Reconstruction of respiratory physiology based on flow dynamics

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Abstract

Since gas exchange in the human lung is mass transports by fluids, respiratory physiology should be based on fluid dynamics. However, current theories of respiratory physiology have been established by regarding the respiratory system as an analogy of electric circuit where the airflow is assumed laminar, and led clinicians to wrong ways. In this paper, two representative cases are introduced. One is a popular pulmonary function test and the other is an artificial ventilation method for severe respiratory failure. Maximum forced expiration test is used for diagnosis of expiratory airflow limitation such as emphysema or chronic obstructive pulmonary disease (COPD). Although the cause of expiratory airflow limitation has been believed to be due to small airway obstruction, its true cause is the collapse of the intra-thoracic large airway. The mechanism of high-frequency ventilation (HFV), one of artificial ventilations with tiny tidal volume, has been believed that high frequency oscillation augments gas dispersion and improves gas exchange in spite of tiny tidal volume. However, recent clinical studies have revealed that HFV is useless for acute respiratory distress syndrome (ARDS) in adults. The true gas transport mechanism with tiny tidal volume is asymmetric airflow profile between inspiration and expiration due to the presence of bronchial bifurcations. In both cases, there are several papers published in famous journals more than 25 years ago, which stated the true mechanisms but currently have been seldom refereed. Reconstruction of respiratory physiology is an urgent task both for medical and engineering researchers.

Keywords : Pulmonary function test, Maximum forced expiration test, Pulmonary emphysema, Chronic obstructive pulmonary disease, Artificial ventilation, High-frequency ventilation, Acute respiratory distress syndrome

1. Introduction

Respiratory physiology is a discipline in medical science regarding respiratory function. The atmosphere is inspired by the action of respiratory muscles, and goes into the alveoli in the lung. The oxygen in the air is moved into the blood in the capillary network located in the alveolar wall. On the other hand, the carbon dioxide in the blood is moved into the air in the alveoli, and exhaled with the expiratory airflow. Since these phenomena are mass transports by fluids (air and blood), fluid dynamics is necessary for studying the respiratory physiology. However, the current respiratory physiology is based on not fluid dynamics but electric circuit analogy where the airflow is regarded laminar. Consequently, clinical diagnoses and treatments for respiratory diseases have been led into inadequate ways for these decades.

In 1960's, it was a consensus among bioengineering researchers majoring in the respiratory system that the origin of airflow resistance in the intra-thoracic airway was a turbulent flow generated in the large airway (Hyatt and Wilcox, 1963). Hence, small airways, defined less than 2 mm in diameter, were called "a silent zone" because its total cross section area was too huge to generate the airflow resistance. At the end of 1960's, a medical group in Canada stated that the small airway obstruction played an important role both in normal and diseased lungs (Holland et al, 1967) and that

high airway resistance in pulmonary emphysema was due to small airway obstruction (Hogg et al., 1968). Their statements were based on the interpretation of nitrogen washout curve in which nitrogen concentration in exhaled air increased suddenly near the end of expiration in normal subjects and the timing of the increase was earlier in smokers and emphysema patients than normal. They interpreted these facts that small airway closure occurred in normal subjects and the degree of closure was severer in emphysema (McCarthy et al., 1972). Since then, the respiratory system has been modeled by an electric circuit analogy in order to express a huge number of bronchi and bronchioles in the human airway tree under the assumption that the airflow through the airway was laminar (Mead, 1969). In the electric circuit analogy, the resistance through the airway tree is easily calculated if sizes of all segments are known, meanwhile application of computational fluid dynamics (CFD) to the airway tree was very difficult before 2000. As a result of the wrong assumption, clinical diagnoses and treatments for respiratory diseases have been led to inadequate ways for these decades. Reconstruction of respiratory physiology based on fluid dynamics is an urgent task for both medical and bioengineering researchers (Kitaoka, 2015).

In this paper, I first explain the lung structure and its modeling for CFD. Then, I introduce two representative cases where the current respiratory physiology has led clinicians to wrong ways. One is a popular clinical respiratory function test, and the other is an artificial ventilation method for severe respiratory failure.

2. The lung structure and its modeling for CFD

The lung consists of the airway tree and the parenchymal tissue in which a huge number of alveoli are included. The trachea is divided into right and left main bronchi, and divided more than ten times like tree branches. The number of terminal branches of the airway tree, the terminal bronchioles, is about 30,000 in the adult human lungs and the diameter is about 0.5 mm. Figure 1 shows an example of the human airway tree model generated by Kitaoka's algorithm (1999).

Fig. 1. An example of the human airway model. There are about 30,000 terminal branches corresponding to the terminal bronchioles. Colors indicate anatomical lung segments.

A popular modeling method for the intra-pulmonary airflow simulation is to extract the airway region from 3D-CT image data. In such a model, the airflow is assigned to go out at the end of terminal branches. However, in reality, there are no outlets in the airway tree. The end of a terminal branch is connected to a kind of air bag which consists of a numerous number of alveoli and changes its volume according to respiratory motion. The air through the airway tree goes into airbags and goes back to the airway tree. The sum of respective air bags is the whole lung, and the incompressible airflow through the airway tree is generated by the volume changes of respective air bags. Therefore, not only the airway tree, but also air space regions should be modelled in order to perform airflow simulation during respiration. It is almost impossible to recognize the relationship between a branch and its air-supplying parenchymal region from real CT images. On the other hand, since Kitaoka's algorithm (1999) assigns positions of a branch and its

air-supplying region simultaneously, the generated airway model is suitable to the airflow simulation. Figure 2 shows an example of the lung model where only one air pathway from the trachea to alveoli is completely modeled and the whole lung parenchyma is expressed as a set of air-supplying regions of respective branches included in the air pathway. Each air space region is approximated by a set of cubes whose side length is equal to its air-supplied branch (Kitaoka 2011). The model consists of a set of tetras so as to perform airflow simulation by the use of finite element method (FEM). Inspiratory airflow simulation from the trachea to alveoli can be performed by this model (Kitaoka, 2014). In order to perform expiratory airflow simulation after inspiration, it is necessary to make a model in which geometric properties of terminal branches are all the same. It requires a vast computing resource to make a 4D lung model with 30,000 terminal branches as shown in Fig.1 and to compute the airflow in it. It is necessary to use a model suitable to the purpose of simulation and available computer resource.

Fig.2. An example of one-pathway model of the human lung. Only one air pathway from the trachea to alveoli is completely modeled with a set of tetras. The whole lung is a set of air space regions which are supplied by respective other-hand branches.

3. Pulmonary function test: maximum forced expiration test

Maximum forced expiration test is the most popular in clinical pulmonary function tests. A subject inspires air as much as possible and then expires as fast as possible. The forced expiratory volume during first one second is called FEV1, and the ratio of FEV1 to the total volume of expired air is called FEV1%. When the FEV1% is below 70 %, the subject is diagnosed as obstructive ventilation disorder. Chronic obstructive pulmonary diseases (COPD) is a disease group whose FEV1% are always below 70 %. Flow-volume curve is obtained from the maximum forced expiration test, where the vertical axis is for airflow rate and the horizontal is for expired air volume (Fig.3). The flow-volume curve in COPD indicates not a simple decrease of the peak flow rate (blue line in Fig.3), but a sudden decrease of flowrate after the peak (red line in Fig.3).

Fig.3. Flow volume curve of maximum forced expiration. In normal subjects (black line), the descending limb is always linear. In COPD (red line), it is not linear but a sudden decrease after the peak.

It has been believed for these three decades that the main cause of low FEV1% in COPD is the small airway obstruction. However, there have been no direct evidences due to lack of live imaging techniques of small airways during forced expiration. We took 4DCT (= dynamic 3D-CT) during maximum forced expiration for COPD patients and found that the trachea and main bronchi in the thoracic space were collapsed just after the beginning of expiration (Fig.4) (Hirata et al, 2014). The collapsed part is the posterior wall of the airway where cartilages are originally absent (called “the membranous part”). This phenomenon was not observed in normal subjects and the degree of collapse had strong correlation to the value of FEV1 (Hirata et al, 2014).

Fig.4 4D-CT images during maximum forced expiration of a COPD patient. Horizontal section images are indicated in the upper row. The trachea at the center of the frame is severely deformed like crescent just after the beginning of expiration. Sagittal section images are indicated in the lower row. The tracheal deformation occurs everywhere in the thorax.

This phenomenon is due to high-speed airflow through the trachea, and never observed by static usual CT images taken under breath hold. Although we found it by 4D-CT images, it was already published in 1963 by the use of cine-bronchography (Rainer et al, 1963). The bronchography is an invasive test and has disappeared after the spread of CT scanners in 1980s. In normal subjects, the high-speed airflow generates negative pressure, too. The difference between normal and COPD is that the tracheal wall can keep its shape against the transmural pressure difference in normal condition but that over-inflated lungs in COPD compress the tracheal wall from outside. If clinicians had recognized this fact a hemi-century ago, the treatment of COPD would have progressed much more than present.

4. Artificial ventilation: High Frequency Ventilation (HFV)

There is a concept in the respiratory physiology called “alveolar ventilation” or “alveolar ventilated volume” which means the effective volume for gas exchange in the tidal volume (= ventilated air volume per one respiratory cycle). In the textbook, the following equation is written;

$$V_T = V_D + V_A$$

, where V_T is tidal volume, V_D is the volume of dead space, and V_A is the alveolar ventilated volume. The dead space means a conductive airway space from the mouth to bronchioles where gas exchange between the air and blood is not performed. For healthy adults, V_T is about 600ml and V_D is about 120 ml. According to the above equation, effective ventilation does not occur when $V_T < V_D$. It is believed that high frequency ventilation ($> 5\text{Hz}$) can realize effective ventilation in spite of low V_T by the mechanism of augmented dispersion (Slutsky et al, 1980) and is useful for acute respiratory distress syndrome (ARDS). However, recent several clinical trials have revealed that HFV has no significant effect except newborn babies (Ferguson et al, 2013).

In terms of mathematics, the above equation has no sense, because V_D is a static volume and is different from two other quantities which indicate changed volumes per one respiratory cycle. In order to validate this equation, V_D should be the changed volume of dead space. In reality, the volume change of dead space during respiratory cycle is negligible and V_A , air volume which goes into the alveolar space, should be nearly equal to V_T . Not only the

mathematical point of view, the statement that effective ventilation does not occur when $VT < VD$ is not correct in terms of clinical experiences. A man close to the end of life after the long struggle with disease breaths with very small tidal volume but the condition is never the same as respiratory arrest.

The above equation is based on a naive idea that the air is not fluid but solid like jelly. The reason why HFV is not effective for adults may be due to the wrong theory. In order to investigate mechanism of HFV, I performed the gas transport simulation by the use of a 4D lung model and CFD (Kitaoka, 2017).

A finite element model for CFD was constructed by adding a tracheal tube to Kitaoka's 4D lung model where the lung parenchyma was divided into 34 regions (corresponding to the lung sub-segments in terms of anatomical nomenclature). The number of tetras is about 2.2 millions. All nodes in the model are displaced according to an assigned oscillatory cycle so as to generate an assigned tidal volume with sine function (time step = 0.001 sec).

Fig.5. Four-dimensional finite element model for the simulation of high-frequency ventilation.

The airflow was computed by solving incompressible Navier-Stokes equation and continuity equation under moving boundary condition (AcuSolve, Altair Engineering, US). Gas partial pressures at the alveolar wall were assumed as the same as those in the capillary blood in the alveolar wall under normal condition. The values for oxygen and carbon dioxide are 100 Torr (equivalent to 13.3 kPa) and 40 Torr, respectively. Those at the inlet were assigned as the same as in the room air (150 Torr for oxygen and 0 Torr for carbon dioxide). The gas distributions in the airway were computed by combining the diffusion equations and Navier-Stokes equation. Transported gas volume was calculated from fluxes at terminal branches.

Figure 6 indicates the temporal change of intra-airway oxygen partial pressure for simulating HFV with tidal volume of 18 ml and frequency of 10 Hz. This ventilation mode is often used for adult ARDS patients. In the first several cycles, the oxygen partial pressure at inlets of air-space regions did not change, but then, increased gradually. When the frequency was assigned at 0.25 Hz (equal to that of normal breath), values of oxygen pressure was almost the same as those for 10 Hz. Furthermore, when the oxygen effusion coefficient is assigned at zero, similar values of oxygen partial pressure were obtained.

I made another lung model which contained 171 terminal branches and obtained similar simulation results to the 34-terminal lung model, although the oxygen partial pressures at terminals were slightly lower. Therefore, if the same simulation were performed by the use of a 30000-terminal lung model, the results would be consistent with those indicated in the present paper.

at the inspiratory end of the 15th terminal branches

Fig. 6. Temporal change of oxygen partial pressure. Green line indicates the mean value for the whole airway and red line indicates that at the end of terminal branches. Right figure shows oxygen distribution in the airway tree at the end of 15th ventilation cycle.

Figure 7 indicates oxygen distribution and velocity distribution in the airway at the first cycle with frequency of 10 Hz and oxygen coefficient of zero. The left half is at early inspiratory phase (0.012 sec) and the right is at late expiratory phase (0.088 sec) with the same flow rate. The velocity profile in the inspiratory phase is almost uniform, meanwhile that in the expiratory phase is irregularly nonuniform due to flow confluences at bifurcations. According to the velocity profiles, oxygen distribution in the airway is translational in the inspiratory phase but nonuniform and more accumulated in the expiratory phase. The accumulated oxygen at the end of ventilation cycle is transported into the lung at the next ventilation cycle, and finally reaches to air space regions and after several cycles. This process is independent of frequency number and even gas diffusion coefficient. It means that gas transport within the airway is purely advective process, which has been already stated by Haselton and Scherer (1980) as "irreversible convection due to bifurcation", four month before the paper regarding augmented dispersion (1980) was on *Science*.

Fig.7. Computed oxygen and velocity distributions in the first ventilation cycle. The left half is in the inspiratory phase and the right half is in the expiratory phase. From left to right, images for oxygen in inspiratory phase, velocity in inspiratory phase, oxygen in expiratory phase, and velocity in expiratory phase.

Transported gas volume was increased proportionally to the frequency, but at the same time, the airway pressure amplitude increases proportionally to the square of frequency (Fig. 8). The high airway pressure amplitude is thought to be the reason why HFV is ineffective for adults. This can never be explained by electric circuit analogy.

Fig.8 Relationship between frequency and intra-airway pressure amplitude.

5. Concluding Remarks

Criticisms against conventional knowledge are essential for the academic advancement. Unfortunately, the academic community of respiratory physiology has excluded researchers against its dogma established a hemi-century ago. Cooperative studies between clinicians and researchers of fluid dynamics are necessary for the reconstruction of respiratory physiology.

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