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# Lung Ventilation Modeling for Assessment of Lung Status: Detection of Lung Disease and Indication for Extubation of Mechanically-Ventilated COPD Patients

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## 1. Introduction

In pulmonary medicine, it is important to detect lung diseases, such as chronic obstructive pulmonary disease (COPD), emphysema, lung fibrosis and asthma. These diseases are characterized in terms of lung compliance and resistance-to-airflow. Another important endeavour of pulmonary medicine is mechanical ventilation of COPD patients and determining when to wean off these patients from the mechanical ventilator. In both these medical domains, lung ventilation dynamics plays a key role.

So in this chapter, we develop the lung ventilation dynamics model in terms of monitored lung volume ( $V$ ) and driving pressure ( $P_L$ ), in the form of a differential equation with parameters of lung compliance ( $C$ ) and resistance-to-airflow ( $R$ ). We obtain the solution of this equation in the forms of lung volume ( $V$ ) function of  $P_L$ ,  $C$  and  $R$ . For the monitored lung volume  $V$  and pressure  $P_L$  data, we can evaluate  $C$  and  $R$  by matching the model solution expression with the monitored lung volume  $V$  and driving pressure  $P_N$  data. So what we have done here is to develop the method for determining lung compliance ( $C$ ) and resistance-to-airflow ( $R$ ) as average values of  $C$  ( $= C_a$ ) and  $R$  ( $= R_a$ ) during the ventilation cycle.

Now in some lung diseases such as in emphysema, the lung compliance ( $C$ ) is high. In other lung diseases such as in asthma, the airway resistance ( $R$ ) is high. So we need to determine the ranges of  $C$  and  $R$  for normal lung status as well as for lung disease states. Then, we can develop a 2-parameter  $R$ - $C$  diagnostic coordinate plane, on which we can demarcate the zones for different diseases. Then, for any patient's ( $R$ ,  $C$ ) value, we can plot the ( $R$ ,  $C$ ) point in the  $R$ - $C$  diagnostic coordinate plane, and based on its location designate the lung disease state of the patient. A more convenient way for detecting lung disease is to combine  $R$  and  $C$  along with some ventilator data (such as tidal volume and breathing rate) into a non-dimensional lung ventilator index ( $LVI$ ). Then, we can determine the ranges of  $LVI$  for normal and disease states, and thereby employ the patient's computed values of  $LVI$  to

designate a specific lung disease for the patient. The *LVI* concept for detecting lung disease is more convenient to adopt in clinical practice, because it enables detection of lung disease states in the form of just one lung-ventilation number.

Now, in this methodology, we need to monitor (i) lung volume, by means of a spirometer, and (ii) lung pressure ( $P_L$ ) equal to  $P_{mo}$  (pressure at mouth) minus pleural pressure ( $P_p$ ). The pleural pressure measurement involves placing a balloon catheter transducer through the nose into the esophagus, whereby the esophageal tube pressure is assumed to be equal to the pressure in the pleural space surrounding it. Now this procedure cannot be carried out non-traumatically and routinely in patients. Hence, for routine and noninvasive assessment of lung ventilation for detection of lung disease states, it is necessary to have a method for determining  $R$  and  $C$  from only lung volume data. So, then, we have shown how we can compute  $R$ ,  $C$  and lung pressure values non-invasively from just lung volume measurement.

Finally, we have presented how the lung ventilation modeling can be applied to study the lung ventilation dynamics of COPD patients on mechanical ventilation. We have shown how a COPD patient's lung  $C$  and  $R$  can be evaluated in terms of the monitored lung volume and applied ventilatory pressure. We have also formulated another lung ventilator index to study and assess the lung status improvement of COPD patients on mechanical ventilation, and to decide when they can be weaned off mechanical ventilation.

## 2. Lung ventilation model

### 2.1 Scope

In this section, we have developed a lung ventilation model by modeling the lung volume response to mouth minus pleural driving pressure (by means of a first order differential equation) in terms of resistance-to-airflow ( $R$ ) and the lung compliance ( $C$ ). The lung volume solution of the differential equation is matched with the clinical volume data, to evaluate the parameters,  $R$  and  $C$ . These parameters' values can help us to distinguish lung disease states, such as obstructive lung and lung with stiffened parenchyma, asthma and emphysema.

### 2.2 Role of lung ventilation

Lung ventilation constitutes inhalation of appropriate air volume under driving pressure (= mouth pressure - pleural pressure), so as to: (i) provide adequate alveolar  $O_2$  amount at

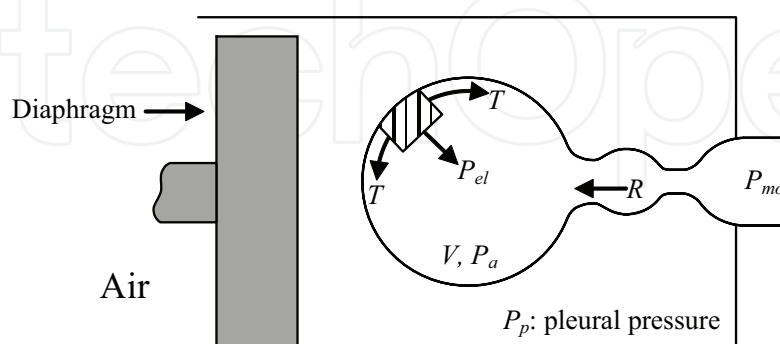


Fig. 1. Lumped Lobule Lung Model. In the figure,  $P_a$  is the alveolar pressure;  $P_{mo}$  is the pressure at the mouth;  $P_p$  is the pleural pressure;  $P_{el} = P_a - P_p = 2h\sigma/r = 2T/r$ , the lung elastic recoil pressure;  $r$  is the radius of the alveolar chamber and  $h$  is its wall thickness;  $T$  is the wall tension in the alveolar chamber;  $V$  is the lung volume;  $R$  is the resistance to airflow; and  $C$  is the lung compliance. This figure is adopted from our work in Ref [1].

appropriate partial pressure, (ii) oxygenate the pulmonary blood, and (iii) thereby provide adequate metabolic oxygen to the cells. Hence, ventilatory function and performance assessment entails determining how much air volume is provided to the alveoli, to make available adequate alveolar oxygen for blood oxygenation and cellular respiration. In this lumped lobule lung model [1], we have (i) a lumped alveolar chamber of volume  $V$  and pressure  $P_a$ , and (ii) lumped airway having airflow resistance  $R$ . In this airway, the pressure varies from  $P_{mo}$  at the mouth to  $P_a$  in the alveolar chamber. The pleural pressure is  $P_p$ .

**2.3 Lung ventilation analysis (using a linear first-order differential equation model)**  
We first analyze Lung Ventilation function by means of a model represented by a first-order differential equation ( $De_q$ ) in lung-volume ( $V$ ) dynamics in response to the driving pressure  $P_L$  (= mouth pressure – pleural pressure). In this model [2], the lung lobes and the alveoli are lumped into one lung lobule, as depicted in Figure 1. Figure 2 displays typical data of lung volume and flow, alveolar and pleural pressure.

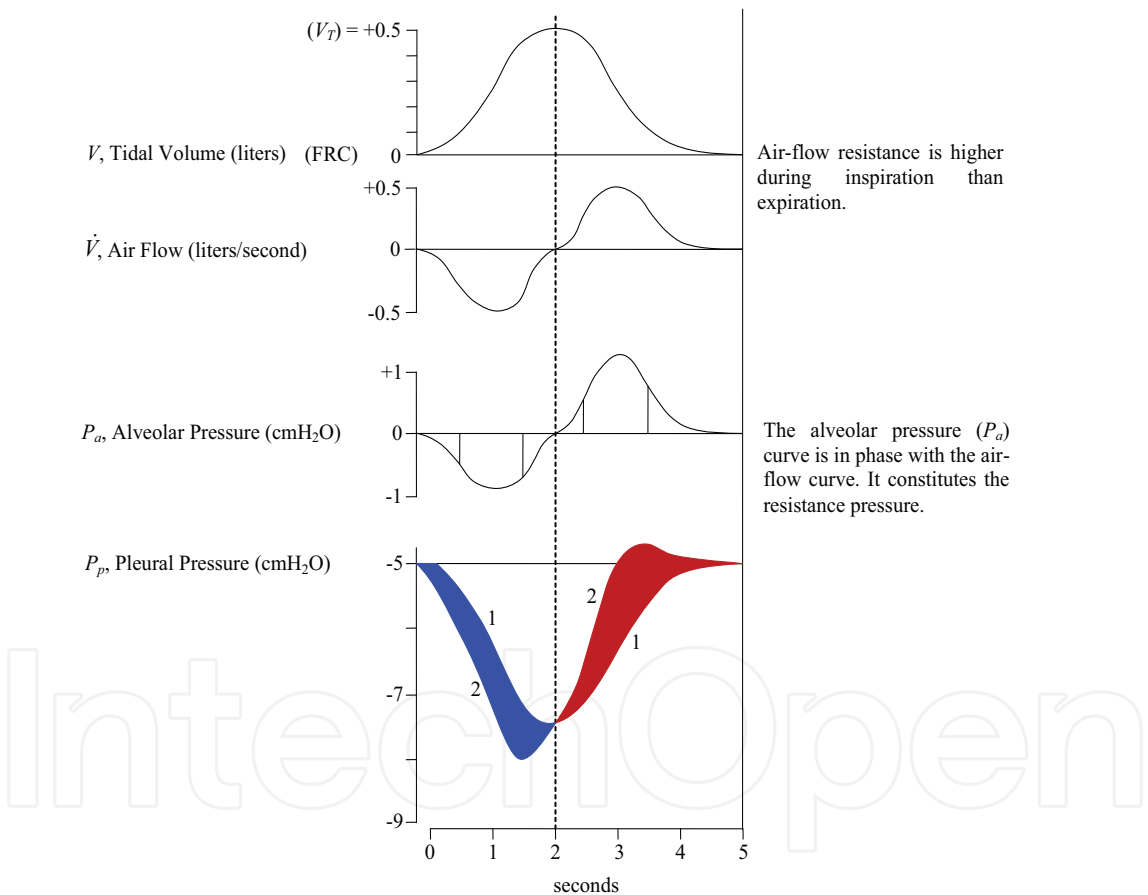


Fig. 2. Lung ventilatory model and lung-volume and pleural-pressure data. In the bottom figure, Curve 1 represents the negative of  $P_{el}$ , the pressure required to overcome lung elastance ( $=1/C$ ) plus elastic recoil pressure at the end of expiration. Curve 2 represents  $P_p = -P_{el} + P_a$ . Now, as can be noted from Figure 1,  $P_a - P_p = P_{el}$ . The lung driving pressure  $P_L = P_{mo} - P_p$ , and the net driving pressure  $P_N(t)$  in Equation (1-b) equals  $P_L$  minus  $P_{el}$  at end-expiration. We define resistance-to-airflow ( $R$ ) as  $(P_{mo} - P_a) / \dot{V}$ . We define lung compliance  $C = V / (P_{el} - P_{el0}) = V / (P_a - P_p) - P_{el0}$ . This figure is adopted from our work in Ref [1].

Based on Figures 1 and 2, we can put:

$$\left. \begin{aligned} \text{(i)} \quad & (P_a - P_p) - P_{el} = 0 \\ \text{(ii)} \quad & P_{el} = (2\sigma h) / R = 2T / R = V / C + P_{el0} \text{ (at end - expiration)} \\ \text{(iii)} \quad & (P_{mo} - P_a) = R(dV / dt) \\ \text{(iv)} \quad & P_L = P_{mo} - P_p = (P_{mo} - P_a) + (P_a - P_p) \\ \text{(v)} \quad & R(dV / dt) + V / C = P_L - P_{el0} \text{ (lung elastic recoil pressure at end - expiration)} \end{aligned} \right\} \quad (1-a)$$

The lung ventilation model governing equation is hence formulated as:

$$R\dot{V} + \frac{V}{C} = P_L(t) - P_{el0} = P_N(t) \quad (1-b)$$

wherein:

- i. the values of pressure  $P_N(t)$  are obtained from the  $P_L (= P_{mo} - P_p)$  data relative to  $P_{el0}$
- ii. the parameters of this Governing Eq are lung compliance ( $C$ ) and airflow-resistance ( $R$ ); in the equation both  $R$  and  $C$  are instantaneous values
- iii.  $V = V(t) - V_0$  (the lung air volume at the end-expiration = lung air volume inspired and expired during a single breath)
- iv.  $P_{el0}$  is the lung elastic-recoil pressure at the end of expiration, and

$$P_{el0} = P_{el} - \frac{V}{C} \quad (1-c)$$

- v. At end-expiration when  $\omega t = \omega T$ ,  $P_L = P_{el0}$

Now, in order to evaluate the lung model parameters  $C$  and  $R$ , we need to simulate this governing equation to lung volume ( $V$ ) and pressure ( $P_N$ ) data. This clinical data is shown in Figure 3. The lung volume is measured by integrating the airflow velocity-time curve, where the airflow velocity can be measured by means of a ventilator pneumatograph; the lung volume can also be measured by means of a spirometer. Inhalation and exhalation pressures are measured by means of a pressure transducer connected to the ventilatory tubing; likewise, a pressure transducer can also be similarly connected to the spirometer tubing. The pleural pressure is measured by placing a balloon catheter transducer through the nose into the esophagus; it is assumed that the esophageal tube pressure equals the pressure in the pleural space surrounding it.

In Equation (1-a), we have put  $P_N(t) = \sum_{i=1}^3 P_i \sin(\omega_i t + c_i)$ , expressed as a Fourier series. The governing equation (1-b) now becomes:

$$R\dot{V} + \frac{V}{C} = P_N(t) = \sum_{i=1}^3 P_i \sin(\omega_i t + c_i) \quad (2-a)$$

where the right-hand side represents the net driving pressure minus pleural pressure:  $P_N = (P_{mo} - P_p) - P_{el0}$ . This  $P_N$  is in fact the driving pressure ( $P_{mo} - P_p$ ) normalized with respect to its value at end-expiration. Equation (2-a) can be rewritten as follows:

$$\dot{V} + \frac{V}{RC} = \frac{1}{R} \sum_{i=1}^3 P_i \sin(\omega_i t + c_i) \quad (2-b)$$

wherein the  $P(t)$  clinical data (displayed in Figure 3) is represented by:

$$P(t) = \sum_{i=1}^3 P_i \sin(\omega_i t + c_i) \quad (3)$$

$$P_1 = 1.581 \text{ cmH}_2\text{O}$$

$$\omega_1 = 1.214 \text{ rad/s}$$

$$c_1 = -0.3132 \text{ rad}$$

$$P_2 = -5.534 \text{ cmH}_2\text{O}$$

$$\omega_2 = 0.001414 \text{ rad/s}$$

$$c_2 = 3.297 \text{ rad}$$

$$P_3 = 0.5523 \text{ cmH}_2\text{O}$$

$$\omega_3 = 2.401 \text{ rad/s}$$

$$c_3 = -2.381 \text{ rad}$$

The pressure curve (in Figure 3) represented by the above Equation (3) closely matches the pressure data of Figure 3. If, in Equation (1), we designate  $R_a$  and  $C_a$  as the average values ( $R$  and  $C$ ) for the ventilatory cycle, then the solution of Equation (2) is given by:

$$V(t) = \sum_{i=1}^3 \frac{P_i C_a [\sin(\omega_i t + c_i) - \omega_i R_a C_a \cos(\omega_i t + c_i)]}{1 + \omega_i^2 (R_a C_a)^2} - H e^{-\frac{t}{R_a C_a}} \quad (4)$$

wherein the term  $(R_a C_a)$  is denoted by  $\tau_a$ . We need to have  $V = 0$  at  $t = 0$ . Hence, putting  $V$  (at  $t = 0$ ) = 0, gives us:

$$H = \sum_{i=1}^3 \frac{P_i C_a [\sin(c_i) - \omega_i R_a C_a \cos(c_i)]}{1 + \omega_i^2 (R_a C_a)^2} \quad (5)$$

Then from Equations (4) and (5), the overall expressions for  $V(t)$  becomes

$$V(t) = \sum_{i=1}^3 \frac{P_i C_a [\sin(\omega_i t + c_i) - \omega_i \tau_a \cos(\omega_i t + c_i)]}{1 + \omega_i^2 \tau_a^2} - \sum_{i=1}^3 \frac{P_i C_a [\sin(c_i) - \omega_i \tau_a \cos(c_i)]}{1 + \omega_i^2 \tau_a^2} e^{-\frac{t}{\tau_a}} \quad (6)$$

We also want that  $dV/dt = 0$  at  $t = 0$ , implying no air-flow at the start of inspiration. So then by differentiating Equation (6), we get the expression for air-flow ( $\dot{V}$ ), as:

$$\dot{V} = \sum_{i=1}^3 \frac{P_i C_a [\omega_i \cos(\omega_i t + c_i) + \omega_i^2 \tau_a \sin(\omega_i t + c_i)]}{1 + \omega_i^2 \tau_a^2} + \sum_{i=1}^3 \frac{P_i C_a [\sin(c_i) - \omega_i \tau_a \cos(c_i)]}{(1 + \omega_i^2 \tau_a^2) \tau_a} e^{-\frac{t}{\tau_a}} \quad (7)$$

For the above values of  $\tau_a = 0.485$  s and for  $\omega$  and  $c_i$  given by Equation (3), we get

$$\dot{V}(t=0) = \sum_{i=1}^3 (P_i / R_a) \sin(c_i) \approx 0, \text{ to satisfy the initial condition.}$$

Now by matching the above  $V(t)$  expression in Equation (6) with the  $V(t)$  data in Figure 3, and carrying out parameter-identification, we can determine the *in vivo* values of  $C_a$ ,  $R_a$  and  $\tau_a$  to be:

$$C_a = 0.218 \text{ L}(\text{cmH}_2\text{O})^{-1}, R_a = 2.275(\text{cmH}_2\text{O})\text{sL}^{-1}, \tau_a = 0.485 \text{ s} \quad (8)$$

The computed  $V(t)$  curve, represented by Equation (6) for the above values of  $C_a$  and  $R_a$ , is shown in Figure 3.



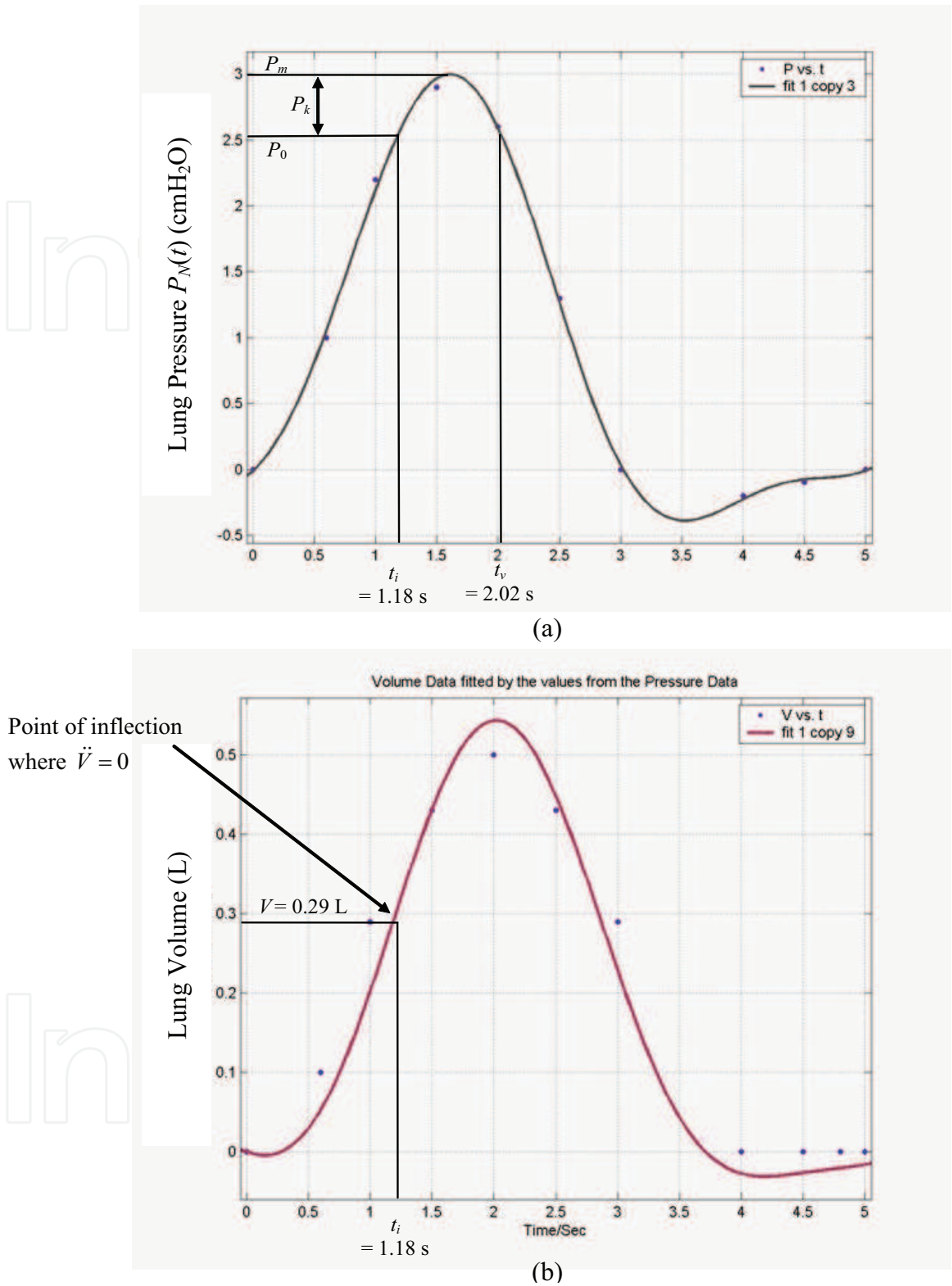


Fig. 3. (a)The pressure curve represented by Equation (3) matched against the pressure data (represented by dots). (b) The volume curve represented by Equation (6), for  $C_a = 0.2132 \text{ L}(\text{cmH}_2\text{O})^{-1}$  and  $R_a = 2.275 \text{ (cmH}_2\text{O)sL}^{-1}$ , matched against the volume data represented by dots. In Figure 3(a), the terms  $P_0$ ,  $P_m$  and  $P_k$  refer to Equation (11). At  $t = t_v$ ,  $V$  is maximum and  $\dot{V}$  is zero. This figure is adopted from our work in Ref [1].

Let us have some validation of the average values of  $C$  and  $R$  obtained by parameter-identification scheme, by determining the values of  $C$  and  $R$  at some specific time instants. For that purpose, we can put down from Equation (1-b),

$$R\ddot{V} + \frac{\dot{V}}{C} = \dot{P}_N(t) \quad (9)$$

Now the volume ( $V$ ) curve in Figure 3(b) has an inflection point at  $t = t_i = 1.18$  s, at which  $\ddot{V} = 0$ . At  $t = 1.18$  s,  $V = 0.29$  L,  $\dot{V} = 0.48$  Ls<sup>-1</sup>,  $P_N = 2.53$  cmH<sub>2</sub>O, and  $\dot{P}_N = 1.66$  (cmH<sub>2</sub>O)s<sup>-1</sup>. Upon substituting these values into Equation (9), we get  $C = 0.289$  L(cmH<sub>2</sub>O)<sup>-1</sup>. Then substituting this value of  $C$  along with the values of  $V$ ,  $\dot{V}$  and  $P_N$  into Equation (1-a), we get  $R = 3.18$  (cmH<sub>2</sub>O)sL<sup>-1</sup>. These values of  $C$  and  $R$  at  $t = t_i = 1.18$  s are of the same order of magnitude as the average values of  $C$  and  $R$  given by Equation (8). This provides us a measure of confidence to our parameter-identification scheme for obtaining the average values  $C_a$  and  $R_a$ .

Now since Lung disease will influence the values of  $R$  and  $C$ , these parameters can be employed to diagnose lung diseases. For instance in the case of emphysema, the destruction of lung tissue between the alveoli produces a more compliant lung, and hence results in a larger value of  $C$ . In asthma, there is increased airway resistance ( $R$ ) due to contraction of the smooth muscle around the airways. In fibrosis of the lung, the membranes between the alveoli thicken and hence lung compliance ( $C$ ) decreases. Thus by determining the normal and diseased ranges of the parameters  $R$  and  $C$ , we can employ this simple Lung-ventilation model for differential diagnosis.

### 3. Non-dimensional ventilatory index

For disease detection, it is more convenient to formulate and employ a non-dimensional number to serve as a ventilatory performance index  $LVI$  (to characterize ventilatory function), as:

$$LVI_1 = \left[ (R_a C_a) (\text{Ventilatory rate in s}^{-1}) 60 \right]^2 = \tau_a^2 (BR)^2 60^2 \quad (10)$$

where  $BR$  is the breathing rate.

Now, let us obtain its order-of-magnitude by adopting representative values of  $R_a$  and  $C_a$  in normal and disease states. Let us take the above computed values of  $R_a = 2.275$  (cmH<sub>2</sub>O)sL<sup>-1</sup> and  $C_a = 0.2132$  L(cmH<sub>2</sub>O)<sup>-1</sup> and  $BR = 12$  m<sup>-1</sup> or  $0.2$  s<sup>-1</sup>, computed by matching Equation (6) to the data of Figure 3.

Then, in a supposed normal situation, the value of  $LVI_1$  is of the order of 33.88. In the case of obstructive lung disease (with increased  $R_a$ ), let us take  $R_a = 5$  (cmH<sub>2</sub>O)sL<sup>-1</sup>,  $C_a = 0.12$  L(cmH<sub>2</sub>O)<sup>-1</sup> and  $BR = 0.3$  s<sup>-1</sup>; then we get  $LVI_1 = 118.6$ . For the case of emphysema (with enhanced  $C_a$ ), let us take  $R_a = 2.0$  (cmH<sub>2</sub>O)sL<sup>-1</sup>,  $C_a = 0.5$  L(cmH<sub>2</sub>O)<sup>-1</sup> and  $BR = 0.2$  s<sup>-1</sup>; then we obtain  $LVI_1 = 144$ . In the case of lung fibrosis (with decreased  $C_a$ ), we take  $R_a = 2.0$  (cmH<sub>2</sub>O)sL<sup>-1</sup>,  $C_a = 0.08$  L(cmH<sub>2</sub>O)<sup>-1</sup> and  $BR = 0.2$  s<sup>-1</sup>; then we obtain  $LVI_1 = 3.7$ .

We can, hence summarize that  $LVI_1$  would be in the range of **2-5** in the case of fibrotic lung disease, **5-50** in normal persons, **50-150** in the case of obstructive lung disease and **150-200** for the case of emphysema. This would of course be needed to be verified by analyzing a big patient population.



Now, all of this analysis requires pleural pressure data, for which the patient has to be intubated. If now we evaluate the patient in an outpatient clinic, in which we can only monitor lung volume and not the pleural pressure, then let us develop a non-invasive method for determining lung compliance ( $C$ ), resistance-to-airflow ( $R$ ) and ventilatory index.

#### 4. For non-invasive assessment of lung status and determination of lung compliance and resistance-to-airflow

Our primary need is to be able to determine lung pressure  $P_N(t)$  non-invasively. If we observe the  $P_N(t)$  curve in Figure 3(a), we can note that, during the period of time from  $t = t_i = 1.18$  s to  $t = t_v = 2.02$  s, we can represent it as:

$$P = P_N = P_k \sin \omega_p(t - t_i) + P_0 \quad (11-a)$$

$$\cong P_k \sin \omega_p(t - 1.18) + 2.5 \quad (11-b)$$

where (i)  $P_k = P_m - P_0$ , and  $P_k = 0.5$  cmH<sub>2</sub>O in Figure 3(a), (ii)  $t = t_i$ , the inflection point on the lung volume curve ( $= 1.18$  s in Figure 3(b)), and (iii)  $P_0 = 2.5$  cmH<sub>2</sub>O.

We can determine the value of  $\omega_p$ , by invoking the condition that the pressure  $P$  becomes maximum ( $= P_m$ ) at  $t = t_m = (t_v + t_i)/2$ . Hence, at  $t = t_m$ ,

$$P_m = P_k \sin \omega_p(t_m - t_i) + P_0$$

But since  $P_k = P_m - P_0$ , we get

$$P_m - P_0 = (P_m - P_0) \sin \omega_p(t_m - t_i)$$

or

$$\sin \omega_p(t_m - t_i) = 1$$

wherein

$$t_m = (t_v + t_i) / 2 = (2.02 + 1.18) / 2 = 1.6$$

Therefore, we have

$$\omega_p(t_m - t_i) = \omega_p(1.6 - 1.18) = \pi / 2 = 1.57 \quad (12)$$

In Equation (12),  $t_m = (t_v + t_i)/2$  and both  $t_v (= 2.02$  s) and  $t_i (= 1.18$  s) can be known from the lung volume curve. Hence,  $\omega_p$  can be determined. For Figure 3 data, we get  $\omega_p = 3.73$  rad/sec.

Hence, in our case of Figure 3 data, we can represent lung pressure  $P_N (= P)$  between  $t_i$  and  $t_v$  as:

$$P = P_k \sin \omega_p(t - t_i) + P_0 \quad (13-a)$$

$$= 0.5 \sin 3.73(t - 1.18) + 2.5 \quad (13-b)$$

and

$$\dot{P} = 1.87 \cos 3.73(t - 1.18) \quad (13-c)$$

So, in general, the parameters of the lung pressure curve are  $P_k$  and  $P_0$ , since  $t_i$  and  $\omega_p$  can be determined in terms of  $t_v$  and  $t_i$ , as per Equation (12) and Figure 3. Likewise, we can also represent lung volume between  $t_i$  and  $t_v$  as:

$$V = V_T \sin \omega_v(t - t_i) + V_0 \quad (14-a)$$

where  $V_T$  is the tidal volume and  $V_0$  is the lung volume at  $t = t_i$ . Based on Figure 3(b) data, we can rewrite Equation (14-a) as follows:

$$V = 0.25 \sin \omega_v(t - 1.18) + 0.3$$

At  $t = t_v = 2.02$  s,  $V = V_T = 0.55$  L. Hence,  $\omega_v(2.02 - 1.18) = 1.57$  (or  $\pi/2$ ), so that  $\omega_v = 1.87$  rad. So then Equation (14-a) can be written as:

$$V = 0.25 \sin 1.87(t - 1.18) + 0.3 \quad (14-b)$$

$$\dot{V} = 0.47 \cos 1.87(t - 1.18) \quad (14-c)$$

$$\ddot{V} = -0.88 \sin 1.87(t - 1.18) \quad (14-d)$$

Now based on Equation (13), we can represent the governing lung ventilation model Equation (1-b) as

$$R\dot{V} + \frac{V}{C} = P_k \sin 3.73(t - 1.18) + P_0 \quad (15-a)$$

or as,

$$R\dot{V} + \frac{V}{C} = 0.5 \sin 3.73(t - 1.18) + 2.5 \quad (15-b)$$

Let us employ this equation to determine the values of  $C$  and  $R$  at some specific points in the ventilation cycle. At  $t = t_i$  (the inflection point) = 1.18 s,  $\ddot{V} = 0$   $\text{Ls}^{-2}$ ,  $\dot{V} = 0.48$   $\text{Ls}^{-1}$  and  $V = 0.3$  L. Now, we can differentiate Equation (15) as:

$$R\ddot{V} + \frac{\dot{V}}{C} = (P_k \omega_p) \cos 3.73(t - 1.18) \quad (16-a)$$

or as,

$$\begin{aligned} R\ddot{V} + \frac{\dot{V}}{C} &= (0.5)(3.73) \cos 3.73(t - 1.18) \\ &= 1.86 \cos 3.73(t - 1.18) \end{aligned} \quad (16-b)$$

Hence, from this Equation (16), we get:

$$\frac{\dot{V}(=0.48)}{C} = 1.86, \text{ or } C = 0.258 \text{ L}(\text{cmH}_2\text{O})^{-1}.$$

Then, upon substituting this value of  $C$  into Equation (15), we get:

$$R(0.48) + \frac{0.3}{0.258} = 2.5, \text{ or } R = 2.79 \text{ (cmH}_2\text{O)sL}^{-1}.$$

Hence at  $t = t_i = 1.18 \text{ s}$ ,  $C = 0.258 \text{ L}(\text{cmH}_2\text{O})^{-1}$  and  $R = 2.79 \text{ (cmH}_2\text{O)sL}^{-1}$ . (17)

Let us now evaluate  $C$  and  $R$  at  $t = t_k = 1.6 \text{ s}$ , the time associated with the peak lung pressure. From Equations (15) and (16), we can put down:

$$R\dot{V} + \frac{V}{C} = 0.5\sin 3.73(1.6 - 1.18) + 2.5 = 3 \quad (18\text{-a})$$

$$R\ddot{V} + \frac{\dot{V}}{C} = 1.86\cos 3.73(1.6 - 1.18) = 0 \quad (18\text{-b})$$

At  $t = t_k = 1.6 \text{ s}$ , we get from Equations (13) and (14),  $V = 0.48 \text{ L}$ ,  $\dot{V} = 0.33 \text{ Ls}^{-1}$ ,  $\ddot{V} = -0.622 \text{ Ls}^{-2}$ ,  $P = 3 \text{ cmH}_2\text{O}$  and  $\dot{P} = 0 \text{ (cmH}_2\text{O)s}^{-1}$ .

Substituting these values into Equations (18-a) and (18-b), we get:

$$0.33R + \frac{0.48}{C} = 3 \quad (19\text{-a})$$

$$-0.622R + \frac{0.33}{C} = 0 \quad (19\text{-b})$$

from which we obtain for  $t = t_k = 1.6 \text{ s}$ ,

$$C = 0.22 \text{ (cmH}_2\text{O)sL}^{-1}, R = 2.51 \text{ (cmH}_2\text{O)sL}^{-1} \quad (20)$$

Finally, let us evaluate  $C$  and  $R$  at  $t = t_v = 2.02 \text{ s}$ . From Equation (15), we get:

$$R\dot{V} + \frac{V}{C} = 0.5\sin 3.73(2.02 - 1.18) + 2.5 \quad (21)$$

Now at  $t = t_v = 2.02 \text{ s}$ ,  $V = 0.55 \text{ L}$ ,  $\dot{V} = 0 \text{ Ls}^{-1}$ . So then, from Equation (21), we obtain:

$$\frac{0.55}{C} = 2.5, \text{ or } C = 0.22 \text{ (cmH}_2\text{O)sL}^{-1} \quad (22)$$

It can be noted that the values of  $C$  and  $R$  given by Equations (17), (20) and (22) are similar to their average values  $C_a = 0.218 \text{ L}(\text{cmH}_2\text{O})^{-1}$  and  $R_a = 2.275 \text{ (cmH}_2\text{O)sL}^{-1}$ . This lends a measure of confidence to our Equation (15), for which  $V$  and  $\dot{V}$  are given by Equations (14-b) and (14-c).

Let us now proceed to how we can determine the values of lung pressure function parameters  $P_k$  and  $P_0$  along with  $R$  and  $C$  from the monitored values of lung volume.

At  $t = t_i = 1.18 \text{ s}$ , we have from Equation (15-a)

$$R\dot{V} + \frac{V}{C} = P_k \sin 3.73(t - 1.18) + P_0 \quad (23)$$

so that by substituting  $V = 0.3$  L,  $\dot{V} = 0.48$  Ls<sup>-1</sup>, we get:

$$R(0.48) + \frac{0.3}{C} = P_0 \quad (24)$$

Also, from Equation (16), we get by substituting the values of  $\dot{V} = 0.48$  Ls<sup>-1</sup> and  $\ddot{V} = 0$  Ls<sup>-2</sup>

$$\frac{0.48}{C} = 3.73P_k \quad (25)$$

At  $t = t_m = 1.6$  s, we have from Equations (15) and (16) as well as by substituting the values of  $V = 0.48$  L,  $\dot{V} = 0.33$  Ls<sup>-1</sup> and  $\ddot{V} = -0.622$  Ls<sup>-2</sup>, we get:

$$0.33R + \frac{0.48}{C} = P_k + P_0 = P_m \quad (26)$$

$$-0.622R + \frac{0.33}{C} = 0, \text{ or } R = 0.53/C \quad (27)$$

Then at  $t = t_v = 2.02$  s, we get from Equation (15), along with  $V = 0.55$  L,  $\dot{V} = 0$  Ls<sup>-1</sup>,

$$\frac{0.55}{C} = P_0 \quad (28)$$

We hence have Equations (24), (25), (26), (27) and (28) to solve and determine the best values of the four unknowns  $R$ ,  $C$ ,  $P_k$  and  $P_0$ . For this purpose, we define the ranges of these four terms, as:

$R$ : 2.1, 2.2, 2.3 (cmH<sub>2</sub>O)sL<sup>-1</sup>;  $C$ : 0.20, 0.21, 0.22 L(cmH<sub>2</sub>O)<sup>-1</sup>;  $P_k = 0.4, 0.5, 0.6$  (cmH<sub>2</sub>O);  $P_0 = 2.4, 2.5, 2.6$  (cmH<sub>2</sub>O)

Then, in order to satisfy these equations, we obtain for the best values of  $R$ ,  $C$ ,  $P_k$  and  $P_0$ , based on the solution in Appendix, as

$$R = 2.29(\text{cmH}_2\text{O})\text{sL}^{-1}, C = 0.22\text{L}(\text{cmH}_2\text{O})^{-1}, P_k = 0.58(\text{cmH}_2\text{O}), P_0 = 2.47(\text{cmH}_2\text{O}) \quad (29)$$

As can be noted, these values of  $C$  and  $R$  correspond to the average values of  $C$  and  $R$  given by Equation (8). This then lends credibility to our procedure for non-invasive determination of  $C$  and  $R$ , for lung disease detection. This procedure enables us to in fact determine lung pressure toward evaluation of  $C$  and  $R$ .

Now since this procedure enables us to determine maximum lung driving pressure  $P_m = P_k + P_0$ , we can also formulate the non-dimensional lung ventilatory index as:

$$LVI_2 = \frac{R}{C} \frac{(TV)^2}{(P_m)^2} (BR)(60)^2 \quad (30)$$

wherein  $BR$  is in s<sup>-1</sup>. For our case,  $R = 2.275$  (cmH<sub>2</sub>O)sL<sup>-1</sup>,  $C = 0.2132$  L(cmH<sub>2</sub>O)<sup>-1</sup>,  $P_m = 3$  cmH<sub>2</sub>O, and  $TV = 0.55$  L. This gives  $LVI_2 = 25.8$ . By using this  $LVI_2$  index, we can

expect its value to be of the order of 30 for normal subjects, 300 for COPD patients, 5 for emphysema patients, and 100 in the case of lung fibrosis.

Here again, we need to determine *LVI* for normal lung states as well as for different lung disease states. We can then compare which of the formulas (10) or (30) enable better separation of lung disease states from the normal state.

*Comments related to values of the ranges of the parameters:* Before proceeding to the next section, let us address the basis of providing the above indicated ranges of parameters. The lung ventilation volume and driving pressure curves in Figure 3 are for a normal case. By carrying out this procedure for other normal subjects, we can define and confirm the above mentioned normal ranges for these parameters, for obtaining their best values.

Now then how do we distinguish subjects with disorders, such as obstructive lung disease (with increased value of  $R_a$ ), emphysema (with enhanced value of  $C_a$ ), lung fibrosis (with decreased value of  $C_a$ )? This can be made out from the shape and values of the lung ventilation volume curve. So then by repeating this procedure for subjects with these disorders, we will be able to characterize the shapes of the lung ventilation curves for normal subjects and for prescribing appropriate ranges of the parameters, for obtaining the best values of these parameters.

## 5. Lung-status evaluation and indicators for extubation of mechanically-ventilated COPD patients

### 5.1 Introduction

In mechanically ventilated patients with chronic-obstructive-pulmonary-disease (COPD), elevated airway resistance and decreased lung compliance (i.e., stiffer lung) are observed with rapid breathing. The need for accurate predictive indicators of lung-status improvement is essential for ventilator discontinuation through stepwise reduction in mechanical support, as and when patients are increasingly able to support their own breathing, followed by trials of unassisted breathing preceding extubation, and ending with extubation.

For this reason, we have developed an easy-to-employ lung ventilatory index (*LVI*), involving the intrinsic parameters of a lung ventilatory model, represented by a first-order differential equation in lung-volume response to ventilator driving pressure. The *LVI* is then employed for evaluating lung-status of chronic-obstructive-pulmonary-disease (COPD) patients requiring mechanical ventilation because of acute respiratory failure.

### 5.2 Scope and methodology

We recruited 13 mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) in acute respiratory failure [3]. All patients met the diagnostic criterion of COPD. The first attempt of discontinuation (or weaning off the ventilator) for every patient was made within a short duration (not exceeding 88 hours). The patients in the study were between the ages of 54-83 years. All the patients were on synchronized intermittent mandatory ventilation (SIMV) mode with mandatory ventilation at initial intubation. Based on the physician's judgment, the modes were changed for eventual discontinuation of mechanical ventilation. The time period for recording observations was one hour. For all purposes in this study, a successful ventilator discontinuation is defined as the toleration to extubation for 24 hours or longer and a failed ventilator discontinuation is defined as either a distress when ventilator support is withdrawn or the need for reintubation. Our *LVI* was then employed to distinguish patients who could be successfully weaned off the mechanical ventilator.

Hence, the scope of this section is that we have developed a lung-ventilatory index (*LVI*), based on a lung-model represented by a first-order differential equation in lung-volume dynamics to assess lung function and efficiency in the case of chronic-obstructive-pulmonary-disease (COPD) patients requiring mechanical ventilation because of acute respiratory failure. Herein, we have attempted to evaluate the efficacy of the *LVI* in identifying improving or deteriorating lung condition in such mechanically ventilated chronic-obstructive-pulmonary-disease (COPD) patients, and consequently if *LVI* can be used as a potential indicator to predict ventilator discontinuation. In our bioengineering study of 13 COPD patients who were mechanically ventilated because of acute respiratory failure, when their *LVI* was evaluated, it provided clear separation between patients with improving and deteriorating lung condition. Finally, we formulated a lung improvement index (*LII*) representative of the overall lung response to treatment and medication, and a parameter *m* that corresponds to the rate of lung improvement and reflects the stability of lung-status with time. This chapter is based on our previous chapter [3] in the book on Human Respiration (edited by V. Kulish and published by WIT Press) and other works on this subject [4-9].

### 5.3 Lung ventilation model

From a ventilatory mechanics viewpoint, the lungs can be considered analogous to a balloon, which can be inflated and deflated (passively). The gradient between the mouth-pressure ( $P_{mo}$ ) and the alveolar pressure ( $P_{al}$ ) causes respiration to occur. During inspiration,  $P_m > P_{al}$ , which causes air to enter the lungs. During expiration  $P_{al}$  increases, and is greater than  $P_{mo}$ ; this causes the air to be expelled out of the lungs passively. These pressure differentials provide a force driving the gas flow. The pressure difference between the alveolar pressure ( $P_{al}$ ) and pleural pressure ( $P_p$ ) counter balances the elastic recoil. Thus the assessment of respiratory mechanics involves the measurement of flows, volumes (flow integrated over time) and pressure-gradients. The lung ventilation model (shown in Figure 1) is based on the same dynamic-equilibrium differential equation (Equation 1-b), expressing lung volume response to pressure across the lung, as:

$$R\dot{V} + \frac{V}{C} = P_L(t) - P_{el0} = B\sin(\omega t) \quad (31)$$

wherein:

- i. the total positive pressure across the lungs,  $P_L = P_{mo} - P_p$ , wherein  $P_p$  is determined by intubating the patient, and assuming that the pressure in the relaxed esophageal tube equals the pressure in the pleural space surrounding it.
- ii. the parameters of the governing Equation (31) are lung compliance (*C*) and airflow-resistance (*R*), with both *R* and *C* being instantaneous values
- iii.  $V = V(t) - V_e$  (wherein  $V_e$  is the end-expiratory lung volume)
- iv.  $P_{el0}$  is the end-expiratory pressure
- v. the net driving pressure  $P_N = P_L - P_{el0}$

Let *B* be the amplitude of the net pressure wave form applied by the ventilator,  $C_a$  be the averaged dynamic lung compliance,  $R_a$  the averaged dynamic resistance to airflow, the driving pressure  $P_L$  be given as  $P_L = P_{el0} + B\sin(\omega t)$ , and the net pressure  $P_N$  be given by  $P_N = B\sin(\omega t)$ , as depicted in Figure 4. The governing equation (31) then becomes:

$$R_a\dot{V} + \frac{V}{C_a} = P_N = B\sin(\omega t) \quad (32)$$



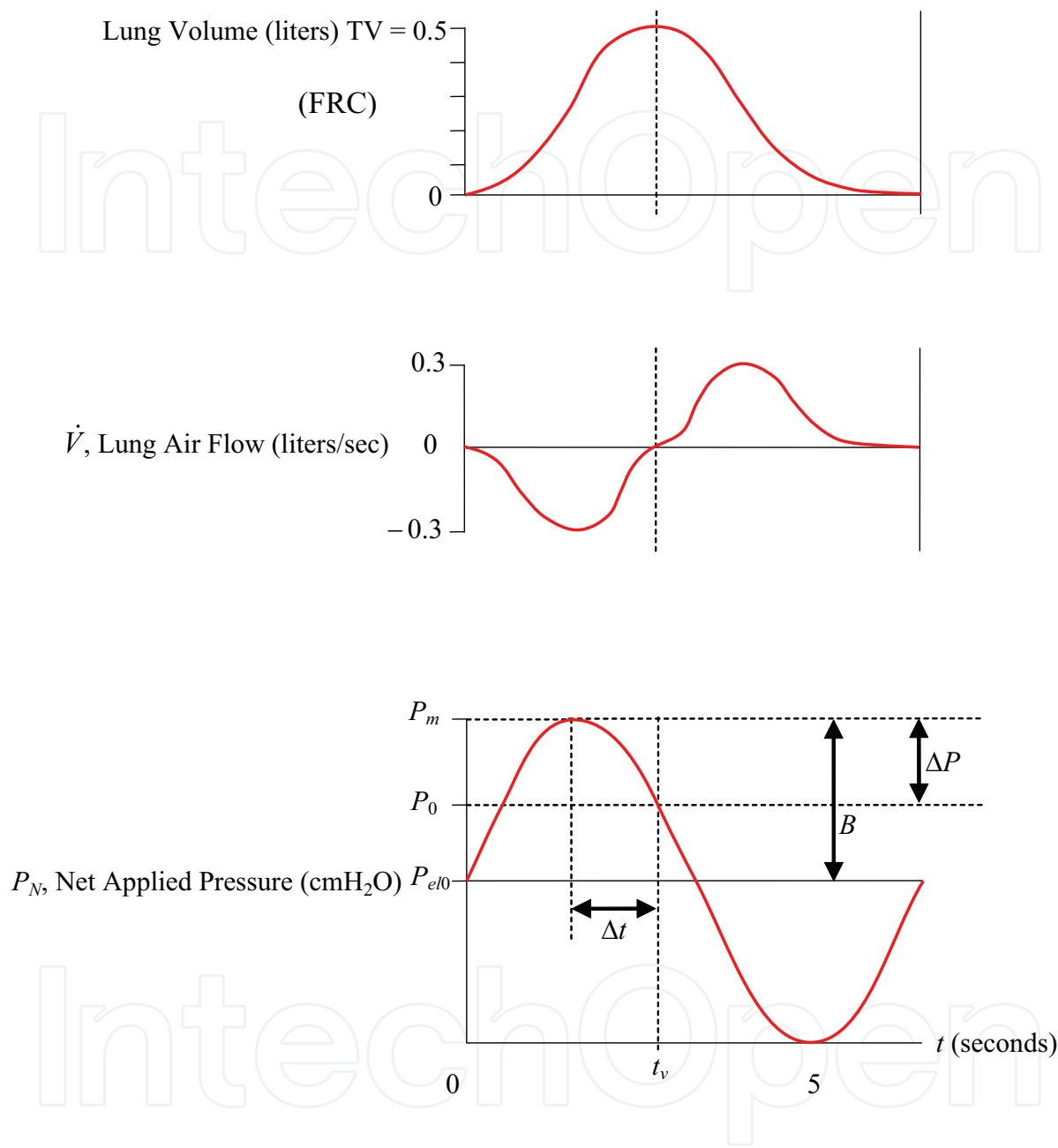


Fig. 4. Lung ventilatory model data shows air-flow ( $\dot{V}$ ) and volume ( $V$ ) and net pressure ( $P_N$ ). Pause pressure ( $P_0$ ) occurs at  $t_v$ , at which the volume is maximum (TV = tidal volume).  $\Delta t$  is the phase difference between the time of maximum volume and peak pressure ( $P_m$ ). It is also the time lag between the peak and pause pressures.  $B$  is the amplitude of the net pressure waveform  $P_N$  applied by the ventilator. This  $P_N$  oscillates about  $P_{el0}$  with amplitude of  $B$ . The difference between peak pressure  $P_m$  and pause pressure  $P_0$  is  $\Delta p$ . This figure is adopted from our work in Ref [3].

The volume response to  $P_N$  (the solution to Equation (32)) is given by:

$$V(t) = \frac{BC_a[\sin(\omega t) - \omega k_a \cos(\omega t)]}{1 + \omega^2 k_a^2} + H e^{\left(\frac{-t}{k_a}\right)} \quad (33)$$

wherein:

- i.  $k_a (= R_a C_a)$  is the averaged time constant,
- ii. the integration constant  $H$  is determined from the initial conditions,
- iii. the model parameters are  $C_a$  and  $k_a$  (i.e.,  $C_a$  and  $R_a$ ), and
- iv.  $\omega$  is the frequency of the oscillating pressure profile applied by the ventilator

An essential condition is that the flow rate is zero at the beginning of inspiration and end of expiration. Hence, the flow rate  $dV/dt = 0$  at  $t = 0$ . Applying this initial condition to our differential Equation (33), the constant  $H$  is obtained as:

$$H = \frac{BC_a \omega k_a}{1 + \omega^2 k_a^2} \quad (34)$$

Then, from Equations (33) and (34), we obtain:

$$V(t) = \frac{BC_a[\sin(\omega t) - \omega k_a \cos(\omega t)]}{1 + \omega^2 k_a^2} + \frac{BC_a \omega k_a}{1 + \omega^2 k_a^2} e^{\left(\frac{-t}{k_a}\right)} \quad (35)$$

For  $t = t_v$ ,  $V(t)$  is maximum and equal to the tidal volume (TV). Now in a normal person,  $k_a$  is of the order of 0.1 and 0.5 in ventilated patients with respiratory disorders, which is relevant to our study of COPD patients. At  $t = t_v$  at which the lung volume is maximum, we note from Figure 4 that  $t_v$  is of the order of 2 s. Hence  $t_v/k_a$  is of the order 20-4, so that  $e^{-t/k_a}$  is of the order of  $e^{-20}$  to  $e^{-4}$ , which is very small and hence negligible. Hence, in Equation (35), we can neglect the exponential term so that,

$$V(t) = \frac{BC_a[\sin(\omega t) - \omega k_a \cos(\omega t)]}{1 + \omega^2 k_a^2} \quad (36)$$

Figure 4 illustrates a typical data of  $V$ ,  $\dot{V}$  and  $P_N$ . For evaluating the parameter  $k_a$ , we will determine the time at which  $V(t)$  is maximum and equal to the tidal volume (TV), Hence, putting  $dV/dt = 0$  in Equation (36), we obtain:

$$\cos(\omega t) + \omega k_a \sin(\omega t) = e^{\left(\frac{-t}{k_a}\right)}, \text{ for } t = t_v \quad (37)$$

Hence from Equation (37), we obtain the following expression for  $k_a$ :

$$\tan(\omega t) = -1 / \omega k_a, \text{ for } t = t_v \quad (38-a)$$

or,

$$k_a = -(1/\omega)\tan(\omega t_v) \quad (38-b)$$

Since both  $\omega$  and  $t_v$  are known, we can evaluate  $k_a$  from Equation (38-b).  
Now from Equation (38-b), we can put down:

$$TV = \frac{BC_a[\sin(\omega t_v) - \omega k_a \cos(\omega t_v)]}{1 + \omega^2 k_a^2} \quad (39)$$

Since  $\omega$ ,  $t_v$  and  $k_a$  are known, we can now determine  $C_a$  in terms of TV and applied pressure amplitude  $B$ .  
Then knowing  $k_a$  and  $C_a$ , we can determine

$$R_a = k_a / C_a \quad (40)$$

For our COPD patients, the ranges of the computed values of these parameters are:

$$R_a = 9 - 43 (\text{cmH}_2\text{O})\text{sL}^{-1}; C_a = 0.020 - 0.080 \text{ L} (\text{cmH}_2\text{O})^{-1} \quad (41)$$

Now that we have determined the expressions for the parameters  $R_a$  and  $C_a$ , the next step is to develop an integrated index lung ventilatory incorporating these parameters.

#### 5.4 Formulating a Lung Ventilatory Index (LVI) incorporating $R_a$ and $C_a$

We believe that the correlations between average airflow-resistance ( $R_a$ ), average lung-compliance ( $C_a$ ), tidal volume (TV), respiratory rate (RF), and maximum inspiratory pressure or peak pressure ( $P_m$ ) can be used as a possible indicator for determining lung-status in a mechanically ventilated COPD patient with acute respiratory failure. We hence propose that a composite index (LVI), incorporating these isolated parameters, can have a higher predictive power for assessing lung status and determining when a patient on a mechanical ventilator.

For this purpose, we note that COPD patients have higher  $R_a$ , lower  $C_a$ , lower TV, higher  $P_m$  and higher respiratory rate (or breathing frequency) RF. If we want the non-dimensional lung-ventilatory index (LVI) to have a high value for a COPD patient, further increasing LVI for deteriorating lung-status and decreasing LVI for improving lung-status in a mechanically ventilated COPD patient in acute respiratory failure, then the non-dimensional lung-ventilatory index (LVI) can be expressed, as given by Equation (30):

$$LVI_2 = \left[ \frac{R_a(TV)^2(RF)}{C_a(P_m)^2} \right] \times (60)^2 \quad (42)$$

where RF is the respiratory-rate frequency.

Let us obtain the order-of-magnitude values of this  $LVI_2$  index for a mechanically ventilated COPD patient in acute respiratory failure (by using representative computed values of the parameters  $R_a$ ,  $C_a$ , RF, TV, and  $P_m$ ), in order to verify that the formula for  $LVI_2$  (given by Equation (42)) can enable distinct separation of COPD patients in acute respiratory failure from patients ready to be weaned off the respirator. For an intubated COPD patient, we have

$$LVI_2 \text{ (Intubated COPD)} = \frac{[15(\text{cmH}_2\text{O})\text{sL}^{-1}][0.5 \text{ L}]^2[0.33 \text{ s}^{-1}]}{[0.035 \text{ L}(\text{cmH}_2\text{O})^{-1}][20 \text{ cmH}_2\text{O}]^2} \times (60)^2 = 318 \quad (43)$$

wherein  $R_a = 15 (\text{cmH}_2\text{O})\text{sL}^{-1}$ ,  $C_a = 0.035 \text{ L}(\text{cmH}_2\text{O})^{-1}$ ,  $RF = 0.33 \text{ s}^{-1}$ ,  $TV = 0.5 \text{ L}$  and  $P_m = 20 \text{ cmH}_2\text{O}$ .

Now, let us obtain the order-of-magnitude of  $LVI$  (by using representative computed values of  $R_a$ ,  $C_a$ ,  $RF$ ,  $TV$ , and  $P_m$ ) for a COPD patient with improving lung-status just before successful discontinuation. For a successfully weaned COPD patient (examined in an outpatient clinic), we have

$$LVI_2 \text{ (Outpatient COPD)} = \frac{[5(\text{cmH}_2\text{O})\text{sL}^{-1}][0.35 \text{ L}]^2[0.33 \text{ s}^{-1}]}{[0.10 \text{ L}(\text{cmH}_2\text{O})^{-1}][12 \text{ cmH}_2\text{O}]^2} \times (60)^2 = 50.5 \quad (44)$$

wherein  $R_a = 5 (\text{cmH}_2\text{O})\text{sL}^{-1}$ ,  $C_a = 0.10 \text{ L}(\text{cmH}_2\text{O})^{-1}$ ,  $RF = 0.33 \text{ s}^{-1}$ ,  $TV = 0.35 \text{ L}$  and  $P_m = 12 \text{ cmH}_2\text{O}$ .

Hence for  $LVI_2$  to reflect lung status improvement in a mechanically ventilated COPD patient in acute respiratory failure, there should be a pronounced decrease in the value of  $LVI_2$ . This shows that the  $LVI$  given by Equation (42) can enable effective decision making to wean off a COPD patient from mechanical ventilator.

## Appendix:

**Solution procedure to obtain the best values of  $R$ ,  $C$ ,  $P_k$  and  $P_0$  provided in Equation (29).**

For the four unknowns  $R$ ,  $C$ ,  $P_k$  and  $P_0$ , where

$R$ : 2.1, 2.2, 2.3 ( $\text{cmH}_2\text{O})\text{sL}^{-1}$ ;

$C$ : 0.20, 0.21, 0.22  $\text{L}(\text{cmH}_2\text{O})^{-1}$ ;

$P_k$ : 0.4, 0.5, 0.6 ( $\text{cmH}_2\text{O}$ );

$P_0$ : 2.4, 2.5, 2.6 ( $\text{cmH}_2\text{O}$ );

we want to find the best values of  $R$ ,  $C$ ,  $P_k$  and  $P_0$  such that they satisfy the following equations:

$$R(0.48) + \frac{0.3}{C} = P_0 \quad (24)$$

$$\frac{0.48}{C} = 3.73 P_k \quad (25)$$

$$0.33 R + \frac{0.48}{C} = P_k + P_0 \quad (26)$$

$$-0.622 R + \frac{0.33}{C} = 0 \quad (27)$$

$$\frac{0.55}{C} = P_0 \quad (28)$$

**Solution:**

We can rewrite Equations (26) to (30) so that the terms are collected at the LHS, i.e.,

$$R(0.48) + \frac{0.3}{C} - P_0 = 0 \quad (\text{A-1})$$

$$\frac{0.48}{C} - 3.73P_k = 0 \quad (\text{A-2})$$

$$0.33R + \frac{0.48}{C} - P_k - P_0 = 0 \quad (\text{A-3})$$

$$-0.622R + \frac{0.33}{C} = 0 \quad (\text{A-4})$$

$$\frac{0.55}{C} - P_0 = 0 \quad (\text{A-5})$$

Since we are trying to find the best values of  $R$ ,  $C$ ,  $P_k$  and  $P_0$ , the RHS of Equations (A-1) to (A-5) can be replaced by an error term so that

$$R(0.48) + \frac{0.3}{C} - P_0 = e_1 \quad (\text{A-6})$$

$$\frac{0.48}{C} - 3.73P_k = e_2 \quad (\text{A-7})$$

$$0.33R + \frac{0.48}{C} - P_k - P_0 = e_3 \quad (\text{A-8})$$

$$-0.622R + \frac{0.33}{C} = e_4 \quad (\text{A-9})$$

$$\frac{0.55}{C} - P_0 = e_5 \quad (\text{A-10})$$

In general, we can represent the overall error incurred at any values of  $R$ ,  $C$ ,  $P_k$  and  $P_0$  by an objective function  $F$  so that

$$F(R, C, P_k, P_0) = \sum_{i=1}^5 \|e_i\| \quad (\text{A-11})$$

We can then find the best values of  $R$ ,  $C$ ,  $P_k$  and  $P_0$  but solving Equation (A-11) as an optimization problem with the aim to minimize  $F$ , subjected to the bounded constraints:

$$2.1 \leq R \leq 2.3$$

$$0.20 \leq C \leq 0.22$$

$$2.4 \leq P_0 \leq 2.6$$

$$0.4 \leq P_k \leq 0.6$$

The optimal solution is obtained at  $F = 0.239539$ , and the associated best values of  $R$ ,  $C$ ,  $P_k$  and  $P_0$  are

$$R = 2.29425 \text{ cmH}_2\text{O}s\text{L}^{-1}$$

$$C = 0.219758 \text{ L}(\text{cmH}_2\text{O})^{-1}$$

$$P_k = 0.57926 \text{ (cmH}_2\text{O)}$$

$$P_0 = 2.46702 \text{ (cmH}_2\text{O)} \quad (\text{A-12})$$

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This innovative book integrates the disciplines of biomedical science, biomedical engineering, biotechnology, physiological engineering, and hospital management technology. Herein, Biomedical science covers topics on disease pathways, models and treatment mechanisms, and the roles of red palm oil and phytochemical plants in reducing HIV and diabetes complications by enhancing antioxidant activity. Biomedical engineering covers topics of biomaterials (biodegradable polymers and magnetic nanomaterials), coronary stents, contact lenses, modelling of flows through tubes of varying cross-section, heart rate variability analysis of diabetic neuropathy, and EEG analysis in brain function assessment. Biotechnology covers the topics of hydrophobic interaction chromatography, protein scaffolds engineering, liposomes for construction of vaccines, induced pluripotent stem cells to fix genetic diseases by regenerative approaches, polymeric drug conjugates for improving the efficacy of anticancer drugs, and genetic modification of animals for agricultural use. Physiological engineering deals with mathematical modelling of physiological (cardiac, lung ventilation, glucose regulation) systems and formulation of indices for medical assessment (such as cardiac contractility, lung disease status, and diabetes risk). Finally, Hospital management science and technology involves the application of both biomedical engineering and industrial engineering for cost-effective operation of a hospital.

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