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THE NATURE OF RECRUITMENT AND DERECRUITMENT AND ITS IMPLICATIONS FOR MANAGEMENT OF ARDS

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Abstract

Recruitment maneuvers (RM) in ARDS are used to improve oxygenation and lung mechanics by apply high airway pressures to re-open collapsed or obstructed peripheral airways and alveoli. In the early 1990’s RMs became a central feature of a variant form of lung protective ventilation (LPV) known as “open-lung ventilation” (OLV). This strategy is based upon the belief that repetitive opening and closing of distal airspaces induces shear injury, and therefore contributes both to ventilator-induced lung injury and ARDS-associated mortality. However, the largest, multi-center randomized controlled trial of OLV in moderate to severe ARDS, wherein RM plateau pressures of 50-60 cmH₂O were used, was associated with significantly higher mortality compared to traditional LPV. Despite being based upon well conducted pre-clinical and clinical RM studies, the higher mortality associated with the OLV strategy requires re-examining the assumptions and conclusions drawn from those previous studies.

This narrative review examines the evidence used to design RM strategies. We also review the radiologic, rheologic, and histopathologic evidence regarding the nature of lung injury, the phenomena of recruitment and derecruitment as it informs our perceptions of recruitment potential in ARDS. Major LPV clinical trial data and other clinical data are also examined to assess the practical necessity of RM in ARDS, and whether a subset of cases might benefit from pursuing RM therapy. Finally, a less a radical approach to RM is offered that might achieve the goals of RM with less risk of harm.
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Introduction

Acute respiratory distress syndrome (ARDS) is characterized by altered permeability pulmonary edema and decreased gas volume (ie. functional residual capacity or FRC) leading to low respiratory system compliance ($C_{RS}$) and hypoxemia both from intrapulmonary shunting and ventilation-perfusion mismatching.\textsuperscript{1-3} Causes of decreased FRC include underinflated, unstable alveoli vulnerable to collapse, as well as atelectatic or “de-recruited” alveoli.\textsuperscript{4} With the advent of low-tidal volume ($V_t$) lung-protective ventilation (LPV) alveolar derecruitment is exacerbated despite moderate levels of PEEP (ie. 10±4 cmH$2$O).\textsuperscript{5}

Recruitment maneuvers (RM) reverse lung collapse in ARDS by applying high airway pressures that overcome a range of “threshold opening pressures” (TOP). Re-opening collapsed or obstructed peripheral airways and alveoli often improves oxygenation, $C_{RS}$, and may enhance alveolar fluid clearance.\textsuperscript{6-10} Historically, RM consisted of 40 cmH$2$O inflations sustained for ~15s (ie. the force needed to achieve Vital Capacity in normal subjects) to reverse intraoperative atelectasis and intrapulmonary shunting.\textsuperscript{11, 12}

RM as an adjunct to LPV was first described in early pre-clinical studies of high frequency oscillatory ventilation for acute lung injury.\textsuperscript{13} In the early 1990’s RM became a central feature of a LPV variant known as “open-lung ventilation” (OLV).\textsuperscript{14, 15} One such technique described brief periods (10 minutes) of continuous mechanical ventilation at a peak airway pressure of 55 cmH$2$O and 16 cmH$2$O PEEP.\textsuperscript{14} Over the intervening years the mechanics, physiology and efficacy of RMs were explored in numerous, clinical and preclinical studies using a variety of strategies, as well as theoretical treatises.\textsuperscript{16}
Some of these findings informed the largest, multi-center randomized controlled trial of OLV that enrolled over 1000 subjects with moderate to severe ARDS. Despite the data-driven protocol, the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial group (ART)\textsuperscript{17} reported significantly higher mortality in the OLV treatment arm compared to the control arm using the National Institutes of Health ARDS Clinical Trials Network (ARDSNet) lower-PEEP protocol.\textsuperscript{18} Particularly vexing was that despite significantly higher oxygenation and $C_{RS}$ in subjects treated with OLV, the need for rescue therapies was not different: suggesting that RM was largely ineffective in stabilizing FRC. Higher mortality in the OLV arm confirmed one of the major findings of the original ARDSNet LPV trial: improved oxygenation is not necessarily a valid signifier for meaningful outcomes.\textsuperscript{18}

Some have interpreted the ART results to suggest abandoning RM in treating ARDS,\textsuperscript{19} whereas others\textsuperscript{20} suggest that ART-related methodologic issues still cloud its interpretation and have instead advocated for a thorough \textit{post hoc} analysis (which to our knowledge has not yet been published). Furthermore, the dramatic failure of a trial based upon numerous well-executed physiologic studies behooves re-examining the nature of recruitment and de-recruitment as well as the validity of inferences drawn from them. This narrative review re-examines the physiology and mechanics of recruitment and de-recruitment in ARDS: the results of which might suggest when and how RM might be incorporated more reasonably into clinical practice.

### Brief overview of RM in ARDS

Different approaches to RM have been developed over the past 30 years (Table 1). One of the earliest and most popular strategies has been the sustained inflation maneuver using
Another strategy (amplitude-modulated ventilation) posited that following a deep inflation the time constants for alveolar closure (of previously collapsed units) were substantially longer than the ventilatory cycle; so that recruitment achieved from a single deep inflation (or short periods of elevated PEEP) could be sustained for a period of time afterwards. This was hypothesized to allow alveolar stabilization without requiring sustained levels of higher PEEP. Strategies based on this approach include intermittent sigh breaths, and intermittent or “fluctuating PEEP”. Another approach is a less intense variation of the RM technique described by Lachmann, in which a brief (2 minute) period of ventilation at a Pplat of 45 cmH₂O and PEEP of 15 cmH₂O is used. Other, more extended, iterations of this approach include “prolonged recruitment maneuver”, and “slow moderate pressure” RM. Other prolonged approaches include the “extended sigh” maneuver, and the “RAMP” technique. These last four techniques most closely resemble what is currently the most widely investigated technique (and the primary focus of this review): the “staircase RM”. The impact of these techniques will be discussed in varying detail throughout the course of this review in terms of what they reveal about the nature of recruitment in ARDS.

RM studies have categorized ARDS subjects as either responders or non-responders according to the presence and magnitude of improvement in oxygenation, resting lung volume, or reduction in non-aerated lung tissue by CT scan, electrical impedance tomography or ultrasonography. This implies RM have a limited application under specific conditions not always discernable at the bedside. ARDS associated with either “direct” epithelial injury (pulmonary or primary ARDS) or “indirect” endothelial injury (extrapulmonary or secondary ARDS) both demonstrate improved oxygenation following the maneuver: those with indirect
injury tended to be more responsive both in the degree of recruitment, oxygenation and reductions in both lung resistance and elastance.\textsuperscript{21, 27, 42} Indirect injury typically coincides with early interstitial edema and higher chest wall elastic forces,\textsuperscript{43, 44} suggesting that RMs are most effective when compressive and congestive atelectasis are major factors versus alveolar flooding and tissue consolidation which are more prominent in direct injury such as pneumonia (see below).

**Physics and physiology of recruitment: pressure and time**

The focus of recruitment has been on alveolar re-inflation. This is a matter of conversational convenience that unintentionally results in an underappreciation of the fact that distal airway injury and inflammation is a prominent feature of ARDS and cannot be separated from alveolar injury.\textsuperscript{45} What follows is a description of the interplay between distal airway and alveolar injury as it relates to recruitment phenomena. In a later section describing the ambiguities surrounding RM, a more in-depth description of associated tissue-related factors (i.e. rheology and histopathology) will be provided.

Distal airway injury (i.e. airways with a diameter $< 2 \text{ mm}$) in ARDS is characterized by bronchiolar epithelial necrosis/sloughing and the rupturing of bronchiolar-alveolar attachments that promotes distal airway instability.\textsuperscript{45, 46} This in turn increases airways resistance and expiratory flow limitation.\textsuperscript{2, 47} Opening collapsed small airways in ARDS is a dynamic process with a variable time course that depends upon several factors including: airway radius, the fraction of functional alveoli providing regional airway stability (i.e. axial wall traction or “tethering”), airway fluid characteristics (i.e. surface tension and viscous forces, as well as film thickness) and the presence of biologically active surfactant.\textsuperscript{48-51} As lining fluid surface tension
increases, so too does the TOP to overcome it; with additional pressure required to overcome viscous forces. As airway fluid viscosity increases both “yield pressures” and time required to effect airway opening also are increased, which may be particularly difficult to achieve in peripheral/terminal airways.

Regarding normal alveolar response to recruitment, an experimental microimaging study of deflated healthy lungs undergoing stepwise inflation from 0 to 35 cmH₂O observed an unusual U-shaped pattern, whereby mean alveolar size first increased, stabilized (at 25 cmH₂O) and then decreased. Simultaneously, the number of inflated alveoli decreased and then markedly increased again at pressures of 25-35 cmH₂O causing a doubling of lung volume size. In other words, at higher pressures alveoli paradoxically become both smaller and more plentiful. It was hypothesized that stretching the alveolar wall increases the diameter of the Pores of Kohn. This in turn thins the alveolar lining fluid normally covering the pores; thus facilitating pressure transmission between adjacent “mother-daughter” alveoli resulting in the latter’s recruitment.

These experimental conditions, however, diverge from those encountered in ARDS such that similar behavior (if it in fact occurs during an RM) might require a prolonged time period. In early ARDS altered permeability pulmonary edema fluid contains protein concentrations similar to plasma. Protein and fibrin-rich alveolar edema, along with oxygen radicals, inactivates surfactant resulting in higher TOP for both distal airways and alveoli.

Depending upon the severity of pulmonary capillary leakage, when alveolar flooding involves the alveolar ducts liquid bridge formation rises exponentially, particularly when FRC decreases and elastic recoil forces increase. Bronchiolar epithelial damage and inflammation
also are present and associated with ARDS severity, thereby increasing the likelihood of inflammatory exudate obstructing both the airway lumen and the Pores of Kohn. Because fluid viscosity increases with increasing protein concentrations, enhanced viscosity of airway and alveolar lining fluid (along with other cellular debris accumulating in the peripheral airspaces) may prolong the time necessary to achieve maximum recruitment for any targeted Pplat during an RM.

The time necessary to reopen collapsed or obstructed small airways also depends upon the extent of menisci formation or plugs in sequentially collapsed or obstructed airways, that may be amplified either by the presence of mucus in pneumonia-associated ARDS, or in those with substantial smoking histories. In other words, the level of recruitment reported at a specific Pplat cited in RM studies that were sustained for 1-2 minutes is not definitive proof of maximal efficacy at that level of applied pressure (see below).

**Temporal aspects of lung recruitment**

Two temporal aspects influence the effectiveness of recruitment: 1) the duration of any particular RM itself, and 2) the clinician-set inspiratory time chosen during the maneuver. Some of what is discussed below reflects this ambiguity as to precisely what occurs when we observe as “recruitment”. Some of this (but by no means all) has been clarified by the advent of lung parenchymal microimaging in animal models discussed above. The following two sections provides a historical narrative on the development of our understanding as well as the persistent ambiguity surrounding “recruitment” between the 1960s to 1990s.

*“Creep”: fast vs. slow pulmonary compartments***
The term “creep” was coined in the 1960s to describe the progressive increase in volume over time when the lungs are subjected to “constant” pressure inflations. More broadly referred to as “hysteresis” or “stress adaptation” it expresses how tissue once deformed resists returning to its former shape. This is attributed to adaptive surface tension forces in the lungs, and intrinsic viscoelastic properties of both lung and chest wall tissue (eg. the presence of elastic fibers in both smooth and skeletal muscle, ligaments and tendons) as well as abdominal organs.

Under normal physiology a two-phase process consisting of “fast” and “slow” compartments was described in animals. During a 10s inflation hold, an initial rapid (2s) phase is followed by a slow (8s) phase of continued “tissue stretching”: the latter attributed primarily to alveolar recruitment and reduced alveolar surface tension, and to a lesser degree alterations in tissue viscoelastic properties. Stress adaptation was directly associated with increasing driving pressures reaching maximal “creep” at 33 cmH₂O. Increasing sustained inflation intensity (ie. 120s at 33 and 39 cmH₂O) effected additional stress adaptation (Fig 1).

Stress adaptation has been observed in anesthetized normal subjects undergoing step inflations (similar to constructing a pressure-volume curve); stabilizing between 5-7s at different volumes. Two-thirds of stress-adaptation was attributed to the lungs, with the chest wall exhibiting a smaller, slower time course. This was ascribed to tissue properties in both structures rather than alveolar recruitment and gas redistribution.

Evidence supporting creep phenomenon in ARDS: stress adaptation, time constants, transient pulmonary states and prone positioning
In ARDS, slow volume changes following a 10 cmH₂O PEEP increase were first reported by Katz et al.⁴ whereby 67% of volume change occurred during the first breath and 90% by the fifth breath. The remaining increase occurred over 40 minutes and was attributed either to stress-adaptation or alveolar recruitment. Similar to other findings,⁶¹ 62% of the changes were attributed to the lungs and 38% to the chest wall.⁴

“Slowly-distensible” pulmonary compartments in severe ARDS have been reported by others.⁶³ Using a 5 cmH₂O PEEP increment only 37% of subjects exhibited a slow recruitment compartment. In contrast 79% displayed a slow de-recruitment compartment: consistent with other studies reporting delayed de-recruitment following step-decreases in PEEP.²⁶ The mean inflation time constant (τ) of the slow compartment was 9.4±7.3s. As 95% equilibration occurs at 3 τ and 99% at 5 τ,⁶⁴ recruitment (or stress-adaptation) of slow pulmonary compartments would reach 95-99% volume equilibration at mean times of 28-47s with an upper 95% confidence limit of 43-72s. As a reference, in normal subjects under general anesthesia atelectasis reversal occurs at τ of 2.6s (95-99% reversal between 8-13s).¹²

In contrast, when oxygenation is the variable of interest, the temporal impact on recruitment is exaggerated. Several studies examined the time required to establish “steady state” oxygenation in ARDS following either a PEEP increase, or initiating sigh breaths.²⁷,⁶⁵,⁶⁶ Setting PEEP above the lower inflection point (PEEP: 14 ± 3 cmH₂O) 90% of maximal improvement occurred at 20 ± 19 m.⁶⁵ However, in another study a 10 cmH₂O PEEP increase produced no apparent oxygenation plateau (ie. PaO₂ progressively increased between 5-60 m).⁶⁶ When augmenting LPV with intermittent sigh breaths (Pplat: 45 cmH₂O; PEEP:14 cmH₂O) maximum improvements occurred at 30m for both PaO₂ and end-expiratory lung volume.²⁷
An intriguing aspect of recruitment are “transient [pulmonary] states” observed in ARDS when the ventilatory pattern was altered.\(^6^7\) Prolonged effects of recruitment were noted after various manipulations: a single PEEP step, a “PEEP wave” maneuver, and an a “undulating PEEP” pattern. One hour following a PEEP increase from 13 to 21 cmH\(_2\)O, FRC rose 150% greater than that predicted by \(C_{RS}\) of the “fast” pulmonary compartment (ie. “baby lung”).\(^6^8\) These results were similar to those reported by Katz et al.\(^4\)

In the “PEEP wave” study, a brief repetitive cycle of incremental ascending and descending PEEP with a maximal PEEP change of 10 cmH\(_2\)O was repeated five times over several hours. When PEEP was returned to the initial settings, \(P_{aO2}\) stabilized at 10 mmHg above the previous baseline. The phenomenon occurred with each successive PEEP wave so that at the end of the experimental run, \(P_{aO2}\) was 80 mmHg higher than at the initial baseline.

The “undulating PEEP” study assessed the upper limit of time constant distributions using a PEEP cycle above and below a baseline PEEP of 14 cmH\(_2\)O. PEEP was titrated in 7 cmH\(_2\)O increments up to 29 cmH\(_2\)O and down to 0 cmH\(_2\)O over nine hours. FRC measured one hour following any PEEP change did not indicate a steady state in terms of recruitment or de-recruitment. The overall impression was: “the length of individual time constants in ARDS may exist in the region of hours.”\(^6^7\)

Slow, progressive lung recruitment frequently observed during prone position therapy supports the existence of slow pulmonary compartments in ARDS.\(^6^9\) Initial improvement in oxygenation typically occurred within 30-60m, yet it is not uncommon for improvements becoming apparent only after 6h; with continuing improvements sometimes observed over 20-36h.\(^6^9\) Prolonged RM (6-14h) reversing profound refractory hypoxemia has been reported.
anecdotally in ARDS complicated by abdominal compartment syndrome\textsuperscript{70} and in pronounced obesity when combined with prone position \textsuperscript{69}

These findings underscore the considerable difference in the time frames chosen to evaluate oxygenation response following an RM. Several RM studies that will be discussed in the next section used two minute equilibration periods between all or some of the PEEP steps,\textsuperscript{17, 40, 71-73} which is consistent with classic physiologic studies.\textsuperscript{60, 67, 74} While the two minute limit allows for stress-adaptation, it also limits exposure to severe respiratory acidemia,\textsuperscript{40} and potential cardiovascular instability from alterations in right and left ventricular function.\textsuperscript{75-78} Most importantly, these necessary time constraints imposed by very high pressure RM techniques limits our ability to fully understand the actual recruitment potential in ARDS.

**Selecting inspiratory time during RM**

The other temporal aspect is whether the inspiratory time per breath impacts the overall effectiveness of RM. This is likely dependent upon whether the clinician-set inspiratory time is appropriate for the inspiratory time constant of individual patients. In general, ARDS subjects have an inspiratory $\tau_{\text{a}}$ of 0.17-0.41s;\textsuperscript{2} which (depending upon syndrome severity) would result in 95% and 99% estimated equilibration between airway and alveolar pressures at $\sim$0.5-1.2s and 0.9-2.1s respectively. However, these estimates are based upon assumptions of mono-exponential functions of constant elastances and resistances throughout inspiration, and therefore neglects the impact of mechanical inhomogeneity in ARDS.\textsuperscript{79} Moreover, they ignore the impact of continued gas mixing and redistribution (ie. *pendelluft* motion) and increased diffusion time on both oxygenation and dead-space ventilation by which RM efficacy often is assessed.
The range of inspiratory time reported in RM studies have varied: 1.5s (single PEEP step),\textsuperscript{63} 2.5±1.1s (for sigh breaths),\textsuperscript{27} between 2-3s\textsuperscript{17, 71, 72, 80} (for “staircase” RM studies) or were not specified,\textsuperscript{40} whereas others used an end-inspiratory pause of 5-7s.\textsuperscript{34, 81} In a lung lavage model of acute lung injury, \textit{in-vivo} microscopic studies of subplueral alveoli during a RM at 40 cmH\textsubscript{2}O found that over a 40s period ~85% of recruitment occurred by 2s.\textsuperscript{82} This data supports clinical use of inspiratory times of 2-3s to maximize per-breath recruitment potential during an RM.

\textbf{Mechanics of recruitment and derecruitment: clinical studies in the 21\textsuperscript{st} Century}

The majority of physiologic and clinical studies investigating recruitment in ARDS began in earnest in the first decade of this century, and thus has produced the majority of our knowledge base and clinical evidence. Because of this, the narrative in this section mostly derives from select studies we believe constitute the most important findings regarding RM and PEEP titration informing current practice.

In 2000 a variant of the original RM used in OLV,\textsuperscript{14} was introduced by Medoff et al.\textsuperscript{83} who applied pressure control ventilation (PCV) at a plateau pressure (Pplat) of 60 cm H\textsubscript{2}O and PEEP of 40 cm H\textsubscript{2}O for two minutes. In a subsequent study comparing PCV-RM to sustained inflation RM (CPAP of 45 cmH\textsubscript{2}O), a 2-minute trial PCV-RM (using a lower Pplat of 45 cmH\textsubscript{2}O and inspiratory time of 2.5s) produced substantially greater oxygenation improvement (80% vs. 19%).\textsuperscript{75}

Since the case report by Medoff et al,\textsuperscript{83} PCV-RM has become a popular approach and was the basis of the strategy used in the ART trial.\textsuperscript{17} A generalized description of this approach
is as follows: an initial Pplat of 40 cm H₂O is slowly increased in 5 cmH₂O increments to levels of 50 or 60 cmH₂O. RM is done using 2-3 minutes stepwise escalation/de-escalation of super PEEP (ie. 20-45 cmH₂O), with a fixed driving pressure (Pplat-PEEP) of 15 cmH₂O (Fig 2).⁴⁰,⁸⁴ This is based upon observations that TOP (Pplat being the clinical correlate) progressively increases from non-dependent to dependent lung between 20-60 cmH₂O.⁴⁰,⁸⁵ A variation of this technique was used in the ART trial but only using 1 or 2 minutes stabilization periods between steps (Fig 3).¹⁷

When absorption atelectasis is pervasive, Pplat up to 70 cmH₂O have been required,⁸⁵ and pressures up to 80 cmH₂O have been used in ARDS associated with blunt chest trauma⁸⁶ or abdominal compartment syndrome.⁷⁰ To place these extraordinary pressures into perspective, the first few post-natal breaths expanding gasless, partially liquid filled lungs (100 times more viscous than air) require TOP of 40 cmH₂O and peak transpulmonary pressures of 60-100 cmH₂O to achieve full inflation.⁸⁷,⁸⁸ The unique circumstances in the moments following birth (in which completely deflated, non-injured lungs are initially expanded) is markedly different from that of heterogenous lung and distal airway injury present in ARDS (in addition to pathological alterations in chest wall mechanics). Nonetheless the physics illustrates the circumstantial necessity that sometimes require applying extraordinarily high transpulmonary pressures to displace liquid and re-expand the lungs under extreme conditions.

**Distribution of threshold opening pressure and recruitment**

Small physiologic studies suggest varying degrees of recruitment occur throughout the lung. An early computed tomography (CT) study found that potentially recruitable lung in
moderate-to-severe ARDS averaged 21±10% and required a Pplat of 45 cmH$_2$O (whereas ~25% remained collapsed). Also, there may exist nodal points whereby full recruitment transitions down the lungs from mid-to-dorsal regions when Pplat of 30, 35 and 45 cmH$_2$O are reached (with the least amount of non-aerated tissue observed at 45 cmH$_2$O). Subsequent studies reaffirmed that TOP varies down the ventral-dorsal axis in ARDS. Upper zones had a negligible TOP of 0-4 cmH$_2$O, whereas middle zones had a TOP of 4-7 cmH$_2$O, and dorsal lung recruitment commenced at ~20 cmH$_2$O.

Similar to initial post-natal breaths, achieving a TOP in ARDS is not synonymous with full recruitment. Early pressure-volume curve studies of ARDS interpreted the lower inflection point as the TOP needed to recruit collapsed peripheral airways and alveoli, but it was misconstrued as the anchoring point for setting “best PEEP”. It later became apparent that recruitment merely commenced in the upper lung zones at the lower inflection point, and continued throughout the inspiratory pressure-volume limb. Likewise, despite TOPs of 4-7 cm H$_2$O (middle) and ~20 cmH$_2$O (dorsal) maximal recruitment in these regions occurs at 20-30 cmH$_2$O and 45 cmH$_2$O respectively.

Other CT imaging studies found nonaerated lung tissue progressively decreased from 55% (at a baseline ventilation with 10 cmH$_2$O of PEEP), to 23% at a Pplat of 40 cmH$_2$O, and 10% at a Pplat of 50 cmH$_2$O. Improved recruitment was observed even when Pplat increased from a baseline of 28-32 cmH$_2$O to 36-41 cmH$_2$O at essentially the same PEEP level. Most importantly (in light of the ART study results), extending RM to a Pplat of 60 cmH$_2$O only reduced nonaerated tissue by 5%. Full recruitment has been reported at Pplat of 40-51 cmH$_2$O, whereas others have reported increasing percentages of subjects achieving full
recruitment as Pplat increased: 46% (40 cmH2O), ~60% (45 cmH2O) and ~70% (50 cmH2O). In the seminal study on the time course of FRC improvement with PEEP in subjects with acute respiratory failure (the majority of whom likely would have met the current definition of ARDS), a Pplat of 40 cmH2O and PEEP of 18 cmH2O was needed to return FRC to normal. Thus, in the context of refractory hypoxemia even at moderate to high levels of PEEP, a RM Pplat of at least 40 cmH2O probably should be targeted.

Furthermore, there is speculation that the recruitable lung represents a “penumbra” of inflamed tissue surrounding a core nidus of compartmentalized injury; constituting a mixture of collapsed or partially flooded air-spaces. The remaining ~25% of nonaerated lung tissue (despite recruiting pressures of 45 cmH2O) likely signifies consolidated tissue, at least in those with normal body habitus (see below).

Interpretive limitations of mechanistic studies of recruitment

Interpreting these RM studies raise several issues. First, confounding factors influence the potential effectiveness of RMs in ARDS. These may include: 1) the inherently heterogenous nature and unique spatial patterns of acute lung injury among individual patients, 2) apparent differences in the response to RM related either to initiating pathways (direct vs. indirect: interstitial vs. alveolar edema) or the severity of injury (e.g. the degree of inflammation and magnitude of edema formation), 3) timing of RM relative to syndrome onset, 4) the ventilatory strategy used prior to initiating RM, 5) alterations in chest wall mechanics, and 6) hemodynamic status (e.g. various vasoactive drugs that might affect cardiac output and pulmonary blood flow distribution). Moreover, mechanistic RM studies require highly complex, clinically
impractical methodologies that limits the number of subjects who can be studied, and thus: the
generalizability of results to individual patients.

Second, variables chosen to signify “full recruitment” differed between studies which
introduces interpretative ambiguity. Borges et al. used a \( P_{aO2} + P_{aCO2} > 400 \text{ mmHg} \). Adjusting for
the range of mean \( P_{aCO2} \) across RM steps (70-95 mmHg) yields a corresponding \( P_{aO2} \) of ~300-330
mmHg. Povoa et al. used a \( P_{aO2} \) of 250 mmHg on an \( F_{IO2} \) of 1, and de Matos et al. reported
the Pplat at which non-aerated alveoli was minimal. Studies by both Crotti et al. and Caironi et
al. merely reported the degree of recruitment observed at a fixed Pplat of 45 cmH\(_2\)O (as a
surrogate measure of total lung capacity).

Third, over the years, RM studies have employed different measurement techniques
that have influenced both the results and their interpretation. Recruitment inferred from
cHEST mechanics (eg. change in end-expiratory lung volume measured during construction of
pressure-volume curves or after step changes in PEEP) reflects increased aeration of partially
and fully inflated alveoli, as well as recruitment of previously collapsed or non-communicating
alveoli. In this review we have focused on CT-based studies. Although ambiguities exist with this
technique, nonetheless it provides a high degree of differentiation between non-, poorly and
well-inflated alveoli (see below). As would be anticipated, recruitment inferred from chest
mechanics analysis estimate much greater recruitment than those based upon CT analysis.

Taken together, numerous potential confounding variables, relatively small numbers of
study subjects, variations in both technique and primary endpoints, all limit the generalizability
of RM study results to individual patients, let alone navigating the contentious discourse
regarding their interpretation.
Sponge theory and superimposed hydrostatic pressures

Setting aside common clinically induced causes (eg. circuit disconnection, endotracheal suctioning, etc.), lung derecruitment in ARDS is thought to be caused largely by super-imposed hydrostatic pressure of overlying edematous lung tissue and mediastinal structures, as well as increased weight of the chest wall (eg. thoracic anasarca, ascites). This is based upon the “sponge theory” posited to explain rapid redistribution of lung densities on CT scans from dorsal to ventral regions during placement in prone position. That this represents a shift in gravitational forces applied to the lungs is supported by two facts. First, overall lung density was unchanged suggesting lung “tissue mass” (ie. edema, blood, cellular content or debris) had remained stable. Second, pulmonary edema clearance in ARDS is severely impaired (6%/hr), regardless of which, edema fluid is removed through the lymphatics system and does not freely redistribute through lung tissue.

PEEP and derecruitment

A recurring, relatively uniform finding in many of the early RM studies was that when ventilation was resumed at the previous PEEP level, oxygenation improvements dissipated rapidly over time despite relatively high baseline PEEP (~ 12-15 cmH2O). In contrast, oxygenation improvements could be sustained following RM when higher post-RM PEEP levels were maintained (eg.~6-7 cmH2O above baseline). Acute lung injury models also found post-RM oxygenation was PEEP-dependent with the highest sustained improvement occurring at PEEP of 16 cm H2O (versus 12 and 8 cmH2O). That sustained improvement was independent of RM methodology suggests recruitment and de-recruitment occur through different mechanisms.
When pleural pressure exceeds alveolar pressure at end-expiration derecruitment occurs over time irrespective of previous volume history. In ARDS, derecruitment is a continuous process that becomes prominent at PEEP < 15 cmH2O. Derecruitment appears to cease in the upper and hilar lung zones at PEEP of 10 cmH2O, whereas it continues in dorsal regions reaching a maximum collapse rate at 5 cmH2O. Derecruitment modeling suggests the speed of collapse also increases as PEEP decreases. Similarly, a decremental PEEP study found pleural pressure exceeded alveolar pressure once PEEP was decreased below ~9 ± 5 cmH2O, whereas in some subjects derecruitment occurred at PEEP < 20 cmH2O.

These findings suggest three potential PEEP targets which might reduce derecruitment during the acute phase of ARDS: 1) minimum PEEP of 10-12 cmH2O, 2) general target of 16 cmH2O, and 3) > 20 cmH2O in very severe cases (particularly those with reduced chest wall compliance). This is similar to the “better PEEP” strategy proposed byGattinoni and colleagues.

Superimposed pressure, derecruitment and ARDS severity

The largest and perhaps most comprehensive CT study reported the maximal range of ventral-dorsal superimposed hydrostatic pressure was 6-18 cmH2O. Interestingly, the mean hydrostatic pressure was similar between Berlin classifications of mild, moderate and severe ARDS (12±3, 12±2, 13±1 cmH2O respectively, P = 0.053). Factoring in PEEP required to counter both superimposed hydrostatic pressure and chest wall elastance yielded PEEP estimates of 16±8, 16±5 and 18±5 cmH2O respectively (P = 0.48).
A particularly interesting finding was PEEP requirements did not differ between those characterized as having low or high recruitment potential and based on the observation that maximum superimposed hydrostatic pressure between the two groups differed by only 1-2 cm H$_2$O. Thus, neither superimposed hydrostatic pressure nor chest wall elastance correlated appreciably with recruitment potential.

This implies that superimposed hydrostatic pressure enters the calculus of setting PEEP to preserve lung stability following recruitment rather than causing recruitment. These observations led the authors to dissuade clinicians from reflexively treating low recruitability (ie. “lobar” ARDS) with PEEP levels of ~ 15 cmH$_2$O simply to prevent shear injury in “a few grams of lung tissue,” given the greater risk of hemodynamic compromise and regional overdistension in middle and ventral lung zones.94

**Elevated Intra-abdominal pressure in ARDS: Implications for RM and setting PEEP**

The ventral-dorsal pleural pressure gradient in supine position determines resting alveolar size and largely reflects gravitational forces imposed by the abdomen: a more dense, fluid-like compartment with a volume twice that of an air-filled thorax.105, 106 Normal intra-abdominal pressure (IAP) is ~5-7 mmHg (7-10 cmH$_2$O), whereas intra-abdominal hypertension is defined as IAP > 12 mm Hg (16 cmH$_2$O) with 20-60% pressure transmission to the thorax.107 Therefore, severe hypoxemia coinciding with intra-abdominal hypertension is a compelling indication for OLV.

**Thorocoabdominal mechanics, derecruitment and intra-abdominal hypertension**
Elevated IAP displaces the diaphragm cephalad into the thorax and stiffens the abdominal portion of the chest wall, such that pleural pressure becomes more positive. This is particularly acute in the dorsal-caudal regions in supine position: the effects being reduced lung and chest wall compliance, increased tissue and airways resistance, and compressive atelectasis.\textsuperscript{108-110} Under these conditions alveolar de-recruitment from tissue compression (versus alveolar consolidation) is more likely the primary cause of refractory hypoxemia, hence RM is more likely to be effective.

Abdominal compartment syndrome (IAP > 25 mmHg; > 34 cmH\textsubscript{2}O),\textsuperscript{111} is associated with substantial non-aerated and poorly aerated lung tissue (23\% and 18\% respectively).\textsuperscript{112} At these extraordinary pressures respiratory system inertance (normally considered negligible) may become significant and therefore would increase TOP.\textsuperscript{113} Inertance, refers to the acceleration of gas molecules as well as displacement of “resting” lung and chest wall tissues (including the abdominal contents).\textsuperscript{110}

During quiet breathing with normal body habitus inertance accounts for < 5\% of driving pressure.\textsuperscript{114} In morbidly obesity, inertance is ~4-fold higher and up to 68\% can be accounted for by chest wall tissue.\textsuperscript{110} Although its relevance to ARDS is unknown, it is notable that in morbidly obese subjects the driving pressure required to overcome inertance alone during “maximal ventilation maneuvers” reaches 40 cmH\textsubscript{2}O.\textsuperscript{110} In a case of ARDS and abdominal compartment syndrome, a similar driving pressure (Pplat: 80 cmH\textsubscript{2}O and PEEP of 45-50 cmH\textsubscript{2}O) was required to increase P\textsubscript{aO\textsubscript{2}} from 23-350 mmHg when surgical decompression could not be attempted.\textsuperscript{70}

**Intra-abdominal hypertension and ARDS**
Intra-abdominal hypertension is common in severe ARDS,\textsuperscript{109} and particularly prevalent in extrapulmonary cases.\textsuperscript{43} It occurs in pulmonary ARDS complicated by morbid obesity (“mass loading”) where IAP is \textasciitilde12-19 cmH\textsubscript{2}O,\textsuperscript{115} as well as other conditions such as ascites from abdominal sepsis, pancreatitis, or hepatic failure.\textsuperscript{116, 117} In acute lung injury models, IAP of 20 cmH\textsubscript{2}O greatly exacerbated pulmonary edema formation and increased intrapulmonary shunting.\textsuperscript{118, 119} Mean IAP of \textasciitilde22 cmH\textsubscript{2}O\textsuperscript{43, 117, 120} and end-expiratory esophageal pressures of \textasciitilde20 cmH\textsubscript{2}O have been reported in severe ARDS.\textsuperscript{121}

IAP is particularly relevant in treating refractory hypoxemia. A pre-clinical study, found that at IAP of 24-35 cmH\textsubscript{2}O, high PEEP (15 cmH\textsubscript{2}O) was equally ineffective as low to moderate PEEP (5-12 cmH\textsubscript{2}O) in improving FRC and P\textsubscript{aO2}/F\textsubscript{I02}.\textsuperscript{122} This lead to a follow-up study of “IAP-matching PEEP” in acute lung injury with intra-abdominal hypertension (ie. 16-25 cmH\textsubscript{2}O). Essentially higher levels of P\textsubscript{plat} and PEEP used in the PCV-RM strategies described above were needed to improve FRC and oxygenation (\textbf{Fig 4}).\textsuperscript{118}

Adding one-half of the measured IAP to the RM pressure targets has been suggested.\textsuperscript{107} For example, a RM of 45 cmH\textsubscript{2}O\textsuperscript{92} applied to IAP representing conditions of intra-abdominal hypertension (16 cmH\textsubscript{2}O), average IAP in reported in ARDS (22 cm H\textsubscript{2}O) or severe abdominal compartment syndrome (\textasciitilde50 cmH\textsubscript{2}O)\textsuperscript{111, 123} would require adjusting P\textsubscript{plat} upwards to 53, 56 and 70 cmH\textsubscript{2}O respectively.

Attempting RM in patients with intra-abdominal hypertension requires assessing overall risk/benefit ratio. Elevated pleural and intra-abdominal pressures impedes hemodynamic function and lymphatic drainage and therefore carries the risk of worsening both pulmonary edema and intra-abdominal hypertension as well as risking hemodynamic collapse.\textsuperscript{124} In the
context of abdominal compartment syndrome it should probably be considered only when surgical decompression carries an even greater risk.

**Impact of PEEP on volume distribution in ARDS**

Finally, regardless of Pplat or PEEP, gas distribution in ARDS steadily decreases down the ventral-dorsal axis with an upper-to-lower lung volume distribution ratio of 2.2:1 at ambient end-expiratory pressure. At PEEP of 20 cmH₂O ventral-dorsal gas distribution was essentially equivalent (1.1:1). For the dorsal regions (ie. those having the greatest impact on gas exchange) this volume redistribution translated into increased end-expiratory lung volumes from ~10 to 25% and end-inspiratory lung volumes from 15 to 35%. These findings were supported by an electrical impedance tomography study of OLV wherein ventral/dorsal V₉ ratio decreased from 2.01±0.36 to 1.19±0.10 (P<0.01).

**The ambiguous and perplexing nature of recruitment phenomena**

In ARDS improvements in radiologic imaging, gas exchange and lung mechanics during and following RM represent complex, histopathologic responses of injured lungs and chest wall forces to applied pressure, and thus are open to interpretation. This section describes some of the vagaries that limits our interpretation of the efficacy of RM.

**Radiologic factors**

CT scans are the gold standard for evaluating topographic distribution of aerated and nonaerated lung tissue in ARDS; inferred by the lungs ability to attenuate X-rays. The radiologic definition of consolidation is markedly increased lung attenuation obscuring pulmonary vessels caused by atelectasis or alveolar filling, whereas in pathology the term
specifically refers to the later. attenuation is measured by the hounsfield linear density scale that assigns a numeric value (hounsfield units or hu) differentiating between bone (+1000 hu), water (0 hu) and air (-1000 hu). values between these three points are used to convey various states of pulmonary tissue with values between -100 and +100 hu considered to represent “collapsed” tissue (table 2).

from these interpretations, pulmonary gas-tissue ratios are calculated and used to infer the response to rm and pEEP. yet, the designation of lung “tissue” also includes extravascular fluid and blood. thus, CT imaging represents “the quantity of air being introduced into a diseased lung”; hence the statement: “one pixel is not an alveolus”. lung CT imaging interpretation relies upon an unprovable assumption of homogenous alveolar filling in “condensed” lung tissue, whereas in reality it likely includes already aerated alveoli. in addition, estimating the reduction in nonaerated tissue is dependent upon the number of CT sections sampled (compared to whole lung scans). for example, a single juxta-diaphragmatic section may result in either over or underestimation of recruitment, whereas adding samples of apical and hilar regions tends to overestimate recruitment.

In spite of the strong associated found between radiological assessment of alveolar recruitment and oxygenation, a complex interaction of other factors contributes to improved oxygenation (eg. increased ventilation-perfusion matching, decreased cardiac output with redistribution of pulmonary perfusion, reduced edema formation, and its redistribution to the peri-vascular spaces). Skeptics claim radiologic evidence supporting lung recruitment are “inferences about alveolar micromechanics from measurements made on a scale several orders of magnitude greater than that of the structures of interest.” The
The volume element of a CT image ("voxel") is ~ 2-2.6 mm$^3$ whereas a single alveolus is ~0.12 mm$^3$. Thus a single voxel may represent a tissue section consisting of ~15 discreet alveoli.

The importance of this limitation becomes apparent from lung microimaging of gas dynamics within alveolar clusters. Animal models of acute lung injury observed pronounced pendelluft motion between adjacent alveoli (some slowly inflating during expiration, some deflating during inspiration), as well as paradoxically simultaneous recruitment/derecruitment, while still others either synchronously inflate and deflate, or appear “stunned” (ie. remaining motionless at a constant volume). This localized inter-alveolar asynchrony and instability results from mechanical interdependency between neighboring alveoli and increases with the severity of injury. Although CT imaging studies provide invaluable information on the nature of recruitment/de-recruitment they are clinically impractical for routine use; beyond which there remains assumptive ambiguity, and therefore a risk of over-interpretation.

**Rheologic factors**

During expiration distal airway derecruitment occurs as increasing surface tension forces cause liquid bridges to reform drawing airway and alveolar walls together. An in vivo study of acute lung injury confirmed the presence of liquid menisci forming dense bridges across small peripheral airways. Therefore, the perception of alveolar recruitment in acutely injured lungs may be explained as the breaking of foam bridges and displacement of pulmonary edema fluid resulting in increased alveolar ventilation. Thus other factors determine the force required to “re-open the lungs”: surface-tension forces (accounting for 50-60% of lung elastance), the presence of biologically active surfactant (in both alveoli and distal airways),
viscosity and thickness of airway edema, and overcoming “strain energy” in collapsed small airways (see below).48-50, 56, 140, 142

Even sponge model proponents acknowledge that “compression atelectasis” likely represents a mixture of alveolar and small airway collapse.81 What remains undisputed is that: 1) specific and reproducible ranges of airway pressures transmitted to the lung parenchyma are required to improve regional aeration and gas exchange in ARDS, and 2) the recruitment of collapsed/obstructed airways and alveoli invariably involves epithelial cell deformation and therefore likely causes shear injury,140, 141 as well as exacerbating baseline airway epithelial injury associated with ARDS.45 Greater injury is thought to occur with reopening collapsed vs. obstructed airways.141

Histopathologic factors

Ambiguity surrounding the effectiveness and appropriateness of RM partly depends upon whether atelectasis (ie. “degassed alveoli”), intra-alveolar edema (“flooded” alveolar units and peripheral airways) or interstitial edema is the predominant lesion causing refractory hypoxemia, as well as the intensity of edema.98 Historically the most prominent autopsy findings in early ARDS included some combination of interstitial and alveolar edema/hemorrhage, and hyaline membranes,143-153 along with a substantial subset reporting atelectasis.145, 146, 148, 150, 154 In what eventually would be called ARDS, the term “congestive atelectasis” was used to describe “diffuse non-obstructive collapse of pulmonary alveoli and intense interstitial edema and pulmonary capillary congestion”;148 leading to excessive surface tension forces causing collapse.149 More recently this has been redefined as “inflammatory atelectasis” (ie. “congestive”) vs. “compression atelectasis”.155
These characteristics defined “diffuse alveolar damage” (DAD): the histopathologic hallmark of ARDS. During the first week of DAD-confirmed ARDS intra-alveolar edema tends to be highest (90% of cases), but remains prevalent during subsequent weeks (74% of cases). Only ~50% of ARDS now present with DAD; its decrease coinciding with the emergence of LPV. Non-DAD ARDS has been associated primarily with pneumonia; characterized less by intra-alveolar edema, but rather intense interstitial edema and alveolar neutrophil infiltration localized in the terminal bronchioles.

A study that matched PEEP responsiveness to lung biopsy and autopsy samples found subjects exhibiting minimal oxygenation response had complete alveolar filling with purulent/hemorrhagic material. Those exhibiting the greatest oxygenation response had less intense alveolar edema and were distinguished by hyaline membrane formation, interstitial edema and atelectasis.

**Recruitment potential: direct vs. indirect injury and injury severity**

Both direct and indirect forms of ARDS include alveolar collapse. Yet direct (alveolar epithelial) injury has been characterized more by intense collapse and alveolar edema but minimal interstitial edema, whereas indirect (capillary endothelial) injury was associated with more intense interstitial edema than alveolar edema. Similar findings were reported in other studies. Moreover, direct injury has been associated with higher pulmonary microvascular permeability that, over a period of days, coincided with higher levels of extravascular lung water. Some evidence suggests that RM (at least when using the sustained inflation technique) might be ineffective in the presence of high extravascular lung water (~16 mL/kg).
Inconsistencies between histologic findings in ARDS likely have many sources due to the limited number of samples, the heterogenous nature of ARDS and associated lesions, and its timing relative to syndrome onset. Irrespective of these, it suggests that simplistic conceptual models guiding RM have limited utility. This is because the varied histopathologic changes in ARDS coexist across a spectrum and that lesions evolve over time. Moreover, direct injury from pneumonia disrupting alveolar membrane integrity (ie. loss of bacterial compartmentalization) can induce indirect, secondary injury to non-infected lung regions through systemic cytokine release. In fact, a substantial number of ARDS subjects with either aspiration or pneumonia as primary etiology also have sepsis as a secondary source of lung injury (20 and 40% respectively).

Furthermore, secondary analysis of several RM CT studies concluded that recruitment is likely determined more by the severity of injury and corresponding edema formation than injury mechanism per-se. As lung injury severity increases, so too does the degree of pulmonary capillary permeability and the magnitude of extravascular lung water. In general, regardless of injury mechanisms, greater recruitment potential is present in ARDS characterized by diffuse vs. predominant dorsal opacities. Unfortunately, this is not a distinction that can be made by clinicians when chest radiographs are the only practical tool available when contemplating whether to pursue treating refractory hypoxemia with RM.

In a secondary analysis of RM studies evaluated by CT, estimates of recruitability were actually higher in direct injury. Several factors were cited that provide important insights into the interpretation of RM studies. First, the timing of RM relative to ARDS onset influences recruitability. Over time, edema fluid is slowly reabsorbed while concurrently fibrotic and tissue
repair mechanisms evolve. Second, the duration and fidelity to LPV prior to initiating a RM will influence recruitment potential regardless of injury mechanism. Third the higher correlation between direct injury and ARDS severity may reflect the degree of “bacterial diffusion throughout the lung parenchyma”. This in turn suggests relatively greater consolidation in direct injury (with a corresponding brisk “reactive” edema formation) possibly producing greater edema than that caused by distant organ injury. However, the investigators stressed that extrapulmonary injury or infection can cause equivalent severity, so that when only a small number of subjects are studied (selection bias) it may produce results suggesting equivalence, relatively greater or lesser lung recruitability between direct vs. indirect injury.

**Pplat and PEEP during LPV: discerning the need for RM**

Oxygenation goals in LPV tend to align with the “least-PEEP” philosophy, whereby the objective is using the lowest PEEP that provides a reasonable $P_{aO2} (\geq 70 \text{ mmHg})$ at a relatively non-toxic $F_{IO2} (\leq 0.60)$. Only when clearly toxic levels of $F_{IO2} (\geq 0.70)$ are necessary are higher PEEP levels generally used ($> 10 \text{ cmH}_2\text{O}$).

In traditional LPV, $V_T$ is titrated to achieve a $P_{plat} < 30 \text{ cmH}_2\text{O}$. Slightly more stringent LPV variants have focused on minimizing the risk of right ventricular dysfunction and cor pulmonale ($P_{plat} \leq 26 \text{ cmH}_2\text{O}$) or the risk of tidal overdistension ($P_{plat} < 27 \text{ cmH}_2\text{O}$). Given the heterogeneity of ARDS and large variability in oxygenation dysfunction, it is important to have some perspective as to how often traditional LPV goals fall short of securing adequate oxygenation at relatively non-toxic $F_{IO2}$ levels.
The mechanistic studies reviewed above suggest a Pplat of 30 cmH2O effects almost complete recruitment in the mid-lung (CT regions 4-7) and simultaneously the largest incremental changes in the dorsal lung (regions 8-10). In addition, derecruitment becomes apparent at PEEP < 15 cmH2O and particularly prominent in the dorsal regions only at PEEP < 10 cmH2O.85,92 Therefore, assuming normal body habitus, a PEEP of 10-15 cmH2O and Pplat to 26-30 cmH2O appears sufficient to ensure adequate oxygenation at relatively non-toxic FIO2 in the majority of ARDS cases.

Data from three major LPV trials174-176 involving over 2,300 subjects with early ARDS compared two PEEP strategies support this interpretation. These studies found that: 1) moderate PEEP of 8-10 cmH2O produced a mean Pplat of 21-25 cmH2O and was generally sufficient to achieve an adequate to normal Pao2 on relatively non-toxic level of FIO2; 2) higher PEEP (ie. ~15 cmH2O) with mean Pplat < 30 cmH2O further improved Pao2 at a decidedly less toxic FIO2, and 3) by the third study day (regardless of PEEP strategy) oxygenation had either stabilized or improved. These findings strongly suggest that RM is unnecessary to manage the majority of ARDS cases and needlessly increases the risk/benefit ratio (Table 3).

Mean data, however, cannot elucidate whether Pplat generated by PEEP levels used during traditional LPV would: 1) likely reach suggested nodal points of TOP associated with “full recruitment” of dorsal regions; 2) estimate the percentage of subjects requiring toxic FIO2 levels; and 3) gauge how many subjects would be reasonable candidates for RM therapy. We examined these issues by querying databases used in our prior studies.164,177 Our results are discussed in detail in online supplementary materials, however the main findings were: 1) VT titration effectively limited Pplat to desired levels despite high PEEP levels and 2) this limited
the likelihood for substantial dorsal lung recruitment in severe refractory hypoxemia, as even at PEEP > 16 cmH₂O only 5% of subjects reached a sufficiently high recruitment threshold of 45 cmH₂O. Thus, there is a subset of severe ARDS cases in which traditional LPV is insufficient and RM would appear a reasonable option to reverse refractory hypoxemia.

**Optimizing oxygenation and its relationship to minimizing the risk of “atelectrauma”**

FRC represents the alveolar volume and is the primary determinant of \( P_{aO2} \). Therefore, increased \( P_{aO2} \) in response to increased PEEP or RM is a “bedside convenience” to infer changes in FRC, and by extension shear injury risk. Unfortunately, the logic linking these three phenomena is precarious.

Depending upon Pplat, a substantial portion of early FRC increase (i.e. the “fast pulmonary compartment”) represents expansion of normally inflated or underinflated alveoli and not recruitment. In addition, arbitrary \( P_{aO2}/F_{I02} \) thresholds used to signify “full recruitment” (250 to 330 mmHg) are literally false. Full recruitment implies normal pulmonary oxygen diffusion function (e.g. \( P_{aO2}/F_{I02} \geq 450 \) mmHg). Essentially this does not occur in ARDS because of varying degrees of tissue consolidation and slow resolution of pulmonary edema. Thus, \( P_{aO2}/F_{I02} \) thresholds of 250 to 330 mmHg used to evaluate RM suggests a tacit acknowledgement that the term “full recruitment” is meant figuratively.

Beyond these vagaries lies the crux of the debate: does OLV materially reduces the risk of repetitive shear injury compared to traditional LPV? This is unlikely for the majority of ARDS cases. First, because a Pplat of \( \geq 40 \) cmH₂O is needed to reopen distal airways and alveoli deep within the dorsal lung. These units remain closed and protected from shear injury when Pplat is
limited to \( \leq 30 \text{ cmH}_2\text{O} \). Second, in ARDS substantial portions of lung tissue appears to reach full recruitment at or below a \( \text{Pplat} \leq 30 \text{ cmH}_2\text{O} \), and its stability appears to be maintained when PEEP is set between 10-15 cm H\(_2\)O. In addition, evidence from several preclinical studies suggests atelectatic areas are relatively protected from shear injury by intra-alveolar edema with most damage caused by excessive stress developed in the peripheral airways.\(^{179}\) In these studies tidal overdistension was a more important contributor to pro-inflammatory cytokine expression than shear injury. Third, microimaging of subpleural alveoli in acute lung injury models revealed that, despite stable levels of driving pressure and PEEP, there exist patterns of recruitment/derecruitment between interdependent alveoli even at high PEEP levels that appear to fluctuate minute-by-minute.\(^{139}\) Thus, the notion of eliminating derecruitment and atelectrauma in ARDS appears illusory.

**Implications of “slow” pulmonary compartments on how to approach RM**

Integrating the temporal issues involved in recruitment, with evidence that most recruitment occurs \( \leq 50 \text{ cmH}_2\text{O} \), and the increased mortality risk reported in the ART study,\(^{17}\) it behooves us to reflect upon the need for RM and how it might be approached going forward. Compelling evidence of slow pulmonary compartments in ARDS is at odds with the current RM strategy and raise questions whether brief recruitment periods reflect the actual effectiveness of a specific \( \text{Pplat} \). By extension, this influences the decision to use higher pressures with increasing risk of injury and hemodynamic compromise. Moreover, limited intensity RM studies such as the “extended sigh”, “prolonged” and “slow moderate” RM cited above all observed substantial recruitment at pressures \( \leq 40 \text{ cmH}_2\text{O} \) over a period of several minutes.\(^{33-35,\ 37,\ 38}\) To date, no study has investigated whether an extended trial of super-PEEP limited to 25-30
cmH₂O and driving pressures of 15 cmH₂O might provide sufficiently stable oxygenation over a period of several hours.

Also, the relative importance of using an inspiratory time of 2-3s during a RM (while supported by preclinical data) has not been evaluated clinically. This strategy substantially limits RM because it restricts minute ventilation in more severe manifestations of ARDS that is associated with highly elevated physiologic dead-space, and also places additional strain on right ventricular function. In pre-clinical studies an inspiratory time of 1.4s is generally sufficient for recruiting the fast pulmonary compartment. And in light of studies describing “transient [pulmonary] states” as well as those on prone positioning, it is worth considering whether more clinically appropriate inspiratory times used during LPV, if not optimal, might be sufficient to effect sufficient recruitment over time to reach oxygenation goals.

Hemodynamic consequences of OLV

Although it is not the focus of this review, the unexpectedly higher mortality in the OLV arm of the ART study, and its association with a higher incidence of hemodynamic impairment, requires a brief review of cardiothoracic inter-relationships in ARDS and the potential impact of OLV strategies. The pulmonary vasculature functions as a low resistance, high capacitance system reflected in the thin walled right ventricle that readily shows signs of dysfunction and eventually fails under sustained work demands imposed by high pulmonary vascular resistance in ARDS.

Acute pulmonary hypertension commonly develops in ARDS due to hypoxemia, hypercapnia, acidosis, and pulmonary vascular obstruction from interstitial edema, and
disseminated arterial and microvascular embolization. Under mechanical ventilation conditions of high end-inspiratory volume (eg. high PEEP, driving pressure or a combination of both) markedly increase pulmonary vascular resistance negatively impacts right ventricular function. Right ventricular function is further compromised due to the simultaneous reduction in venous return and ventricular preload. Acute cor pulmonale develops when the right ventricle becomes ischemic from sustained excessive workloads and occurs in 22-25% of patients with ARDS, with the incidence increasing to 50% in severe ARDS. Thus higher PEEP strategies and the potential for RM overuse of in response to incidences of desaturation risks developing either short-term transient hemodynamic instability (which is a common finding in RM studies), or more importantly, the potential for longer term problems of right ventricular dysfunction and the development of cor pulmonale (which increases mortality risk in ARDS).

**RM and the potential risk of ventilator-induced lung injury**

A brief comment also seems appropriate regarding the potential risk of PCV-RM strategies on ventilator-induced lung injury. Although driving pressure is controlled at a seemingly safe level during stepwise increases of super-PEEP (ie. 15 cmH₂O), the overall magnitude of step-changes in airway pressure increase abruptly from 5 or 10 cmH₂O to 20cmH₂O as PEEP increases from 25 to 45 cmH₂O, or by continuous incremental changes of 10 cmH₂O. Regardless, these manipulations culminate in extraordinarily high end-inspiratory pressures of 60 cmH₂O. More concerning is that during the subsequent PEEP decrement trials in some studies, once the optimal PEEP level is determined: “patients underwent another recruitment maneuver using the same recruiting pressures used in the last step of the maximum recruitment maneuver” [italics added]. This procedure was incorporated into the
ART trial.\textsuperscript{17} As others have noted, regardless of the perceived safety of limiting driving pressure to 15 cmH\textsubscript{2}O, there is an upper limit of lung stress that can be tolerated without resulting in severe lung injury.\textsuperscript{141} As described in this review there appears to exist highly circumspect situations in which this might be appropriate (e.g. morbid obesity, abdominal compartment syndrome) however clinicians should always be cognizant of this danger.

**Implications of the ART Study**

Finally, the discouraging results of the ART trial underscores the primary clinical problem with RM therapy in ARDS: namely the necessary reliance upon chest radiographs and inferences drawn from mechanistic studies that limits clinicians to mere speculation about the likelihood of therapeutic success. In consequence the vexing problem for clinicians is discerning whether an apparent “non-responder” reflects inadequate TOP, insufficient time allotted for recruitment or simply poor recruitment potential. From what little we are able to discern from the ART trial, this appears to have been what occurred. The majority of ARDS cases were from direct injury exhibiting only “mild responses” to RM.\textsuperscript{17} There was a correspondingly higher incidence of lung overdistension (surmised from the incidence of barotrauma and need for vasopressor therapy) that was significantly associated with mortality risk in the OLV study arm.\textsuperscript{17}

As mentioned above, the gold standard for assessing lung recruitment is CT imaging which provides superior information to identify both whom RM most likely would benefit (eg. diffuse injury pattern) and demarcating the limits of Pplat and PEEP based upon real time imaging. Unfortunately, this is clinically impractical and therefore we remain in the same predicament as the ART study investigators. However, the utilization of bedside
ultrasonography in the assessment of lung recruitment is a promising tool and should be incorporated into clinical management when assessing the effectiveness of RM.

Summary

In the context of severe ARDS consideration of RM should be reserved for a minority of cases with persistent or recurring bouts of hypoxemia that occur despite PEEP levels of 15-20 cmH₂O and require prolonged exposure (ie. days) to F₁O₂ ≥ 0.70 in order to stabilize oxygenation: particularly in those with either intra-abdominal hypertension or severe obesity. Under these circumstances the risk of exacerbating lung injury from oxidative stress from prolonged exposure to toxic levels of F₁O₂, enters prominently into the calculus. When elevated IAP is not a prominent factor, a prolonged trial of super PEEP and low driving pressures that generate a Pplat of 40-45 cmH₂O (perhaps in concert with prone position) may be a more prudent approach to stabilize oxygenation. Finally, RM in those with direct injury and a higher likelihood of pronounced tissue consolidation is probably of limited benefit and has been associated with greater mortality risk.
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**Figure Legends**

**Fig 1.** Association between increasing driving pressures and alveolar stress adaptation in an animal model with normal chest mechanics (Reference 60).

**Fig 2.** Representation of a “staircase” recruitment maneuver inflation steps ($P_{dr} = \text{alveolar driving pressure or plateau pressure} - \text{PEEP}$) as described in Reference 84.

**Fig 3.** Representation of a “staircase” recruitment maneuver inflation steps ($P_{dr} = \text{alveolar driving pressure or plateau pressure} - \text{PEEP}$) as used initially during the ART trial (Reference 17).

**Fig 4.** Relationship between PEEP, plateau pressure ($P_{plat}$) and chest wall elastance ($E_{cw}$) at increasing levels of intra-abdominal pressure (IAP) in an animal model of acute lung injury (Reference 118).

**Supplementary Fig 1.** Clinical management data of plateau pressure ($P_{plat}$) associated with the ARDSNet lung protective ventilation protocols. The green line represents $P_{plat}$ associated with major recruitment in the dorsal lung and the red line is associated with the lower range of full recruitment in the most dorsal lung aspects in ARDS. (Reference 1)

**Supplementary Fig 2.** Percentage of ARDS subjects with plateau pressure ($P_{plat}$) ranges meeting proposed nodal points of alveolar recruitment in the dorsal lung regions associated with PEEP when using the ARDSNet lung protective ventilation protocols (Reference 1).
**Table 1.** Different recruitment maneuver strategies for the treatment of moderate to severe ARDS.

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>Description</th>
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<tbody>
<tr>
<td>Sustained Inflation (SI)</td>
<td>CPAP is increased in 5 cmH₂O steps every 5-10 s until a target recruitment pressure between 30-50 cmH₂O is achieved, and then sustained for 30-40s. Deflation is achieved with the same stepwise decrement in airway pressure until CPAP reaches baseline PEEP level (or a new targeted baseline). The technique is based upon numerous clinical and pre-clinical studies.</td>
</tr>
<tr>
<td>Intermittent Sighs</td>
<td>Programmed, consecutive sigh breaths (1-3/m) targeting a Pplaat of 35-45 cmH₂O. The technique is based upon small clinical studies.</td>
</tr>
<tr>
<td>Intermittent PEEP/“Fluctuating” PEEP</td>
<td>Programmed, consecutive breaths in which PEEP is elevated from baseline to a higher level for either a specific number of breaths per minute (1-3), every few minutes, or for an extended time period (6m). The technique is based upon several pre-clinical studies without a targeted Pplaat and a case report with a targeted Pplaat was 50 cmH₂O in ARDS and abdominal compartment syndrome.</td>
</tr>
<tr>
<td>Brief RM on CMV</td>
<td>Volume or pressure control ventilation producing a Pplaat of 45 cmH₂O at PEEP of 15 cmH₂O. Several clinical studies on the physiologic effects of RM.</td>
</tr>
<tr>
<td>Prolonged RM</td>
<td>Repeated periodic (2 m) PEEP elevation to 15 cmH₂O upon which the Pplaat plateau pressure was then increased step-wise from 30, 35 and 40 cmH₂O (30, 35 and 40 cmH₂O) during successive 2 minute maneuvers</td>
</tr>
</tbody>
</table>
Pre-clinical study

Slow Moderate Pressure RM

PEEP is increased to 15 cmH₂O for 15 min at a Vₜ of 10mL/kg (producing a Pplat ~ 27 cmH₂O) in which a 7s end-inspiratory pause is applied every 30s.

Pre-clinical study

Extended Sigh

Two approaches:

1) Increasing PEEP to 10 cmH₂O above LIP and Pplat < UIP. If UIP unidentifiable then Vₜ adjusted to maintain Pplat < 35 cmH₂O. Duration: 15 min.

2) Increasing PEEP (5 cmH₂O/30s) while simultaneously reducing Vₜ in 2mL/kg steps until reaching a PEEP of 25 cmH₂O and a Vₜ of 2 mL/kg. This is followed by CPAP of 30 cmH₂O and then a deflationary phase pattern returning to baseline settings or to PEEP set 2 cmH₂O above the LIP.

The technique is based upon several small clinical studies.

RAMP RM

Two approaches:

1) CPAP is increased 1 cmH₂O/s to reach 40 cmH₂O

2) PIP and PEEP simultaneously increased 1-2 cmH₂O every 2-3m. “Open Lung” stopping criteria based on reaching oxygenation goals at F₁O₂ ≤ 0.25 (neonatal model) P

Pre-clinical study

Staircase RM

Pressure control ventilation with a fixed driving pressure of 15 cmH₂O starting at a PEEP of 25 cmH₂O. This strategy uses 2 minute periods of alternating increasing/decreasing
incremental PEEP steps that ramp up from 5 to 10 and 15 cmH2O to achieve a Pplat of 60 cmH2O.

Post RM PEEP is set according to a decremental trial with optimal PEEP defined as the level just above the threshold when deterioration in either oxygenation or compliance is observed.

Several iterations of this general approach exist using different maximum levels of PEEP and Pplat (e.g. 25 and 45-50 cmH2O respectively.

The technique is based upon multiple small and large clinical studies as well as pre-clinical studies.

**Key:** CMV = continuous mechanical ventilation, FIO2 = inspired oxygen fraction, LIP = lower inflection point, PIP = peak inspiratory airway pressure, Pplat = plateau pressure, RM = recruitment maneuver, UIP = upper inflection point, VT = tidal volume.

<table>
<thead>
<tr>
<th>Radiologic Quantification Hounsfield Units</th>
<th>Used to signify</th>
</tr>
</thead>
<tbody>
<tr>
<td>+1000</td>
<td>Bone</td>
</tr>
<tr>
<td>0</td>
<td>Tissue (defined as 50% tissue,50% air)</td>
</tr>
<tr>
<td>-1000</td>
<td>Air</td>
</tr>
<tr>
<td>-1000 to -900</td>
<td>Hyperinflated tissue</td>
</tr>
<tr>
<td>-900 to -500</td>
<td>Normally aerated tissue</td>
</tr>
<tr>
<td>-500 to -100</td>
<td>Poorly aerated tissue</td>
</tr>
<tr>
<td>-100 to +100</td>
<td>Non-aerated tissue</td>
</tr>
</tbody>
</table>
Table 3. Oxygenation and plateau pressure differences in three multi-centered randomized controlled trials of lower vs. higher PEEP during lung-protective ventilation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Day 1</th>
<th>Day 3</th>
<th>PEEP (cmH₂O)</th>
<th>Lower PEEP</th>
<th>Higher PEEP</th>
<th>PEEP (cmH₂O)</th>
<th>Lower PEEP</th>
<th>Higher PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVEOLI174*</td>
<td></td>
<td></td>
<td>9 ± 4</td>
<td>15 ± 4</td>
<td>9 ± 4</td>
<td>13 ± 5</td>
<td>24 ± 7</td>
<td>27 ± 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 ± 7</td>
<td>27 ± 6</td>
<td>24 ± 6</td>
<td>26 ± 7</td>
<td>0.54 ± 0.18</td>
<td>0.44 ± 0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>78 ± 22</td>
<td>85 ± 28</td>
<td>77 ± 22</td>
<td>74 ± 20</td>
<td>168 ± 66</td>
<td>220 ± 89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.52 ± 0.18</td>
<td>0.40 ± 0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOVS176†</td>
<td></td>
<td></td>
<td>10 ± 3</td>
<td>16 ± 4</td>
<td>9 ± 3</td>
<td>12 ± 4</td>
<td>25 ± 5</td>
<td>30 ± 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 ± 6</td>
<td>29 ± 6</td>
<td></td>
<td></td>
<td>0.58 ± 0.17</td>
<td>0.50 ± 0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80 ± 26</td>
<td>88 ± 32</td>
<td>76 ± 16</td>
<td>75 ± 15</td>
<td>149 ± 61</td>
<td>187 ± 69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.41 ± 0.12</td>
<td>0.52 ± 0.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXPRESS175‡</td>
<td></td>
<td></td>
<td>8 ± 2</td>
<td>16 ± 3</td>
<td>8 ± 2</td>
<td>15 ± 4</td>
<td>21 ± 5</td>
<td>28 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 ± 5</td>
<td>27 ± 4</td>
<td></td>
<td></td>
<td>0.66 ± 0.21</td>
<td>0.55 ± 0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>89 ± 34</td>
<td>108 ± 43</td>
<td>91 ± 37</td>
<td>102 ± 38</td>
<td>150 ± 69</td>
<td>218 ± 97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.58 ± 0.20</td>
<td>0.46 ± 0.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>175 ± 81</td>
<td>245 ± 98</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: 
- F<sub>O₂</sub> = inspired oxygen fraction,
P<sub>AO₂</sub> = arterial oxygen tension,
- PEEP = positive end-expiratory pressure,
P<sub>plat</sub> = end-inspiratory plateau pressure,
- *After the first interim analysis the Higher PEEP protocol was amended to require a minimum PEEP of 14 cmH₂O for 48h due to a lack of difference in PEEP requirements in the two treatment arms. In addition, the first 80 subjects in the Higher PEEP arm underwent 1-2 sustained inflation recruitment maneuver of continuous positive airway pressure of 35-40 cmH₂O for 30s during the first 4 study days. This sub-study was discontinued for lack of
sustained oxygenation response. †Higher PEEP arm included Pplat limit of 40 cmH2O and use of a sustained inflation recruitment maneuver of continuous positive airway pressure of 40 cmH2O for 40s. ‡Total PEEP rather than set PEEP reported. Pplat was limited to 30 cmH2O in higher PEEP arm.

**Supplementary Table 1.** Subjects ventilated at elevated PEEP levels and toxic oxygen concentrations on the day following ARDS onset categorized by arterial oxygen tension ranges.

<table>
<thead>
<tr>
<th>PEEP Range (cmH2O)</th>
<th>N</th>
<th>FIO2 ≥ 0.70</th>
<th>Pao2 &lt; 60°</th>
<th>Pao2 60-79†</th>
<th>Pao2 80-100‡</th>
<th>Pao2 &gt; 100§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>PaO2 (mmHg)</td>
<td>mean±sd</td>
<td>PaO2 (mmHg)</td>
<td>mean±sd</td>
<td>PaO2 (mmHg)</td>
</tr>
<tr>
<td>11-13</td>
<td>174</td>
<td>116 (67%)</td>
<td>52 ± 11</td>
<td>36 (31%)</td>
<td>70 ± 6</td>
<td>30 (26%)</td>
</tr>
<tr>
<td>14-16</td>
<td>208</td>
<td>166 (80%)</td>
<td>54 ± 6</td>
<td>14 (8%)</td>
<td>70 ± 6</td>
<td>68 (41%)</td>
</tr>
<tr>
<td>17-19</td>
<td>40</td>
<td>35 (88%)</td>
<td>48 ± 8</td>
<td>8 (23%)</td>
<td>67 ± 6</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>≥20</td>
<td>20</td>
<td>19 (95%)</td>
<td>50 ± 4</td>
<td>3 (16%)</td>
<td>64 ± 5</td>
<td>3 (16%)</td>
</tr>
</tbody>
</table>

**Key:** FIO2 = fractional oxygen concentration, Pao2 = arterial oxygen tension, PEEP = positive end-expiratory pressure. Oxygenation classifications: * refractory hypoxemia, † clinically adequate oxygenation, ‡ normal oxygenation, § super normal oxygenation, ‡ represents the percentage of those cases requiring an FIO2 ≥ 0.70 within that PEEP range.
Fig 1
Fig 2
Fig 3
Supplementary Fig 1

[Graph showing Pplat (cm H₂O) against PEEP Ranges (cm H₂O)]
Supplementary Fig 2

PEEP Ranges (cmH₂O)

- Pplat Ranges
  - 35-39
  - 40-44

Tri

0%  5%  10%  15%  20%  25%  30%  35%  40%

11-13 14-16 17-19 20+