
#### **High flow rates :-**

- \*\* ↓ inspiratory time .
- \*\* ↑ PIP ( more turbulent flow ) .
- \*\* May lead to maldistribution of gases .
- \*\* Required for high minute ventilatory demands .

7- Wave form :-

If the flowmeter is set at **high rate** ,the PIP will be reached rapidly and a square wave form is produced ,but with **low rate** , the PIP is reached more slowly and a sine wave form is produced .<sup>35</sup>

**Table - 5** Flow wave pattern.<sup>35</sup>

<b><i>Label</i></b>	<b><i>Flow wave pattern</i></b>	<b><i>Description</i></b>
<b>1- Square .</b>		<ul style="list-style-type: none"> <li>- Peak flow rate is delivered immediately at the onset of inspiration ,maintained throughout the inspiratory phase ,and abruptly terminated at the onset of expiration.</li> <li>- Most commonly used flow wave form pattern .</li> </ul>
<b>2- Sinusoidal</b>		<ul style="list-style-type: none"> <li>- Inspiratory flow rate gradually accelerates to peak flow and then tapers off .</li> <li>- Believed to mimic spontaneous inspiratory patterns .</li> <li>- May ↑ PIP .</li> </ul>
<b>3- Accelerating (ascending ramp ).</b>		<ul style="list-style-type: none"> <li>- Flow gradually accelerates in linear fashion to the set peak flow rate .</li> </ul>
<b>4- decelerating (descending ramp )</b>		<ul style="list-style-type: none"> <li>- Flow is at peak at onset of inspiration and gradually decelerates throughout inspiratory phase .</li> <li>- Flow ceases and ventilator cycles to expiratory phase when flow decays to a percentage of peak flow usually 25% .</li> <li>- May improve the distribution of gases when there is inhomogeneity of alveolar ventilation</li> <li>- ↓ dead space, ↑ arterial O<sub>2</sub> tension , ↓ PIP.</li> </ul>

**Table - 6 Effects of changing ventilator setting .<sup>25</sup>**

<b>Increasing</b>	<b>PaO<sub>2</sub></b>	<b>PaCo<sub>2</sub></b>	<b>PH</b>	<b>Complications</b>
Fio <sub>2</sub>	↑	0	0	Oxygen toxicity (BPD), retrolental fibroplasia , absorption atelectasis .
CPAP / PEEP	↑	0/↑	0/↓	Hypoventilation with respiratory acidosis , decreased cardiac output with metabolic acidosis , air leaks .
PIP	↑	↓	↑	Barotrauma with air leaks and BPD, respiratory alkalosis .
Rate	↓	↓	↑	Respiratory alkalosis .
I/E ratio 1 to 1.3	↑	0	0	Increased intrapleural pressure , decreased venous return .

**BPD** = bronchopulmonary dysplasia

## **RESPIRATORY DISTRESS SYNDROM** **( HYALINE MEMBERANE DISEASE )**

### **► Epidemiology :-**

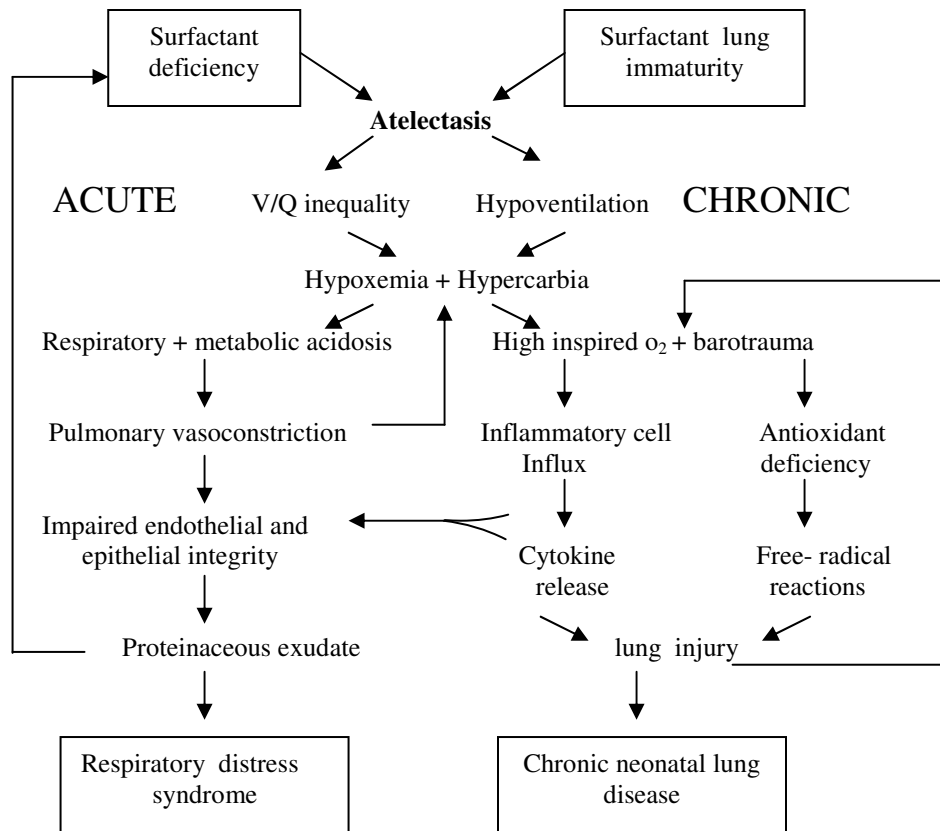
Respiratory distress syndrome occurs throughout the world with a slight male predominance .The greatest risk factor appears to be low gestational age.<sup>36</sup> Other risk factors include maternal diabetes and perinatal asphyxia .<sup>37</sup>

Hack et al have reported that 56% of infants between 501 and 1500 gm were noted to have RDS and /or respiratory insufficiency of prematurity {including 86% between 501 and 750 gm , 79% between 751 and 1,000 gm, 48% between 1,001 and 1,250 gm and 27% between 1,250 and 1,500 gm .<sup>38</sup>

The incidence is 60% at 29 weeks , gestation but declines with maturation to near 0 by 39 weeks .The condition is more common in male than in female infants<sup>39</sup>; it is more common in white than in nonwhite infants.<sup>40</sup> At each level of gestational age , RDS is less common in black infants ,and this phenomenon is not explained by other factors that may influence lung maturity.<sup>41</sup> At any given gestational age,the incidence is higher for cesarean section without labor than for vaginal delivery.<sup>42</sup> There is a significantly increased risk if elective cesarean section is performed before completion of 39 week gestation.<sup>43</sup>

### **► Pathophysiology:-**

The development of RDS begins with impaired or delayed surfactant synthesis followed by a series of events that may progressively increase the severity of the disease for several days ( Fig - 5 ). Surfactant synthesis is a dynamic process that depends on factors such as pH, temperature,and perfusion and may be compromised by cold stress,hypovolemia, hypoxemia, and acidosis.Other unfavorable factors, such as exposure to high inspired oxygen concentration and the effects of barotrauma from assisted ventilation (volutrauma),may further damage the alveolar epithelial lining,resulting in reduced surfactant synthesis and / or function .<sup>4</sup>



**Fig.-5:-** A schematic representation of the complex series of acute and chronic events that lead to neonatal RDS and the accompanying lung injury secondary to therapeutic intervention in these infants .

In HMD, the respiratory rate is elevated, so despite a reduction in each tidal volume, the minute ventilation initially is increased. The functional residual capacity, analyzed by nitrogen washout, is reduced; the greater the need for oxygen, the smaller is the measured value for functional residual capacity.<sup>44</sup>

Edberg and coworkers (1991) found decreased compliance, increased resistance, decreased lung volume, and reduced gas mixing efficiency in very-low-birth-weight infants with RSD. From these data, it can be approximated that the overall time constant in RSD would be less than 0.05 second.<sup>45</sup>

### ► Clinical Diagnosis:-

The classic clinical presentation of RDS comprises grunting respirations, retractions, nasal flaring, cyanosis, and increased oxygen requirement, together with diagnostic radiographic findings and onset of symptoms before 6 hours of age. The full-blown picture is modified in many low birth weight infants as a result of the early administration of surfactant and immediate assisted ventilation.<sup>36</sup>

The infant with HMD is almost always premature and is cyanotic in room air. There is rapid or labored breathing, beginning at or immediately after birth. The severity of respiratory distress can be represented by the Silverman score (Fig.- 6).

**Fig - 6:-** The Silverman score for assessing the magnitude of respiratory distress. ( From Avery ME, Fletcher BD: The lung and its Disorders in the Newborn. Philadelphia, WB Saunders, 1974. Courtesy of WA Silverman. )

There are five signs gathered by Silverman as a score, each of the five signs has being ascribed a value of 0,1,or 2 .This score can be established at various steps in the evolution of the disease in order to facilitate follow up of the RDS . The signs are:-

- 1- Intercostal chest retractions and xiphoid retraction due to action of respiratory muscles on a cartilaginous ,poorly rigid skeleton.
- 2- Thoracic - abdominal saw pattern which corresponds to the possibility of thoracic distension with respiratory movements.
- 3- Expiratory grunting due to prolonged expiration time with a semiclosed glottis.
- 4- Nares dilatation ( flaring ) due to efforts by infants to obtain more air through the airway .
- 5- A score of 0 indicates no RD.  
 A score of >7 indicates impending RD.  
 A score of 10 indicates severe RDS,with impending respiratory failure.

**Downes et al, (1970)** proposed a scoring system consisting of 5 items for assessment of RDS ( **Table - 7** ).

**Table - 7**

<b>Downes scoring ( Clinical RDS Scoring System ) .<sup>46</sup></b>			
<b>Grade</b>	<b>0</b>	<b>1</b>	<b>2</b>
<b>RR</b>	60	60-80	>80 or apneic episodes in 40% O <sub>2</sub>
<b>Cyanosis</b>	None	In air	in 40% O <sub>2</sub>
<b>Retractions</b>	None	Mild	Moderate to severe
<b>Grunting</b>	None	Audible by stethoscope	Audible by naked ear
<b>Air entry</b>	Clear	Delayed or --	Barely audible

A score >6 is an indication of blood gas analysis but as in all clinical situations assessment of the infant may indicate blood gas analysis at lower scores .

Infants usually have a characteristic grunt during expiration , caused by closure of the glottis , the effect of which is to maintain lung volume and gas exchange during exhalation . The urine output is low for the first 24 to 48 hours, but soon after this time a diuresis ensues. The very-low-birth-weight infant (<1500g ) usually requires mechanical ventilation and has a more prolonged course. A few infants with RDS also appear to have persistent pulmonary hypertension of the newborn ( PPHN ); they are easy to ventilate , especially after exogenous surfactant, but are difficult to oxygenate , and they have severe pulmonary hypertension as evaluated by echocardiographic criteria .<sup>47,48,49,50</sup>

### ► **Laboratory Diagnosis:-**

Based on arterial blood gas values, infants with HMD have a moderate to severe oxygenation defect , significant hypercarbia, and a mild metabolic acidosis with elevation of blood lactate.<sup>51</sup> The lecithin / sphingomyelin (L/S) ratio and phosphatidylglycerol (PG) remain low in serial tracheal aspirate samples for 48 hours , then increase with recovery; the saturated phosphatidylcholine (PC) levels remain low in RDS and reach normal levels after 4 to 7 days; the surfactant protein A (SP-A) / saturated PC (SPC) ratio is low in RDS and is even lower in infants destined to develop bronchopulmonary dysplasia (BPD) .<sup>52</sup>

**Stevens and colleagues (1992 )** showed that SP-A in tracheal aspirate samples was low in infants with RDS , remained low for 3 to 4 days, and then rose in survivors but remained low in nonsurvivors .<sup>53</sup>

**Moya and colleagues (1994)** also found a low SP-A / SPC ratio in infants with RDS, but they detected increasing SP-A in tracheal aspirate samples as early as 12 to 24 hours.<sup>54</sup> **Gerdes and colleagues (1992)** found that SP-A in tracheal aspirate samples increased after Exosurf administration; because Exosurf does not contain surfactant protein , they attributed this phenomenon to increased lung expansion and therefore increased secretion of endogenous surfactant and SP-A.<sup>55</sup>

Another study found that the SP-A / albumin ratio in tracheal aspirate samples was low in infants with RDS; it rose into the normal range at 48 to 72 hours of age but was not changed by the administration of bovine surfactant.<sup>56</sup> Because all of the surfactant proteins are developmentally regulated, it is likely that infants with HMD are also deficient in SP-B and SP-C.

► **Radiographic Diagnosis:-**

The extension of the radiological features depends on the severity of the disease , the initiation of artificial ventilation ,and the gestational age of the infant .At a precocious stage of the disease,the signs may attenuatedor may be masked by the presence of abundant unabsorbed alveolar fluid .At a later stage in the most severe forms , the opacities become confluent opacifying the total parenchyma and erasing the cardiac edges.<sup>57</sup>The use of controlled mechanical ventilation and PEEP modifies this images, favoring a better alveolar aeration .

Radiographic assessment of the pulmonary disease was made with the use of following classification system.<sup>58</sup>

1- Minimal Disease: Good lung expansion, fine reticular pulmonary densities,and slight air bronchogram.

2-Moderate Disease: More dense and confluent parenchymal reticular pattern and definite widespread air bronchogram .

3- Severe Disease: Homogenous consolidation of lungs , marked air bronchogram and poor expansion .

Edwards, et al ( 1985 ) also assessed a scoring system for the severity of RDS on the basis of radiologic evaluation ( Table - 8 ) .<sup>59</sup>

Table - 8 :

<b>Sign</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
<b>Granularity</b>	Faint ,requiring close observation to detect	Easily seen	Prominent light and dark areas of lung approximately equal	Marked ,lungs substantially light than dark	Lungs essentially opaque
<b>Air bronchogram</b>	None beyond centre of chest	Faint at the bases	Obvious	Marked	Sharp and distinct or absent
<b>Cardiac and diaphragmatic silhouettes</b>	Sharp	Sharp	Slight fuzzy	Indistinct	Indiscrenible
<b>Aeriation</b>	Normal	Normal	Normal to slightly decreased	Decreased	Impo

[ 1 ] Signifies the mildest RDS and [ 5 ] the most severe

### ► **Etiology:-**

HMD is the consequence of ventilation of lungs that have not achieved the capacity to synthesize the pulmonary surfactant, with failure to develop a functional residual capacity and the tendency of affected lung to become atelectatic.<sup>60</sup>

Differentiation of type II alveolar cells, which are the sole site of surfactant synthesis, usually occurs at about 32 weeks' gestation. The time of differentiation is, in part, under genetic control, and is regulated by both endocrine and paracrine hormones. Thus, infants who have had intrauterine stress (such as those of whose mothers are toxemic or who smoke and are SGA) have presumably been in a high glucocorticoid milieu before birth. They have less respiratory distress than expected. Conversely, infants of diabetic mother, whose intrauterine environment was hyperinsulinemic, have a relative delay in lung maturation because of the antagonistic effect of insulin and cortisol on type II cell differentiation.<sup>61</sup>

It has been suggested that surfactant function in infants with HMD is inhibited by plasma proteins<sup>62</sup>, which leak into the respiratory bronchioles at the sites of overdistention and epithelial damage. In particular, a plasma protein of relative molecular weight 110,000 has been implicated. Fibrinogen, hemoglobin, and albumin are potent inhibitors of surfactant.<sup>63</sup> It is of critical importance to the lungs to have adequate surfactant at the gas-liquid interface from the earliest possible moment after birth; otherwise, acute lung injury and surfactant inhibition supervene rapidly and contribute to a cycle of worsening disease.<sup>64</sup> Thus RDS is due to a developmental deficiency of surfactant at birth, but associated lung injury results in surfactant dysfunction as well.

### ► **Prevention:-**

Because HMD is a problem of insufficient lung maturity, the best way to prevent it is to prevent premature birth; for this purpose, the effective strategies are thought to be cervical cerclage, discovery and treatment of bacteriuria, and liberal use of tocolytics. At present, however, the two major approaches to the problem are (1) prediction of the risk for HMD by antenatal testing of amniotic fluid samples and (2) antenatal treatment of women in preterm labor with glucocorticoid hormones to accelerate fetal lung maturation. In addition, the prophylactic administration of exogenous surfactant at birth is designed to prevent RDS, and this strategy has been quite successful.<sup>65</sup>

### ► **Prenatal Prediction:-**

Before birth , the surfactant system can be assessed in amniotic fluid because some fetal lung fluid enters the amniotic cavity. The most common material measured is lecithin or PC, in particular ,SPC. Because changes in amniotic fluid volume may alter the concentration of SPC, it is standardized to the concentration of sphingomyelin, which remains relatively constant throughout gestation ;it is expressed as the L/S ratio.

In normal pregnancy , the L/S ratio display a remarkably stable pattern , increasing slowly to 1 at 32 weeks,rising more rapidly to 2 at35 weeks, and accelerating rapidly thereafter.<sup>66</sup> In abnormal pregnancy, there is much wider scatter, reflecting conditions that accelerate or decelerate lung maturation .The ratio may reach 2 as early as 28 weeks or remain at 1 until close to term . The incidence of HMD is only 0.5% for an L/S ratio of 2 or more but 100% for an L/S ratio less than 1; between 1 and 2 , the risk of HMD decreases progressively. Elective cesarean section delivery of infants having an unrecognized low L/S ratio carries an unnecessary risk of HMD.<sup>67</sup>

Phosphatidylinositol (PI) in amniotic fluid progressively increases until 36 weeks and then decreases .<sup>68</sup>At about this time ,PG appears and increases until term .The appearance time of PG may be accelerated or delayed in the same way as the L/S ratio .The presence of PG at 1% of total phospholipid indicates a remarkably low risk for HMD, less than 0.5%.If a patient has both an L/S ratio of less than 2 and a PG of less than 1% the risk for HMD is greater than 80%.<sup>69</sup> Besides an L/S ratio below 1,this combination is the best predictor of HMD available to the clinician .In certain pregnancies characterized by diabetes and Rh isoimmunization ,the L/S ratio has proved less reliable, the risk of HMD at a value between 2 and 3 still being approximately 13%. In those with both an L/S ratio above 2 and PG of 1% or more, however ,the risk has been reduced to 0.There are other factors to be considered in the interpretation of the L/S ratio: A low L/S ratio carries a much smaller risk at a more advanced gestation ,and in black infants the risk of RDS is low with an L/S ratio of more than 1.2.<sup>40</sup>

### ► **Early Postnatal Prediction:-**

The L/S ratio may be used on tracheal aspirate samples to predict RDS, but the threshold level of 2.0 must be raised to 3.0.<sup>70</sup> The measurement of PG on tracheal aspirate samples is also useful,and the combination of low L/S ratio and absent PG on tracheal aspirate samples gives a positive test predictive value of 89%.The measurement of static lung compliance is also useful for this purpose ; if the

measurement is less than 1.8 mL/cm H<sub>2</sub>O/m body length, the positive test predictive value is 100%, and if the measurement is more than 1.8, the negative test predictive value is 92%.<sup>71</sup> This test, however, is complex and expensive.

► **Prophylaxis with Antenatal Glucocorticoid Hormones:-**

Crowley and associates concluded that maternal steroid therapy significantly reduced the incidence of RDS, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death; in addition, they concluded that the duration and costs of hospital care for the newborn infant were greatly decreased. The benefits applied to all infants at a gestational age of 24 to 34 weeks, and this was not affected by race or gender or by the presence of prelabor rupture of amniotic membranes.<sup>72</sup>

The National Institutes of Health (NIH) concluded that the incidence of RDS, intraventricular hemorrhage, and neonatal death was significantly reduced (odds ratios 0.5, 0.5, and 0.6), and it regarded the evidence as compelling. The benefits were not affected by race or gender or by the presence of premature rupture of membranes, and, most important, was less than 24 hours. In infants of 24 to 28 weeks, the evidence for a reduced incidence of RDS was less certain, but the severity of RDS and the incidence of severe intraventricular hemorrhage were significantly decreased.<sup>73</sup>

There is no reasonable evidence that the incidence of infection is increased in either the mother or the infant. The results of long-term follow-up studies have shown no problems with general health or neurodevelopment that could be attributed to the use of hormone therapy.<sup>74</sup>

**The recommendations of the NIH panel are as follows :**

(1) All fetuses between 24 and 34 weeks' gestation are candidates for this therapy; (2) the decision should not be influenced by race, gender, premature rupture of membranes, or anticipated surfactant therapy; (3) all patients eligible for tocolytic therapy should receive steroids; (4) because therapy for less than 24 hours is effective, all patients should be treated unless immediate delivery is anticipated; (5) patients of less than 30 weeks' gestation should be treated because of the reduction in intraventricular hemorrhage; (6) treatment may be withheld in the presence of overt amnionitis; (7) treatment consists of **betamethasone** 12 mg every 24 hours for two doses or **dexamethasone** 6 mg every 12 hours for four doses.<sup>75</sup>

Liggins and Howie (1972) reported a higher incidence of RDS in infants delivered more than 7 days after maternal steroid treatment, which means that the beneficial effect is reversible. Routine retreatment after 7 days is not recommended, however,<sup>76</sup> unless the mother is still in active labor and imminent delivery before 34 weeks' is still a likely possibility.<sup>77</sup>

### ► **Treatment:-**

#### **1 - Resuscitation :-**

The mortality among all infants, including those with HMD is increased by asphyxia . Therefore, the presence of a skilled resuscitation team at delivery can reduce the morbidity and mortality of RDS .<sup>78</sup>

#### **2 - Lung Expansion :-**

Since secretion of surfactant is impaired by inadequate expansion of the lung at birth, many believe that it is appropriate to selectively intubate all infants under 1000 gms at birth and initiate mechanical ventilation with PEEP, and instillation of prophylactic surfactant therapy .<sup>79</sup>

#### **3 - Surfactant Replacement :-**

Infants less than 1000 g birth weight should be treated prophylactically with exogenous surfactant within 15 to 30 minutes of birth but only after adequate stabilization .Larger Infants should be treated as early as possible , preferably before the age of 2 hours and certainly before the age of 6 hours . A mammalian surfactant is currently preferred . The dose should be 100 mg / kg, the interval between doses should be 12 hours, and two to three doses should be given but omitted when the inspired oxygen decreases below, 30%. The dose should be given as rapidly as possible followed by bag - tube ventilation to insure even distribution, but it should not be given so rapidly as to obstruct the airways and promote hypercarbia; the number of aliquots for each dose does not matter.<sup>80</sup>

#### **4 - Thermal Neutrality :-**

Infants should be nursed in a warm environment so that oxygen consumption is maintained at minimal levels . This usually means servo-controlling the anterior abdominal skin temperature at 36.5 °C, but small premature infants may need to be servo-controlled at 36.9 °C to maintain the rectal temperature at 37 °C. The

measured energy expenditure is 55 calories / kg per day during the first 4 days <sup>81</sup>; the caloric intake is usually only 25 calories / kg per day,so it is important to minimize increased caloric expenditure.

### **5 - Blood Gas Monitoring :-**

Infants with HMD require monitoring of blood pressure, blood gases, electrolytes, calcium,and glucose. Blood samples may be obtained from an umbilical arterial catheter.<sup>4</sup>

### **6 - Oxygen :-**

An increase in  $F_{iO_2}$  is the minimal level of respiratory support that can be given to an infant with RDS.

Increased inspired oxygen produces (1) a rise of alveolar oxygen pressure in open low V/Q units,(2)relief of regional hypoxic vasoconstriction in this compartment, (3) a reduction in true right -to - left shunt, and (4) an increase of arterial oxygen saturation.<sup>82</sup>

Frequently the unventilated infant requires 40 % to 50 % oxygen after birth for relief of central cyanosis but then develops an increasing oxygen requirement over 24 to 48 hours;this may reach as high as100 %. In other infants ,the oxygen requirement transiently decreases as acidosis or hypothermia is corrected or fetal lung fluid is cleared ; the oxygen requirement begins to increase only after 3 to 6 hours. More severely affected infants have an immediate high oxygen requirement that progresses rapidly to 100 %; without mechanical ventilation,they may die within 24 hours . Another group of larger infants needs less oxygen initially and manifests a slowly progressive course of generalized atelectasis over 48 to 72 hours . If HMD is uncomplicated , recovery starts after 48 hours .The decline in oxygen requirement is relatively rapid after 72 hours ,and usually oxygen can be discontinued after 1 week.<sup>47, 48, 49, 50</sup>

### **7 - Fluid Restriction and Attention to Serum Electrolytes :-**

Because HMD is characterized by high surface tension pulmonary edema<sup>83</sup> and high permeability pulmonary edema,<sup>84</sup> fluid restriction to 50 mL/kg per day is indicated for many infants with HMDfor the first 48 hours or until the onset of diuresis. A controlledtrial of this kind of fluid restriction, compared with a modest increase in the fluid intake, showed a significant reduction in the incidence of BPD at the age of 1 month and at a postconceptional age near term.<sup>85</sup> Close

attention should be paid to fluid intake, urine output, urine concentration, and serum electrolytes. Premature infants have an excess of extracellular fluid and are expected to lose at least 10% of body weight by the end of the 1st week of life. It is not necessary or beneficial to administer sodium in the first few days of life.<sup>86</sup> Potassium should also be restricted because hyperkalemia may be troublesome.<sup>87</sup> In the very immature infant (24 to 26 weeks' gestation) with extremely permeable skin, there may be excessive evaporative losses, and much higher amounts of fluid may be required. If the serum sodium rises sharply, especially if it approaches 150 mEq/L, it can be assumed that insensible water losses through the skin are excessive, and the fluid intake should be liberalized accordingly. To minimize insensible water losses, it is useful to manage the infant in a humidified incubator.<sup>4</sup>

## **8 - Minimal Stimulation :-**

Manipulation, such as heel sticks, tracheal suctioning, diaper changes, and even weighing, should be kept to a minimum because these procedures have been shown to reduce arterial oxygen tension<sup>88</sup>; they probably also increase oxygen consumption and may contribute to the genesis of cerebral hemorrhage by rapidly raising arterial blood pressure to excessive levels. It is not appropriate to give enteral feedings to infants with HMD because this condition is usually accompanied by poor intestinal motility.<sup>89</sup>

## **9 - Blood Pressure Support :-**

Premature infants with RDS frequently have a low arterial blood pressure in the first 12 hours of life, as defined by normative data.<sup>90</sup> Many extremely-low-birth-weight infants with RDS probably have a low blood pressure for many days after birth, and this may predispose them to brain injury.<sup>91</sup> In small premature infants without intraventricular hemorrhage, the normal mean blood pressure is more than 30 mmHg during the 1st week of life.<sup>92</sup> Intraventricular hemorrhage is more common in those who have a mean blood pressure less than 30 mmHg<sup>93</sup>, and a mean blood pressure less than 30 mmHg is more common in those who develop an intraventricular hemorrhage.<sup>94</sup>

## **10 - Alkali Therapy :-**

Severe metabolic acidosis may increase pulmonary vascular resistance, impair surfactant synthesis, reduce cardiac output, and ultimately reduce ventilation. An early trial showed that continuous infusion of glucose-bicarbonate solutions reduced the mortality of HMD.<sup>95</sup> With the introduction of better methods for

oxygenating infants, however, bicarbonate therapy no longer appears to have much benefit<sup>96</sup>, and it may be harmful in infants who are not being ventilated adequately and have a high arterial Pco<sub>2</sub>.<sup>97</sup>

## 11 - Continuous Positive Airway Pressure :-

The inability to maintain a Pao<sub>2</sub> higher than 50 to 60 mmHg in an Fio<sub>2</sub> of 0.4 to 0.7 constitutes adequate indication for initiating CPAP in infants with RDS in many nurseries. CPAP is a technique with which a sustained continuous pressure is applied to the airways throughout both the inspiratory and expiratory cycles.<sup>98</sup> Use of CPAP appears to reduce the need for subsequent mechanical ventilation.<sup>99</sup> CPAP increases lung volume in part by increasing alveolar size, preventing atelectasis, and recruiting collapsed alveoli. The increased lung volume results in better oxygenation by improving ventilation - perfusion relationships and decreasing intrapulmonary right-to-left shunting. However, there can be a variable effect on lung compliance, which may decrease, particularly at high levels of distending pressure. This suggests that, in addition to recruitment of some alveoli, there also may be overdistension of others. With the application of CPAP the breathing pattern becomes slower and more regular while grunting generally ceases. Because of the rapidity with which these frequency changes occur, they are most likely mediated by the increase in functional residual capacity via the Hering Breuer reflex. Hypoxemia remains the most universally accepted indication for institution of CPAP. Because CPAP has a variable effect on Paco<sub>2</sub>, blood gases must be monitored closely, and if respiratory failure ensues (i.e., Paco<sub>2</sub> higher than 50 to 60 mmHg, pH less than 7.20 to 7.25), endotracheal intubation with mechanical ventilation should be instituted.<sup>4</sup>

In the traditional approach to the use of CPAP support, endotracheal CPAP is frequently used in larger infants (>1500 g) in the hope that mechanical ventilation will not be necessary; it should be started when the oxygen requirement reaches 50%. Many believe that endotracheal CPAP alone is not likely to be successful in smaller infants (>1500 g) and proceed directly to mechanical ventilation. In the larger infants, the initial level of endotracheal CPAP used is 5 cm H<sub>2</sub>O at an oxygen requirement of 50%, and the pressure is increased in 1 cm H<sub>2</sub>O steps for each 10% increase in the oxygen requirement. The incidence of pulmonary air leak with this regimen is no higher than the spontaneous rate for RDS.<sup>100</sup> Infants who require oxygen concentration of more than 80% with endotracheal CPAP of 8 to 10 cm H<sub>2</sub>O usually need mechanical ventilation.

Because CPAP may overdistend the lung and impair the pulmonary circulation, attempts have been made to identify optimal levels.<sup>101</sup> The optimal level of CPAP may be defined as that airway pressure at which oxygen saturation and  $P_{aO_2}$  are optimized without adverse effects on cardiac output. If the pressure is increased above this level, cardiac output decreases and oxygen transport is impaired. Furthermore,  $P_{aCO_2}$  usually rises, probably due to the overdistention of and decrease in lung compliance. Esophageal pressure rises sharply when optimum lung compliance is achieved because of enhanced transmission of airway pressure to the intrapleural space. The optimum level of CPAP is not static in a given patient but varies as disease severity changes.<sup>4</sup> As CPAP is increased and approaches optimum, the aA.Dco<sub>2</sub> falls significantly, but as the optimal level is exceeded, both the aA.Dco<sub>2</sub> and the arterial Pco<sub>2</sub> rise significantly.<sup>101</sup> Under clinical conditions, increased hypercarbia may indicate excessive CPAP, which should be recognized and corrected before oxygenation deteriorates.

Early administration of CPAP to infants with established RDS results in a reduction in the subsequent need for mechanical ventilation.<sup>99</sup> However, prophylactic early use of CPAP soon after delivery has not resulted in reduction in the development of RDS, the need for mechanical ventilation, or complications of mechanical ventilation, including chronic lung disease.<sup>102</sup> In infants with moderate to severe RDS, a single dose of surfactant given during a short intubation, plus early nasal CPAP, has been shown to improve gas exchange and reduce the need for mechanical ventilation when compared with early nasal CPAP in the absence of exogenous surfactant therapy.<sup>103</sup>

## **12 - Mechanical Ventilation :-**

Infants with HMD who weigh less than 1500g and infants treated with exogenous surfactant usually require mechanical ventilation.<sup>104</sup>

In the absence of conclusive clinical studies we recommend initiation of assisted ventilation if any of the following is present:-

- (1) Respiratory acidosis with a pH of less than 7.20 to 7.25.
- (2) Severe hypoxemia with a  $P_{aO_2}$  less than 50 to 60 mmHg despite a high  $F_{iO_2}$  (0.6 to 0.7) (often while on CPAP in infants with RDS).
- (3) Severe apnea.

Although a controversial practice, elective intubation may increase survival of very low birth weight infants.<sup>105</sup>

**The aim** is to correct the blood gas abnormalities with as little lung injury and circulatory compromise as possible. Because the time constant in RDS is short, long inspiration times are not necessary and may be associated with pulmonary air leaks. Oxygenation is dependent on the level of mean airway pressure; in a condition characterized by low lung volume and low lung compliance, it is efficient to use generous levels of PEEP. Many clinicians allow modest hypercarbia to avoid excessive peak pressures and tidal volumes; it is high tidal volumes that injure the lung, not high peak pressures. Under isocarbic conditions, smaller tidal volumes can be used if the rate is higher. Two controlled trials have shown that there is an advantage to ventilating at a rate of 60 breaths/min with a short inspiratory time compared with 30 breaths/min; in each case, there was a significant reduction in the incidence of lung injury with pneumothorax.<sup>106,107</sup>

To prevent gas trapping, sufficient time must be allowed for expiration, so there is a limit on how high the rate can be increased; most infants can be managed at a rate of 60 breaths / min initially. If the infants' breathing is asynchronous, especially if the blood pressure is low, it is common to find that the blood pressure wave fluctuates,<sup>108</sup> a phenomenon associated with an increased incidence of intraventricular hemorrhage.<sup>109</sup> Asynchrony is also associated with an increased incidence of pneumothorax. Sometimes an increase in the rate to 70 or 80 breaths/min may promote adequate synchrony,<sup>110</sup> or breathing can be suppressed with narcotics.<sup>111</sup> If narcotics are given, expiratory braking may be impaired, so it is again important to use generous levels of PEEP to promote the maintenance of lung volume.<sup>112</sup>

### **13 - Closure of the Patent Ductus Arteriosus :-**

Especially in infants less than 1000g birth weight, a patent ductus arteriosus may contribute significantly to the overall problem during recovery from RDS and may predispose the infant to the development of BPD. If the ductus is demonstrated to be patent at the age of 3 to 4 days by two-dimensional echocardiography and pulsed Doppler ultrasonography, the evidence suggests that it is unlikely to close spontaneously within a reasonable time,<sup>113</sup> and therefore it should be closed, either with indomethacin therapy or with surgery. In infants greater than 1000g birth weight, in whom the risk for BPD is much less, it is reasonable to close the patent ductus arteriosus later, if signs of a significant left-to-right shunt develop, usually at the age of 5 to 10 days.<sup>65</sup>

#### **14 - Corticosteroids :-**

There has been considerable interest in the use of dexamethasone in the treatment of RDS, with the emphasis being on the prevention of BPD in very small infants.<sup>65</sup>

#### **► Prognosis :-**

The chances of survival in HMD are directly related to birth weight and gestational age and are affected by prenatal treatment with glucocorticoids, by surfactant replacement therapy, and by the severity and complications of the disease.<sup>65</sup>

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