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**Airway Pressure Release  
Ventilation in the Acute  
Respiratory Distress Syndrome  
Following Traumatic Injury**

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Respiratory insufficiency that occurs following a traumatic injury is due to both mechanical and physiological disruption of pulmonary integrity. Although an overall decrease in pulmonary compliance ( $\Delta V/\Delta P$ ) is a component of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS)\*, this may not be a *homogeneous* process. Changes in compliance may actually occur at varying degrees throughout the lung parenchyma in a *heterogeneous* fashion. Attempting to open or “recruit” collapsed alveoli without causing lung injury by overdistention or stretch of alveoli with more normal compliance remains a clinical challenge. Airway pressure release ventilation (APRV) is a ventilator mode that incorporates features that optimize the spectrum of alveolar mechanics present in ARDS/ALI. In the past, the focus on ventilator support was on conforming the patient to the ventilator; alternatively, APRV accommodates the patient’s breathing pattern and superimposes ventilation onto a pressure framework to support spontaneous breathing,<sup>1-3</sup> and thereby conforms the ventilator to the patient. APRV differs from other modes of positive-pressure ventilation in that it delivers a continuous positive airway pressure (CPAP) that releases periodically to augment CO<sub>2</sub> exchange. The patient’s breathing is spontaneous and unrestricted throughout the entire ventilator cycle, allowing infinite inspiratory/expiratory ratios. Studies have shown that APRV can augment ventilation with lower pulmonary artery pressures and improved efficiency compared to traditional modes of ventilatory support; these elements may reduce the risk of ventilator-associated lung injury while improving oxygenation. After a brief

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\*ALI and ARDS as referred to in this text are as defined by the American-European Consensus Conference on ARDS, Barcelona, September 2000. (personal correspondence, Dr. Roy Brower, participant)

review of the incidence and outcome of traumatic ARDS, we will present basic concepts of ventilator management with APRV and then will address the use of APRV in the patient with respiratory failure secondary to trauma.

### ■ ARDS Following Traumatic Injury

The incidence of ARDS in the general population has been estimated to be 6.9–18%,<sup>4–6</sup> while the incidence in the trauma population is reported to be 12–39%.<sup>7</sup> Despite advances in technology and treatment (i.e., new ventilator modes, noninvasive ventilation, intermittent prone positioning, extracorporeal support) and the implementation of new drug therapies (i.e., steroids, surfactant, liquid ventilation, nitric oxide, antibiotics), the mortality from this disease has not changed appreciably in the past several decades.<sup>8,9</sup> To date, the largest prospective, randomized published study to show a significant decrease in mortality in ALI/ARDS is the multicenter ARDSnet trial, which demonstrated a mortality of 31% in patients treated with low tidal volumes (6 mL/kg) versus 39.8% in those randomized to “traditional” tidal volume (12 mL/kg) ventilation ( $P = .007$ ).<sup>10</sup> Enrollment was stopped after 861 patients due to the significant difference in mortality. There is some evidence to suggest that an integrated approach, incorporating several modalities, may actually improve outcome,<sup>11,12</sup> but larger prospective, randomized trials are needed. It also appears that there may be a lower mortality from ARDS in trauma patients than in nontrauma patients with the disease.<sup>8,9,13</sup>

While most authors do not separate traumatic from nontraumatic etiologies when analyzing their data—which makes defining the incidence of ARDS secondary to trauma complex—a few recently published studies have done so. In addition, it may be important to differentiate between early and late ARDS, as they seem to be two distinct clinical entities.<sup>9</sup> Early ARDS (<48 hours after admission) has been characterized by hemorrhagic shock and capillary leak, while late ARDS (>48 hours after admission) follows pneumonia and is associated with multiple organ system failure. Of the risk factors identified as independent variables associated with subsequent development of ARDS, most are present early following trauma, a few develop later in the hospital course, and others may occur at any time during hospitalization (Table 1). Analysis is made problematic by the fact that many trauma patients have multiple risk factors and it is therefore more difficult to accurately predict the chance of developing severe respiratory failure in any given patient.

In a prospective trial that followed 3,289 trauma patients from admission, those who developed ARDS were compared to those who did not.<sup>14</sup> The variables shown to be significant risk factors by logistic regression analysis were Injury Severity Score more than 16, Trauma Score less than

**Table 1.** Risk Factors for ARDS

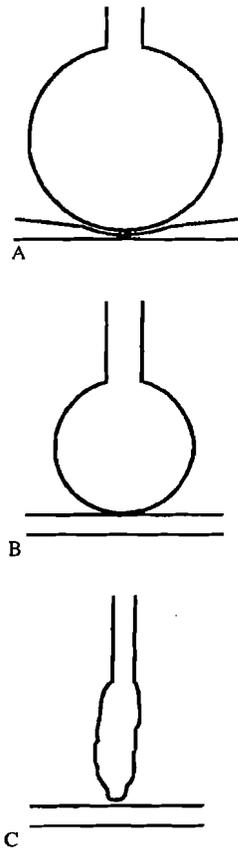
Early	Late
Pulmonary contusion	Pneumonia
Fractures	Sepsis
Near-drowning	Disseminated intravascular coagulation
Smoke inhalation	
Injury severity score >16	
Trauma score <13	
Metabolic acidosis on admission	
Blunt mechanism of injury	
Shock	→
Multiple transfusions	→
Gastric aspiration	→
Surgery to the head	→

13, surgery to the head, and blunt mechanism of injury. In addition to these variables, a more recent publication demonstrated that the degree of metabolic acidosis on presentation (base deficit  $-8.85$  vs.  $-5.65$ ,  $P < .01$ ) predicts development of ALL.<sup>15</sup> Previous studies have shown inconsistent findings with respect to base deficit, lactate, pH, and serum bicarbonate concentration on admission in multiply injured patients.<sup>16-18</sup> A later trial demonstrated that the  $\text{PaO}_2/\text{FiO}_2$  ratio on the third, fifth, and seventh days post-ARDS, high-volume resuscitation, APACHE III score, and the development of multisystem organ failure were independent variables that were associated with an increase in mortality in victims of trauma.<sup>19</sup>

### ■ Pathophysiology

During the initial stages of ARDS, increased capillary permeability results in lung edema. Positive pressure must exceed the sum of the superimposed hydrostatic pressure and the threshold opening pressure to reopen lung units. Following the initial phase of injury, alveolar edema becomes organized and is replaced by fibrinous material. Recruitment maneuvers to open collapsed alveoli become less effective as the response to pressure increases on the ventilator begin to favor overdistention. Therefore, complete lung recruitment needs to be instituted early in the course of respiratory failure.

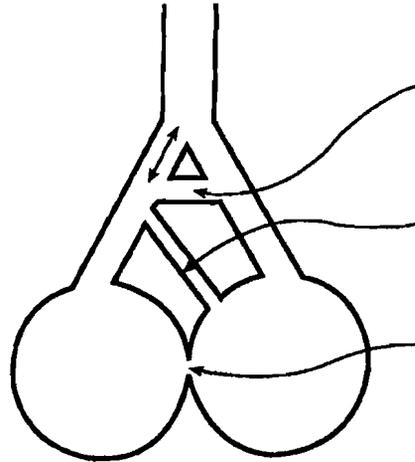
Overdistention creates dead space. Progressive overdistention initiates capillary compression and blood flow is redistributed to less ventilated regions, aggravating hypoxemia (Fig. 1). Recruitment of lung tissue requires sufficient airway pressures to exceed the threshold (critical) opening pressure of the airspaces. Lung recruitment also requires time in



**Figure 1.** (a) Nondependent alveolus overdistended ( $V/Q > 1$ ). (b)  $V/Q = 1$ . (c) dependent, collapsed alveolus ( $V/Q < 1$ ).

addition to threshold opening pressure. As this pressure is reached and maintained, time allows redistribution of delivered gas volume (Fig. 2).

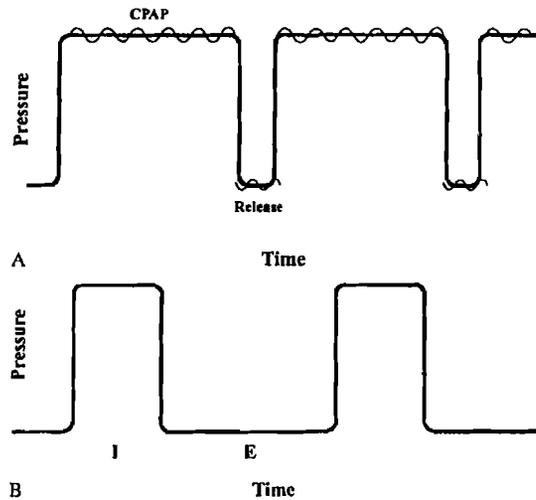
Ideally, mechanical ventilation should achieve complete alveolar recruitment, optimizing intrapulmonary gas distribution and narrowing time constant discrepancies. Ideal ventilator management should distribute pressure and volume to dependent and nondependent regions proportionally. Continuous rather than intermittent short bursts of high airway pressure minimize out-of-phase inflation of lung regions with different time constants. Inflation pressure should be interrupted minimally in frequency and duration. APRV allows continuous airway pressure, providing sustained recruitment, once threshold opening pressures are exceeded and maintained. The use of APRV also provides greater surface area for gas exchange. At least one study using multiple inert gas techniques has documented reduced shunt and dead space ventilation during APRV.<sup>20</sup>



**Figure 2.** *Distribution of volume (Pressure) over time between pores of Kohn, channels of Lambert, and channels of Martin.*

### ■ Basic Concepts of APRV

The distinguishing characteristic of APRV is that augmented ventilation is accomplished by passive lung deflation from the higher volume established by CPAP. An intermittent decrease rather than an increase in airway pressure and lung volumes means that peak airway pressure in APRV never exceeds the set CPAP level ( $P_{\text{HIGH}}$  or  $P_1$ ). APRV is a pressure-limited, time-cycled, time-initiated, volume-variable mode of ventilation that limits peak airway pressure but unlike traditional pressure-control modes allows spontaneous breathing to occur throughout the entire ventilator cycle. One of the basic concepts to understand with APRV is that rather than the ventilator delivering gas flow to initiate inspiration, and then allowing passive expiration to occur by the opening of an expiratory valve, gas flow at 90 to 100 L/min is available continuously due to the "floating" valve.  $P_{\text{HIGH}}$  and the CPAP level are maintained through the use of this threshold resistor valve, which permits spontaneous breathing. Oxygenation is achieved by maintaining mean airway pressure ( $P_{\text{AW}}$ ) with CPAP, and ventilation by the release of the continuous pressure level to  $P_{\text{LOW}}$  (or  $P_2$ ); this solenoid release valve attains the fully open or closed position within 10 msec. So rather than thinking in terms of inspiration and expiration, APRV fundamentally is CPAP with release. The patient continues his or her own inspiratory/expiratory ratio at both levels of support (Fig. 3a). It is as if the traditional positive-pressure ventilation pressure waveform has been inverted (Fig. 3b) with the addition of spontaneous breathing throughout. Because the release period typically comprises only about 30% of the ventilatory cycle and is much shorter than the expiratory time achieved with conventional ventilatory techniques, air-space closure is minimized, preserving end expiratory lung volumes and



**Figure 3.** Pressure waveforms and inspiratory (I)/expiratory (E) ratios. (a) I/E ratio with airway pressure release ventilation (b) traditional (conventional) ventilation.

alveolar recruitment established during the CPAP ( $P_1$ ) level. An estimate of mean airway pressure is determined by the set pressures and their duration:

$$P_{AW} = \frac{(P_1 \times T_1) + (P_2 \times T_2)}{(T_1 + T_2)}$$

In diseased lungs, traditional mechanical ventilation utilizes positive end-expiratory pressure (PEEP) to maintain functional residual capacity (FRC). Subsequent tidal ventilation increases lung volume above FRC. During APRV, lung volume and FRC have been restored by the CPAP level ( $P_1$ ) and lung volume falls to provide exhalation and  $\text{CO}_2$  removal. Conceptually, the CPAP level is limited to the upper inflection point, achieving complete recruitment and releasing airway pressure briefly for ventilation, thus limiting the risk of overdistention and high-volume lung injury (baro/volutrauma). Alveolar collapse or "derecruitment" and low-volume lung injury are limited as the duration of the release is brief to maintain end-expiratory lung volume. Worsening of ventilation/perfusion (V/Q) mismatch has not been borne out in clinical trials.<sup>1,3,21</sup>

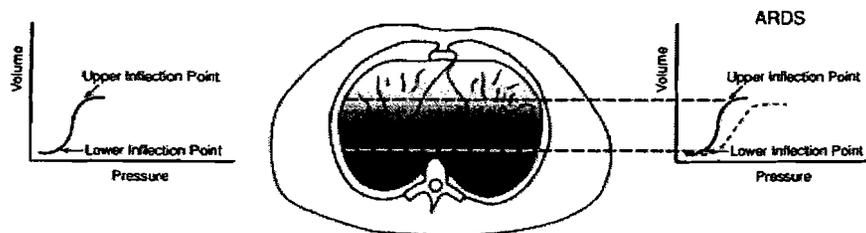
### ■ Management Techniques

APRV is a recruiting mode because it maintains a constant pressure to overcome the closing forces superimposed on the lungs. Application of CPAP decreases the work of breathing in patients with decreased FRC and

may unload inspiratory muscles.<sup>22</sup> By limiting  $T_2$  to a short release time (<1 sec), end-expiratory lung volume is maintained, preventing collapse of dependent lung units. Because of an improved FRC (greater surface area for gas exchange),  $\text{CO}_2$  clearance is enhanced.

Initial descriptions of settings for APRV suggested an expiratory time ( $T_2$ ) of 1.5 seconds.<sup>21-24</sup> This was due to the finding that after 1 sec, complete emptying of the lung occurs and that after 2 secs, airway pressure remained stable but no further pressure left the lungs. Many of the early trials were done in patients with relatively normal pulmonary compliance or ALI only. In the patient with ARDS, a decreased compliance, by definition, shifts the pressure-volume (PV) curve to the right, and adjustments are needed to maintain ventilation on the optimal area of the curve (without causing overdistention "high-volume" lung injury, or alveolar collapse and "low-volume" lung injury secondary to shear force stress) (Fig. 4). As compliance decreases with worsening ARDS (or any restrictive disease), elastic recoil increases, resulting in an increase in expiratory flow rate;  $T_2$  will need to be shortened to prevent complete emptying of the lungs. In this way, a short  $T_2$  will ensure that the critical closing pressure of the alveoli is exceeded, maintaining end-expiratory lung volume.<sup>25</sup> By viewing the flow/time waveform on the ventilator screen,  $T_2$  can be set before cessation of expiratory flow; by shortening  $T_2$  below this point, the solenoid valve closes before the end of complete lung emptying and maintains a higher mean airway pressure (Fig. 5). Adequate expiratory time is determined by the expiratory time constant of the patient's lung/thorax (defined as the product of compliance times resistance). When lung compliance is low, a shorter release time is needed.<sup>26</sup>

Many studies have shown higher  $\text{PaO}_2$  and lower  $\text{PaCO}_2$  at similar minute ventilation ( $V_E$ ) with APRV. Because of the maintenance of a CPAP level above the critical opening pressure, the mean airway pressure pattern of APRV may effect more uniform distribution of gas in injured lungs (see Fig. 2). Pores of Kohn, channels of Lambert, and channels of Martin allow gas distribution to occur between alveoli with differing time



**Figure 4.** Pressure-volume curve (left) and pressure-volume curve (right) demonstrating areas at risk of overdistention injury (above upper inflection point) and shear injury (below lower inflection point).

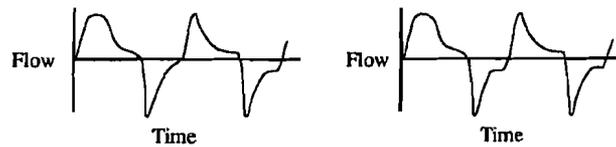


Figure 5. Inspiratory and expiratory flow patterns without air trapping (left) with expiratory flow to zero; and with air trapping (on right) as desired on airway pressure release ventilation.

constants. Sustaining  $P_1$  for a significant time will allow this phenomenon to take place. In addition, spontaneous breathing may improve the distribution of ventilation, enhancing dependent lung recruitment.

“Lower mean  $P_{aCO_2}$  during APRV may be secondary to decreased deadspace. The longer  $T_{I_{NSP}}$  ( $T_1$ ) during APRV may have enhanced distribution of inspired gas and thus promoted a lower  $P_{aCO_2}$  at the same  $V_E$ .”<sup>27</sup> In a study comparing V/Q distribution between intermittent mandatory ventilation; pressure support ventilation, and APRV,  $P_{aCO_2}$  was similar in patients on APRV despite lower  $V_E$  compared with intermittent mandatory and pressure support ventilation, likely due to a decrease in deadspace ventilation.

### ■ Spontaneous Breathing

Spontaneous breathing is a much-ignored and yet crucial aspect to improve V/Q matching, as there is a significant difference in the distribution of gas flow (V) between controlled mechanical ventilation and spontaneous breathing. Mechanical ventilation results in a tidal volume delivered to nondependent, poorly perfused lung units (West's zone I), whereas spontaneous breathing is preferentially directed to dependent lung regions where blood flow (Q) is higher.<sup>28-30</sup> In addition, allowing the diaphragm to move helps to maintain its muscular tone, enabling it to perform one of its functions: keeping the abdominal contents out of the thorax. Relaxation of the diaphragm into the posterior (dependent) chest in a supine patient exacerbates alveolar collapse. Underventilation of these lung units can then lead to shunt. Also, spontaneous breathing does not increase oxygen consumption ( $VO_2$ ).<sup>31</sup>

When setting  $T_1$  and  $T_2$ , it is important not to override the patient's respiratory drive and not to sedate the patient too heavily, in order to sustain the patient's respiratory effort. This is because spontaneous breathing superimposed on mechanical ventilation has been shown to improve the distribution of ventilation and significantly increase  $P_{aO_2}$ , cardiac output, and oxygen delivery, without an increase in oxygen consumption ( $VO_2$ ) or  $V_E$ .<sup>32</sup> In this study, spontaneous breathing accounted for only 10% of total  $V_E$  but resulted in decreased blood flow to shunt

units and increased blood flow to normal V/Q units (as shown by multiple inert gas elimination technique).

### ■ APRV Following Traumatic Injury

Following traumatic injury, the patient is immobilized in the supine position on a long backboard and may remain in this position for several hours during prehospital transport and the initial diagnostic workup. Dependent atelectasis is seen early (on admission chest computed tomography) in trauma patients or within minutes after induction of anesthesia,<sup>33</sup> even in those without pulmonary injury or massive volume resuscitation (Fig. 6). Obesity or decreases in thoracic or abdominal compliance compound the reduction of FRC. In patients with rib fractures, "splinting" due to pain will lead to atelectasis and subsequent hypoxemia. Pulmonary contusions, if severe, can be life-threatening early in the hospital course, and the disruption of pulmonary integrity may be exacerbated by the need for massive blood and crystalloid replacement, adding further insult to the already "leaky" capillaries and parenchyma. APRV will recruit the collapsed alveoli without overdistention of the nondependent alveoli. As seen in Figure 4, a shift of the PV curve to the right requires adjustments to ventilator management to prevent both low-end shear and high-end overdistention lung injury. As ARDS progresses, less of the lung parenchyma is recruitable, compliance worsens, and often the physician is left with progressively increasing peak airway pressures in an attempt to oxygenate the patient, or, if the patient is placed on pressure controlled-

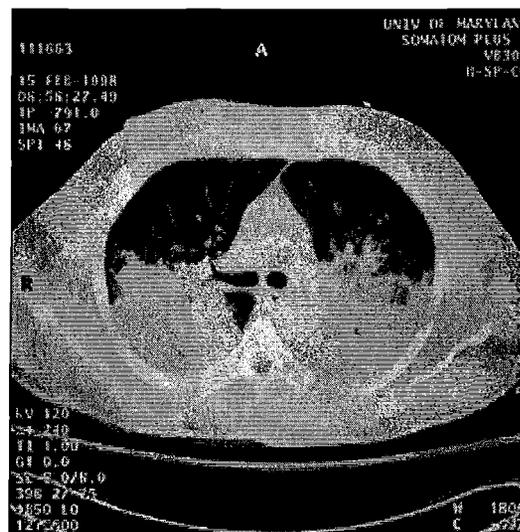


Figure 6. Dependent atelectasis.

inverse ratio ventilation (PC-IRV), paralysis and heavy sedation are required. With APRV, no paralytics are needed, and peak inspiratory pressure is limited by the set  $P_1$ , thereby avoiding ventilator-associated lung injury.

### ■ Cardiovascular, Pulmonary, and Intracranial Pressure Issues

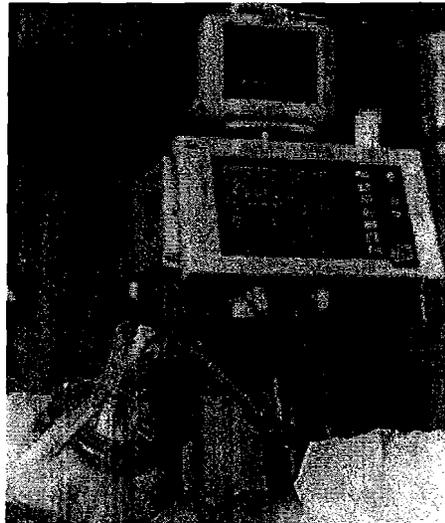
Previous studies suggest initial APRV settings that titrate CPAP to its "optimal level", defined as the pressure that is associated with the highest  $P_{aO_2}/F_{iO_2}$  ratio without cardiovascular compromise,<sup>21</sup> or titration to  $ETCO_2$ .<sup>34</sup> Although studies have shown no adverse cardiovascular consequences secondary to higher mean airway pressure with CPAP,<sup>34-36</sup> institution of APRV during the resuscitation phase may result in hypotension until intravascular volume is restored. Trauma patients undergoing continued resuscitation, or those with blunt myocardial injury (and resultant decreased cardiac output), may initially have a decrease in blood pressure following institution of APRV; this can be thought of as a "thoracic compartment syndrome" secondary to high intrathoracic pressure. If the patient's oxygenation requires a higher mean airway pressure, then further volume replacement and the addition of inotropes may be necessary to maintain blood pressure. Patients who demonstrate a decrease in arterial oxygen saturation when first placed on APRV may also require further volume loading—until collapsed alveoli are recruited, the initial effect of a higher  $P_{AW}$  may be an increase in zone I and a subsequent collapse of adjacent vasculature, leading to worsening V/Q mismatch (see Fig. 1).

One of the largest, prospective, multicenter clinical trials to date to use APRV in comparison to conventional ventilation studied 50 patients with acute respiratory failure. When converted to APRV, there was a significant decrease in peak inspiratory pressures ( $P < .0001$ ), an increase in  $P_{AW}$  ( $P < .05$ ), and smaller tidal volumes ( $P < .001$ ), with equivalent oxygenation and ventilation.<sup>21</sup> Unfortunately, patients were treated for only 30 minutes. An investigation into longer-term effects conducted the following year<sup>37</sup> studied 18 patients with ALI for 24 hours on volume control inverse ratio ventilation, and then for 24 hours on APRV. Eleven of the subjects were multiple trauma patients with lung contusions or ARDS. In addition to confirming prior study findings of a significant decrease in peak inspiratory pressure ( $P < .01$ ), a further decrease in peak inspiratory pressure was seen after 24 hours ( $P < .05$ ), likely due to effective recruitment over time. Alveolar-arterial gradient and venous admixture also improved with APRV ( $P < .01$ ). Of importance, this was the first study to report a decrease in the use of sedative agents during APRV. Patients on inverse ratio ventilation required a Ramsey score of 6, but those on APRV were comfortable with a Ramsey of 2 to 5 and were not given paralytics.

APRV has also been studied in trauma patients with ARDS, again with

findings of decreased peak inspiratory pressure and higher  $P_{AW}$ , without the derangements in gas exchange.<sup>38</sup> Of interest in this report, release time ( $T_2$ ) was adjusted to "prevent auto-PEEP." The authors hypothesized that the previously recommended and studied expiratory time of 1.5 sec was insufficient and resulted in auto-PEEP (which is known to improve oxygenation), although they believed it to be undesirable. This highlights two important points. First, as the ARDS process evolves in any given patient, lung mechanics change. Therefore, frequent assessment of the patient and frequent ventilator changes need to be made to adjust for the changing pattern. It is unlikely that any two patients will require the exact same pressure and time settings initially. Secondly, by decreasing the time ( $T_2$ ) at  $P_2$ , airspace closure is prevented. Even when  $P_2$  is set to 0 cm  $H_2O$ , assuming a short  $T_2$  (<1 sec), this does not correspond to a PEEP of 0 cm  $H_2O$ —intrinsic PEEP can be measured directly on some of the ventilators that perform APRV and will always be above 0 (and dependent on trapped volume).

Several recent trials of noninvasive positive-pressure ventilation have shown multiple benefits over conventional ventilation (decreased incidence of pneumonia, decreased length of stay in the intensive care unit) and illustrate that not all patients require endotracheal intubation.<sup>39</sup> In patients with intact airway reflexes, NIPPV may be an alternative to invasive ventilation, or may provide adequate support for a patient recently extubated who requires a short period of positive pressure. CPAP levels up to 15 cm  $H_2O$  can be maintained using a tight-fitting mask. APRV may also be used for NIPPV.<sup>40</sup> Facial fractures or an altered mental status may preclude its use (Fig. 7). A retrospective review of trauma patients with



**Figure 7.** *Noninvasive positive-pressure ventilation with airway pressure release ventilation.*

acute respiratory failure showed an improved P/F ratio, an increase in tidal volume, and a decrease in respiratory rate when treated with NIPPV; the time range was 6 to 144 hours.<sup>41</sup>

Classic teaching in the management of patients with elevated intracranial pressure (ICP) is that PEEP should be avoided due to the concern that an increase in intrathoracic pressure will result in a further increase in ICP. APRV may be effective at lowering ICP compared to conventional mechanical ventilation at similar  $V_E$ ,  $ETCO_2$ , and  $PaCO_2$ . In a preliminary report in patients with elevated ICP secondary to head trauma, ICP either remained constant or decreased, and peak airway pressure decreased in the first four patients studied.<sup>42</sup>

Some trauma patients with severe pulmonary injury progress rapidly to life-threatening hypoxemia requiring extracorporeal life support.<sup>43,44</sup> APRV can be used for patients during extracorporeal life support, and CPAP with extracorporeal  $CO_2$  removal has been shown experimentally to provide a better environment for recovery of lung injury than conventional ventilation.<sup>45</sup>

## ■ Conclusion

Despite advances in the multimodal approach to managing ARDS in the trauma patient, morbidity and mortality remain high. With progression of this disease process, worsening lung compliance may result in parenchyma that is at increased risk of ventilator-associated lung injury. APRV minimizes high airway pressures associated with ventilator-associated lung injury and maintains improved oxygenation and sustained  $CO_2$  clearance, despite a lower minute ventilation. Spontaneous breathing during APRV results in lower sedative and neuromuscular blockade use, exercises the diaphragm, and improves V/Q matching.

## ■ References

1. Garner W, Downs JB, Stock CS, et al. Airway pressure release ventilation: A human trial. *Chest* 1988;94:779-781
2. Floreto OG, Banner MJ, Banner TE, et al. Airway pressure release ventilation in a patient with acute pulmonary injury. *Chest* 1989;96:579-683
3. Cane RD, Peruzzi WT, Shapiro BA. Airway pressure release ventilation in severe acute respiratory failure. *Chest* 1991;100:460-463
4. Roupie E, Lepage E, Wysocki M, et al. Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. *Intens Care Med* 1999;25:920-925
5. Reynolds HN, McCunn M, Borg U, et al. Acute respiratory distress syndrome: estimated incidence and mortality rate in a 5 million-person population base. *Crit Care [serial online]* 1998;2:29-34
6. Luhr OR, Antonsen K, Karlsson M, et al. Incidence and mortality after acute respiratory

- failure and acute respiratory distress syndrome in Sweden, Denmark and Iceland. *Am J Respir Crit Care Med* 1995;159:1849–1861
7. Garber BG, Hevert PC, Yelle JD, et al. Adult respiratory distress syndrome: A systematic overview of incidence and risk factors. *Crit Care Med* 1996;24:687–695
  8. Milberg JA, Davis DR, Steinberg KP, et al. Improved survival of patients with acute respiratory distress syndrome (ARDS) 1983–1993. *JAMA* 1995;273:306–309
  9. Croce MA, Fabian TC, Davis KA, et al. Survival in patients with severe acute respiratory distress syndrome: Two distinct clinical entities. *J Trauma* 1999;46:361–368
  10. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308
  11. Ullrich R, Lorber C, Roder G, et al. Controlled airway pressure therapy, nitric oxide inhalation, prone position and extracorporeal membrane oxygenation (ECMO) as components of an integrated approach to ARDS. *Anesthesiology* 1999;91:1577–1586
  12. McIntyre RC, Pulido EJ, Bensard DD, et al. Thirty years of clinical trials in acute respiratory distress syndrome. *Crit Care Med* 2000;28:3331
  13. DiRusso SM, Nelson LD, Safcsak K, et al. Survival in patients with severe acute respiratory distress syndrome treated with high-level positive end-expiratory pressure. *Crit Care Med* 1995;23:1485–1496
  14. Hoyt DB, Simons RK, Winchell RJ, et al. A risk analysis of pulmonary complications following major trauma. *J Trauma* 1993;35:524–531
  15. Eberhard LW, Morabito DJ, Matthay MA, et al. Initial severity of metabolic acidosis predicts the development of acute lung injury in severely traumatized patients. *Crit Care Med* 2000;28:125–131
  16. Sauaia A, Moore FA, Moore EE, et al. Early predictors of postinjury multiple organ failure. *Am J Surg* 1982;144:124–130
  17. Roumen RM, Redl H, Schlag G, et al. Scoring systems and blood lactate concentrations in relation to the development of adult respiratory distress syndrome and multiple organ failure. *J Trauma* 1993;35:349–355
  18. Davis JW, Parks SN, Kaups KL, et al. Admission base deficit predicts transfusion requirements and risk of complications. *J Trauma* 1996;41:769–774
  19. Navarro AP, Bailen MR, Fernandez RR, et al. Acute respiratory distress syndrome in trauma patients: ICU mortality and prediction factors. *Intens Care Med* 2000;26:1624–1629
  20. Putensen C, Mutz NJ, Putensen-Himmer G, et al. Spontaneous breathing during ventilatory support improves ventilation perfusion distributions in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;159:1241–1248
  21. Rasanen J, Cane RD, Downs JB, et al. Airway pressure release ventilation during acute lung injury: a prospective multicenter trial. *Crit Care Med* 1991;19:1234–1241
  22. Petrol B, Lagare M, Goldberg P, et al. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Crit Care Med* 1990;141:179–188
  23. Stock CM, Downs JB. Airway pressure release ventilation: A new approach to ventilatory support during acute lung injury. *Resp Care* 1987;32:517–524
  24. Rasanen J. Airway pressure release ventilation. In: Tobin M (ed). *Principles and practice of mechanical ventilation*. New York: McGraw-Hill, 1994:341–345
  25. Habashi NM. New directions in ventilatory management. In: Franco KL, Putman JB, eds. *Advanced Therapy in Thoracic Surgery*. Ontario, Canada: BC Decker, 1998
  26. Stock CM. Airway pressure release ventilation: a new concept in ventilatory support. *Crit Care Med* 1987;15:459–461
  27. Stock CM. Airway pressure release ventilation: a new concept in ventilatory support. *Crit Care Med* 1987;15:459–461

28. Froese AB, Bryan AC. Effects of anesthesia and paralysis on diaphragmatic mechanics in man. *Anesthesiology* 1974;41:242-255
29. Rheder K, Knopp TJ, Sessler AD, et al. Ventilation-perfusion relationship in young healthy awake and anesthetized-paralyzed man. *Appl Physiol* 1979;47:745-753
30. Wagner PD, Rodriguez-Roisin R. Clinical advances in pulmonary gas exchange. *Am Rev Resp Dis* 1991;143:883-888
31. Neumann P, Hedenstierna G. Ventilatory support by continuous positive airway pressure breathing improves gas exchange as compared with partial ventilatory support with airway pressure release ventilation. *Anesth Analg* 2001;92:950-958
32. Putensen C, Rasanen J, Lopez FA. Ventilation-perfusion distributions during mechanical ventilation with superimposed spontaneous breathing in canine lung injury. *Am J Respir Crit Care Med* 1994;150:101-108
33. Brismar B, Hedenstierna G, Lundquist H, et al. Pulmonary densities during anesthesia with muscular relaxation—a proposal of atelectasis. *Anesthesiology* 1985;62:422-428
34. Bratzke E, Downs JB, Smith RA. Intermittent CPAP: A new mode of ventilation during general anesthesia. *Anesthesiology* 1998;89:334-340
35. Rasanen J, Downs JB, Stock MC. Cardiovascular effects of conventional positive pressure ventilation and airway pressure release ventilation. *Chest* 1988;93:911-915
36. Martin L, Wetzel RV, Bilenki AL. Airway pressure release ventilation in a neonatal lamb model of acute lung injury. *Crit Care Med* 1991;19:373-378
37. Sydow M, Burchardi H, Ephraim E, et al. Long-term effects of two different ventilatory modes of oxygenation in acute lung injury: comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. *Am J Respir Crit Care Med* 1994;49:1550-1556
38. Davis K, Johnson DJ, Branson RD, et al. Airway pressure release ventilation. *Arch Surg* 1993;128:1348-1352
39. Antonelli M, Cinti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998;339:429-435
40. Jousela IT, Nikki P, Tahvananainen J. Airway pressure release ventilation by mask. *Crit Care Med* 1988;93:795-799
41. Beltrame F, Lucangelo U, Gregori D, et al. Noninvasive positive pressure ventilation in trauma patients with acute respiratory failure. *Monaldi Arch Chest Dis* 1999;54:109-114
42. Sestito J, Gradwell L, Reily D. Airway pressure release ventilation (preliminary report). *Resp Manage*; 21:133-134
43. Michaels AJ, Schreiner RJ, Lolla S, et al. Extracorporeal life support in pulmonary failure after trauma. *J Trauma* 1999;46:638-645
44. McCunn M, Reynolds HN, Cottingham CA, et al. Extracorporeal support in an adult with severe carbon monoxide poisoning and shock following smoke inhalation: a case report. *Perfusion* 2000;15:169-173
45. Borelli M, Kolobow T, Spatola R, et al. Severe acute respiratory failure managed with continuous positive airway pressure and partial extracorporeal carbon dioxide removal by an artificial membrane lung. *Am Rev Respir Dis* 1988;138:1480-1487