

# ANESTHESIOLOGY

## Respiratory Physiology for the Anesthesiologist

Luca Bigatello, M.D., Antonio Pesenti, M.D.

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Anesthesiologists take control of the respiratory function of millions of patients throughout the world each day. We learn to maintain gas exchange and use respiration to administer anesthetic gases through the completion of surgery, when we return this vital function to its legitimate owners, ideally with a seamless transition to a healthy postoperative course. With this being the nature of our trade, it is no surprise that a number of anesthesiologists have provided major contributions to the advancement of respiratory physiology, from early pioneers of the measurement of respiratory mechanics and gas exchange during anesthesia, to investigators of acute respiratory failure and extracorporeal gas exchange. Yet this article is for the clinical anesthesiologist: residents, educators, and those who fly solo, assisting them in perfecting their practice so that they can rouse every day healthy and happy individuals improved by their surgery. Aware that we cannot review every facet of this physiology, we focused our work on gas exchange and respiratory mechanics, developing four main themes (fig. 1): hypoxemia, hypercarbia, respiratory mechanics, and the mechanics of the lung and chest wall. To start, we recommend reading from classic textbooks of physiology.<sup>1–3</sup>

### Gas Exchange

#### Hypoxemia

Hypoxemia deprives cells of their main source of energy—oxygen. When the  $P_{aO_2}$  decreases below normal levels, the gradient that drives oxygen from the blood into the interstitium and finally to the cell narrows, and may eventually compromise oxygen uptake. It is important in this context to differentiate the unique danger of a low  $P_{aO_2}$  versus a decreased oxygen content; increasing oxygen content through, e.g., additional transfusions of red cells, will provide little help to the crucial lack of sufficient partial pressure. In situations of acute severe hypoxemia,

### ABSTRACT

Respiratory function is fundamental in the practice of anesthesia. Knowledge of basic physiologic principles of respiration assists in the proper implementation of daily actions of induction and maintenance of general anesthesia, delivery of mechanical ventilation, discontinuation of mechanical and pharmacologic support, and return to the preoperative state. The current work provides a review of classic physiology and emphasizes features important to the anesthesiologist. The material is divided in two main sections, gas exchange and respiratory mechanics; each section presents the physiology as the basis of abnormal states. We review the path of oxygen from air to the artery and of carbon dioxide the opposite way, and we have the causes of hypoxemia and of hypercarbia based on these very footpaths. We present the actions of pressure, flow, and volume as the normal determinants of ventilation, and we review the resulting abnormalities in terms of changes of resistance and compliance.

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swift treatment is often simple: administer oxygen! In less immediate but often complex situations such as severe acute respiratory failure or intraoperative one-lung ventilation, understanding the physiology leading to hypoxemia is essential for choosing effective therapy.

*What Determines  $P_{aO_2}$ : How Oxygen Gets from Air to Arteries (fig. 2).* Oxygen constitutes 21% of the air that we breathe and exerts 21% of the atmospheric pressure. At sea level (atmospheric pressure, 760 mmHg) once fully saturated by water vapor (47 mmHg),  $P_{O_2}$  in the inspired air ( $P_{iO_2}$ ) can then be calculated:

$$P_{iO_2} = (760 - 47) \text{ mmHg} \times 0.21 \approx 150 \text{ mmHg} \quad (1)$$

In the alveoli, oxygen is exchanged for carbon dioxide at a ratio of approximately 1.25:1, because a little more oxygen is used than carbon dioxide is produced. This phenomenon reflects the physiologic respiratory quotient (RQ), the ratio between carbon dioxide production ( $\dot{V}_{CO_2}$ ) and oxygen consumption ( $\dot{V}_{O_2}$ ), normally approximately 0.8 when using a balanced diet. With a normal  $P_{aCO_2}$  of 40 mmHg,  $P_{aO_2}$  at steady state will be

$$P_{aO_2} = P_{iO_2} - P_{aCO_2} \times (1 / RQ) \approx 102 \text{ mmHg}$$

This is a simplified version of the alveolar air equation suitable for clinical use. Further development includes  $\dot{V}_{O_2}$  and  $\dot{V}_{CO_2}$ :

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**Mini-Summaries / Take Home Points**

**Hypoxemia.**

- Hypoxemia is low arterial oxygen tension and harms by impeding oxygen transfer from blood to cells. Increasing oxygen content by, *e.g.*, transfusion, does not cure hypoxemia.
- Most common mechanism of hypoxemia is ventilation/perfusion inequality, present in acute respiratory failure, chronic lung diseases, and during general anesthesia.
- Induction of anesthesia reduces functional residual capacity predisposing to atelectasis. PEEP restores lung volume, prevents atelectasis, and avoids hypoxemia.

**Hypercarbia.**

- Hypercarbia *per se* threatens life only when severe enough to cause obtundation. With cerebral edema, even mild hypercarbia can precipitate brain herniation.
- The danger of hypercarbia in hypoventilation is in the development of hypoxemia via decrease of alveolar  $P_{O_2}$ .
- Dead space indicates lung ventilated but not perfused that causes hypercarbia. Standard computation of physiologic dead space includes  $P_{aCO_2}$  from shunt and low ventilation.

**Mechanics of Ventilation.**

- Air moves in and out of the lungs by changes of pressure, flow, and lung volume. Air movement is impeded by airways' resistance and respiratory elastance (stiffness).
- Respiratory mechanics can be measured during mechanical ventilation with an inspiratory pause (compliance and resistance) and an expiratory pause (auto-PEEP).
- Auto-PEEP is positive pressure in the alveoli at end expiration, generally caused by high flow resistance. It may recruit or overstretch alveoli and increases work of breathing.

**Mechanics of Lung and Chest Wall.**

- Lung and chest wall move in series during respiration. Inward recoil of the lung balances expanding of the chest wall at functional residual capacity, and alveolar pressure is 0.
- Measuring pressure between lung and chest wall by an esophageal balloon allows to estimate transpulmonary pressure, which may vary in different regions of the lung.
- Positive transpulmonary pressure keeps alveoli open; increasing it with PEEP during anesthesia opposes atelectasis in the dependent lung and prevents hypoxemia

**Fig. 1.** Mini summaries/take home points from the four main themes of the review. PEEP, positive end-expiratory pressure.

$$P_{AO_2} = (760 - 47) \times F_{IO_2} - P_{aCO_2} \times (\dot{V}_{O_2} / \dot{V}_A) \\ = 713 \times F_{IO_2} - P_{aCO_2} \times (\dot{V}_{O_2} / \dot{V}_A \times K)$$

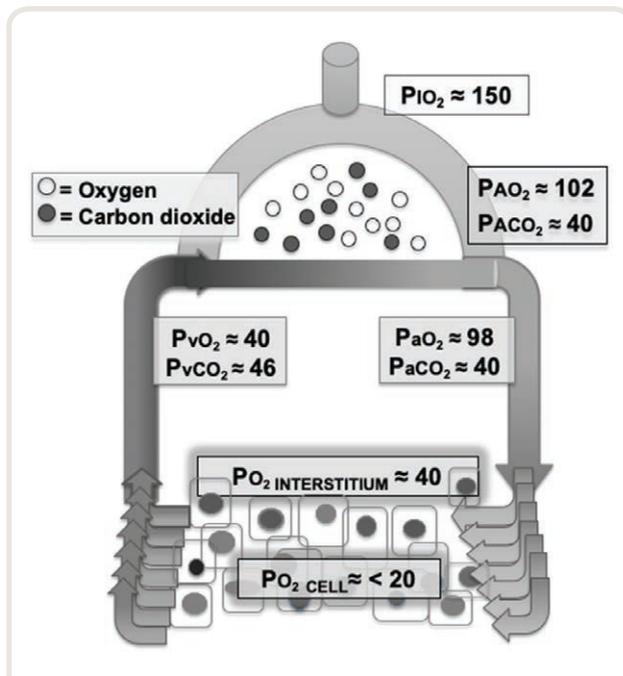
where  $\dot{V}_{CO_2}$  is alveolar ventilation ( $\dot{V}_A$ )  $\times$  its carbon dioxide concentration, with  $K = 1/760$  mmHg; hence:

$$P_{AO_2} = 713 \times F_{IO_2} - \dot{V}_{O_2} / \dot{V}_A \times K \quad (2)$$

Under normal conditions, past the pulmonary capillaries, arterialized blood receives a small fraction of venous blood from minimal alveolar shunt (2 to 3%, increasing with age) and anatomic sources like bronchial, Thebesian, and some

diaphragmatic veins, so that  $P_{aO_2}$  decreases just under 100 mmHg. Equation 2 also explains how hyperventilation may increase  $P_{aO_2}$  above 100 mmHg. The following paragraphs differentiate the main causes of hypoxemia based on the above schematic.

**Low  $P_{IO_2}$ .** The most common cause of low  $P_{IO_2}$  is breathing at high altitude<sup>4</sup>; in La Paz, Bolivia, and in Lhasa, Tibet (both approximately 12,000 feet/3,600 meters),  $P_{IO_2} \approx 100$  mmHg, versus 150 mmHg at sea level (fig. 2). At high altitudes, the main concern for the anesthesiologist who treats native populations or transient workforces is hypoxemia; supplemental oxygen will be necessary for most patients and may be beneficial for the medical staff to maintain full



**Fig. 2.** The oxygen pathway of respiration. Drawing of an alveolus adjoining a pulmonary capillary, where oxygen ( $O_2$ ) and carbon dioxide ( $CO_2$ ) are exchanged; blood flow exiting the alveolus enters the arterial circulation (right), crosses through the interstitium and tissues, and returns to the pulmonary capillary through the venous system (left). Partial pressure values are in mmHg.  $PiO_2$ ,  $PiO_2$  in the inspired air;  $PvCO_2$ , mixed venous carbon dioxide tension;  $PvO_2$ , mixed venous oxygen tension.

physical and mental performance. Hypoxemia stimulates  $\dot{V}_A$  mainly through carotid chemoreceptors<sup>4</sup>; hyperventilation may be profound, and the consequent decrease in  $PACO_2$  will limit the reduction of  $PAO_2$  according to equation 2. Near the summit of Mount Everest, at approximately 27,000 feet/8,200 meters and a barometric pressure of 284 mmHg,  $PAO_2$  and  $PACO_2$  measured in climbers breathing air were 25 and 13 mmHg, respectively.<sup>5,6</sup>

A low  $PiO_2$  at sea level may be related to the accidental administration of a hypoxic mixture. The remarkable level of safety of anesthesia machines and portable field devices makes accidental delivery of a hypoxic mixture an exceptional event.

**Low  $PAO_2$ .** In addition to causes of low  $PO_2$  upstream from the alveoli (low  $PiO_2$ ),  $PAO_2$  decreases mainly in relation to an increase in  $PACO_2$ . As per equation 2,  $PAO_2$  falls when  $\dot{V}_A$  decreases, at any given  $\dot{V}O_2$  and any starting  $PACO_2$ . Table 1 applies the alveolar air equation to representative physiologic situations. Also, from equation 2, we appreciate the effect of fraction of inspired oxygen ( $FiO_2$ ): a simple increase from 21 to 30%  $FiO_2$  raises  $PiO_2$  by 64 mmHg, which may restore  $PAO_2$  to a value around 100 mmHg even in the presence of extreme hypoventilation.

In modern intensive care, we learn to take into account the possible contribution of extracorporeal carbon dioxide

removal and carbon dioxide dialysis.<sup>7,8</sup> The lung of a patient undergoing low-flow, high-efficiency carbon dioxide removal for severe acute respiratory failure will maintain a comparatively high natural lung  $\dot{V}O_2$  while achieving a very low  $\dot{V}_A$  (low natural lung  $\dot{V}CO_2$ ) thanks to the high rate of carbon dioxide removal by the artificial lung. Very low respiratory quotient values, well below 0.5, are thus possible, requiring increased  $FiO_2$  to maintain a constant  $PAO_2$ , despite an artificially normal or low  $PACO_2$ .

**Impaired Diffusion.** Oxygen transfer from the alveolus to the circulating hemoglobin is very rapid and seldom the cause of hypoxemia.<sup>9</sup> The high partial pressure gradient and the thinness of the alveolo-capillary membrane allow ample time for oxygen transfer to reach steady state within the normal capillary blood transit time. Hence, transfer of oxygen is limited by pulmonary blood flow rather than diffusing capacity. However, regional capillary blood flow can vary substantially due to factors such as posture, alveolar pressure, and disease. Lung regions with short capillary transit time will then yield desaturated blood, which will not be compensated by areas with prolonged transit time, because hemoglobin will not saturate above 100%. Hence, any measurement of diffusion capacity, such as carbon monoxide diffusion, will be affected primarily by regional flow abnormalities rather than diffusion. Just like for oxygen, abnormal transfer of carbon monoxide is mostly due to ventilation/perfusion ratio ( $\dot{V}/\dot{Q}$ ) inequality, and carbon monoxide diffusion may be used as a generic index of abnormal pulmonary function, typically in the preoperative evaluation of patients scheduled to undergo pulmonary resections.<sup>10</sup>

**Shunt (or Venous Admixture) and  $\dot{V}/\dot{Q}$  Inequality.** The basic principle for alveoli to work as gas exchangers is to match ventilation (provides inflow and outflow for gases from and to the air) with perfusion (provides inflow and outflow of gases to and from the tissues). The two systems cross paths in the alveoli, where blood enters with different  $PO_2$  and  $PCO_2$  from the alveolar gas and exits with near equal concentrations. Normal  $\dot{V}_A$  is approximately 4 l/min, and normal pulmonary blood flow (cardiac output) approximately 5 l/min, giving a  $\dot{V}/\dot{Q}$  of 0.8. In reality, each individual alveolus's  $\dot{V}/\dot{Q}$  may differ substantially, from 0, that is shunt, to  $\infty$ , that is dead space and infinite combinations in between.

The most practical approach to  $\dot{V}/\dot{Q}$  distribution is still the three compartments model proposed by Riley and Cournand<sup>11,12</sup> more than half a century ago: an ideal compartment, a nonventilated compartment, and a nonperfused compartment. In the nonventilated compartment, capillary blood reaches the pulmonary venous side (oxygenated blood) without participating at all in gas exchange. The proportion of nonoxygenated blood mixing into the arterialized side is defined as shunt or venous admixture and represents the amount of blood that would justify the deficit in arterial oxygenation if it were to cross the lung

**Table 1.** Effects of Changes of Variables that Determine  $PAO_2$  According to the Alveolar Air Equation:  $PAO_2 = P_{iO_2} - (\dot{V}_{O_2} / K \times \dot{V}_A)$

	$P_{atm} - P_{H_2O}$ mmHg	$F_{iO_2}$	$P_{iO_2}$ mmHg	$\dot{V}_{O_2}$ ml/min	$\dot{V}_A$ ml/min	$PAO_2$ mmHg
Normal	713	0.21	150	250	4,000	102
Hypoventilation	713	0.21	150	250	2,000	55
Hypoventilation, higher $F_{iO_2}$	713	0.30	214	250	2,000	119
Shivering	713	0.21	150	500	4,000	55
Shivering, higher $\dot{V}_A$	713	0.21	150	500	8,000	102
Altitude 27,000 feet	237	0.21	50	250	4,000	2
27,000 feet, higher $\dot{V}_A$	237	0.21	50	250	8,000	26
27,000 feet, higher $\dot{V}_A, F_{iO_2}$	237	0.30	71	250	8,000	47

The  $P_{atm}$  value at 27,000 feet is taken from West.<sup>4</sup> The changes in  $\dot{V}_{O_2}$  and in  $\dot{V}_A$  are double or half of baseline for easy comparisons. Note how the same increase of  $F_{iO_2}$  from 21 to 30% is much less effective at high altitude because of the lower  $P_{atm}$ .  $F_{iO_2}$ , fraction of inspired oxygen;  $P_{atm}$ , atmospheric pressure;  $P_{H_2O}$ , water vapor pressure;  $P_{iO_2}$ , partial pressure of inspired oxygen;  $\dot{V}_A$ , alveolar ventilation;  $\dot{V}_{O_2}$ , oxygen consumption.  $K = 1/760$ .

without participating to gas exchange. The degree of shunt is computed when mixed venous blood gases are available:

$$\dot{Q}_{VA} / \dot{Q}_{TOT} = (C_{CO_2} - C_{AO_2}) / (C_{CO_2} - C_{VO_2}) \quad (3)$$

where  $\dot{Q}_{VA}$  is the fraction of pulmonary blood flow exposed to ventilation,  $\dot{Q}_{TOT}$  is the total pulmonary blood flow,  $C_{CO_2}$  is the oxygen content of ideal capillary blood computed from  $PAO_2$  of the ideal compartment (equation 2),  $C_{AO_2}$  is the oxygen content of arterial blood, and  $C_{VO_2}$  is the oxygen content of venous blood.

In reality, hypoxemia and hypercarbia in lung disease result from infinite combinations of  $\dot{V}/\dot{Q}$  relationships that lie somewhere between shunt and dead space. The structure of the lung tends to predispose to  $\dot{V}/\dot{Q}$  inequality, with both perfusion and ventilation being more efficient at the bases of the lungs, but the gradient of perfusion being steeper than ventilation, creating a situation prone to mismatch.<sup>13,14</sup> It is important to appreciate that although  $\dot{V}/\dot{Q}$  inequality affects both oxygen and carbon dioxide exchange, the end result of is primarily hypoxemia, for two main reasons:

**Increased  $P_{ACO_2}$  Stimulates Ventilation.** When low  $\dot{V}/\dot{Q}$  develops in a portion of the lung, it decreases  $PO_2$  and increases  $PCO_2$  of arterialized blood. In spontaneously breathing patients, the higher  $P_{ACO_2}$  stimulates ventilation, and  $P_{ACO_2}$ —but not  $PAO_2$ —will return toward baseline. If hypoxemia is severe, as at high altitudes, an additional stimulus to hyperventilation will further decrease  $P_{ACO_2}$ . In fully ventilated patients, who cannot increase their minute ventilation,  $P_{ACO_2}$  will indeed increase, but the gradient between venous and arterial  $P_{CO_2}$  (46 to 40 = 6 mmHg) is very small, and the change is difficult to detect.

**Opposite Changes in  $\dot{V}/\dot{Q}$  Do Not Cancel Each Other Out.** At first glance, it would seem that comparable but opposite changes of  $\dot{V}/\dot{Q}$  would cancel each other out and yield normal gas exchange. This does not occur, and

hypoxemia is the main result; this phenomenon is explained in terms of blood oxygen content and the hemoglobin–oxygen dissociation curve:

$$\begin{aligned} \text{Arterial oxygen content } (Ca_{O_2}) \\ = [Hb] \times 1.34 \times Sa_{O_2} + Pa_{O_2} \times 0.003 \end{aligned} \quad (4)$$

In an alveolo–capillary unit with normal  $\dot{V}/\dot{Q}$ ,  $Ca_{O_2}$  is = 14 g/dl  $\times$  1.34  $\times$  1 + 0.3  $\approx$  19 ml of oxygen per dl, also expressed as 19 ml %. In a unit with low  $\dot{V}/\dot{Q}$  and, e.g., arterial oxygen saturation ( $Sa_{O_2}$ ) of 0.85,  $Ca_{O_2}$  will be 16 ml %, close to a normal venous oxygen content ( $C_{VO_2}$ ) of 14 ml %. In a unit with high  $\dot{V}/\dot{Q}$  and a  $Pa_{O_2}$  of, e.g., 400 mmHg,  $Ca_{O_2}$  is almost 20 ml %, only slightly above normal. The high  $\dot{V}/\dot{Q}$  unit cannot carry much more than 19 ml % of oxygen because once full saturation of hemoglobin is reached, a higher  $Pa_{O_2}$  only increases dissolved oxygen, which contributes minimally to  $Ca_{O_2}$ .

**Clinical Evaluation of  $\dot{V}/\dot{Q}$  Distribution.** Measuring regional  $\dot{V}/\dot{Q}$  distribution is a complex task. The accepted standard has been the Multiple Inert Gas Elimination Technique, based on the infusion of a mixture of six dissolved inert gases with a known range of solubility, then measuring their concentrations in arterial blood and expired gas.<sup>15,16</sup> This technique has never been simplified enough for clinical use, nor does it provide spatial information of the areas of  $\dot{V}/\dot{Q}$  inequality. Recently, the evolution of lung imaging with high–definition computerized tomography scan, positron emission tomography, and electrical impedance tomography<sup>17</sup> is taking the visualization of  $\dot{V}/\dot{Q}$  distribution closer to the clinical arena, although not yet to a quantitative evaluation of the precision provided by the Multiple Inert Gas Elimination Technique.

**Clinical Indices of Oxygenation and the Effect of  $F_{iO_2}$ .**  $PAO_2$  and  $Sa_{O_2}$  are precise measurements of their respective physiologic entity, but alone do not provide adequate description

of an ongoing respiratory impairment, nor allow accurate comparison among patients. It is important to know partial pressure (mmHg) or fraction (%) of oxygen upstream from the artery at which a certain  $P_{aO_2}$  is obtained<sup>18</sup>: a  $P_{aO_2}$  of 100 mmHg has different physiologic implications whether obtained at a  $P_{iO_2}$  of 600 mmHg ( $F_{iO_2}$  100%) versus a  $P_{iO_2}$  of 150 mmHg ( $F_{iO_2}$  21%). The **alveolo-arterial oxygen gradient** is the most time-honored index of oxygenation, where  $P_{aO_2}$  is estimated from equation 2; the wider the alveolo-arterial oxygen gradient, the worse the performance of the lung as an exchanger. The most accurate application for this index is in patients intubated and breathing high  $F_{iO_2}$ , where the linearity between this index and the level of venous admixture is best.<sup>18</sup> More recently, the **ratio between  $P_{aO_2}$  and  $F_{iO_2}$  ( $P_{aO_2}/F_{iO_2}$ , or “P/F”)** has largely substituted **alveolo-arterial oxygen gradient** because it does not require equation 2 and its relationship with venous admixture is less affected by  $F_{iO_2}$ .<sup>19,20</sup>

**Low Mixed Venous Oxygen Tension ( $P_{vO_2}$ ).** Normally, transfer of oxygen from air to blood reaches full equilibrium within the alveolo-capillary unit, and  $P_{aO_2} \approx P_{vO_2}$ . Such degree of efficiency allows for even a low  $P_{vO_2}$  to yield a normal  $P_{aO_2}$ . However, in patients with intrapulmonary shunt, blood with low  $P_{vO_2}$  enters the arterial stream without being saturated by alveolar oxygen and will decrease  $P_{aO_2}$  to a degree depending on the magnitude of the shunt fraction: the higher the shunt, the more the  $P_{aO_2}$  becomes dependent on the  $P_{vO_2}$ .

**The Physiology of Mixed Venous  $P_{vO_2}$ .** The next logical question is what causes a low  $P_{vO_2}$ . The following equation (Fick's equation) illustrates the relationship between oxygen delivery to the tissues ( $Ca_{O_2} \times$  cardiac output) and oxygen utilization, or  $\dot{V}_{O_2}$ :

$$\text{Cardiac output} = \dot{V}_{O_2} / (Ca_{O_2} - Cv_{O_2}) \quad (5)$$

$P_{vO_2}$  and mixed venous oxygen saturation ( $S_{vO_2}$ ) contribute to  $Cv_{O_2}$  (equation 4) and are used interchangeably as indices of tissue oxygen utilization.<sup>21</sup> Unless indicated otherwise,  $P_{vO_2}$  and  $S_{vO_2}$  refer to mixed venous blood, which is blood distal to the right atrium, where full mixing has occurred. Mixed venous blood can be sampled only via a pulmonary artery catheter. Central venous blood  $P_{vO_2}$  obtained via a standard central venous catheter has been used as a surrogate, but it is not consistently accurate because is affected by separate currents of blood coming from venous districts with different  $P_{vO_2}$ .<sup>22</sup>

$P_{vO_2}$  may decrease for a defined number of factors: a low  $P_{aO_2}$ , low hemoglobin concentration, low cardiac output, or a high  $\dot{V}_{O_2}$ . With a low  $P_{aO_2}$ , the lower  $P_{vO_2}$  will further decrease  $P_{aO_2}$  until a new equilibrium of lower  $P_{vO_2}$  and  $P_{aO_2}$  is reached. Normally, a  $Ca_{O_2}$  of  $\sim 19$  ml/100 ml of blood  $\times$  cardiac output of 5 l/min yields a delivery of oxygen of  $\sim 1,000$  ml/min; with a resting  $\dot{V}_{O_2}$  of  $\sim 250$  ml/min, the  $(Ca_{O_2} - Cv_{O_2}) \times$  cardiac output term is 750 ml/min, meaning

that under normal circumstances, approximately 25% of the available oxygen is taken up by tissues. With a lower cardiac output or hemoglobin concentration and constant  $\dot{V}_{O_2}$ , the term  $Ca_{O_2} - Cv_{O_2}$  widens and  $P_{vO_2}$  decreases, indicating an increased extraction of oxygen by the tissues. Note that increased extraction does not automatically indicate insufficient perfusion; hence, monitoring  $P_{vO_2}$  or  $S_{vO_2}$ <sup>22</sup> provides information on the status of oxygen tissue delivery but does not necessarily indicate a need to normalize oxygen delivery. It is important to note that the mathematical effect of the same change of each component of oxygen delivery on  $P_{vO_2}$  may differ greatly from the clinical effect. This is shown in table 2, where halving any of the terms of the equation will equally half oxygen delivery and decrease  $P_{vO_2}$ . However, while halving hemoglobin concentration may be a relatively minor event in many critically ill patients, halving  $Sa_{O_2}$  may be deadly. Furthermore, the physiologic relationship among the variables in discussion is complex and cannot be evaluated simply by the Fick's equation. For example, accurate measurement of  $\dot{V}_{O_2}$  is elusive in the clinical setting,<sup>23</sup> and it is often referred to from tables; also, an increase in cardiac output in the presence of moderate shunt will generally increase shunt itself, negating the assumption that the other variables are constant.<sup>24,25</sup>

**General Anesthesia and Hypoxemia.** A succession of physiologic events decreases  $P_{aO_2}$  during general anesthesia.<sup>26</sup> Shortly after induction of anesthesia, the resting volume of the lung (functional residual capacity [FRC]), which is a reserve of oxygen, decreases by an average of 500 ml in adults; added to the volume lost by going from the erect to the supine position,<sup>27</sup> FRC is reduced from approximately of 3,000 ml to just more than 2,000, i.e., close to residual volume. The main cause is a loss of muscle tone with consequent cephalad displacement of the diaphragm; it is largely independent of the type of anesthesia and unrelated to neuromuscular blockade,<sup>28</sup> and is aggravated by pregnancy, obesity, and abdominal distention.<sup>29</sup> The decrease in resting lung volume causes a decrease in lung compliance, promotes cyclic airway closure at end-expiration and gas reabsorption, rapidly leading to atelectasis. Persistent blood flow during cyclic airway closure and through atelectasis causes areas of low  $\dot{V}/\dot{Q}$  and shunt, contributing to hypoxemia. In the supine position, atelectases are prevalently located in the dorsal areas of the lung; normally limited to less than 10% of the lung volume, they may extend to 15 to 30% of it and be associated with persistent hypoxemia and respiratory complications.<sup>30</sup> Almost paradoxically, a high  $F_{iO_2}$  may add to lung collapse (absorption atelectasis) by substituting alveolar nitrogen with oxygen, the former not taking part in gas exchange. An  $F_{iO_2}$  of 80% may limit the degree of absorption atelectasis compared to 100%. The combination of an  $F_{iO_2}$  not higher than 60%, and positive end-expiratory pressure (PEEP) during awakening from general anesthesia, may limit the degree of atelectasis and the incidence and duration of hypoxemia in the postoperative period.<sup>31,32</sup>

**Table 2.** Effects of Changes in the Determinants of Oxygen Delivery on Mixed Venous Oxygen Partial Pressure (PvO<sub>2</sub>) and Saturation (Svo<sub>2</sub>)

	CO, l/min (× 10)	Hb, g/dl (× 1.34)	Sao <sub>2</sub> %	Oxygen delivery ml/min	ṠO <sub>2</sub> 250 ml/min	PvO <sub>2</sub> /Svo <sub>2</sub> mmHg, %
Normal	5	14	100	938	26%	37/70
Severe anemia (50% Hb)	5	7	100	469	52%	23/40
Severe anemia (50% Hb), compensated	6	7	100	562	44%	29/55
Severe anemia (50% Hb), myocardial dysfunction	3.5	7	100	328	65%	20/30
Cardiogenic shock (50% CO)	2.5	14	100	469	52%	23/40
Severe hypoxemia (50% Sao <sub>2</sub> )	5	14	50	469	52%	23/40

The values of PvO<sub>2</sub> and Svo<sub>2</sub> are estimated on the normal hemoglobin oxygen dissociation curve and may show variability in the clinical setting because of the steep slope of the curve, and the situational effects of temperature and pH. Note how an identical decrease of oxygen delivery from 938 to 469 ml/min, and identical decrease in PvO<sub>2</sub> / Svo<sub>2</sub>, may produce radically diverging clinical implications: in the case of a hemoglobin of 7 g/dl, the clinical picture is hardly critical, but in the case of Sao<sub>2</sub> of 50% (Pao<sub>2</sub> ~ 27 mmHg), the picture is deadly. For the case of severe anemia, we show the effects of normal physiologic compensation (increased cardiac output) and how the lack of such compensation (myocardial dysfunction) may significantly affect PvO<sub>2</sub> / Svo<sub>2</sub>. CO, cardiac output; Hb, hemoglobin serum concentration; ṠO<sub>2</sub>, oxygen consumption. Oxygen delivery = oxygen content × cardiac output; oxygen extraction = oxygen consumption / oxygen delivery.

### Hypercarbia

Different from hypoxemia, hypercarbia is generally well tolerated unless severe enough (above 80 to 100 mmHg) to cause obtundation and respiratory arrest. In susceptible patients, hypercarbia may be perilous through various mechanisms, by increasing intracranial pressure in patients with cerebral edema or exacerbating pulmonary hypertension in adults with right ventricular dysfunction and in children with congenital heart disease. On the other hand, moderate hypercarbia may be a favorable condition in a number of pathologic situations, such as in circulatory shock by improving local blood flow, and in acute respiratory distress syndrome (ARDS) as an accepted consequence of a ventilatory strategy of limited tidal volume.<sup>33</sup>

**What Determines Hypercarbia: How Carbon Dioxide Gets from Cells to Air.** Carbon dioxide and water are the end-products of aerobic metabolism; carbon dioxide is the main source of acid in the body and requires a highly efficient system for removal. In plasma, dissolved carbon dioxide (Paco<sub>2</sub> × 0.03) is in equilibrium with carbonic acid, hydrogen ions (buffered by hemoglobin), and bicarbonate ions, and is measured in mEq/l as “total CO<sub>2</sub>” in a standard metabolic profile.<sup>34</sup> From the pulmonary capillary, carbon dioxide transfers to the alveolus by the same physical forces that transfer oxygen the other way. By the end of the capillary, carbon dioxide is in equilibrium in the two phases, and normally Paco<sub>2</sub> ≈ Pao<sub>2</sub>. At steady state, Paco<sub>2</sub> results from the equilibrium of production by cellular metabolism (ṠCO<sub>2</sub>) and elimination by Ṡ<sub>A</sub>,

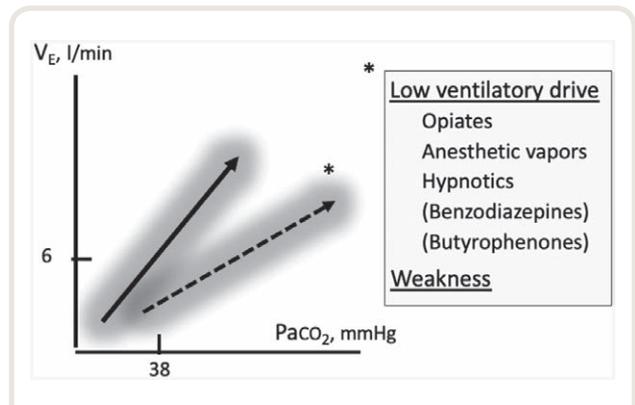
$$Paco_2 = \dot{V}CO_2 / \dot{V}_A K \tag{6}$$

where K = 1/760 as in equation 2.

Elimination of carbon dioxide is the essential target of breathing. Paco<sub>2</sub> and Ṡ<sub>A</sub> are tightly bound, and small

increases in Paco<sub>2</sub> have immediate effect on the total minute ventilation: for each 1 mmHg Paco<sub>2</sub>, minute ventilation increases by 1 to 2 l/min, returning Paco<sub>2</sub> to its normal value (fig. 3). Based on the above schematic, we can differentiate the main causes of hypercarbia.

**High ṠCO<sub>2</sub>.** Increased aerobic metabolism occurs in hypermetabolic states such as exercise, fever, shivering, hyperthyroidism, excessive caloric/carbohydrate intake and, to its maximum extent, in neuroleptic malignant syndrome and malignant hyperthermia. Except for the latter two entities, increase of ṠCO<sub>2</sub> is either mild, as in high carbohydrate intake, or transient, as in shivering, and most of the time offset by the increase of Ṡ<sub>A</sub>. When ventilation is limited by disease, sedation or residual anesthesia, an episode of high fever or shivering may overwhelm the capability



**Fig. 3.** The close relationship of arterial carbon dioxide (Paco<sub>2</sub>, independent variable) and minute ventilation (Ve). The continuous line is the normal, and the hashed line represents the effect of different conditions. The glow around both lines is a qualitative representation of the variance present in both healthy and affected individuals. Medications in parentheses have a less pronounced effect.

of the respiratory system and result in levels of hypercarbia that require mechanical ventilatory support.  $\dot{V}_{CO_2}$  may also change abruptly under non-steady state condition by changes in body carbon dioxide stores (bicarbonate and carbonic acid) or by exogenous infusion. For example, the rapid administration of sodium bicarbonate with the aim of neutralizing a metabolic acidemia (*i.e.*, converting bicarbonate to carbon dioxide and water) results in a stoichiometric increase in carbon dioxide production: 100 mEq of sodium bicarbonate more than 20 min may cause up to 50% increase in  $\dot{V}_{CO_2}$  of the same duration (5 mEq/min).

**Low  $\dot{V}_A$ .** Hypoventilation causes hypercarbia and hypoxemia, particularly at low  $F_{IO_2}$ . Looking at equation 2, at constant  $\dot{V}_{O_2}$ , a decrease in  $\dot{V}_A$  implies a decreased delivery of oxygen to the alveolus, while  $P_{ACO_2}$  increases because a higher carbon dioxide concentration in the expired air is necessary to eliminate the same amount of carbon dioxide per unit time at constant  $\dot{V}_{CO_2}$ . Common causes of hypoventilation include a decreased central drive to breathe, as it occurs with hypnotics, volatile anesthetics, and opiates (fig. 3); respiratory muscle weakness, as in Guillain-Barré syndrome, myasthenia, and polyneuropathy of critical illness; and high resistive (severe asthma) or elastic (abdominal distention) ventilatory loads.

**Dead Space Ventilation and  $\dot{V}/\dot{Q}$  Inequality.** Ventilation is a to and fro process that starts in the airways, which are one-way conduits not involved in gas exchange. This fraction of tidal ventilation (150 to 200 ml in adults) is thus “dead volume” or *anatomic dead space* of the airways ( $V_D/V_{TAW}$ ). In mechanically ventilated patients,  $V_D/V_{TAW}$  also includes any additional respiratory equipment where flow of gas is bidirectional, such as masks and corrugated tubing added distally to the Y-piece. In addition to  $V_D/V_{TAW}$ , where no carbon dioxide is ever exchanged, dead volume may also occur at the alveolar level or *alveolar dead space* ( $V_D/V_{TALV}$ ), where normally all carbon dioxide is exchanged, and represents a wasted fraction of  $\dot{V}_A$ . In analogy with shunt in the three compartments model of Riley and Cournand,<sup>11,12</sup>  $V_D/V_{TALV}$  is the proportion of alveolar ventilation that could justify the observed decrease in mixed  $P_{ACO_2}$  if it were to be expired with a  $P_{CO_2}$  equal to the one of the inspired air.  $V_D/V_{TAW} + V_D/V_{TALV}$  is *physiologic dead space* ( $V_D/V_{T PHYS}$ ).

Measurement of  $V_D/V_{T PHYS}$  is commonly obtained from a modification of the Bohr equation<sup>35</sup> where  $P_{ACO_2}$  substitutes  $P_{ACO_2}$ , the latter being difficult to measure:

$$V_D / V_{T PHYS} = (P_{ACO_2} - P_{ECO_2}) / P_{ACO_2} \quad (7)$$

$P_{ECO_2}$  is the mixed expired  $P_{CO_2}$ , which includes both alveolar ( $\approx$  arterial)  $CO_2$  and airways ( $\approx 0$ )  $CO_2$ , where a normal value of 30 mmHg gives a  $V_D/V_{T PHYS} = (40 - 30)/40 = 1/4 = 25\%$ , *i.e.*, 150 to 200 ml. The availability of continuous capnography allows estimation of  $P_{ECO_2}$  from the midpoint of the initial rise of expired trace, or Phase

I, and alveolar  $P_{CO_2}$  from the highest point (also *end-tidal*  $P_{CO_2}$ ,  $P_{ETCO_2}$ ); substituting  $P_{ECO_2}$  with  $P_{ETCO_2}$  in equation 7, we measure  $V_D/V_{TALV}$  continuously and noninvasively.<sup>36</sup> However, using  $P_{ACO_2}$  as a surrogate of  $P_{ACO_2}$  adds to  $V_D/V_{T PHYS}$  a source of carbon dioxide that does not contribute to  $P_{ACO_2}$  because it is not dead space but shunt and  $\dot{V}/\dot{Q}$  inequality.<sup>35,37</sup> Shunt widens the A - a gradient for carbon dioxide just like the A - a gradient for oxygen, but the effect of shunt on  $P_{ACO_2}$  will be less visible than on  $P_{aO_2}$  because the difference in  $P_{CO_2}$  between venous and arterial blood is much smaller than the difference in  $P_{O_2}$ . For example, a 30% shunt would increase  $P_{ACO_2}$  by only 2 mmHg, a barely noticeable change; however, that would correspond to an increase in calculated  $V_D/V_{T PHYS}$  larger than 30% because of the increase in gradient, not in absolute  $P_{ACO_2}$  value. Differentiating the mechanism leading to hypercarbia may be important; for example, the magnitude of  $V_D/V_{T PHYS}$  has been correlated with the rate of mortality in ARDS,<sup>38</sup> given the high shunt fraction present in severe ARDS, part of the increase in  $P_{ACO_2}$  that contributes to the high calculated  $V_D/V_{T PHYS}$  may be due to decreased ventilation and not decreased blood flow. Similarly, in lung disease characterized by major alterations in  $\dot{V}/\dot{Q}$  relationship, such as severe chronic obstructive pulmonary disease (COPD), a low  $P_{ETCO_2}$  may reflect the overall  $\dot{V}/\dot{Q}$  inequality in addition to dead space.

Occasionally, alveolar units with altered mechanics may empty throughout expiration and add carbon dioxide, increasing  $P_{ACO_2}$  and  $P_{ETCO_2}$  may exceed  $P_{ACO_2}$ , the limit being mixed venous carbon dioxide tension ( $P_{vCO_2}$ ). This is rare, and  $P_{ETCO_2}$  is normally equal to or lower than  $P_{ACO_2}$ ; as long as the expired carbon dioxide trace on the capnogram shows a stable plateau, the  $P_{ETCO_2}$  can be accepted as representative of alveolar carbon dioxide.

**Dynamic Changes of Carbon Dioxide.** The above discussion refers to steady state conditions, but we should also take into account the peculiarities of dynamic or transient carbon dioxide changes.<sup>39</sup> When ventilation increases,  $P_{CO_2}$  decreases rapidly, the rate of decrease being governed primarily by  $\dot{V}_A$ . When ventilation decreases, the process is overall different, because the rate of increase of  $P_{CO_2}$  is governed only by  $\dot{V}_{CO_2}$ . When an individual holds breath for several seconds (apnea), an initial increase of  $P_{ACO_2}$  toward the  $P_{vCO_2}$  value (an additional 6 mmHg or 21 ml of carbon dioxide with an FRC is 2.5 l) will take place rapidly—less than 6 s at constant cardiac output. However, past this equilibration time, any further increase of  $P_{CO_2}$  takes place at a much slower speed (3 to 6 mmHg/min) due to the high capacity of the body stores for carbon dioxide. Important dynamic changes in carbon dioxide occur also with changes in pulmonary blood flow. A fall in cardiac output at constant  $V_E$  causes a decrease in carbon dioxide transferred to the alveoli, reflected by lower  $P_{ETCO_2}$  and increased  $V_D/V_{TALV}$ .

## Respiratory Mechanics

Air moves in and out of the lungs by the cyclic action of the respiratory muscles. Each breath starts with **pressure** applied by the respiratory muscles (negative pressure) or by a ventilator (positive pressure), generating a **flow** of gas through the airways that expands the **volume** of the lung and surrounding structures. This process is **opposed** each time by **resistance** to gas flow in the airways and **elastance** (**stiffness**) of the lung and surrounding structures. Note that the term elastance is seldom used in clinical lingo, in favor of its **reciprocal**, **compliance**; thus, an increased stiffness of the lung is a low compliance. These **five variables**—pressure, flow, volume, resistance, and compliance—are intimately intertwined in determining the mechanical process of breathing, whether it is during relaxed breathing, during arduous exercise, or supplied by a ventilator.<sup>40</sup>

### Bedside Measurement of Respiratory Mechanics Can Be Carried Out with Nearly Any Modern Ventilator

#### Mechanics of Inspiration.

$$\text{Resistance} = (\text{peak [PIP]} - \text{plateau [P}_{\text{PLAT}}\text{] pressure}) / \text{flow rate} \quad (8)$$

$$\text{Compliance} = \text{tidal volume} / (\text{P}_{\text{PLAT}} - \text{PEEP}) \quad (9)$$

Normal airway resistance ( $R_{\text{aw}}$ ) is 1 to 3 cm H<sub>2</sub>O/l/s; normal compliance of the respiratory system ( $C_{\text{RS}}$ , *i.e.*, lung plus chest wall, is 80 to 100 ml/cm H<sub>2</sub>O.<sup>41</sup> Separating PIP and  $P_{\text{PLAT}}$  is key for the correct measurement of  $R_{\text{aw}}$  and  $C_{\text{RS}}$ .<sup>42</sup> PIP is the highest pressure measured at the airway during a mechanical breath and is determined by size of the tidal volume ( $V_{\text{T}}$ ), inspiratory flow rate,  $R_{\text{aw}}$ , and  $C_{\text{RS}}$ .  $P_{\text{PLAT}}$  is the pressure measured at the end of inspiration when flow is held, *i.e.*, zero flow, and is determined solely by  $V_{\text{T}}$  and  $C_{\text{RS}}$ . Basic ventilatory settings do not separate PIP and  $P_{\text{PLAT}}$ , but most ventilators provide ways to measure and visualize them. An **end-inspiratory pause** closes the inspiratory valve without opening the expiratory valve, pausing flow for an adjustable period of 0.5 to 2 s, and displays the values of  $R_{\text{aw}}$  and  $C_{\text{RS}}$ . A typical inspiratory pause is executed with the ventilator on **volume control**, constant flow rate (“square flow waveform”); if possible, setting the flow rate at 60 l/min (1 l/s) simplifies  $R_{\text{aw}}$  calculation. We caution the practitioner to examine the actual traces on the ventilator screen, because inaccuracies do occur from unplanned changes in settings or artifacts due to spontaneous respiration, coughing, or leaks. Most critical care ventilators add the pause to a single breath without altering other parameters, thus allowing measurement on the ongoing ventilatory settings. Most anesthesia ventilators incorporate an end-inspiratory pause as a percentage of the set inspiratory time to all subsequent breaths; by doing so, the delivery of the breath changes, and with that the mechanics of the breath. Figure 4 shows such

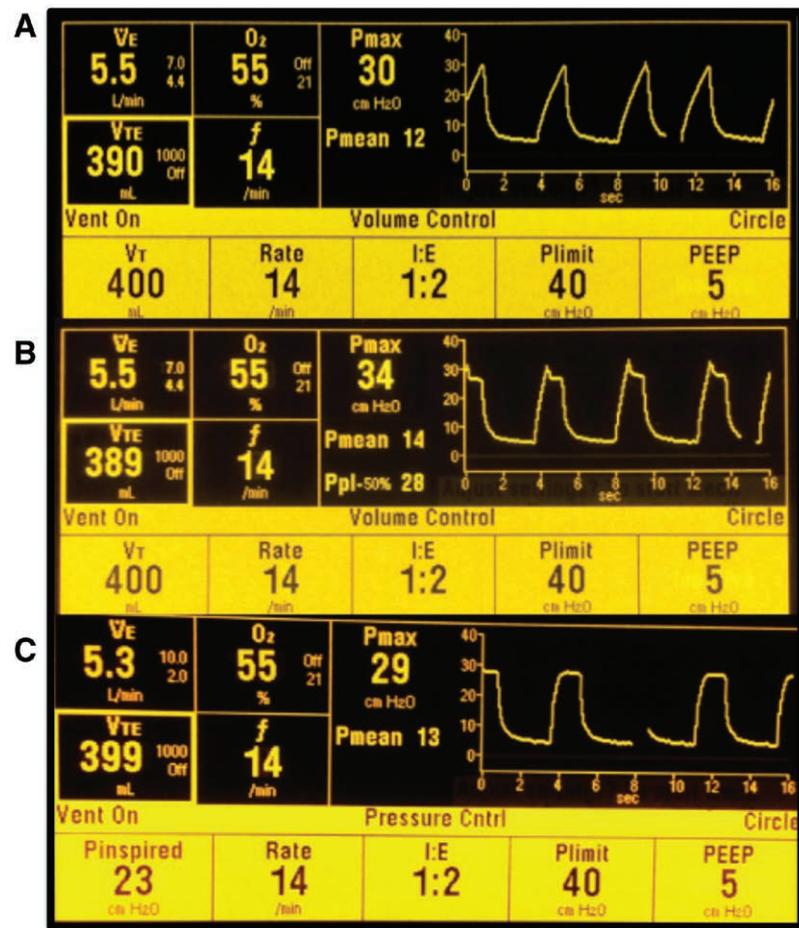
occurrence: by including the zero-flow pause in the set inspiratory time, the ventilator must deliver the set volume in a shorter time, which can only be done by increasing inspiratory flow, which in turn will result in higher PIP and sometimes in changes of  $P_{\text{PLAT}}$  and  $V_{\text{T}}$ , altering the measurement of  $R_{\text{aw}}$  and  $C_{\text{RS}}$ . Most anesthesia ventilators do not display the actual value of  $R_{\text{aw}}$ , but one can still get an approximate idea by assessing the difference between PIP and  $P_{\text{PLAT}}$ : when  $R_{\text{aw}}$  is increased by, *e.g.*, bronchospasm, separation of PIP and  $P_{\text{PLAT}}$  is clearly noticeable, and may subsequently change with an intervention such as administering a bronchodilator. Under the appropriate circumstances,  $C_{\text{RS}}$  (but not  $R_{\text{aw}}$ ) can be estimated without performing an inspiratory pause, provided that the pressure trace shows an identifiable plateau, as in figure 4C. This happens when flow is delivered with an initial peak followed by progressive decay throughout inspiration (“descending ramp” pattern), ideally reaching zero flow. This is the rule in **pressure control ventilation** and may be obtained also in volume control under appropriate settings.

As the mechanics of alveolar units vary, the time required to move air in and out may also vary both within and among areas of the lung. The time required by the respiratory system to change volume is described by the concept of **time constant** ( $\tau$ ):<sup>43</sup>

$$\tau = R_{\text{aw}} (\text{cmH}_2\text{O/l/s}) \times C_{\text{RS}} (\text{l/cmH}_2\text{O}) \quad (10)$$

Time constants are used to describe the **exponential time change of a dynamic system to reach a new steady state**, in our case filling or emptying of the lung or a lung unit. **One  $\tau$**  is the time in seconds taken to achieve 63% of maximal volume change of the lung unit; **every successive  $\tau$  will change 63% of the previous volume**; hence it takes **4  $\tau$** s to reach about 95% of the new steady state. The clinical relevance of this concept is that it allows to distinguish different forms of respiratory failure from a mechanical standpoint. For example, asthma and COPD have **slow  $\tau$**  because they have **high  $R_{\text{aw}}$**  and normal or high  $C_{\text{L}}$ ; conversely, ARDS has **fast  $\tau$**  because  $C_{\text{L}}$  is **low** and  $R_{\text{aw}}$  only moderately increased. The slow  $\tau$  of asthma and COPD is responsible for lung hyperinflation and expiratory flow limitation. The fast  $\tau$  of ARDS is responsible for the **short inspiratory time** (when not assisted by the ventilator) and **tendency to de-recruit**.

**Mechanics of Expiration.** During expiration, the most relevant measurement is **auto-PEEP**—also “intrinsic PEEP” or “occult PEEP.”<sup>44</sup> **Auto-PEEP** is positive alveolar pressure ( $P_{\text{ALV}}$ ) at end expiration, where normally we expect it to be equal to the pressure measured at the airway opening ( $P_{\text{PLAT}}$ ), *i.e.*, 0 cm H<sub>2</sub>O (atmospheric pressure) or PEEP. Auto-PEEP occurs by **two main mechanisms**, shown in figure 5. First, there is **insufficient time to exhale** the full  $V_{\text{T}}$  because the relaxation time of the respiratory system is longer than the allocated expiratory time, be it spontaneous or set on the ventilator. Such is the situation of **long  $\tau$**  in



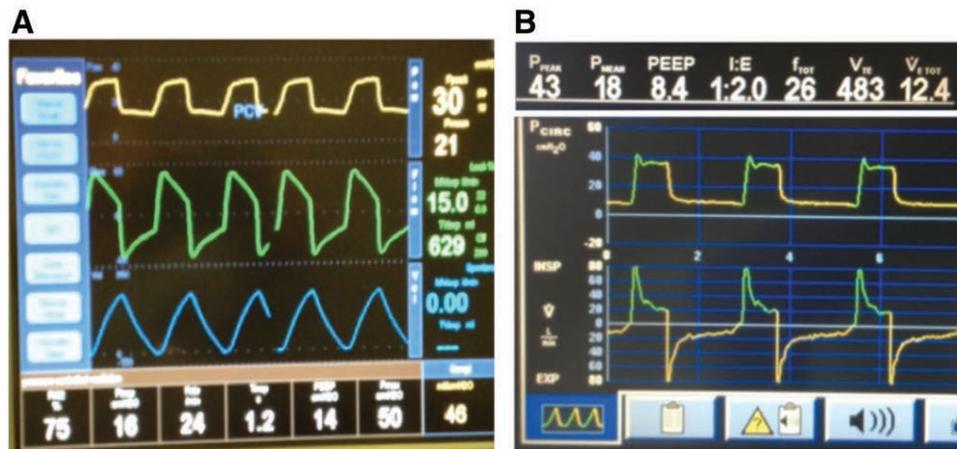
**Fig. 4.** Photographs of anesthesia ventilator screens during robotic abdominal hysterectomy; abdomen is insufflated, position steep Trendelenburg; traces are of airway pressure over time. Measured variables are in yellow over black background, set variables in black over yellow. (A) Volume control constant flow ventilation; note peak inspiratory pressure ( $P_{MAX}$ ) of 30 cm H<sub>2</sub>O. (B) Same mode of ventilation with end-inspiratory pause of 50% of inspiratory time. Note the higher  $P_{max}$  (34 cm H<sub>2</sub>O) generated by the higher inspiratory flow necessary to compensate for the pause in inspiratory flow. Tidal volume ( $V_{te}$ ) remained the same, and plateau pressure ( $P_{pl-50\%}$ , 28 cm H<sub>2</sub>O) nearly the same as the  $P_{max}$  prior to inducing the inspiratory pause. (C) Pressure control ventilation set to generate the same  $V_{te}$  is nearly equal to  $P_{pl-50\%}$ , indicating that (1) with pressure control, the peak inspiratory pressure ( $P_{max}$  in the figure) is the plateau pressure; and (2) the pressure that generates a certain tidal volume, which is the plateau pressure, is nearly the same in all three conditions.  $\dot{V}_E$  minute ventilation.

pure bronchospasm. Second is by the presence of expiratory flow limitation, characteristic of COPD due to loss of elastic recoil of the lung and supporting structure of the airways. As the volume of the lung decreases during exhalation, so does the diameter of the airways, possibly down to full collapse; this is often further amplified when the expiratory muscles are activated and generate a positive pressure around the airways.

Auto-PEEP has some of the effects of set PEEP: it may recruit the lung and may damage the lung. When generated during mechanical ventilation by prolonging inspiratory time, auto-PEEP may improve  $PaO_2$  through alveolar recruitment<sup>45</sup>; when generated by trapped gas in status asthmaticus, auto-PEEP may overstretch and damage the

lung.<sup>46</sup> Just like set PEEP, auto-PEEP may decrease cardiac output and arterial blood pressure.<sup>41</sup> Differently from set PEEP, auto-PEEP increases work of breathing; when breathing normally from FRC or from a set PEEP, a minimal negative pressure starts inspiratory flow and initiates a breath; with auto-PEEP, this negative pressure has to overcome the positive  $P_{ALV}$  before decreasing to less than 0 and starting inspiratory flow. This added pressure constitutes wasted effort because it does not generate any volume, and may ultimately cause fatigue in susceptible patients.<sup>47</sup>

Measurement of auto-PEEP is carried out on a ventilator through an expiratory pause,<sup>42</sup> which closes the expiratory valve without opening the inspiratory valve, and equilibrates  $P_{ALV}$  across different lung units; the positive



**Fig. 5. Mechanisms of auto-PEEP:** persistence of expiratory flow at the end of expiration. In both panels, mode of ventilation is pressure control; upper trace is pressure, lower trace is flow; bottom trace in (A) is volume. (A) The flow trace is abruptly interrupted in both inspiration and expiration, suggesting an insufficient time to maintain a high minute ventilation (15 l/min), likely compounded by increased airway resistance. (B) At a slightly lower minute ventilation (12.4 l/min), the expiratory flow trace shows an initial rapid drop followed by a long, nearly flat portion, eventually interrupted by the beginning of the successive breath. This pattern is suggestive of expiratory flow limitation characteristic of chronic obstructive respiratory disease. Note that at the time of expiratory flow changing direction upwards to pursue inspiration, flow rate is still substantial, 20 l/min, suggesting a considerable amount of residual alveolar pressure at end expiration, auto-PEEP.  $V_{TE}$ , tidal volume;  $\dot{V}_{E\text{TOT}}$ , minute ventilation.

airway pressure trace will rise to a plateau above 0 or PEEP, the difference being auto-PEEP. Just like an inspiratory pause, this maneuver is optimal in the absence of spontaneous efforts and with a low respiratory frequency. Of note, even during a pause, the value of positive airway pressure will still be the lowest measured, and if the pause is not sufficiently long, there may be areas of the lung where  $P_{ALV}$  is still higher than the measured auto-PEEP.<sup>48</sup> When this maneuver is not available, as in most anesthesia ventilators, the presence of auto-PEEP can be inferred, but not quantified, by examining the expiratory flow trace, which will be truncated before reaching zero flow at end expiration, as shown in both panels of figure 5.

**Regional Lung Mechanics: The Inhomogeneous Lung.** Bedside measurements of respiratory mechanics provide values that pertain to the respiratory system as a whole. Similar to  $\dot{V}/\dot{Q}$ , minor mechanical inequalities develop during normal respiration, and their impact is trivial; however, regional changes in mechanics develop with the onset progression of respiratory disease, affect respiratory function, and may invalidate standard measurements.

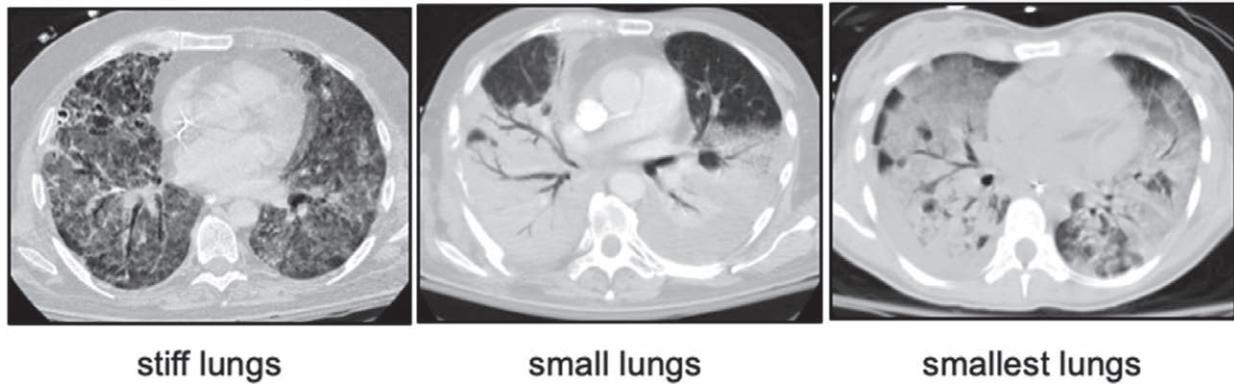
*Regional inhomogeneity in  $R_{aw}$*  develops in asthma and COPD due to weakened elastic recoil, active bronchospasm, inflammatory changes, and trapping of gas. A common result is regional lung hyperinflation, described during spontaneous as well as general mechanical breathing,<sup>48,49</sup> and visually confirmed by advanced imaging techniques.<sup>50</sup> Dynamic reduction in airway caliber may progress to complete obstruction and exclude hyperinflated areas of the lung from standard measurements, underestimating the

potential for lung damage, hypoventilation, and hemodynamic compromise.

*Regional inhomogeneity of  $C_{RS}$*  during general anesthesia and respiratory failure was demonstrated with the introduction of lung computerized tomography in the 1980s,<sup>51,52</sup> opening the way to the understanding of alveolar recruitment and damage during mechanical ventilation, and to the development of innovative strategies of lung protective ventilation.<sup>53</sup> Figure 6 shows computerized tomography scans of patients with acute respiratory failure and severe hypoxemia with similarly diminished  $C_{RS}$  by bedside measurement, whose regional mechanical characteristics are manifestly different. The “stiff” lungs will require high ventilating pressures that will distribute throughout severely diseased lung tissue, possibly causing diffuse damage. The “small” lungs will receive ventilating pressures intended to the entire lung but delivered mainly to a small portion of it, possibly causing damage to the small lung and doing very little to the consolidated lung. The last set of lungs seems impossible to ventilate, which was indeed the case: this patient was treated by extracorporeal membrane oxygenation for three weeks.

Further attention to ventilatory mechanics during anesthesia and intensive care requires understanding the interaction between lung and chest wall.<sup>54</sup>  $C_{RS}$  measured ordinarily at the bedside comprises the compliances in series of lung ( $C_L$ ) and chest wall ( $C_{CW}$ ). Like electrical capacitances in series, the reciprocal of each compliance adds up to the reciprocal of the total:

$$\frac{1}{C_L} + \frac{1}{C_{CW}} = \frac{1}{C_{RS}} \quad (11)$$



**Fig. 6. Regional inhomogeneity of lung compliance.** High resolution computerized tomography scans of three patients with acute respiratory failure and low lung compliance, with noticeably different patterns of distributions of lung injury. The patient on the *left* had fungal pneumonia in the setting of prolonged immunosuppression. The patient in the *middle* had bibasilar dorsal pneumonic infiltrates and a sizable left pleural effusion; note the stark demarcation between affected and (at least by imaging) spared lung. The patient on the *right* was approximately 10 days into the course of acute respiratory distress syndrome after near drowning; only small areas of apparently inflated lung are visible ventrally and possibly in the dorsal aspect of the left lung; also notice right subpleural loculated pneumothoraces, possibly indicative of barotrauma.

Normal values in  $\text{ml/cm H}_2\text{O}$  are:  $C_{RS} = 100$ ,  $C_L = 200$ , and  $C_{CW} = 200$ . During mechanical ventilation, we are interested in the lung; it is the lung that we want to expand and we do not want to damage. By measuring  $C_{RS}$ , we extrapolate to the lung what we are actually measuring on the lung and chest wall, and for the most part, the information is valuable.

Under certain circumstances, understanding the mechanics of ventilation may require knowledge of the separate contributions of lung and chest wall. During normal respiration, at FRC the inward elastic force of the lung is equally balanced by the outward elastic force of the chest wall, resulting in a  $P_{ALV}$  equal to atmospheric (0) pressure, and a pressure in the pleural cavity ( $P_{PL}$ ) slightly less than atmospheric pressure. Due in part to gravity,  $P_{PL}$  is more negative in ventral than dorsal areas of the lung in the supine position, reversed in the prone position,<sup>55</sup> and again more negative in the nondependent lung than in the dependent lung in the lateral position.<sup>47</sup> As FRC decreases after induction of general anesthesia,  $P_{PL}$  increases toward and above 0, promoting airway closure and atelectasis.<sup>26</sup> The key physiologic parameter here is the pressure generated across the lung, or *transpulmonary pressure* ( $P_{TP}$ ):

$$P_{TP} = P_{ALV} - P_{PL} \quad (12)$$

A positive  $P_{TP}$  keeps the alveoli open: under normal circumstances at FRC,  $P_{ALV}$  is 0 and  $P_{PL}$  slightly negative, hence  $P_{TP}$  is positive; with PEEP,  $P_{ALV}$  is positive and  $P_{PL}$  less positive than  $P_{ALV}$ ; with anesthesia, pulmonary edema, and abdominal distention,  $P_{PL}$  increases above  $P_{ALV}$  and  $P_{TP}$  turns negative, causing alveolar collapse and atelectasis.<sup>56</sup>

Clinically,  $P_{ALV}$  is reliably estimated by  $P_{PLAT}$  but  $P_{PL}$  requires indirect measurement by means of special thin-walled balloons positioned *via* the nares into the esophagus (esophageal pressure).<sup>57</sup> The value of esophageal pressure as a measurement of  $P_{PL}$  has been somewhat controversial, but recent studies have confirmed its reliability in selected situations with close attention to proper positioning and calibration.<sup>58,59</sup> Measuring  $P_{TP}$  as the target to PEEP titration in patients with ARDS has revealed the need for higher PEEP to provide effective recruitment of regional lung collapse and allow protective ventilation.<sup>60,61</sup> Under general anesthesia, the use of a lung protective strategy of higher PEEP with or without direct measurement of  $P_{TP}$  seems to ideally suit morbidly obese patients<sup>62,63</sup> and patients undergoing laparoscopic surgery, particularly in the steep Trendelenburg position, where  $P_{PL}$  increases further.

**Contrasting Spontaneous Breathing and Controlled Mechanical Ventilation.** During a spontaneous inspiration, the chest wall expands by its elastic recoil and by the action of the inspiratory muscles, making  $P_{PL}$ , the pressure surrounding the lung, more negative than at end expiration. Since at the airway opening the pressure remains atmospheric,  $P_{TP}$  is positive and lung volume increases. During controlled mechanical ventilation, pressure is positive,  $P_{ALV}$  increases,  $P_{PL}$  increases a fraction of  $P_{ALV}$ , and  $P_{TP}$  is again positive. For the same pressure applied and constant respiratory mechanics, changes in  $P_{TP}$  will be the same, and  $V_T$  will be the same in spontaneous and mechanical breathing. During assisted breathing, where tidal ventilation is the result of a cooperative effort of patient and ventilator, the mechanical situation is more complex, with a few points worth noting.

First, for the same  $V_T$ , the change in  $P_{TP}$  will be the same, independent of the mode of ventilation (fig. 4), and so will be the potential degree of lung damage. Second, when the lung volume increases during spontaneous ventilation,  $P_{PL}$  becomes more negative; when the lung volume increases during controlled tidal ventilation,  $P_{PL}$  becomes more positive; in both cases,  $P_{ALV}$  must be lower than the pressure in the airways for inspiratory flow to occur. Therefore, while during controlled mechanical ventilation  $P_{ALV}$  is higher than the set end expiratory pressure throughout the respiratory cycle, during spontaneous inspiration,  $P_{ALV}$  must become lower than the end expiratory pressure.

These differences have profound influences on the interaction between heart and lung function, and ultimately on hemodynamics and on the fluid balance of the lung interstitium. In particular, when spontaneous breathing generates significant decreases in intrathoracic and/or alveolar pressures, these may contribute to the generation of pulmonary edema, cardiogenic and not,<sup>64,65</sup> and may worsen lung injury.<sup>66</sup>

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## Competing Interests

The authors declare no competing interests.

## Correspondence

Address correspondence to Dr. Bigatello: Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, 800 Washington Street, Boston, Massachusetts 02115. lbigatello@gmail.com. Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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