Dynamic Hyperinflation and Auto–Positive End-Expiratory Pressure

Lessons Learned over 30 Years

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Auto–positive end-expiratory pressure (auto-PEEP; AP) and dynamic hyperinflation (DH) may affect hemodynamics, predispose to barotrauma, increase work of breathing, cause dyspnea, disrupt patient–ventilator synchrony, confuse monitoring of hemodynamics and respiratory system mechanics, and interfere with the effectiveness of pressure-regulated ventilation. Although basic knowledge regarding the clinical physiology and management of AP during mechanical ventilation has evolved impressively over the 30 years since DH and AP were first brought to clinical attention, novel and clinically relevant characteristics of this complex phenomenon continue to be described. This discussion reviews some of the more important aspects of AP that bear on the care of the ventilated patient with critical illness.

Keywords: dynamic hyperinflation; gas trapping; auto–positive end-expiratory pressure; intrinsic positive end-expiratory pressure; airflow obstruction; mechanical ventilation; monitoring

Caregiver awareness of the wide-ranging importance of dynamic hyperinflation (DH) has been comparatively recent. Although basic principles of its management are now well recognized, understanding of the clinical nuances of DH continues to evolve. This overview—admittedly a selective and personal perspective—approaches the topic from a physiologic standpoint directed toward interpretation and management of DH in the mechanically ventilated patient.

TERMINOLOGY

Several terms related to incomplete deflation of the lung during mechanical ventilation have been used in the medical literature, but not always consistently. Alveolar pressure at the end of passive expiration may exceed set positive end-expiratory pressure (PEEP) when the expiratory phase cannot be completed to the fully relaxed position of the respiratory system before the next inspiration initiates (1–4) (Figure 1). The resulting pressure gradient driving end-expiratory flow (auto-PEEP, from the Greek word *autos* for "self") persists until interrupted by inspiratory forces generated by patient or ventilator (5–7). Total end-expiratory alveolar pressure (total PEEP) is the sum of the applied PEEP and auto-PEEP (AP). Unlike applied PEEP, AP (and therefore total PEEP), which is generated distally in lung units with diverse mechanical properties, may not distribute uniformly throughout the diseased lung.

Confusion has arisen regarding the alternative term "intrinsic PEEP," a label suggested after AP was first described (4) and often regarded as synonymous (6, 8). AP and intrinsic PEEP can logically be used interchangeably when no PEEP is set. (In fact, to avoid overlap with already well-established, preexisting physiologic abbreviations, both AP and intrinsic PEEP are usually abbreviated "PEEPi.") Using this alternative nomenclature, PEEP set by the clinician is termed extrinsic PEEP, whereas intrinsic PEEP usually refers to total (internal) PEEP, not just the dynamically generated pressure component (6, 7). (When doing so, AP would correspond to the difference between intrinsic and extrinsic PEEP). Such intrinsic/extrinsic terminology is frequently used in research (8). Clinically, however, set PEEP is seldom referred to as extrinsic PEEP, whereas end-expiratory pressure in excess of the applied value continues to be called AP by most caregivers. This makes good sense for several reasons: (*1*) PEEP is the traditional term for applied end-expiratory pressure; (*2*) the primary connotation of intrinsic evokes an innate or inherent property rather than one that changes with resistance, position, and breathing pattern; and (*3*) intrinsic/extrinsic labeling invites the parallel with internal (total)/external (applied)—leaving the dynamic component unnamed. For clarity in the remainder of this paper, the dynamic component of total PEEP will be consistently termed auto-PEEP and abbreviated AP.

Air (or gas) trapping is also interpreted with varied meanings. In the context of passive ventilation, air trapping and DH are usually used interchangeably. Yet, insufficient deflation time may produce DH without physically trapping gas (1), and gas trapping may occur without generalized DH. For example, persistence of inspiratory muscle activity during early expiration and glottic braking are common contributors to DH in nonintubated patients with asthma (9–12), whereas dependent gas trapping that reverses at modest tidal inspiratory pressures may be observed in settings such as obesity (13–15) and acute respiratory distress syndrome (ARDS) (16–18), especially in recumbency (see further).

Flow limitation (FL) describes the dynamic condition that occurs when gas flow cannot be increased further by raising alveolar pressure or reducing airway opening pressure (19–21), due either to wave speed limitation (22, 23) or to small airway collapse at a critical closing pressure (23, 24). Because the lungs cannot decompress during tidal exhalations of any sustainable duration, true gas trapping very often results from FL and airway closure (functional or physical, global or regional; *see* below).

RELATIONSHIP OF AP TO DH

AP-driven end-expiratory flow encountered in a passive individual invariably implies DH in proportion to respiratory system

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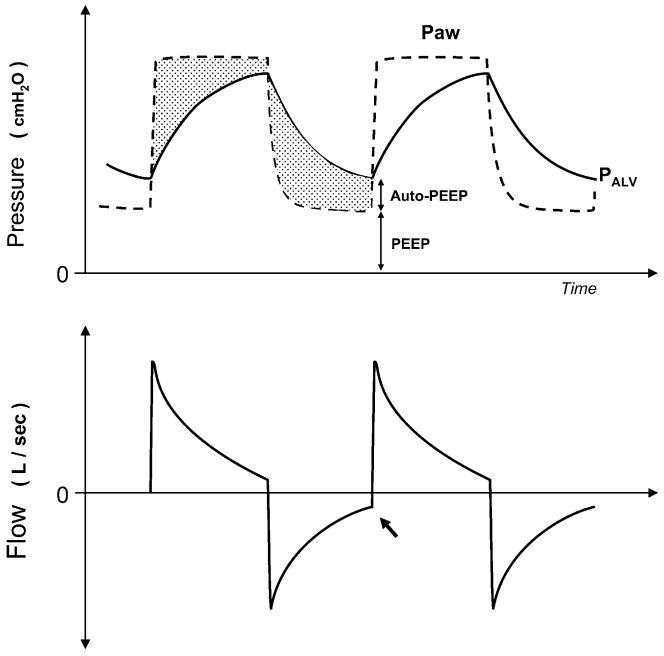

Figure 1. Relationship of auto–positive end-expiratory pressure (AP) to PEEP, driving pressure, and terminal expiratory flow during pressure-controlled ventilation. *Shaded areas* indicate the flow driving pressure gradients during inspiration and expiration. When exhalation terminates before equilibration can be achieved between airway (Paw) and alveolar (Palv) pressures, end-expiratory flow (*arrow*) persists, and total PEEP exceeds the set value, producing dynamic hyperinflation that can be modified with changes of breathing pattern.

compliance. Expiratory muscular activity, however, invalidates this assumption. For example, during vigorous aerobic exercise, flow persists to the very end of expiration even in healthy individuals, as expiratory effort compresses the respiratory system to a volume lower than relaxed FRC (25). By doing so, compression shares the work of chest inflation with the expiratory muscles, which temporarily store inflation energy as the potential for outward recoil of the chest wall (26).

MEASUREMENT OF AP AND DH

In cooperative outpatients with chronic airflow obstruction, inspiratory capacity (IC) tracks changes in DH, as TLC remains relatively fixed over the short term (27–29). Partial relief of DH by bronchodilators often improves IC and vital capacity more than flow-related spirometric indices (30). In spontaneously breathing but poorly cooperative persons, the cumulated inspired volume using a one-way inspiratory valve is a research-validated measure of IC (31, 32), which, although feasible, is seldom undertaken in ventilated patients.

End-expiratory flow reliably implicates AP during passive ventilation; however, the magnitude of flow bears little relation to the level of AP that drives it through an undetermined upstream resistance. At present, measuring static airway pressure after airway occlusion timed at end-exhalation remains the method most commonly used to quantify total PEEP and to index DH during passive ventilation (4). Under passive conditions, total PEEP can be measured by delaying a breath as precisely timed airway occlusion terminates flow at the very end of the usual expiratory period. Unfortunately, this maneuver cannot be performed reliably when the patient controls the breathing rhythm because of variations in the expiratory cycle length and/or muscular effort (33–35). This occlusion estimate is neither the highest nor lowest regional end-expiratory alveolar pressure during tidal breathing but rather the measurable volume-averaged value.

The positive airway pressure that just neutralizes expiratory flow at the exact onset of passive inflation (the zero-flow pressure), another estimate of AP (6), characterizes those compartments with less impeded deflation and, therefore, may reflect the difficulty of breath triggering while underestimating the extent of gas trapping (36). During unaided spontaneous breaths, the deflection of esophageal balloon pressure required to initiate flow has been used in research, but this value requires correction to account for the influence of expiratory muscle effort (34, 35). These latter methods are rarely used for this purpose in everyday practice. Moreover, however precise they might be, the resulting determinations of measurable AP may be unnecessary and misleading as indicators of DH. By contrast, an occlusion of brief duration to obtain a reproducible plateau at end-inspiration can be recorded by modern ventilators even when the breath is gently triggered. This end-inspiratory value may better reflect most hazards associated with DH than would AP itself (37).

CONSEQUENCES OF AP

AP may affect hemodynamics, predispose to barotrauma, increase work of breathing, cause dyspnea, disrupt patient–ventilator synchrony, confuse monitoring of hemodynamics and respiratory system mechanics, and interfere with the effectiveness of pressure-regulated ventilation (4–6, 38–42). Barotrauma risk and the hemodynamic and energetic costs of AP largely relate to any accompanying expansion of lung and chest wall volumes (DH), not to alveolar pressure *per se* (42). Therefore, as with the end-inspiratory plateau pressure, AP that occurs in association with stiff lungs or chest wall is less likely to be consequential for hemodynamics or muscle efficiency than the same value measured in a setting of better respiratory system compliance.

An important and occasionally overlooked point is that it is not total PEEP that risks overdistention, but rather the associated end-inspiratory alveolar pressure. This simple fact carries weight when confronting the trade-off between frequency and V_T to meet a specific minute ventilation ($\dot{V}_E$) target. In ventilated patients with airflow obstruction, flows in late expiration are disproportionately slow when compared with those of early expiration, especially in the presence of FL. Consequently, increasing frequency (as opposed to V_T) to achieve the same $\dot{V}_E$ tends to boost AP to a greater extent. However, differences among AP values with $\dot{V}_E$ held constant are typically modest across a wide range of frequency/tidal volume combinations (42, 43). Moreover, because higher frequency is paired with lower V_T, the resulting plateau pressure is usually less (44).

DH increases the inspiratory work of breathing for two primary reasons. First, initiation of inflow requires inspiratory force to counterbalance AP (5). During spontaneous efforts, AP raises tidal elastic pressure throughout inspiration. Second, the lung and chest wall are less compliant at high lung volumes. Inward recoil of the chest cage adds to lung recoil at thoracic volumes greater than 60% of predicted vital capacity (45). DH also compromises efficiency of the inspiratory pump, as muscle fibers foreshorten and the inspiratory geometry becomes less conducive to force generation (46). It is no surprise, then, that dyspnea correlates strongly with DH (47–49). Independently of associated DH, AP of itself may cause dyssynchronous ventilation, impaired triggering, and less effective inspiratory pressures, with attendant consequences for ventilation efficiency and comfort (40, 50).

In patients with acutely exacerbated chronic obstructive pulmonary disease (COPD) or *status asthmaticus*, relative hypotension almost invariably follows intubation and ventilation with positive pressure. Hypotension relates in part to sedation and to the cessation of the markedly negative inspiratory pleural pressure deflections that otherwise occur during labored spontaneous breathing (51). DH itself makes an important contribution, however, as it not only increases pulmonary vascular resistance and right ventricular afterload, but the associated AP elevates pleural and right atrial pressures, impeding venous return (4, 52). Because the proportion of alveolar pressure transmitted to the pleural space is determined by the ratio of chest wall elastance to total respiratory system elastance, pulmonary vascular, pleural, and right atrial pressures elevate more when the lungs are flexible than when they are not. During cardiopulmonary resuscitation of patients with airflow obstruction, AP generated by overzealous "bagging" impairs ventricular loading and can result in pulseless electrical activity reversible by reducing ventilation (53, 54).

DETERMINANTS OF DYNAMIC HYPERINFLATION AND AP

Under passive conditions, the addressable variables that tend to increase DH and AP are increased airway resistance, long inspiratory duty cycle (T_I/T_{tot}), and high $\dot{V}_E$ (55, 56). Among these targets for therapy, perhaps the most effective strategy is to reduce ventilation (43). Lessening $\dot{V}_E$ and accepting associated hypercapnia was adopted as a life-saving approach for the treatment of intubated patients with asthma well before permissive hypercapnia was implemented for ARDS (57).

Manipulation of the ventilatory pattern also influences DH, but reducing Ti/Ttot is generally of limited effectiveness when $\dot{V}_E$ remains unchanged (44, 56). Many who require ventilatory assistance for airflow obstruction have biphasic flow curves during tidal exhalation, with the second phase much slower than the first. Tidal FL is present in a large proportion of such patients (58, 59). Such biphasic deflation patterns are more often observed in COPD than in acute asthma but do occur in both (60, 61). Under these circumstances, increasing frequency may help take advantage of the relatively faster kinetics of early deflation. When $\dot{V}_E$ is kept unchanged, increasing frequency may negligibly worsen (or even benefit) global (44) or regional gas trapping (*see below*).

For many didactic purposes, the respiratory system is modeled as a single compartment characterized by unique parameters of mechanics: resistance (R) and compliance (C). In such a simplistic model, their RC product—the time constant—succinctly characterizes the rate of passive, uniexponential expiratory flow decay, whatever the lung size may be. But because they are expressed in absolute units, individual values of R and C should be referenced to the size (capacity) of the aerated compartment (62–64). During ARDS, for example, R is high and C is low, whereas the specific R and specific C per unit of air-containing lung are much closer to normal levels (63). Therefore, although it is technically accurate to describe resistance as "high" in ARDS (65–68), it is an error to infer that the dimensions of the functioning airways are proportionately compromised at usual levels of PEEP (*see* below). Although compression of dependent airways and tissue viscoelastance almost certainly contribute (69, 70), AP detected in ARDS may owe primarily to the relatively high $\dot{V}_E$ that flows through a reduced number of conducting airways of the functional "baby" lung (71). Some modest level of AP is demonstrable even in nonobstructed patients at high $\dot{V}_E$ (e.g., during sepsis) due in part to the endotracheal tube, especially when it is partially kinked or soiled (72).

HETEROGENEITY OF AP

Diverse mechanical environments often exist within the diseased lung (Figure 2). A tendency for dependent airway closure, already evident in normal individuals (73, 74), is accentuated in recumbency, obesity, acute lung injury, and emphysema (13, 14, 75–77) (Figure 3). In all conditions, airway biofluids pool in dependent zones, further increasing their resistance. Dependent airway closure tends to occur before end-expiration, trapping gas at alveolar pressures that exceed the measurable AP (37). Because of such "early" airway closure, AP (which is measured through air channels that remain patent), may dramatically underestimate DH and barotrauma risk in patients with asthma.

With all airways open, an unambiguously stable value of AP is achieved within 2 to 3 seconds of airway occlusion (4, 35, 78). This is not the case, however, when extensive dependent airway closure occurs, as gas trapped in these zones gradually decompresses into the central airways, raising AP with a characteristic pressure wave signature that continues to slowly rise for many seconds after occlusion (Figure 4) (37, 66). It is interesting to note that this regional gas trapping signature may only appear when $\dot{V}_E$ (and therefore overall lung dimensions) falls to relatively low values, allowing dependent airway closure that is otherwise prevented by interdependence of the hyperinflated lung. It is not surprising, therefore, that regional trapping and its slowly rising waveform signature can be eliminated by raising PEEP or $\dot{V}_E$. As already noted, for a fixed tidal volume, end-inspiratory plateau pressure is a better guide than the measurable AP to DH severity and treatment response (37).

One implication of zonal airway closure is that sitting, supine, and lateral decubitus positions may be associated with disparate degrees of dyspnea, gas trapping, FL, and PEEP responsiveness (49, 77, 79). The need to avoid positional volume loss and gas trapping helps account for orthopnea experienced by patients with asthma and COPD (49, 79).

VARIANTS OF OBSTRUCTED AIRFLOW, AP

AP may develop despite structurally normal airways (e.g., lung resection, external airway compression, hyperpnea), in narrowed

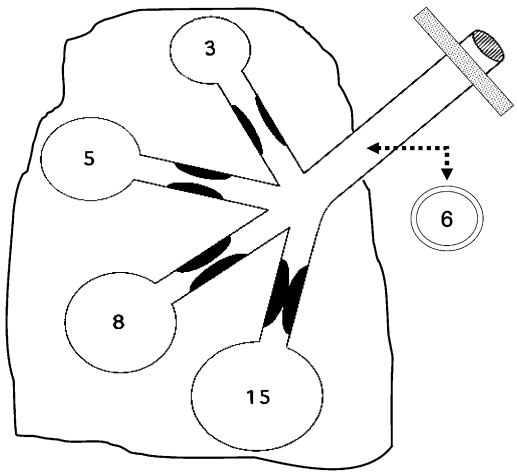

Figure 2. Spectrum of end-expiratory pressures within a mechanically heterogeneous lung and their relationship to measured auto–positive end-expiratory pressure (AP). When the external circuit is closed at end-expiration, the measured value for AP is the volume-weighted average of pressures within lung units that communicate with it. Some units that effectively close before the end of expiration is reached have higher regional AP values that elude clinical measurement.

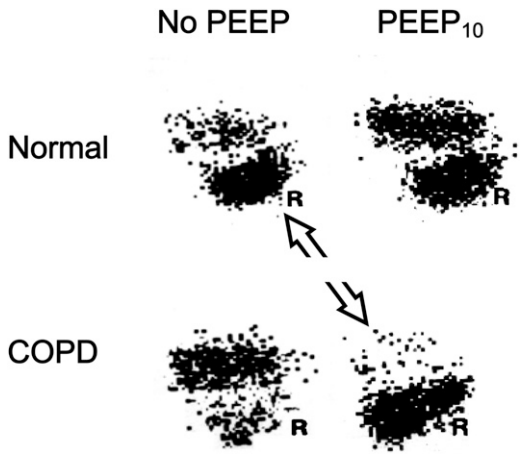

Figure 3. Radioisotope ventilation scan of a normal subject and a patient with chronic obstructive pulmonary disease (COPD) in the left lateral decubitus position at two levels of positive end-expiratory pressure (PEEP; 0 and 10 cm H_2O). The dependent lung of the patient with COPD ventilates poorly at ambient airway pressure. Application of 10 cm H_2O PEEP restores the normal distribution of dependent ventilation, presumably because the dependent airways are prevented from collapse (modified by permission from Reference 77.)

airways without FL, and in obstructed airways with FL (5, 80). It is generally accepted that FL during tidal breathing is more likely to occur during an exacerbation of COPD than an acute asthmatic attack (81). During unaided spontaneous breathing, tidal FL closely associates with dynamic hyperinflation; DH may not occur in outpatients with COPD until tidal expiratory flow encroaches on the maximal flow volume envelope, making the costs of hyperinflation energetically worthwhile (27, 28). Individuals with flow-limited DH often respond to an inhaled bronchodilator by reducing end-tidal lung volume in preference to improving maximal spirometric rates of airflow (e.g., FEV_1) (30). Failure of expiratory flow to accelerate as a gentle negative pressure (negative 3–5 cm H_2O) is applied to the airway is a test of FL seldom conducted apart from research protocols (20). Observing the flow responses to gentle epigastric pressure or PEEP has been recommended to more simply gauge FL and may offer clinical application in the ventilated patient (82).

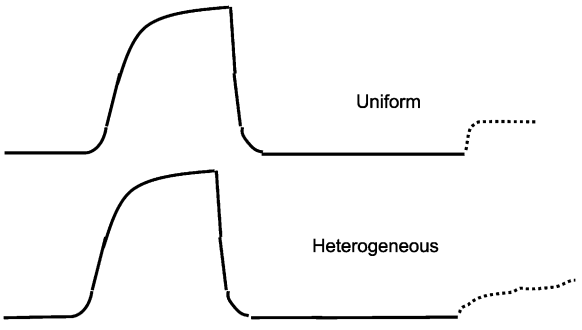

Figure 4. Comparison of the airway pressure signatures during airway occlusion (*dashed segments*) of lungs with airways that are uniformly open at end-expiration (*top panel*) and those composed of mechanically heterogeneous subunits, a proportion of which decompress very slowly into the central airway during central airway occlusion (*bottom panel*). *See* text and Figure 2.

PEEP ON AP

Whether adding PEEP benefits the ventilated patient with AP depends critically on the level of PEEP used and whether tidal expiration is flow limited (5, 24, 80). Unless airway recruitment occurs, adding PEEP to lungs without FL simply distends them further. If tidal deflation is flow limited, however, applying PEEP less than the critical closing pressure—reasonably estimated as about 80% of the occlusion-measured original AP (83)—narrows the difference between alveolar and airway opening pressures without a proportionate rise in lung volume. Assuming flow-limited exhalation, adding PEEP to the airway of a patient receiving flow-controlled, volume-cycled ventilation exerts little impact on the plateau pressure until AP is nearly counterbalanced. Beyond that level, however, adding PEEP while maintaining V_T causes plateau pressure to rise in proportion to the PEEP increment. In contrast, in pressure-targeted ventilation with the set inspiratory pressure referenced to the applied PEEP (driving airway pressure held constant), adding PEEP less than AP will increase the effective driving pressure and the resulting VT. Once AP is counterbalanced, further PEEP increments do not increase VT and may even decrease it as the hyperinflated lung stiffens further. In either mode, judicious reduction of AP with added PEEP improves triggering sensitivity and lessens the work of breathing, even as the end-expiratory dimensions of the lung remain little affected (5). Monitoring the plateau pressure during volume-cycled ventilation or the delivered tidal volume during pressure-controlled ventilation helps the clinician determine when the added PEEP is optimized.

Counterbalancing AP in flow-limited patients may have a defensible rationale in fully controlled as well as in patient-triggered ventilation. Applied PEEP tends to improve the ventilatory distribution of V_T by narrowing the range of regional total-PEEP values (84, 85). Adding PEEP may occasionally liberate sufficient volume from the most severely trapped zones to allow their partial decompression (Figure 5). In such cases,

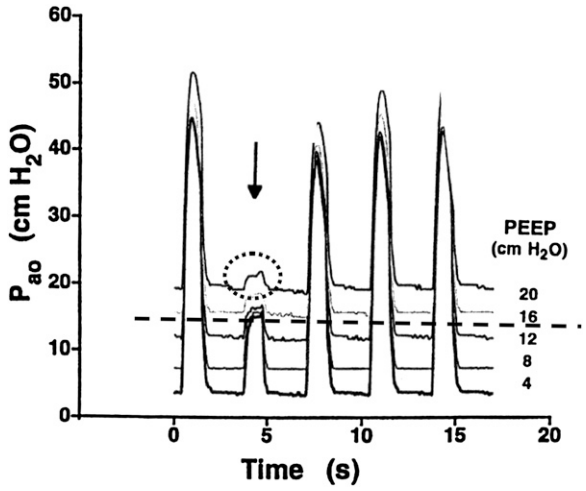

Figure 5. Superimposed airway pressure tracings during controlled ventilation with constant flow at multiple levels of positive end-expiratory pressure (PEEP). At each PEEP level, end-expiratory occlusion occurred after the first breath of each sequence (*arrow*). With no PEEP applied, the measured auto-PEEP (AP) was approximately 16 cm H_2O (*dashed line*) and diminished progressively with each step increment of PEEP less than that value. Total PEEP changed little until the original level of AP was exceeded. Note that some AP reemerged at 20 cm H_2O PEEP (*dashed circle*), indicating the reopening of units that had remained closed at lower airway pressures.

total PEEP rises little and in rare instances may even decline, albeit slightly (85). Hemodynamics are little changed (85, 86)

INTERACTIONS WITH VENTILATION

Dyssynchronous interactions between the neural controller and machine response are associated with discomfort, increased use of sedation, and adverse outcomes (40, 87–89). Incomplete lung emptying associated with DH presents challenges for breath-to-breath matching of power requirements during mechanical ventilation, because variations of effort caused by fluctuating AP are imperfectly matched by fixed targets for trigger threshold, maximal pressure, or flow. Moreover, in a real sense, DH that results from excessive pressure support is responsible for many adverse patient–ventilator interactions that relate to breath timing—both triggering and termination (40, 87). Nowhere is this more evident than in the application of pressure-regulated ventilation.

Pressure regulation underpins certain time-tested modes (pressure assist-control, pressure support) as well as modes that only now are gaining traction at the bedside (90). Because AP reduces the effective driving pressure resulting from the applied inspiratory airway pressure (41), increasing frequency may be accompanied by a decreasing V_T, so that V_E does not rise as much as anticipated. Conversely, a slowing of breathing frequency lessens AP, boosts inspiratory driving pressure, and may result in unintended increases of V_T. In comparison to patients with restrictive diseases, those with severe airflow obstruction exhibit greater V_T sensitivity to selections of both inspiratory time and cycling frequency (41).

An unintended lengthening of the inspiratory cycle time may occur in severely obstructed patients receiving pressure support if the flow criterion for cycling to the expiration phase is inappropriately low for that condition. In such instances, inspiratory flow decelerates relatively slowly, crowding the available time for exhalation and contributing to AP that, in turn, competes with the applied inspiratory pressure. If detected, this problem can be addressed by either raising the "off-switch" cycling percentage of the peak flow or by directly setting an appropriate inspiratory time length after a change to pressure assist-control.

Interactions between airway pressures and AP may result in a variable V_T when AP fluctuates with airway resistance or episodic tachypnea. Moreover, owing to the linkage between V_T and AP, serial breaths may differ with respect to effective driving pressure and V_T during pressure-supported breathing. In fact, chaotic breathing patterns may emerge at some flow off-switch settings, even when patient effort per cycle, R and C, and pressure support remain unchanged (91, 92).

AP AND MONITORING

AP was first described as occult because it surreptitiously boosted pleural and pulmonary vascular pressures, elevated pulmonary artery wedge pressure, and led to false clinical impressions of excessive left ventricular filling pressure (4). A similarly misleading effect of AP on routine measurements of respiratory system compliance was brought to clinical attention only shortly afterward (6). With total PEEP unmeasured, calculated tidal driving pressure is falsely high and respiratory system compliance underestimated (6). True physiologic effects of unsuspected AP may also contribute to the misinterpretation of systemic hemodynamics. For example, DH amplifies the respiratory variation of arterial pulse pressure and is a key contributor to *pulsus paradoxus* (and undulation of the pulse oximetry tracing) in mechanically ventilated patients (93), with entirely different implications regarding cardiac performance, pericardial compromise, and the logical next steps in hemodynamic management.

SUMMARY

Knowledge regarding the clinical physiology and management of AP during mechanical ventilation has evolved impressively over the 30 years since DH and AP were first brought to clinical attention. Awareness of their implications for hemodynamics, barotrauma, work of breathing, patient–ventilator interactions, and monitoring now seems integral to the scientific management of ventilated patients in a wide variety of clinical settings. Better understanding of DH has helped construct a solid—yet still incomplete—framework for cardiopulmonary management of several common forms of life-threatening critical illness requiring ventilatory assistance.

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References

1. Bergman NA. Intrapulmonary gas trapping during mechanical ventilation at rapid frequencies. *Anesthesiology* 1972;37:626–633.
2. Jonson B, Nordström L, Olsson SG, Akerback D. Monitoring of ventilation and lung mechanics during automatic ventilation: a new device. *Bull Physiopathol Respir (Nancy)* 1975;11:729–743.
3. Kimball WR, Leith DE, Robins AG. Dynamic hyperinflation and ventilator dependence in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1982;126:991–995.
4. Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction (the auto-PEEP effect). *Am Rev Respir Dis* 1982;126:166–170.
5. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. *J Appl Physiol* 1988;65:1488–1499.
6. Rossi A, Gottfried S, Zocchi L, Higgs BD, Lennox S, Calverley PM, Begin P, Grassino A, Milic-Emili J. Measurement of static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation. *Am Rev Respir Dis* 1985;131:672–677.
7. Gottfried SB, Reissman H, Ranieri VM. A simple method for the measurement of intrinsic positive end-expiratory pressure during controlled and assisted modes of mechanical ventilation. *Crit Care Med* 1992;20:621–629.
8. Brochard L. Intrinsic (or auto-) positive end-expiratory pressure during spontaneous or assisted ventilation. *Intensive Care Med* 2002;28:1552–1554.
9. Collett PW, Brancatisano T, Engel LA. Upper airway dimensions and movements in bronchial asthma. *Am Rev Respir Dis* 1986;133:1143–1149.
10. Shee CD, Ploy-Song-Sang Y, Milic-Emili J. Decay of inspiratory muscle pressure during expiration in conscious humans. *J Appl Physiol* 1985;58:1859–1865.
11. Muller N, Bryan AC, Zamel N. Tonic inspiratory muscle activity as a cause of hyperinflation in asthma. *J Appl Physiol* 1981;50:279–282.
12. Citterio G, Agostoni E, Del Santo A, Marazzini L. Decay of inspiratory muscle activity in chronic airway obstruction. *J Appl Physiol* 1981;51:1388–1397.
13. Holley HS, Milic-Emili J, Becklake MR, Bates DV. Regional distribution of pulmonary ventilation and perfusion in obesity. *J Clin Invest* 1967;46:475–481.
14. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol* 2010;108:206–211.
15. Koutsoukou A, Koulouris N, Bekos B, Sotiropoulou C, Kosmas E, Papadima K, Roussos C. Expiratory flow limitation in morbidly obese postoperative mechanically ventilated patients. *Acta Anesthesiol Scand* 2004;48:1080–1088.
16. Koutsoukou A, Armaganidis A, Stavrakaki-Kallergi C, Vassilakopoulos T, Lymberis A, Roussos C, Milic-Emili J. Expiratory flow limitation and intrinsic positive end-expiratory pressure at zero positive end-expiratory pressure in patients with adult respiratory distress syndrome. *Am J Respir Crit Care Med* 2000;161:1590–1596.
17. Richard JC, Brochard L, Breton L, Aboab J, Vandelet P, Tamion F, Maggiore SM, Mercat A, Bonmarchand G. Influence of respiratory

rate on gas trapping during low volume ventilation of patients with acute lung injury. *Intensive Care Med* 2002;28:1078–1083.
18. de Durante G, del Turco M, Rustichini L, Cosimini P, Giunta F, Hudson LD, Slutsky AS, Ranieri VM. ARDSNet lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002;165:1271–1274.
19. Hyatt RE. The interrelationships of pressure, flow and volume during various respiratory maneuvers in normal and emphysematous subjects. *Am Rev Respir Dis* 1961;83:676–683.
20. Valta P, Corbeil C, Lavoie A, Campodonico R, Koulouris NG, Chassé M, Braidy J, Milic-Emili J. Detection of expiratory flow limitation during mechanical ventilation. *Am J Respir Crit Care Med* 1994;150: 1311–1317.
21. Gay PC, Rodarte JR, Hubmayr RD. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. *Am Rev Respir Dis* 1989;139: 621–626.
22. Dawson SV, Elliot EA. Wave-speed limitation on expiratory flow: a unifying concept. *J Appl Physiol* 1977;43:498–515.
23. Hyatt RE. Expiratory flow limitation. *J Appl Physiol* 1983;55:1–8.
24. Tobin MJ, Lodato RF. PEEP, auto-PEEP, and waterfalls. *Chest* 1989;96: 449–451.
25. Grimby G, Bunn J, Mead J. Relative contribution of rib cage and abdomen to ventilation during exercise. *J Appl Physiol* 1968;24:159–166.
26. Martin JG, Shore S, Engel LA. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. *Am Rev Respir Dis* 1982;126:812–817.
27. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158:1557–1565.
28. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation: the role of lung hyperinflation. *Am Rev Respir Dis* 1993;148:1351–1357.
29. Yan S, Kaminski D, Sliwinski P. Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;156:55–59.
30. Paré PD, Lawson LM, Brooks LA. Patterns of response to inhaled bronchodilators in asthmatics. *Am Rev Respir Dis* 1983;127:680–685.
31. Marini JJ, Rodriguez RM, Lamb VJ. Involuntary breath stacking: an alternative method for vital capacity estimation in poorly cooperative subjects. *Am Rev Respir Dis* 1986;134:694–698.
32. Baker WL, Lamb VJ, Marini JJ. Breath-stacking increases the depth and duration of chest expansion by incentive spirometry. *Am Rev Respir Dis* 1990;141:343–346.
33. Lessard MR, Lofaso F, Brochard L. Expiratory muscle activity increases intrinsic positive end-expiratory pressure independently of dynamic hyperinflation in mechanically ventilated patients. *Am J Respir Crit Care Med* 1995;151:562–569.
34. Ninane V, Yernault JC, de Troyer A. Intrinsic PEEP in patients with chronic obstructive pulmonary disease: role of expiratory muscles. *Am Rev Respir Dis* 1993;148:1037–1042.
35. Zakynthinos SG, Vassilakopoulos T, Zakynthinos E, Roussos C. Accurate measurement of intrinsic positive end-expiratory pressure: how to detect and correct for expiratory muscle activity. *Eur Respir J* 1997; 10:522–529.
36. Hernandez P, Navalesi P, Maltais F, Gursahaney A, Gottfried SB. Comparison of static and dynamic measurements of intrinsic PEEP in anesthetized cats. *J Appl Physiol* 1994;76:2437–2442.
37. Leatherman JW, Ravenscraft SA. Low measured auto-positive end-expiratory pressure during mechanical ventilation of patients with severe asthma: hidden auto-positive end-expiratory pressure. *Crit Care Med* 1996;24:541–546.
38. Georgopoulos D, Mitrouska I, Markopoulou K, Patakas D, Anthonisen NR. Effects of breathing patterns on mechanically ventilated patients with chronic obstructive pulmonary disease and dynamic hyperinflation. *Intensive Care Med* 1995;21:880–886.
39. Thille AW, Cabello B, Galia F, Lyazidi A, Brochard L. Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure-support ventilation. *Intensive Care Med* 2008;34:1477–1486.
40. Epstein SK. Optimizing patient-ventilator synchrony. *Semin Respir Crit Care Med* 2001;22:137–152.
41. Marini JJ, Crooke PS, Truwit JD. Determinants and limits of pressure preset ventilation: a mathematical model of pressure control. *J Appl Physiol* 1989;67:1081–1092.
42. Leatherman JW, McArthur C, Shapiro RS. Effect of prolongation of expiratory time on dynamic hyperinflation in mechanically ventilated patients with severe asthma. *Crit Care Med* 2004;32:1542–1545.
43. Williams TJ, Tuxen DV, Scheinkestel CD, Czarny D, Bowes G. Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. *Am Rev Respir Dis* 1992;146:607–615.
44. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis* 1989;140:5–10.
45. Mead J. Respiration: pulmonary mechanics. *Annu Rev Physiol* 1973;35: 169–192.
46. Roussos C, Macklem PT. The respiratory muscles. *N Engl J Med* 1982; 307:786–797.
47. Palange P, Valli G, Onorati P, Antonucci R, Paoletti P, Rosato A, Manfredi F, Serra P. Effect of heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. *J Appl Physiol* 2004;97:1637–1642.
48. Stevenson NJ, Walker PP, Costello RW, Calverley PM. Lung mechanics and dyspnoea during exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:1510–1516.
49. Eltayara L, Ghezzo H, Milic-Emili J. Orthopnea and tidal expiratory flow limitation in patients with stable COPD. *Chest* 2001;119:99–104.
50. de Wit M. Monitoring of patient-ventilator interaction at the bedside. *Respir Care* 2011;56:61–72.
51. Stalcup SA, Mellins RB. Mechanical forces producing pulmonary edema in acute asthma. *N Engl J Med* 1977;297:592–596.
52. Oddo M, Feihl F, Schaller MD, Perret C. Management of mechanical ventilation in acute severe asthma: practical aspects. *Intensive Care Med* 2006;32:501–510.
53. Lapinsky SE, Leung RS. Auto-PEEP and electromechanical dissociation. *N Engl J Med* 1996;335:674–675.
54. Rogers PL, Schlichtig R, Miró A, Pinsky M. Auto-PEEP during CPR: an "occult" cause of electromechanical dissociation? *Chest* 1991;99:492–493.
55. Marini JJ, Crooke PS III. A general mathematical model for respiratory dynamics relevant to the clinical setting. *Am Rev Respir Dis* 1993;147: 14–24.
56. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis* 1987;136:872–879.
57. Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. *Am Rev Respir Dis* 1984;129:385–387.
58. Kondili E, Alexopoulou C, Prinianakis G, Xirouchaki N, Georgopoulos D. Pattern of lung emptying and expiratory resistance in mechanically ventilated patients with chronic obstructive pulmonary disease. *Intensive Care Med* 2004;30:1311–1318.
59. Calverley PMA, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. *Eur Respir J* 2005;25:186–199.
60. Boczkowski J, Murciano D, Pichot M-H, Ferretti A, Pariente R, Milic-Emili J. Expiratory flow limitation in stable asthmatic patients during resting breathing. *Am J Respir Crit Care Med* 1997;156:752–757.
61. Pellegrino R, Violante B, Nava S, Rampulla C, Brusasco V, Rodarte JR. Relationship between expiratory airflow limitation and hyperinflation during methacholine induced bronchoconstriction. *J Appl Physiol* 1993;75:1720–1727.
62. Kallet RH, Katz JA. Respiratory system mechanics in acute respiratory distress syndrome. *Respir Care Clin N Am* 2003;9:297–319.
63. Pesenti A, Pelosi P, Rossi N, Virtuani A, Brazzi L, Rossi A. The effects of positive end expiratory pressure on respiratory resistance in patients with the adult respiratory distress syndrome and in normal anesthetized subjects. *Am Rev Respir Dis* 1991;144:101–107.
64. Gattinoni L, Pesenti A. The concept of "baby lung". *Intensive Care Med* 2005;31:776–784.
65. Koutsoukou A, Bekos B, Sotiropoulou C, Koulouris NG, Roussos C, Milic-Emili J. Effects of positive end-expiratory pressure on gas exchange and expiratory flow limitation in adult respiratory distress syndrome. *Crit Care Med* 2002;30:1941–1949.

66. Vieillard-Baron A, Jardin F. The issue of dynamic hyperinflation in acute respiratory distress syndrome patients. *Eur Respir J* 2003;22: 43s–47s.
67. Wright PE, Carmichael LC, Bernard GR. Effect of bronchodilators on lung mechanics in the acute respiratory distress syndrome (ARDS). *Chest* 1994;106:1517–1523.
68. Pelosi P, Cereda M, Foti G, Giacomini M, Pesenti A. Alterations of lung and chest wall mechanics in patients with acute lung injury: effects of positive end-expiratory pressure. *Am J Respir Crit Care Med* 1995; 152:531–537.
69. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;149:8–13.
70. Eissa NT, Ranieri VM, Corbeil C, Chassé M, Robatto FM, Braidy J, Milic-Emili J. Analysis of behavior of the respiratory system in ARDS patients: effects of flow, volume, and time. *J Appl Physiol* 1991;70: 2719–2729.
71. Marini JJ. Auto-positive end-expiratory pressure and flow limitation in adult respiratory distress syndrome–intrinsically different? *Crit Care Med* 2002;30:2140–2141.
72. Wright PW, Marini JJ, Bernard GR. *In vitro* versus *in vivo* comparison of endotracheal tube airflow resistance. *Am Rev Respir Dis* 1989;140: 10–16.
73. Hedenstierna G. Atelectasis formation and gas exchange impairment during anaesthesia. *Monaldi Arch Chest Dis* 1994;49:315–322.
74. Craig DB, Wahba WM, Don HF, Couture JG, Becklake MR. "Closing volume" and its relationship to gas exchange in seated and supine positions. *J Appl Physiol* 1971;31:717–721.
75. Hurewitz AN, Susskind H, Harold WH. Obesity alters regional ventilation in lateral decubitus position. *J Appl Physiol* 1985;59:774–783.
76. Gattinoni L, Bombino M, Pelosi P, Lissoni A, Pesenti A, Fumagalli R, Tagliabue M. Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA* 1994;271:1772–1779.
77. Shim C, Chun K, Williams MH Jr, Blaufox MD. Positional effects on distribution of ventilation in chronic obstructive pulmonary disease. *Ann Intern Med* 1986;105:346–350.
78. Blanch L, Bernabé F, Lucangelo U. Measurement of air trapping, intrinsic positive end-expiratory pressure, and dynamic hyperinflation in mechanically ventilated patients. *Respir Care* 2005;50:110–123.
79. Marini JJ, Tyler ML, Hudson LD, Davis BS, Huseby JS. Influence of head-dependent positions on lung volume and oxygen saturation in chronic airflow obstruction. *Am Rev Respir Dis* 1984;129:101–105.
80. Marini JJ. Should PEEP be used in airflow obstruction? *Am Rev Respir Dis* 1989;140:1–3.
81. Armaganidis A, Stavrakaki-Kallergi K, Koutsoukou A, Lymberis A, Milic-Emili J, Roussos C. Intrinsic positive end-expiratory pressure in mechanically ventilated patients with and without tidal expiratory flow limitation. *Crit Care Med* 2000;28:3837–3842.
82. Ninane V, Leduc D, Kafi SA, Nasser M, Houa M, Sergysels R. Detection of expiratory flow limitation by manual compression of the abdominal wall. *Am J Respir Crit Care Med* 2001;163:1326–1330.
83. Ranieri VM, Giuliani R, Cinnella G, Pesce C, Brienza N, Ippolito EL, Pomo V, Fiore T, Gottfried SB, Brienza A. Physiologic effects of positive end-expiratory pressure in COPD patients during acute ventilatory failure and controlled mechanical ventilation. *Am Rev Respir Dis* 1993;147:5–13.
84. Hotchkiss JR, Crooke PS, Adams AB, Marini JJ. Implications of a biphasic two-compartment model of constant flow ventilation for the clinical setting. *J Crit Care* 1993;9:114–123.
85. Caramez MP, Borges JB, Tucci MR, Okamoto VN, Carvalho CR, Kacmarek RM, Malhotra A, Velasco IT, Amato MB. Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation. *Crit Care Med* 2005;33: 1519–1528.
86. Baigorri F, de Monte A, Blanch L, Fernández R, Vallés J, Mestre J, Saura P, Artigas A. Hemodynamic responses to external counterbalancing of auto-positive end-expiratory pressure in mechanically ventilated patients with chronic obstructive pulmonary disease. *Crit Care Med* 1994;22:1782–1791.
87. Tobin MJ, Jubran A, Laghi F. Patient-ventilator interaction. *Am J Respir Crit Care Med* 2001;163:1059–1063.
88. Kondili E, Prinianakis G, Georgopoulos D. Patient-ventilator interaction. *Br J Anaesth* 2003;91:106–119.
89. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med* 2006;32:1515–1522.
90. Branson RD, Johannigman JA. Innovations in mechanical ventilation. *Respir Care* 2009;54:933–947.
91. Hotchkiss JR, Adams AB, Stone MF, Dries DJ, Marini JJ, Crooke PS. Oscillations and noise: inherent instability of pressure support ventilation? *Am J Respir Crit Care Med* 2002;165:47–53.
92. Hotchkiss JR, Adams AB, Dries DJ, Marini JJ, Crooke PS. Dynamic behavior during noninvasive ventilation: chaotic support? *Am J Respir Crit Care Med* 2001;163:374–378.
93. Hartert TV, Wheeler AP, Sheller JR. Use of pulse oximetry to recognize severity of airflow obstruction in obstructive airway disease: correlation with pulsus paradoxus. *Chest* 1999;115:475–481.