Ventilatory management of acute respiratory distress syndrome: A consensus of two

John J. Marini; Luciano Gattinoni

Objective: **To synthesize the emerging body of experimental, observational, and clinical trial data into a practical guideline for safe and effective ventilatory management of acute respiratory distress syndrome.**

Data Sources: **Relevant, peer-reviewed, scientific literature and personal observations from clinical practice.**

Study Selection: **Relevant experimental studies and high-impact observational and clinical trials of acute respiratory distress syndrome management.**

Data Extraction: **Detailed review of information contained in published scientific work.**

Data Synthesis: **Interactive discussions between the authors that culminated in our consensus view of appropriate management.**

Conclusions: **Prevention of ventilator-induced lung injury while accomplishing the essential life-supporting roles of mechanical ventilation is a complex undertaking that requires application of principles founded on a broad experimental and clinical database and on the results of well-executed clinical trials. At the bedside, execution of an effective lung-protective ventilation strategy remains an empirical process best guided by integrated physiology and a readiness to revise the management approach depending on the individual's response. (Crit Care Med 2004; 32:250–255)**

KEY WORDS: ventilatory management; acute respiratory distress syndrome; ventilator-induced lung injury; lung-protective ventilation

Acute respiratory distress syndrome, a diagnosis based on physiologic and radiographic criteria, is a category comprising patients with varied patho-anatomy and mechanical characteristics. This diversity presents a challenge to developing a common strategy for safe and effective ventilatory management, as experimental studies have clearly shown that excessive mechanical stresses developed during mechanical ventilation can inflict injury on both normal and acutely injured lungs (1–4). The potential for iatrogenic injury includes extra-alveolar gas leaks (barotrauma), damage to small airways, inflammatory edema, and alveolar hemorrhage. The purpose of this communication is to describe our current approach to lung-protective ventilation. Definitive answers for many important clinical questions related to this topic are not available; what we present here reflects our understanding of the pathophysiology of ventilator-induced lung injury (VILI) and is not intended to preclude or invalidate other interpretations.

VILI. We view VILI as a complex process initiated by the repetitive application of excessive stress or strain to the lung's fibroskeleton, microvasculature, terminal airways, and delicate juxta-alveolar tissues (Fig. 1). Defining the linkage between stress, strain, and diffuse alveolar damage is currently a subject of intense investigation (5–7). On the strength of excellent laboratory evidence, however, it seems undeniable that high levels of mechanical stress may disrupt the normal functioning of cells that populate the pulmonary micro-environment and that sufficient dimensional strain triggers the release of inflammatory mediators and destructive metaloproteinases (5, 6, 8). Under moderate degrees of strain, such mechanosignaling may be the primary injury pathway. When the applied mechanical stress is very high, fibro-elastic structural integrity may be directly breached, with the inflammatory process a consequence rather than initiator of the observed histopathology.

From an engineering perspective, mechanical stress is a function of transstructural tension; strain is the dimension-altering consequence of high transstructural pressure, conditioned by the elastance of the element in question. The measurable analog of the stress across the entire lung is transpulmonary pressure—crudely estimated as the difference between static airway pressure (plateau pressure) and average pleural pressure (often estimated by use of an esophageal balloon). Although not directly measurable, strain correlates with aerated volume as a fraction of aeratable capacity.

Regional transpulmonary pressures vary considerably because of the influence of gravity, chest wall irregularities, intraabdominal pressure, mediastinal weight, and vascular filling pressure, among other factors (9). Modifying the characteristics of the chest wall (e.g., by prone positioning (10, 11)) is a potent mechanism for altering regional differences of transpulmonary pressure. Even within the same small region, inflationary stresses can vary markedly in magnitude and even in direction between structures situated within microns of one another. Shearing forces, one of the varied forms of mechanical stress resulting from lung inflation, intensifies at the junctions of tissues with different compliance values and anchoring attachments (12). Minimizing or eliminating such irregularities reduces the potential for adverse "stress focusing" and tissue

From the University of Minnesota, Regions Hospital, St. Paul, MN (JJM); and the Istituto di anestesia e Rianimazione, Università di Milano, Milano, Italia (LG).

Address requests for reprints to: John J. Marini, University of Minnesota, Regions Hospital, 640 Jackson Street, St. Paul, MN 55101. E-mail: John.j.marini@healthpartners.com

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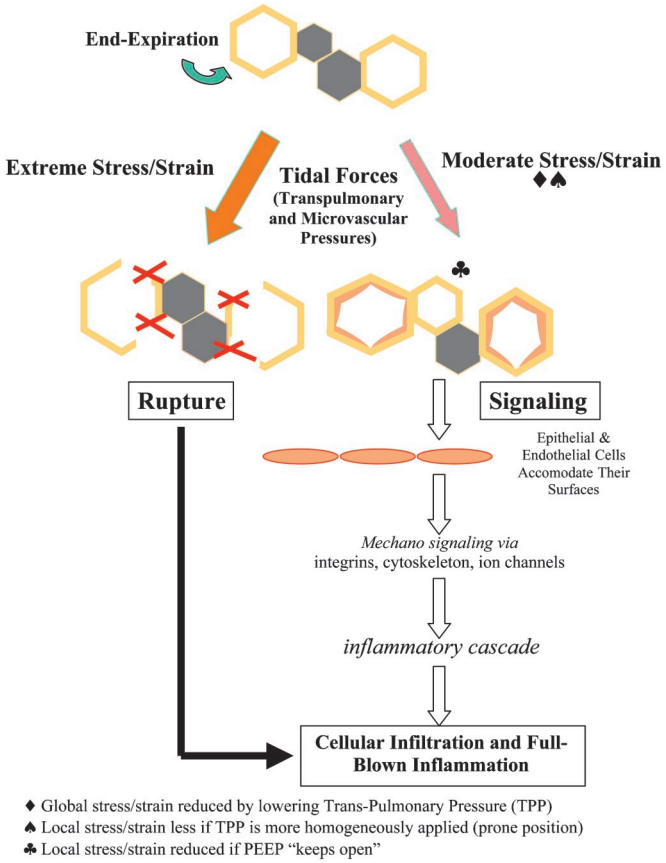

Figure 1. Pathogenesis of ventilator-induced lung injury.

strain. In such a microenvironment, limiting end-tidal alveolar pressure assumes major importance for two primary reasons: 1) a high plateau pressure may overstretch open alveoli, and 2) perhaps more importantly, because junctional tension rises in nonlinear proportion to airway pressure (12), the plateau pressure acts as a potent lever arm at stress focus points.

By reducing the number of junctional interfaces, recruitment of lung tissue, defined as the sustained reversal of atelectasis on whatever scale it occurs, may be lung protective. When nearly all of potentially recruitable tissue is aerated, the lung is said to be "open" (13). A given transpulmonary pressure applied to a fully open lung should be associated with less stress than the same pressure applied to a lung with closed units juxtaposed to open ones. Whereas some authors argue that the injured lung should be fully opened to reduce the potential for repetitive opening and reclosure (13), it is not presently clear that this should always be given highest priority; to what extent repetitive opening and closure of small airways produces injury and whether the prevention of such behavior is the key to lung protection remain debatable. In addition, some lung units are unable to be recruited, some degree of tidal recruitment may be unavoidable, and modest airway pressures may not inflict shearing injury. Therefore, how much of the lung should be opened and what pressure cost is acceptable are key unresolved questions.

Although the highest prevalence of lung unit opening may occur at pressures of <25 cm H_2O, some refractory units of the acutely injured lung may require much higher pressures to establish patency (14, 15). To reach the "yield" pressures of refractory lung units requires the initial application of pressures that would be hazardous during tidal ventilation (14, 15). To consolidate the benefit after a successful recruiting maneuver, end-expiratory pressure must remain high enough to keep open these newly recruited units once safe tidal plateau pressures are resumed (16). With few exceptions, this stabilizing value of positive end-expiratory pressure (PEEP) is generally higher than the initial one (17, 18). Although the majority of unstable lung units can be kept open with end-expiratory lung pressures of <10 cm H_2O, some units close at pressures considerably higher than those that are safe to consistently apply (15). We caution that it is a fallacy to consider all injured tissue as potentially recruitable. Unlike most experimental models of acute lung injury (14, 19), only a small fraction of the lungs of pneumonia-caused (primary) acute respiratory distress syndrome, for example, can be opened (15).

Experimentally, a variety of co-factors apart from end-inspiratory and end-expiratory tidal transpulmonary pressures are important in the generation or prevention of VILI. As already mentioned, prone positioning seems to confer a protective advantage in both normal and pre-injured animals (20, 21). As other examples, higher precapillary (22) and lower postcapillary (23) vascular pressures intensify the injury inflicted by a fixed ventilatory pattern. For identical tidal inflation and end-expiratory pressures, reducing respiratory frequency attenuates or delays damage, provided that the tidal ventilatory stress is sufficiently high (24).

What level of transpulmonary pressure is likely to be damaging, therefore, depends on multiple variables other than the tidal plateau pressure. Moreover, when the lung is composed of large numbers of recruitable units, PEEP attenuates the tendency for high plateau pressures or tidal volumes to cause injury (25, 26). It is therefore difficult to specify an exact level of transpulmonary pressure that serves as an appropriate threshold criterion for safety. From a theoretical standpoint, a transpulmonary pressure of 20 cm H_2O (corresponding in a patient with a normal chest wall to a plateau pressure that may be in the range of 25–35 cm H_2O) gives cause for concern, as some higher compliance regions of the injured lung may approach their elastic limits at this pressure. It is worth noting that a transpulmonary pressure of only 15 cm H_2O subjects the normal lung to approximately two thirds of its total capacity and is associated with a tidal volume exceeding 2500 mL (27).

PEEP has the potential to maintain recruitment of unstable lung units (thereby reducing the stress amplification factor). However, when tidal driving pressure is preserved, PEEP raises both mean and peak tidal pressures, distends lung units that are already open, redirects blood flow, and alters cardiac loading conditions. Moreover, those lung units that continue to undergo repeated

tidal recruitment, despite an increase of PEEP, are subjected to any PEEP-related elevation of end-inspiratory pressure, increasing the tendency for damage to those specific units. Thus, PEEP has the clear potential for benefit or harm, depending on the balance among its multiple effects. Prone positioning tends to even the distribution of ventilation and reduce the gradient of transpulmonary pressure across the lung (11, 28), facilitating the selection of a single combination of PEEP and tidal volume that achieves a protective strategy for the entire organ. Preservation of spontaneous breathing efforts during assisted ventilation may help to improve ventilation/perfusion matching by preferentially ventilating the peridiaphragmatic regions (29–32). Whether this redistribution of ventilation reduces or augments the tendency for VILI currently remains unknown.

Clinical Trials of Lung Protection. Acknowledging the imprecision of disease definition, the theoretical importance of chest wall compliance characteristics, and the dependence of strain magnitude on the interactions among the main determinants of VILI, the results of clinical trials that have addressed lung-protective strategies can be placed into a schema that is internally consistent (33–37). Studies in which the highest tidal volumes and pressures were applied in the control arm have shown benefit from low tidal volume ventilation (33, 34). Results were particularly impressive when higher PEEP was used in conjunction with small tidal volumes in a setting in which emphasis was placed on maintained recruitment and consistent management of clinical co-interventions (34).

Only one of the studies that randomized selectively on tidal volume—by far the largest yet published—succeeded in demonstrating mortality benefit for a smaller tidal volume approach (33). However, a recent provocative meta-analysis of all such published trials suggested that lower is not necessarily better (38). Knowing that tidal volume is only very indirectly linked to tissue strain, inflammation, and rupture (consider the noninjurious effects of high tidal volumes during exercise), it is interesting to speculate that the recruiting effects of higher tidal volumes might actually have a salutary effect on inflammatory signaling if peak transpulmonary pressure were kept below the overstretch signaling threshold and an appropriate level of PEEP were utilized. Whatever the validity of that controversial argument, the collective results of these clinical studies have focused attention on transalveolar stresses rather than on tidal volume *per se*. They have also demonstrated that the levels and effects of hypercapnia experienced during low tidal volume ventilation, although complex (39, 40), are generally modest and well tolerated. Precise numerical guidelines for selecting PEEP, tidal volume, and ventilatory position that are applicable to any given individual patient should not be expected from the results of studies conducted in a diverse sample population. What follows is our approach to the care of the individual patient with acute respiratory distress syndrome. It is based on our understanding of the physiologic principles just outlined, which must be brought to bear in the complex clinical environment that applies to the given individual receiving care.

RECOMMENDATIONS FOR PRACTICE

General Principles

Certain principles guide our own approach, and they include the following. 1) Adjust ventilatory variables empirically, rather than by formula-driven rules, and prioritize patient comfort and safety; 2) assign the prevention of mechanical trauma precedence over maintenance of normocapnia and avoidance of oxygen toxicity. Although no exact upper limits for acceptable plateau pressure or F_{IO_2} can be specified, very high values for F_{IO_2} risk absorption atelectasis and oxygen toxicity. Therefore, we suggest that F_{IO_2} be held at <0.7 whenever possible. 3) Consider the impact of chest wall stiffness on transpulmonary pressure and gas exchange efficiency. In concerning cases, determine abdominal (bladder) or esophageal pressures (41). 4) Monitor hemodynamics, mechanics, and gas exchange when regulating ventilatory therapy. A surrogate for measuring hemodynamics directly may be to monitor the central venous oxygen saturation. A value of $>70\%$ and a difference of $\leq 25\%$ between arterial and mixed venous saturations is almost invariably associated with an adequate cardiac index ($>2.5\ L \cdot m^{-2} \cdot min^{-1}$). 5) In severe cases, attempt to minimize ventilatory demands and thereby reduce airway pressures, high rates of gas flow, and cardiac output requirements. 6) Incorporate the "challenge" principle in making therapeutic decisions, both regarding the intensification and the withdrawal of therapeutic measures. Examples of such challenges include recruiting maneuvers to assess lung-unit instability and closely monitored challenges of fluid administration or removal. 7) Unless otherwise contraindicated, utilize prone positioning when high values for ventilatory pressure, PEEP, and F_{IO_2} are needed to maintain adequate supine arterial oxygen tension. 8) Assess pulmonary interventions in the volume-control mode of ventilation so as to better track thoracic mechanics and the lung's gas-exchanging efficiency for CO_2. At other times, employ pressure-limited forms of ventilation (e.g., pressure-control, pressure-support, or bilevel positive airway pressure/airway pressure release ventilation) for ongoing management.

Ventilatory Objectives

Targets for Ventilation and Oxygenation. As a general rule, the desired goal is to use the least PEEP and tidal volume necessary to achieve acceptable gas exchange while avoiding tidal collapse and reopening of unstable lung units. Knowing that moderate hypercapnia is generally well tolerated, our therapeutic targeting priorities are directed toward lung protection and maintenance of appropriate hemodynamics and oxygen delivery. We utilize recruiting maneuvers to characterize PEEP responsiveness, to determine the relative status of intravascular filling and response to altered cardiac loading conditions, and to set the PEEP–tidal volume combination. During the trial, a recruiting inflation should *immediately* precede each adjustment of PEEP to avoid (to the extent possible) collapse of the newly recruited volume. Prone positioning is strongly considered in all but the least severe cases and those that rapidly improve. On rare occasions, noninvasive mechanical ventilation, using a full facemask or a helmet, may overcome short-lived deficits of oxygen exchange without the need for intubation. In practice, however, the needs to control the airway, to reduce ventilatory requirements, to apply high levels of end-expiratory pressure, and to sustain support for extended periods usually preclude its use.

In the first phase of ventilatory support, we believe that patient comfort must be ensured and ventilatory effort kept to a minimum. Modes such as airway pressure release ventilation, bilevel

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positive airway pressure, and high frequency oscillation have their persuasive advocates and considerable theoretical appeal (31, 32, 42, 43). However, the existing database and our own personal experience has not convinced us that they offer a great deal beyond that which can be accomplished with carefully adjusted, pressure-controlled ventilation in a well-sedated patient.

All patients should be assessed for severity of disease and for recruitment potential. We measure bladder pressure as a surrogate of intraabdominal pressure in the most severe cases or when the chest wall compliance is suspected to be abnormal; the physical examination alone cannot reliably predict its magnitude or influence on airway pressure. After deficits of intravascular volume have been addressed and hemodynamics have been optimized, recruitment potential is gauged by applying high-level pressure-controlled ventilation: PEEP of 15–20 cm H_2O, driving pressure of 30 cm H_2O, plateau pressure of 50 cm H_2O for 1–2 mins, as tolerated. Even higher pressures may be appropriate for a patient with a very stiff chest wall (e.g., in a burn victim). Although sustained inflation with high pressure has been traditionally used, widely employed, and selected for most reported research, it is no more effective and tends to be less well tolerated hemodynamically than a recruiting method based on pressure-controlled ventilation that achieves lower average pressure but similar peak pressure during its inspiratory phase (44). If oxygenation and lung mechanics do not improve substantially with high-level pressure-controlled ventilation as a recruiting technique, the patient is considered to have low recruiting potential *in that position and at that specific time*. Management goals in the recruitable group emphasize the maintenance of high-level end-expiratory pressure, whereas in poorly recruitable patients, PEEP is maintained as low as feasible—generally in the range of 5–10 cm H_2O. In both groups, end-inspiratory plateau pressure is kept at <30 cm H_2O, except when chest wall compliance is very low.

Patients with an extensive recruitable population of lung units should respond to increased PEEP and recruiting maneuvers by demonstrating improved alveolar mechanics and improved gas exchange, reflected both by increased Pa_{O_2} and reduced V_E/Pa_{CO_2}. Inspiratory crackles (rales) audible over the dependent zones of the chest suggest that recruitment and derecruitment are occurring with each breath and indicate that recruitment maneuvers and higher levels of end-expiratory pressure may be indicated to silence them. Crackles late in inspiration are of particular concern, as they may originate in units opening under relatively high pressures. In gauging response to PEEP, it is important to consider CO_2 exchange and oxygenation response. With rare exception (e.g., when a PEEP-impaired cardiac output causes mixed venous oxygen content to fall), Pa_{O_2} tends to increase when PEEP is applied. However, this oxygenation improvement may be accounted for either by recruitment of lung units or by redirected blood flow within the injured lung. In the latter circumstance, Pa_{CO_2} may also increase. When recruitment is the explanation for improved oxygenation, however, CO_2 exchange is not compromised and may even improve, reflecting increased alveolar ventilation. Similar principles apply during prone positioning.

We initiate the prone position in those patients with severe gas exchanging impairment, regardless of their recruiting test result using high-level pressure-controlled ventilation in the supine position. We place in the prone position those requiring >10 cm H_2O PEEP at F_{IO_2} of ≥ 0.6 to maintain oxygen saturation at $\geq 90\%$, unless there is a clear contraindication or the patient is rapidly improving. Tidal thoracic compliance (tidal volume/[plateau pressure–total PEEP]) of <0.040 L/cm H_2O also signals sufficiently severe disease to warrant a prone position trial. The prone position should be considered independently of supine recruiting potential, as prone positioning will help lymphatic drainage and secretion removal and release the lower lobes of the lungs from the need to support the weight of the heart. Although provocative experimental data have recently challenged the concept (45), the preferred angle for head elevation in supine patients is 30 degrees to horizontal (Fowler) with frequent (at least every 2–4 hrs) lateral turning. Similar rules apply in the prone position; reverse Trendelenberg at 15–30 degrees is preferred to flat (0 degrees) horizontal. Tidal volume is adjusted to the same value used in the supine position. An increase of plateau pressure strongly suggests that chest wall compliance has been altered by prone positioning. In those instances, a proportional increase of PEEP may also be justified.

Sequence of Management Decision Making (Fig. 2)

Initial Phase of Stabilization and Support.

1. Determine whether the patient with oxygenation impairment is in acute respiratory distress syndrome, and if so, assign a primary or secondary etiology.
2. Initiate ventilation with facemask or intubate, as severity warrants.
3. Decide on controlled vs. spontaneous ventilation, using controlled or nearly controlled ventilation to subdue respiratory efforts for the most severely affected patients during the early stage of support.
4. Initial ventilatory settings: F_{IO_2}, 0.8; PEEP, 5–8 cm H_2O (depending on concern regarding hemodynamic tolerance); tidal volume, 6–10 mL/kg (depending on inspiratory plateau pressure).
5. Estimate volemic status initially from arterial blood pressure, respiratory variations of pulmonary and systemic arterial pulse pressure, central venous pressure, urinary output, and urinary electrolytes.
6. Confirm adequacy of intravascular volume utilizing echocardiography, results from a volume challenge, and central venous and pulmonary artery catheter data (cardiac index, mixed venous oxygen saturation, and occlusion pressure), if available.
7. Replete any volume deficits and

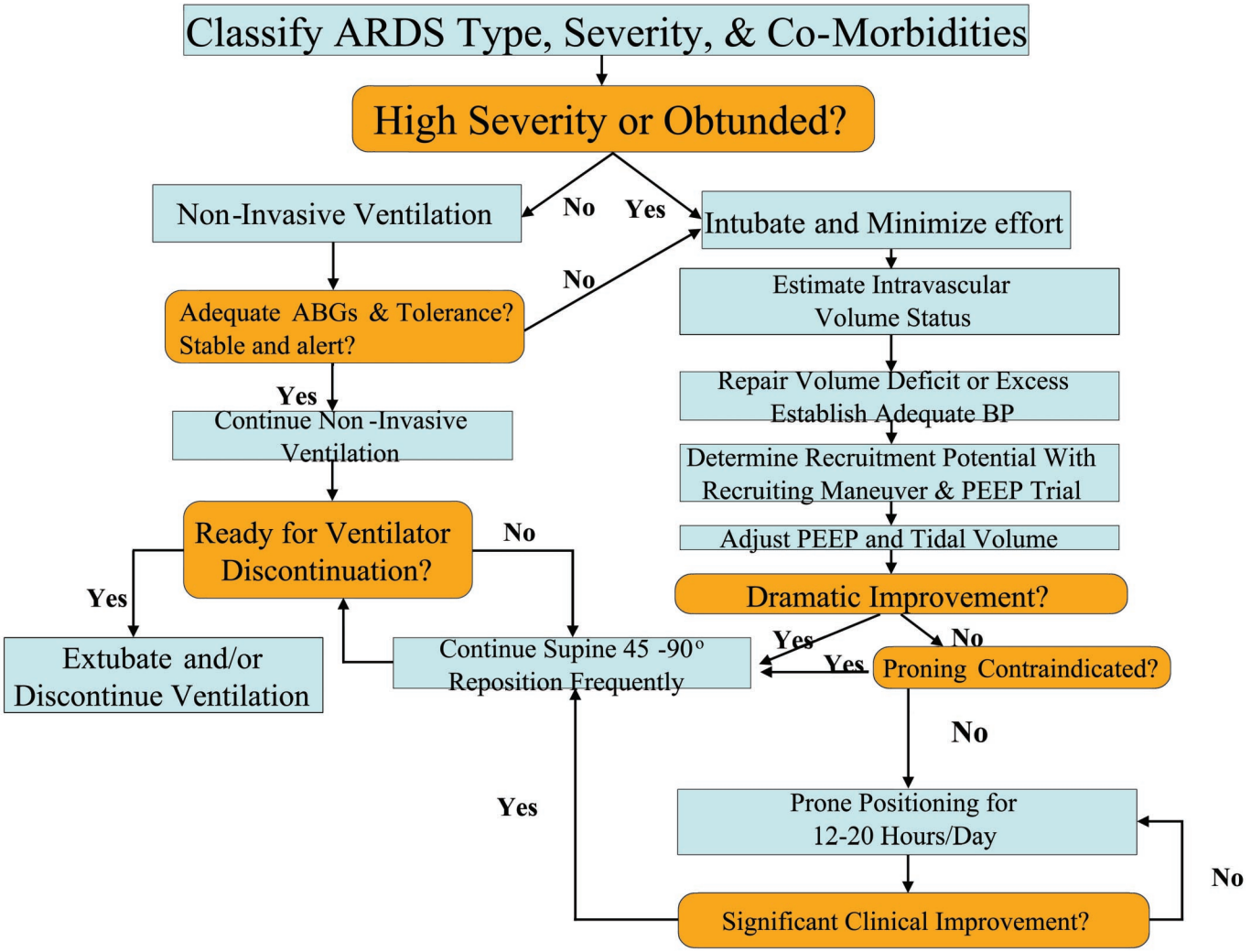

Figure 2. Acute respiratory syndrome type, severity, and co-morbidity.

support the circulation with pressors and inotropes to the extent necessary to safely perform the ventilatory manipulations.

8. Determine the recruitment potential of the patient by using a recruiting maneuver/PEEP trial. During the PEEP trial, consider together the oxygenation change, the $Paco_2$ change, the alterations of mechanics, and the hemodynamic response. Adjust the PEEP and tidal volume combination to the lowest tolerated values that sustain the recruitment benefit.
9. We recommend using the prone position in those with no contraindication and moderate-to-severe disease (as defined earlier), regardless of recruiting test, unless they are already improving rapidly. If the patient does not respond to the prone position, another recruiting maneuver is attempted while prone. The PEEP and tidal volume combination is readjusted, as before.
10. When the prone position is used, scheduled reversion to the supine position is conducted at least once per day for cleanup, dressing changes, edema clearance, diagnostic procedures, transport to imaging, etc. Many patients require almost continuous prone positioning to maintain adequate gas exchange during the first several days of illness. Prone positioning can be discontinued when it no longer makes an impressive difference to oxygenation and plateau pressure can be kept in a safe range when supine. Therefore, supine ventilation is resumed when the alterations in Pao_2 observed during position changes are <10%, status is clearly improved, or no obvious benefit to proning has been achieved after a lengthy trial (>48 hrs).

Subsequent Care. Recovery onset is recognized by improving Pao_2/Fio_2 and $V_E/Paco_2$ ratios, clearing radiographic opacity, and increasing thoracic compliance. Appropriate adjustments are then made to sedation and ventilating pressures and spontaneous breathing encouraged by conversion to pressure-support ventilation or to pressure-controlled ventilation with lower driving pressures, as tolerated. Reductions in Fio_2 are undertaken before cutbacks of PEEP, and PEEP is weaned very slowly when Fio_2 is ≤40% and Pao_2 is ≥80 mm Hg.

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