M. R. Pinsky · L. Brochard · J. Mancebo

Applied Physiology in Intensive Care Medicine

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With 116 Figures and 21 Tables

Springer

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The articles in this book appeared in the journal „Intensive Care Medicine“ between 2002 and 2006.

ISBN-10 3-540-37361-6 Springer-Verlag Berlin Heidelberg NewYork
ISBN-13 978-3-540-37361-2 Springer-Verlag Berlin Heidelberg NewYork

Library of Congress Control Number: 2006930741

Springer is a part of Springer Science+Business Media
springer.com

Editor: Dr. Ute Heilmann
Desk Editor: Meike Stoeck
Production: LE-TeX Jelonek, Schmidt & Vöckler GbR, Leipzig
Cover Design: Frido Steinen-Broo, eStudio Calamar, Spain

Printed on acid-free paper 21/3100/YL 5 4 3 2 1 0

Introduction

The practice of intensive care medicine is at the very forefront of titration of treatment and monitoring response. The substrate of this care is the critically ill patient who, by definition, is at the limits of his or her physiologic reserve. Such patients need immediate, aggressive but balanced life-altering interventions to minimize the detrimental aspects of acute illness and hasten recovery. Treatment decisions and response to therapy are usually assessed by measures of physiologic function, such as assessed by cardio-respiratory monitoring. However, how one uses such information is often unclear and rarely supported by prospective clinical trials. In reality, the bedside clinician is forced to rely primarily on physiologic principles in determining the best treatments and response to therapy. However, the physiologic foundation present in practicing physicians is uneven and occasionally supported more by habit or prior training than science.

A series of short papers published in Intensive Care Medicine since 2002 under the heading Physiologic Notes attempts to capture the essence of the physiologic perspectives that underpin both our understanding of disease and response to therapy. This present volume combines the complete list of these Physiologic Notes up until July 2006 with the associated review articles over the same interval that also addressed these central issues. This volume was created to address this fundamental unevenness in our understanding of applied physiology and underscore what is known and how measures and monitoring interact with organ system function and response to therapy. This collection of physiologic perspectives and reviews, written by some of the most respected experts in the field, represent an up-to-date and invaluable compendium of practical bedside knowledge essential to the effective delivery of acute care medicine. Although this text can be read from cover to cover, the reader is encouraged to use this text as a reference source reading individual Physiologic Notes and Review articles as they pertain to specific clinical issues. In that way the relevant information will have immediate practical meaning and hopefully become incorporated into routine practice.

We hope that the reader finds these papers and reviews useful in their practice and enjoy reading them as much as we enjoyed editing the original articles that it comprises.

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Physiological Notes 1

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Laurent Brochard

Intrinsic (or auto-) PEEP during controlled mechanical ventilation

Introduction

Extrinsic positive end-expiratory pressure (PEEP) applied to the patient at the airway opening is used artificially to increase end-expiratory lung volume. Extrinsic PEEP is increased or decreased in small increments in ventilator-dependent patients because of its marked effects on cardiorespiratory status. Unintentional or unmeasured end-expiratory hyperinflation, called intrinsic or auto-PEEP, can also occur and have similarly marked profound cardiorespiratory effects in ventilator-dependent patients during controlled mechanical ventilation. Ventilatory settings can interact with the passive process of expiration and generate intrinsic or auto-PEEP [1, 2].

What is intrinsic (or auto-) PEEP?

During passive expiration of the lungs the elastic forces of the respiratory system are the driving forces and can be described by the relationship between lung volume and the elastic recoil pressure of the respiratory system. The lower the elastic forces, or the higher the resistive forces, the longer will be the time needed to fully expire the inspired tidal volume. In a single-compartment model of the lung in which the lung behaves as if it has a single resistance and compliance, the volume at any given time during expiration (V) is described by the monoexponential equation, $V=V_o-Ve^{-kt}$, where k is the time constant of the equation and is the product of resistance times compliance (the reverse of elastance), and V_o is the end-inspiratory volume. In practical terms a time constant is the time required for the lungs to expire 63% of their initial volume. Thus the time needed passively to expire the inspired tidal volume is determined by the two main characteristics of the respiratory system: elastance and resistance. If expiration is interrupted before its natural end, i.e., by occurrence of the next inspiration, end-expiratory lung volume is higher than the so-called relaxation volume of the respiratory system, usually referred to as functional residual capacity. As a result the alveolar pressure at the end of expiration is higher than zero (zero being the atmospheric pressure), as predicted by the relationship between lung volume and the elastic recoil pressure of the respiratory system. This process is called dynamic hyperinflation, and the positive end-expiratory alveolar pressure associated with a higher than resting lung volume, is called intrinsic or auto-PEEP. Importantly for the clinician, this pressure is not directly measured at the airway opening and is thus not shown on the pressure dial of the ventilator. What the ventilator measures is the pressure in the ventilator circuit. Because the direction of the flow is still expiratory, the pressure measured by the ventilator at the end of expiration reflects only the relationship between flow and the resistance of the expiratory line, above the set PEEP. It does not give the clinician any information about the real alveolar pressure.

How one can suspect the presence of intrinsic (or auto-) PEEP

The presence of a positive alveolar pressure higher than the atmospheric pressure or higher than the external PEEP set on the ventilator (which is a new "reference pressure" for the lungs) can be identified by inspection of the expiratory flow-time curve. When the expiratory time is sufficient for lung emptying, expiratory flow de-

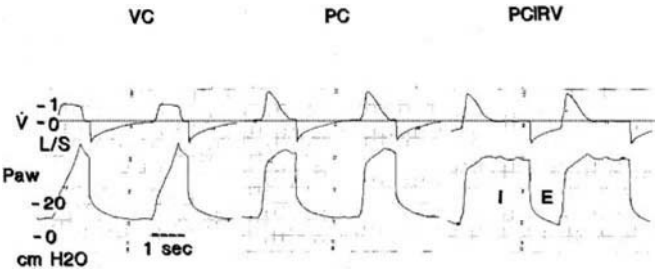

Fig. 1 Tracings of flow ($\dot{V}$) and airway pressure (*Paw*) at the airway opening during volume controlled (*VC*), pressure-controlled (*PC*), and pressure-controlled inverse ratio ventilation (*PCIRV*). In the first two situations the expiratory flow declines gradually to zero; in the third case inspiration is lengthened by the inverse ratio setting and expiration shortened; the expiratory flow is abruptly interrupted, indicating the presence of dynamic hyperinflation and intrinsic or auto-PEEP. (From Lessard et al. [3])

clines from a maximum to zero or to the set PEEP. An interruption in this process results in an abrupt change in the slope of this curve, immediately continued by the next inspiratory flow. In other words, the next "inspiration" starts during "expiration." Since the ventilator, which cannot generate flow into the patient's lungs until the pressure at the airway opening exceeds the end-expiratory alveolar pressure, one way in which to measure intrinsic or auto-PEEP is to determine the airway pressure at the exact time of inspiratory flow. One can measure the intrinsic PEEP level by simultaneously recording airway pressure and flow data using a high-speed tracing. Figure 1 illustrates how shortening the expiratory phase generates such dynamic hyperinflation [3].

Is the level of intrinsic (or auto-) PEEP predictable?

If one assumes the respiratory system to be homogeneous and behave as a single compartment, a monoexponential equation can be used. By simple mathematics it takes three time constants (one being the product of resistance and compliance) to expire 96% of the inspired tidal volume. Therefore any longer expiratory time minimizes or fully avoids incomplete emptying. For instance, a resistance of 10 $cmH_2O.l^{-1}.s^{-1}$ and a compliance of 100 $ml.cmH_2O^{-1}$ (0.1 $l.cm\ H_2O^{-1}$) results in a time constant of 1 s. Thus 3 s represents the minimal expiratory time needed to avoid intrinsic or auto-PEEP. Unfortunately, the diseased lungs are not only frequently inhomogeneous, making this calculation overly simplistic, but the presence of small airway collapse during expiration, also referred to as expiratory flow limitation, makes this even more complicated. Because of an abnormal structure of the small airways, when the pressure surrounding these conducts becomes higher than the pressure inside the airway, these small conducts collapse. The relationship between the "driving pressure" (pressure in the alveoli minus pressure at the airway opening) on which is based the equation, disappears. In the setting of expiratory flow-limitation, the expiratory time required to minimize intrinsic PEEP is much longer than predicted by the time constant alone. By minimizing inspired minute ventilation the clinician can minimize intrinsic (auto-) PEEP.

Can intrinsic (or auto-) PEEP be reliably measured?

Since the reason for the presence of intrinsic PEEP is flow-dependent pressure gradients from the alveolus to the airway opening, occluding of the expiratory port of the ventilator at the exact end of expiration causes airway pressure to equilibrate rapidly with alveolar pressure and reliably measure the end-expiratory alveolar pressure. This occlusion takes place at the exact time where the next inspiration should start and is now available on most modern ventilators ("expiratory hold or pause"). If the patient is fully relaxed, this pressure measurement reflects the mean alveolar pressure at the end of expiration. Most of the time a plateau is reached after less than 1 s, but in the case of inhomogeneous lungs this pressure may require a few seconds to also reflect some very slow compartments. This airway occlusion pressure may not be homogeneously present in the whole lung but represents an average pressure of all regional levels of end-expiration alveolar pressure. Usually the difference between the expiratory pause airway pressure and the set external PEEP is called intrinsic or auto-PEEP, while the measured pressure is referred to as total PEEP.

Can the set external PEEP influence the total PEEP in the case of dynamic hyperinflation?

A frequent confusion is the belief that external PEEP could be useful in reducing the level of dynamic hyperinflation because it helps to reduce the value of auto- or intrinsic PEEP. Obviously this is not the case. The effect of external PEEP is to minimize the difference between the alveolar and the ventilator proximal airway pressure. This difference being called intrinsic or auto-PEEP, external PEEP application results in a decreased intrinsic or auto-PEEP. The level of dynamic hyperinflation, however, depends on the level of total PEEP and is either not influenced by external PEEP when external PEEP is less than intrinsic PEEP or is even worsened if external PEEP is set higher than the minimal level of regional intrinsic PEEP.

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Intrinsic (or auto-) positive end-expiratory pressure during spontaneous or assisted ventilation

Introduction

The mechanisms generating intrinsic or auto-positive end-expiratory pressure (PEEP) during controlled mechanical ventilation in a relaxed patient also occur during spontaneous breathing or when the patient triggers the ventilator during an assisted mode [1, 2]. These include an increased time constant for passive exhalation of the respiratory system, a short expiratory time resulting from a relatively high respiratory rate and/or the presence of expiratory flow limitation. Whereas dynamic hyperinflation and intrinsic or auto-PEEP may have haemodynamic consequences, this is not frequently a major concern in spontaneously breathing patients or during assisted ventilation because the spontaneous inspiratory efforts result in a less positive or more negative mean intrathoracic pressure than during controlled mechanical ventilation. The main consequence of dynamic hyperinflation during spontaneous and assisted ventilation is the patient's increased effort to breathe and work of breathing [1, 2].

To what extent does intrinsic (or auto-) positive end-expiratory pressure influence work of breathing?

For air to enter the lungs, the pressure inside the chest has to be lower than the pressure at the mouth (spontaneous breathing) or at the airway opening (assisted ventilation). In the case of intrinsic (or auto-) PEEP, by definition, the end-expiratory alveolar pressure is higher than the pressure at the airway opening. When the patient initiates the breath, there is an inevitable need to reduce airway pressure to zero (spontaneous breathing) or to the value of end-expiratory pressure set on the ventilator (assisted ventilation) before any gas can flow into the lungs. For this reason, intrinsic or (auto-) PEEP has been described as an inspiratory threshold load. In patients with chronic obstructive pulmonary disease (COPD) this load has sometimes been measured to be the major cause of increased work of breathing [3].

During assisted ventilation, is the trigger sensitivity important to reduce intrinsic (or auto-) positive end-expiratory pressure?

Because the problem of intrinsic or (auto-) PEEP has to do with the onset of inspiration, one may reason that increasing the inspiratory trigger sensitivity to initiate a breath with a lower pressure or flow deflection should reduce the work of breathing induced by hyperinflation. These systems are based on the detection of a small pressure drop relative to baseline (pressure-triggering system) or on the presence of a small inspiratory flow (flow-triggering systems). Unfortunately, increasing the trigger sensitivity induces only a small reduction in the total work of breathing. The reason for this lack of effect relates to the need for the inspiratory trigger to sense changes in airway pressure or in inspiratory flow. Thus, intrinsic PEEP needs to be counterbalanced first by the

effort of the inspiratory muscles, in order for this effort to generate a small pressure drop (in the presence of a closed circuit) or to initiate the inspiratory flow (in an open circuit) [4]. The consequence of intrinsic or (auto-) PEEP is that the inspiratory effort starts during expiration. This is easily identified by inspection of the expiratory flow-time curve [1]. As a consequence, it cannot be detected by any of the commercially available trigger systems.

Can the set external positive end-expiratory pressure reduce dynamic hyperinflation and work of breathing?

Responses to these two questions are the same as during controlled mechanical ventilation in a relaxed patient [1]. Their consequences are, however, very different. External PEEP reduces the difference between the alveolar and the ventilator proximal airway pressure, i.e., intrinsic (or auto-) PEEP. The inspiratory threshold load resulting from intrinsic (or auto-) PEEP is thus reduced by addition of external PEEP. Thus, the total work of breathing is reduced, especially in patients with high levels of intrinsic (or auto-) PEEP, such as those subjects with COPD [5, 6].

Although external PEEP reduces work of breathing, it does not minimise hyperinflation. The level of dynamic hyperinflation is not modified by external PEEP, unless this PEEP is set higher than the minimal level of regional intrinsic PEEP, and then hyperinflation increases. Increasing hyperinflation can aggravate the working conditions of the respiratory muscles by placing them at a mechanical disadvantage and can result in significant haemodynamic compromise by decreasing venous return and increasing right ventricular outflow resistance. Hyperinflation in excess of intrinsic (or auto-) PEEP occurs usually when the set PEEP is positioned at values above 80% of the mean "static" intrinsic PEEP [7]. For this reason, titration of external PEEP based on measuring intrinsic (or auto-) PEEP would be desirable. Unfortunately, a reliable measurement of intrinsic (or auto-) PEEP in the spontaneously breathing subject is much more difficult to obtain than in passive positive-pressure ventilation conditions.

Can standard ventilatory settings influence intrinsic (or auto-) positive end-expiratory pressure?

During assisted ventilation, the patient is supposed to determine the respiratory rate freely, and one may suppose that he/she will govern his/her respiratory rate to control expiratory time and minimise hyperinflation. Unfortunately, most patients will not be able to counteract fully the effects of a ventilator inspiratory time longer than their own inspiratory time [8]. Although some compensatory mechanism may exist, it will frequently be insufficient. Every setting influencing the ventilator inspiratory time may thus influence the level of dynamic hyperinflation.

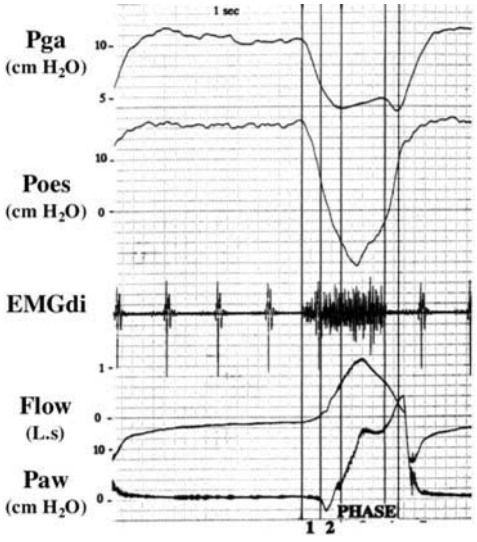

Fig. 1 Tracings of gastric (*Pga*), oesophageal (*Poes*) and airway (*Paw*) pressures, flow and diaphragmatic electromyographic activity (*EMGdi*) during an assisted breath (pressure-support ventilation). The *vertical lines* help to delineate the different phases of the inspiratory effort. During phase 1, the flow is still expiratory: the start of EMGdi and the abrupt decrease in both Pes and Pga all indicate that the patient performs an active inspiratory effort against intrinsic positive end-expiratory pressure (PEEP) at the same time that his/her expiratory muscles relax. Phase 2 is the triggering of the ventilator and occurs once intrinsic (or auto-) PEEP has been counterbalanced

Is intrinsic (or auto-) positive end-expiratory pressure always synonymous with dynamic hyperinflation?

In patients with spontaneous respiratory activity, recruitment of the expiratory muscles frequently participates in generating intrinsic (or auto-) PEEP independently of dynamic hyperinflation. In the case of airflow obstruction, the main consequence of an activation of the expiratory muscles is to augment intrathoracic pressure, whereas their effects on expiratory flow may be very modest, especially in the case of airflow limitation, thus promoting small airways to collapse. The activation of the expiratory muscles results from an increase in respiratory drive. Many patients with COPD already have a recruitment of their expiratory muscles at rest. This expiratory muscle recruitment results in a measurable increase in alveolar pressure. However, such expiratory muscle recruitment, although creating an intrinsic (or au-

to-) PEEP, does not contribute to the inspiratory threshold load and the increased work of breathing. Indeed, at the same time that the inspiratory muscles start to decrease intrathoracic pressure, the expiratory muscles relax and their release almost immediately abolishes this part of intrinsic (or auto-) PEEP due to the expiratory muscles [9]. This is illustrated in Fig. 1.

Can intrinsic (or auto-) positive end-expiratory pressure be reliably measured?

The commonly applied end-expiratory airway occlusion method that measures intrinsic (or auto-) PEEP in patients on controlled ventilation cannot be readily applied to the patient making spontaneous inspiratory efforts. For example, it is not possible to determine which amount of measured positive airway occlusion pressure, if not all, is due to expiratory muscle activity [9]. Setting the external PEEP based on this measurement could induce considerable mistakes by overestimating intrinsic (or auto-) PEEP. The only readily available and reliable method of measuring intrinsic (or auto-) PEEP in the spontaneously breathing subject is to measure the drop in oesophageal pressure occurring before flow becomes inspiratory, and subsequently subtract the part due to expiratory muscle activity determined from an abdominal pressure signal [9]. The reasoning is as follows: any rise in abdominal pressure occurring during expiration is transmitted to the intrathoracic space and increases alveolar pressure.

Intrinsic PEEP is measured from the abrupt drop observed on the oesophageal pressure signal until flow becomes inspiratory (phase 1 on Fig. 1). Part of this drop in oesophageal pressure is caused by the relaxation of the expiratory muscles. This part needs to be subtracted from the oesophageal pressure drop, in order to evaluate a "corrected" intrinsic PEEP due to hyperinflation. Two main possibilities exist: to subtract the rise in gastric pressure that occurred during the preceding expiration [9] or to subtract the concomitant decrease in gastric pressure at the onset of the effort [10]. Because the correction of intrinsic (or auto-) PEEP for expiratory muscle activity has not been used in early studies, one can hypothesise that the magnitude of intrinsic (or auto-) PEEP has often been overestimated. This combined oesophageal and gastric pressure measuring technique requires the insertion of a nasogastric tube equipped with both oesophageal and gastric balloon catheters. This technique is often used for research purposes but cannot be easily used at the bedside for routine clinical monitoring.

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Work of breathing

Introduction

The main goal of mechanical ventilation is to help restore gas exchange and reduce the work of breathing (WOB) by assisting respiratory muscle activity. Knowing the determinants of WOB is essential for the effective use of mechanical ventilation and also to assess patient readiness for weaning. The active contraction of the respiratory muscles causes the thoracic compartment to expand, inducing pleural pressure to decrease. This negative pressure generated by the respiratory pump normally produces lung expansion and a decrease in alveolar pressure, causing air to flow into the lung. This driving pressure can be generated in three ways: entirely by the ventilator, as positive airway pressure during passive inflation and controlled mechanical ventilation; entirely by the patient's respiratory muscles during spontaneous unassisted breathing; or as a combination of the two, as in assisted mechanical ventilation. For positive-pressure ventilation to reduce WOB, there needs to be synchronous and smooth interaction between the ventilator and the respiratory muscles [1, 2, 3]. This note will concentrate on how to calculate the part of WOB generated by the patient's respiratory muscles, especially during assisted ventilation.

Esophageal pressure and the Campbell diagram

Measuring WOB is a useful approach to calculate the total expenditure of energy developed by the respiratory muscles [4]. In general, the work performed during each respiratory cycle is mathematically expressed as WOB = $\int$ Pressure $\times$ Volume, i.e. the area on a pressure–volume diagram. Esophageal pressure, which is easily measured, is usually taken as a surrogate for intrathoracic (pleural) pressure. The dynamic relation between pleural pressure and lung volume during breathing is referred to as the Campbell diagram [5] (Fig. 1). Esophageal pressure swings during inspiration are needed to overcome two forces: the elastic forces of the lung parenchyma and chest wall, and the resistive forces generated by the movement of gas through the airways. One can calculate these two components (elastic and resistive) by comparing the difference between esophageal pressure during the patient's effort during the breath and the pressure value in passive conditions, represented by the static volume–pressure curve of the relaxed chest wall. This passive volume–pressure curve is a crucial component of the Campbell diagram. It is calculated from the values of esophageal pressure obtained over lung volume when the airways are closed and the muscles are completely relaxed. Unfortunately, as this is difficult to do (because it requires passive inflation and often muscle paralysis), a theoretical value for the slope of this curve is frequently used. However, if a patient is passively ventilated and an esophageal balloon is placed, a true value for the volume–pressure relationship of the chest wall during passive tidal breathing can be obtained [6]. This passive pressure–volume relationship can be used as a reference value for subsequent calculations when the patient develops spontaneous inspiratory efforts.

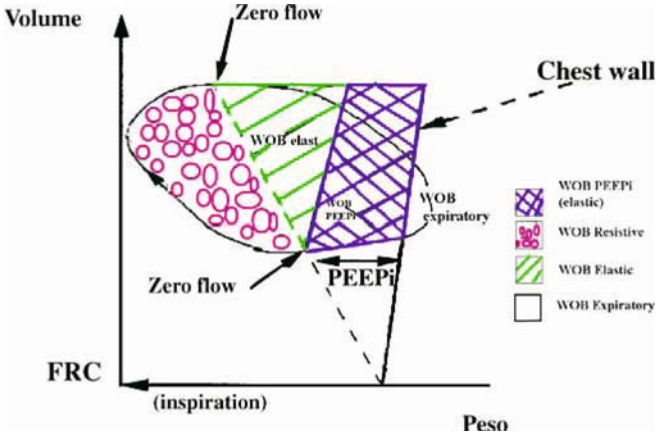

Fig. 1 Campbell's diagram. Work of breathing measured by the esophageal pressure: resistive WOB (W_{resist}), elastic WOB (W_{elast}), WOB related to active expiration (*WOB expiratory*) and WOB related to intrinsic PEEP (W_{PEEPi}). *Chest wall*: this *thick line* (the chest wall compliance) represents the pleural (esophageal) pressure obtained when muscles are totally relaxed and lung volume increases above functional residual capacity, measured in static conditions

The WOB is normally expressed in joules. One joule is the energy needed to move 1 l of gas through a 10-cmH_2O pressure gradient. The work per liter of ventilation (J/l) is the work per cycle divided by the tidal volume (expressed in liters). In a healthy subject the normal value is around 0.35 J/l [7]. Lastly, WOB can be expressed in work per unit of time, multiplying joules per cycle by the respiratory rate (expressed in breaths per minute) to obtain the power of breathing (joules/minute). In a healthy subject the normal value is around 2.4 J/min [7]. As illustrated by the Campbell diagram, two other phenomena affect the WOB: intrinsic PEEP (positive end-expiratory pressure, or PEEPi) and active expiration.

PEEPi and active expiration

The distending pressure of the lungs is called the transpulmonary pressure and it can be estimated as the difference between airway and esophageal (pleural) pressure. At the end of a normal expiration, alveolar and airway pressures are zero relative to atmosphere, and esophageal pressure is negative, reflecting the resting transpulmonary pressure (around 5 cmH_2O in normal conditions). However, in the presence of PEEPi, the alveolar pressure remains positive throughout expiration, because of either dynamic airway collapse or inadequate time to exhale [8]. This implies that some degree of dynamic hyperinflation does exist (lung volume at end-expiration is higher than passive functional residual capacity). Importantly, for lung volume to further increase in a patient with PEEPi, the inspiratory muscles contract to an amount equal to PEEPi before any volume is displaced.

PEEPi can be quite high in patients with chronic obstructive pulmonary disease (COPD) and may represent a high proportion of the total WOB [9]. For example, a patient who displaces 0.5 l of tidal volume through a 7-cmH_2O pressure gradient will perform an amount of work of 0.35 J/cycle. If nothing else changes except that this patient develops 5 cmH_2O of PEEPi, 0.25 J will be required to counterbalance this, meaning that the total WOB will be 0.60 J (0.35 + 0.25), which represents around 40% of the total work required for the inspiration. The PEEPi value is measured as the drop in esophageal pressure occurring during expiration when the inspiratory muscles start contraction, until the flow reaches the point of zero (see Fig. 1).

In the case of ineffective respiratory efforts, that is, muscle contraction without volume displacement, WOB cannot be measured from the Campbell diagram, since this calculation is based on volume displacement. In this situation, measurement of the pressure–time product (PTP) may more accurately reflect the energy expenditure of these muscles. The PTP is the product of the pressure developed by the respiratory muscles multiplied by the time of muscle contraction, expressed in cmH_2O per second. The relevant pressure is again the difference between the measured esophageal pressure and the static relaxation curve of the chest wall.

Expiration normally occurs passively. However, the coexistence of PEEPi and active expiration is common, especially in COPD patients [10]. Positive expiratory swings in gastric pressure are observed during active expiration as a consequence of abdominal muscle recruitment. When the patient starts contracting the inspiratory muscles, the expiratory muscles also start to relax. The drop in esophageal pressure used to estimate PEEPi is therefore also due to the relaxation of the expiratory muscles. To avoid overestimating the value of PEEPi, the abdominal pressure swing resulting from the active expiration must thus be subtracted from the initial drop in esophageal pressure [10].

Technical aspects of WOB calculation

Two other calculations can be obtained from pressure and volume measurements: airway pressure WOB and transpulmonary pressure WOB. The airway pressure WOB displays the energy dissipated by the ventilator to inflate the respiratory system. The transpulmonary pressure WOB shows the energy needed to inflate the lung parenchyma and reflects the mechanical characteristics of the pulmonary tissue. The limitation of these two measurements is that the amount of WOB performed by the patient's respiratory muscles is ignored.

The main tools used to measure the WOB are a double-lumen polyethylene gastro-esophageal catheter–balloon system and a pneumotachygraph. The catheter has an esophageal and a gastric balloon, usually filled with

0.5 and 1 ml of air to measure the esophageal and gastric pressures, respectively. Correct positioning of the esophageal balloon is assessed by an occlusion test: when the airways are closed at the end of expiration and an active inspiration occurs, a drop in esophageal pressure occurs. In this scenario, there are no changes in lung volume and the decrease in esophageal pressure equals the decrease in airway pressure (because in the absence of volume displacement, the transpulmonary pressure has to be nil) [11]. The catheter–balloon system should be placed to obtain a ratio between airway pressure and esophageal pressure changes as close as possible to 1. Also, the correct positioning of the gastric balloon needs to be checked [12].

Limitations

The calculation of WOB has several limitations. The first is that it requires insertion of a double-balloon gastro-esophageal catheter system. The second is the validity of the esophageal pressure value. Since pleural pressure is influenced by gravity, it can be modified by the weight of the thoracic content and by the posture. In the supine position, end-expiratory esophageal pressure is usually positive because of the weight of the heart and mediastinum on the esophagus. However, the amplitude of the changes in esophageal pressure is not usually affected. The third limitation is that the theoretical value for chest wall compliance is often used rather than a true measured value. Furthermore, chest wall deformation can occur if levels of ventilation are high [13]. Lastly, it is difficult to determine what the optimal WOB level should be for each patient on clinical grounds.

Conclusion

From the standpoint of clinical research, the measurement of WOB is extremely useful in the field of mechanical ventilation, having contributed to important progress in the management of patients for optimizing and understanding the effects of ventilator settings such as trigger, external PEEP, peak inspiratory flow, etc. WOB has also been used to evaluate the physiological effects of a number of agents such as helium and bronchodilators [9, 14, 15, 16, 17, 18, 19]. Studies on WOB have given us greater insight into the pathophysiology of weaning failure [3] and have also contributed to the progress made in the field of non-invasive mechanical ventilation [20, 21]. Bedside measurements of WOB in clinical practice, however, should be reserved for individuals in whom assessment of this parameter can provide further insight into the patient ability to breath and the patient–ventilator interactions.

Acknowledgements. The authors wish to thank Carolyn Newey for her help in editing the manuscript. Belen Cabello is the recipient of a research grant from the Instituto de Salud Carlos III (expedient CM04/00096, Ministerio de Sanidad) and the Institut de Recerca Hospital de la Santa Creu i Sant Pau.

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Interpretation of airway pressure waveforms

Abstract Most mechanical ventilators display tracings of airway pressure (Paw) volume (V) and flow ($\dot{V}$). In volume preset modes, Paw informs about the mechanical properties of the respiratory system and about the activity of respiratory muscles acting on the system. When monitoring ventilator waveforms, it is important to appropriately scale the tracing so that nuances in time profiles may be appreciated. In this short monograph, we offer three examples of how clinicians may use this information for patient assessment and care.

The Paw waveform

The interactions between a ventilator and a relaxed intubated patient can be modeled as a piston connected to a tube (flow-resistive element) and balloon (elastic element). Accordingly, at any instant in time (t), the pressure at the tube inlet reflects the sum of a resistive pressure (*Pres*) and an elastic pressure (*Pel*) [1]. *Pres* is determined by the product of tube resistance with $\dot{V}$, while *Pel* is determined by the product of balloon elastance (a measure of balloon stiffness) with volume [1]. In this model, the resistive element reflects the properties of the intubated airways, while the elastic element reflects those of lungs and chest wall. When applied to volume preset ventilation with constant inspiratory $\dot{V}$ and a short post-inflation pause, the resulting *Paw* tracing has three distinct components: (1) an initial step change proportional to *Pres*; (2) a ramp that reflects the increase in *Pel* as the lungs fill to their end-inflation volume; and (3) a sudden decay from a pressure maximum (*Ppeak*) to a plateau (*Pplat*) that reflects the elastic recoil (*Pel*) of the relaxed respiratory system at the volume at end-inflation. Since in this example flow is held constant throughout inflation, *Pres* must remain constant unless flow resistance changes volume and time. Consequently, the initial step change in *Paw* and its decay from *Ppeak* to *Pplat* are of similar magnitude. Fig. 1a demonstrates these features. Since, in pneumatic systems, there are invariable delays in the pressure and flow transients, in practice the step changes in pressure are never as sudden as they are depicted in Fig. 1a [2]. Nevertheless, the amplitude of transients can be easily estimated by extrapolating the tracing relative to the slope of the pressure ramp. Finally, while the principles that govern the interactions between pressure, volume and flow apply to all modes of mechanical ventilation, the specific pressure waveforms depicted in Fig. 1 refer only to constant flow inflation (square wave) and look very different when other flow profiles (e.g., decelerating, sine wave) are used. Our use of square wave profiles in Fig. 1 should not be interpreted as an endorsement of a specific mode, but rather as the most convenient means to present this information.

The tracing in Fig. 1b differs in several important respects: the *Paw* ramp is steeper and it is nonlinear with respect to time. Since $\dot{V}$ is constant the nonlinearity between *Paw* and t means that the relationship between *Paw* and V

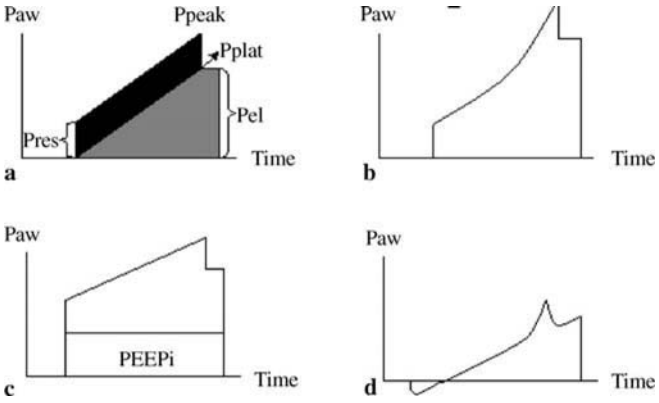

Fig. 1 Schematic illustration of the Paw profile with time during constant-flow, volume-cycle ventilation. **a** Passive respiratory system with normal elastance and resistance. Work to overcome the resistive forces is represented by the *black shaded area*, and the *gray shaded area* represents the work to overcome the elastic forces. **b** Up-sloping of the *Paw tracing* representing increased respiratory system elastance. **c** *Paw tracing* in the presence of inadvertent PEEP. **d** scalloping of the *Paw tracing* generated by a large patient effort (*Paw* airway pressure, *Pel* elastic pressure, *Ppeak* pressure maximum, *Pplat* pressure plateau, *PEEPi* inadvertent PEEP, *Pres* resistive pressure)

must be nonlinear as well. Assuming identical ventilator settings as in Fig. 1a the increased steepness of the ramp and its convexity to the time axis indicates a stiffening of the respiratory system with volume and time and suggests that the lungs may be overinflated to volumes near or exceeding their capacity. At the bedside, such an observation should raise concern for injurious ventilator settings [2].

The tracing in Fig. 1c is characterized by a larger-than-expected initial step change in *Paw* that exceeds the peak-to-plateau pressure difference. In an otherwise relaxed patient, such an observation should raise suspicion for dynamic hyperinflation and inadvertent PEEP (*PEEPi*). If *Pel* at end-expiration is greater than *Paw* at that time (i.e., *PEEPi* is present), then gas will flow in the expiratory direction. The step change in *Paw* during the subsequent inflation will therefore not only reflect *Pres* but also *PEEPi* that must be overcome to reverse flow at the tube entrance [1]. Tracings like the one in Fig. 1c should therefore alert the clinician to the presence of dynamic hyperinflation and provide an estimate of the extrinsic PEEP necessary to minimize the associated work of breathing. *PEEPi* is invariably associated with a sudden transient in expiratory flow prior to ventilator-assisted lung inflation [3]. However, this flow transient need not be associated with dynamic hyperinflation, because it is also seen in patients with increased respiratory effort and active expiration.

The tracing in Fig. 1d represents a significant departure from relaxation patters. There is no initial step change in *Paw*; the ramp is nonlinear, and the end-inspiratory pressure plateau is lower than expected. This tracing suggests that the inspiratory muscles are active throughout machine inflation and that their work represents a considerable fraction of the work performed on the respiratory system. This pattern should alert clinicians to the presence of a potentially fatiguing load.

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L. Blanch

Dead space

Introduction

Dead space is that part of the tidal volume that does not participate in gas exchange. Although the concept of pulmonary dead space was introduced more than a hundred years ago, current knowledge and technical advances have only recently lead to the adoption of dead space measurement as a potentially useful bedside clinical tool.

Concept of dead space

The homogeneity between ventilation and perfusion determines normal gas exchange. The concept of dead space accounts for those lung areas that are ventilated but not perfused. The volume of dead space (Vd) reflects the sum of two separate components of lung volume: 1) the nose, pharynx, and conduction airways do not contribute to gas exchange and are often referred to as anatomical Vd or herein as airway Vd (Vd_{aw}); 2) well-ventilated alveoli but receiving minimal blood flow comprise the alveolar Vd (Vd_{alv}). Mechanical ventilation, if present, adds additional Vd as part of the ventilator equipment (endotracheal tubes, humidification devices, and connectors). This instrumental dead space is considered to be part of the Vd_{aw}. Physiologic dead space (Vd_{phys}) is comprised of Vd_{aw} (instrumental and anatomic dead space) and Vd_{alv} and it is usually reported in mechanical ventilation as the portion of tidal volume (Vt) or minute ventilation that does not participate in gas exchange [1, 2].

A device that measures partial pressures (PCO_2) or fractions (FCO_2) of CO_2 during the breathing cycle is called a capnograph. The equation to transform FCO_2 into PCO_2 is $PCO_2 = FCO_2$ multiplied by the difference between barometric pressure minus water-vapour pressure. Time-based capnography expresses the CO_2 signal as a function of time and from this plot mean expiratory (Douglas bag method) or end-expiratory (end-tidal) CO_2 values can be obtained. The integration of the volume signal using an accurate flow sensor (pneumotachograph) and CO_2 signal (with a very fast CO_2 sensor) is known as volumetric capnography. Combined with the measurement of arterial PCO_2 ($PaCO_2$) it provides a precise quantification of the ratio of Vd_{phys} to Vt. The three phases of a volumetric capnogram are shown in Fig. 1 and Fig. 2. The combination of airflow and mainstream capnography monitoring allows calculation of breath by breath CO_2 production and pulmonary dead space. Therefore, the use of volumetric capnography is clinically more profitable than time-based capnography.

Measurement of dead space using CO_2 as a tracer gas

Bohr originally defined Vd/Vt [2] as: $Vd/Vt = (F_ACO_2 - F_ECO_2)/F_ACO_2$, where F_ACO_2 and F_ECO_2 are fractions of CO_2 in alveolar gas and in mixed expired gas, respectively. End-tidal CO_2 is used to approximate F_ACO_2,

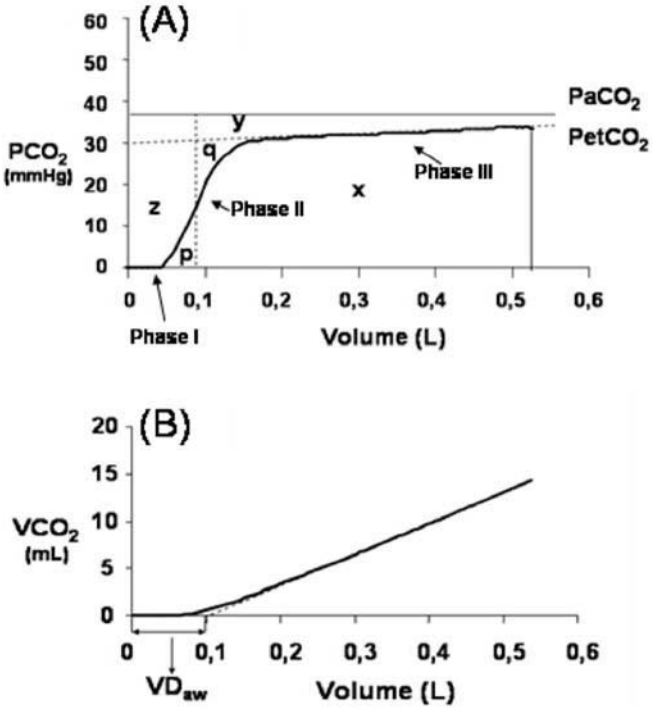

Fig. 1 **A** Single-breath expiratory volumetric capnogram recorded in a healthy patient receiving controlled mechanical ventilation. Dead-space components are shown graphically and equations are depicted and explained in the text. Phase I is the CO_2 free volume which corresponds to Vd_{aw}. Phase II represents the transition between airway and progressive emptying of alveoli. Phase III represents alveolar gas. $PaCO_2$ is arterial PCO_2; $PetCO_2$ is end-tidal PCO_2. Drawings adapted from [2]; **B** Single-breath expiratory carbon dioxide volume (VCO_2) plotted as a function of exhaled tidal volume. The alternative method to measure airway dead space (Vd_{aw}) described by Langley et al. [3] is graphically shown in a healthy patient receiving controlled mechanical ventilation

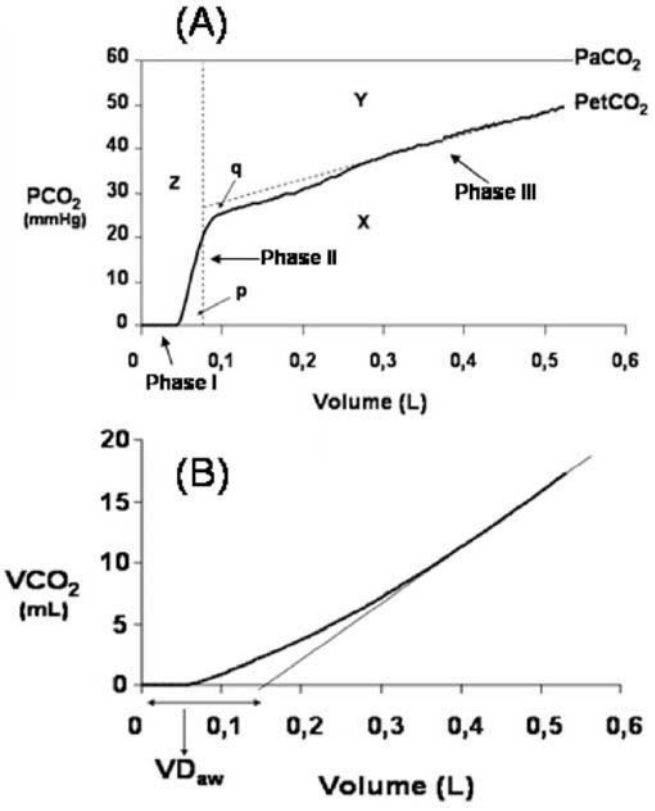

Fig. 2 **A** Single-breath expiratory volumetric capnogram recorded in a chronic obstructive pulmonary disease patient receiving controlled mechanical ventilation. The three phases of the volumetric capnogram are depicted. The transition from phase II to III is less evident due to heterogeneity of ventilation and perfusion ratios. Dead-space components are shown graphically and equations are depicted and explained in the text. $PaCO_2$ is arterial PCO_2; $PetCO_2$ is end-tidal PCO_2. Drawings adapted from [2]; **B** Single-breath expiratory carbon dioxide volume (VCO_2) plotted as a function of exhaled tidal volume. The alternative method to measure airway dead space (Vd_{aw}) described by Langley et al. [3] is graphically shown in a chronic obstructive pulmonary disease patient receiving controlled mechanical ventilation

assuming end-tidal and alveolar CO_2 fractions are identical. Physiologic dead space calculated from the Enghoff modification of the Bohr equation uses $PaCO_2$ with the assumption that $PaCO_2$ is similar to alveolar PCO_2 [2], such that: $Vd_{phys}/Vt = (PaCO_2–P_ECO_2)/PaCO_2$, where P_ECO_2 is the partial pressure of CO_2 in mixed expired gas and is equal to the mean expired CO_2 fraction multiplied by the difference between the atmospheric pressure and the water-vapour pressure. Since Vd_{phys}/Vt measures the fraction of each tidal breath that is wasted on both Vd_{alv} and Vd_{aw}, the Vd_{aw} must be subtracted from Vd_{phys}/Vt to obtain the Vd_{alv}/Vt. Vd_{phys}/Vt is the most commonly and commercially (volumetric capnographs) formula used to estimate pulmonary dead space at the bedside.

Additional methods mostly used in research to calculate all the Vd components are shown in Fig. 1A and Fig. 2A. Fowler [1] introduced a procedure for measuring Vd_{aw} based on the geometric method of equivalent areas (p = q), obtained by crossing the back extrapolation of phase III of the expired CO_2 concentration over time with a vertical line traced so as to have equal p and q areas. Airway dead space is then measured from the beginning of expiration to the point where the vertical line crosses the volume axis [1]. By tracing a line parallel to the volume axis and equal to the $PaCO_2$, it is possible to determine the readings from areas y and z, which respectively represent the values of alveolar and airway dead space. Referring these values to the Vt, it is possible to single out several Vd components [2]:

$$Vd_{phys}/Vt=(Y+Z)/(X+Y+Z)$$

$$Vd_{alv}/Vt=Y/(X+Y+Z)$$

$$Vd_{aw}/Vt=Z/(X+Y+Z)$$

An alternative method to measure airway dead space introduced by Langley et al. [3] is based on determination of the VCO_2 value, which corresponds to the area inscribed within the CO_2 versus volume curve (indicated in Fig. 1A and Fig. 2A as X area). Figure 1B and Fig. 2B are examples of Vd_{aw} calculation using the Langley et al. [3] method. Briefly, VCO_2 is plotted versus expired breath volume. Thereafter, Vd_{aw} can be calculated from the value obtained on the volume axis by back extrapolation from the first linear part of the VCO_2 versus volume curve.

Although these indexes are clinically useful, they are always bound to visual criteria for the definition of phase III of the expired capnogram. Often, the geometric analysis establishing the separation between the phase II and phase III is hardly seen and the rate of CO_2 raising of the phase III is nonlinear in patients with lung inhomogeneities (Fig. 2A).

Utility of dead space in different clinical scenarios

The CO_2 tension difference between pulmonary capillary blood and alveolar gas is usually small in normal subjects and end-tidal PCO_2 is close to alveolar and arterial PCO_2. Physiologic dead space is the primary determinant of the difference between arterial and end-tidal PCO_2 (ΔPCO_2) in patients with a normal cardio-respiratory system. Patients with cardiopulmonary diseases have altered ventilation to perfusion (V_A/Q_T) ratios producing abnormalities of Vd, as well as in intrapulmonary shunt, and the latter may also affect the ΔPCO_2. A ΔPCO_2 beyond 5 mmHg is attributed to abnormalities in Vd_{phys}/Vt and/or by an increase in venous admixture (the fraction of the cardiac output that passes through the lungs without taking oxygen) or both. The increase in Vd_{phys}/Vt seen in normal patients when anaesthetised may be attributed to muscle paralysis, which causes a reduction of functional residual capacity and alters the normal distribution of ventilation and perfusion across the lung [2, 4, 5, 6].

Ventilation to regions having little or no blood flow (low alveolar PCO_2) affects pulmonary dead space. In patients with airflow obstruction, inhomogeneities in ventilation are responsible for the increase in Vd. Shunt increase VD_{phys}/Vt as the mixed venous PCO_2 from shunted blood elevates the $PaCO_2$, increasing VD_{phys}/Vt by the fraction that $PaCO_2$ exceeds the nonshunted pulmonary capillary PCO_2 [7]. Vd_{alv} is increased by shock states, systemic and pulmonary hypotension, obstruction of pulmonary vessels (massive pulmonary embolus and microthrombosis), even in the absence of a subsequent decrease in ventilation and low cardiac output. Vd_{aw} is increased by lung overdistension and additional ventilatory apparatus dead space. Endotracheal tubes, heat and moisture exchangers, and other common connectors may increase ventilator dead space and induce hypercapnia during low Vt or low minute ventilation. Vd_{aw} calculations include the ventilator dead space. Because the anatomic dead space remains relatively constant as Vt is reduced, very low Vt is associated with a high Vd/Vt ratio [1, 2, 7, 8, 9].

Positive end-expiratory pressure (PEEP) is used to increase lung volume and to improve oxygenation in patients with acute lung injury. Vd_{alv} is large in acute lung injury and does not vary systematically with PEEP. However, when the effect of PEEP is to recruit collapsed lung units resulting in an improvement of oxygenation, Vd_{alv} may decrease, and alveolar recruitment is associated with decreased arterial minus end-tidal CO_2 difference [4, 5, 6]. Conversely, PEEP-induced overdistension may increase Vdalv and widen this difference [7].

In patients with sudden pulmonary vascular occlusion due to pulmonary embolism, the resultant high V_A/Q_T mismatch produces an increase in Vd_{alv}. The association of a normal D-dimer assay result plus a normal Vd_{alv} is a highly sensitive screening test to rule out the diagnosis of pulmonary embolism [9].

Dead space and outcome prediction

Characteristic features of acute lung injury are alveolar and capillary endothelial cell injuries that result in alterations of pulmonary microcirculation. Consequently, adequate pulmonary ventilation and blood flow across the lungs are compromised and Vd_{phys}/Vt increases. A high dead-space fraction represents an impaired ability to excrete CO_2 due to any kind of V_A/Q_T mismatch [7]. Nuckton et al. [10] demonstrated that a high Vd_{phys}/Vt was independently associated with an increased risk of death in patients diagnosed with acute respiratory distress syndrome.

Conclusions

The advanced technology combination of airway flow monitoring and mainstream capnography allows breath-by-breath bedside calculation of pulmonary Vd and CO_2 elimination. For these reasons, the use of volumetric capnography is clinically more useful than time capnography. Measurement of dead-space fraction early in the course of acute respiratory failure may provide clinicians with important physiologic and prognostic information. Further studies are warranted to assess whether the continuous measurement of different derived capnographic indices is useful for risk identification and stratification, and to track the effect of a therapeutic intervention during the course of disease in critically ill patients.

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