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MECHANICAL VENTILATION IN ARDS: QUO VADIS?

The First Robert M Kacmarek Scientific Memorial Lecture

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Abstract

Contemplating the future should be grounded in history. The rise of post-Polio intensive care units was inextricably related to mechanical ventilation. Critically-ill patients who developed acute respiratory failure often had "congestive atelectasis" (ie. a term used to describe ARDS prior to 1967). Initial mechanical ventilation strategies for treating this condition and others inadvertently led to ventilator-induced lung injury. Both injurious ventilation and later use of overly cautious weaning practices resulted from both limited technology and understanding of ARDS and other aspects of critical illness. The resulting misperceptions, misconceptions and missed opportunities took decades to rectify, and in some instances still persist. This suggests a reluctance to acknowledge that all therapeutic strategies reflect the historical period in which they were developed and the corresponding limited understanding of ARDS pathophysiology at that time. We are at the threshold of a revolutionary moment in critical care. The confluence of enormous clinical data production, massive computing power, advances in understanding the biomolecular and genetic aspects of critical illness and the emergence of neural networks will have enormous impact on how critical care is practiced in the decades to come. Therefore, it is imperative we understand the long-crooked path needed to reach the era of protective ventilation in order to avoid similar mistakes moving forward. The emerging era is as difficult to fathom as our current practices and technologies were to those practicing 60 years ago. This review explores the history of mechanical ventilation in treating ARDS, describes current protective ventilation strategies and speculates how ARDS management might look 20 years from now.

Introduction

"You can't really know where you are going until you know where you have been."

Maya Angelou[1]

"The past is never dead. It's not even past. … Haunted by wrong turns and roads not taken, we pursue images perceived as new but whose providence dates to the dim dramas … which are themselves but ripples of consequence echoing down the generations."

William Faulkner[2]

I am deeply honored to deliver the first scientific memorial lecture for my colleague and friend Bob Kacmarek, and to speak on a subject I know Bob would have relished delivering himself. When I began thinking about this topic, what came to mind was something the poet Maya Angelou said. I believe speculating about the future without discussing what has transpired over the past 60 years would be of marginal value. And towards completion of this project I was reminded of a passage by novelist William Faulkner. Although written in a different context it nonetheless alludes to the crooked path taken to reach the current era of protective ventilation.

In no small measure respiratory care arose from the rapid expansion of intensive care units (ICU) in the early to mid-1960s; largely driven by the need to safely deliver mechanical ventilation. Bob and I entered respiratory care during what could be called the "prehistoric period" of ICU mechanical ventilation (1965-1975). There was no history because it was all new and happening while we were doing it. History helps us reflect upon why specific approaches came about and subsequently were abandoned, retained, and sometimes rediscovered. Reckoning with our past allows us to appreciate all too human tendencies to misperceive, misconceive, and miss opportunities that have occurred along the way.

I believe we stand at the threshold of a truly revolutionary era in our understanding and management of ARDS. One that will challenge our profession to adapt moving deeper into the 21st Century. Therefore, it's imperative we recognize the tenacious hold outdated approaches and beliefs have had and (in some cases) continue to have. Thus preparing us for what lies ahead. I will also review the current state and scope of protective ventilation practices in ARDS before attempting to answer the question: "whither goest thou?"

Origins of Ventilator-Induced Lung Injury

Absorption Atelectasis, Large Tidal Volumes and Acute Respiratory Failure

In the post-Polio period of 1958-1961 small intensive care units (ICU) with 5-6 bed capacities emerged in major university-associated hospitals (eg. Oxford, John Hopkins, Harvard, and the Universities of Toronto, Pittsburgh, and Southern California).[3, 4] By the mid-1960s ICUs had expanded widely in Western countries. During this period the indications for mechanical ventilation also expanded to treat acute respiratory failure across a wide array of medical, surgical and trauma cases. Beginning in 1963 these early experiences began to appear in the medical literature highlighting the problems encountered in managing acute respiratory failure.[5-7] These patients differed from those with polio who were characterized by respiratory muscle paralysis, normal lung mechanics and gas exchange, low minute ventilation ($V_{\dot{E}}$) demand, and in whom triggering and asynchrony were essentially non-factors.

The customary practice of supine positioning with mechanical ventilation using atmospheric expiratory pressure and a physiologic V_T based upon the Radford nomogram (developed for use during general anesthesia and in managing polio patients),[8] resulted in

progressive atelectasis and hypoxemia from intrapulmonary shunting. The predominant clinical model for treating hypoxemia was that based upon the reversal of post-operative absorption atelectasis.[7] This involved sustained ("sigh") inflations of 30 to 40 cmH_2O for 15 seconds that was adopted for ICU practice.

For practical reasons the sustained inflation approach was modified by simply using large V_T ventilation to treat atelectasis, hypoxemia and also to meet elevated $V_{\dot{E}}$ demands.[7] The later justification was that the Radford nomogram grossly underestimation $V_{\dot{E}}$ requirements as physiologic dead-space and CO_2 production are markedly elevated in acute respiratory failure (as predicted by the nomogram's authors).[5, 8] And despite the use of predicted normal V_T, patients often complained of dyspnea or appeared in distress that was quickly relieved once V_T was increased.[3] In addition, using pressure ventilators designed to treat patients with polio were inadequate as they could only achieve peak airway pressures of 15-20 cmH_2O.[7]

By the mid-1960s a mean V_T of ~11-13 mL/kg with ambient expiratory pressure was the standard of care,[5, 6] as had been recommended.[7] And in patients presenting with (or subsequently developing) severe acute respiratory failure, the only *perceived* options were to increase V_T and fractional inspired oxygen concentration (F_{IO2}) to toxic levels (ie, $\geq$ 0.70).[9] Moreover, in subjects who now would be classified as "primary ARDS", increasing V_T to $\geq$ 15 mL/kg increased alveolar ventilation, but was ineffective in reversing hypoxemia.[6]

Thus, the absorption atelectasis paradigm supporting high V_T ventilation for refractory hypoxemia was not conceptually appropriate. And during this period it was also discovered that the venturi air-entrainment mechanisms used to control F_{IO2} at 0.40 were deeply flawed. When

peak inspiratory pressures reached 30 cmH_2O measured F_{IO2} ranged from 0.65 to 0.95.[10] Thus as compliance or resistance worsened, patients often endured prolonged exposure to toxic levels of F_{IO2}.

1967: ARDS, PEEP and Oxygen Toxicity

Nineteen sixty-seven was a watershed year because of two studies. Ashbaugh and colleagues [11] introduced the concept of ARDS and proposed treating it with PEEP. ARDS replaced previously terms (eg. "congestive atelectasis", "wet lung", etc.) that had described the phenomenon without a unifying concept. These investigators made the initial step towards understanding the underlying pathophysiology that evolved into the concept of acute lung injury.[12]

Equally important was the introduction of PEEP, representing the first effective therapy for treating refractory hypoxemia in ARDS and potentially avoiding O_2 toxicity. Its initial use was a desperate attempt to save a young trauma patient when pressure-cycled ventilation failed. An experimental Engstrom volume ventilator with high-pressure capability was retrieved from storage. Although the "expiratory retard control" was unfamiliar to the authors, it was set to 10 cmH_2O resulting in rapidly improved oxygenation.[13] This was largely responsible for the adoption of volume-cycled ventilation in treating ARDS requiring high ventilating pressures and $V_{\dot{E}}$ demand (eg. ~ 16 L/min).[14]

In the other study Nash and colleagues[15] described O_2 toxicity as a clinical problem. However, they raised the possibility that prolonged exposure to high V_T and peak airway pressures may have been contributory; thus anticipating the concept of ventilator-induced lung

injury (VILI). Unfortunately, soon afterwards the authors dismissed their own speculation.[16] However, evidence of VILI was apparent (but unrecognized) when early ARDS investigators reflected on "pre-PEEP" practices. They noted radiographic opacities first appeared "patchy in nature", becoming "more diffuse" over time and ultimately requiring "inspiratory pressures of 60-70 cmH_2O" with atmospheric expiratory pressure "permit[ting] collapse of more alveoli."[14] And until the early 1990's this was plausibly interpreted as simply representing underlying disease progression.

Missed Opportunity for Lung Protective Ventilation

In hindsight, the reluctance to use PEEP before and after 1967 reflected the enormous influence of Cournand's[17] 1947 study describing its adverse effects on cardiac output. However, that study focused not on manipulating end-expiratory pressure but on altered inspiratory:expiratory (I:E) ratios in which inadvertent PEEP was a consequence. When I:E ratio was $\geq$ 1:1 during large V_T ventilation, a prolonged expiratory retard (up to 2.4 sec) was responsible for decreased venous return, whereas nadir end-expiratory pressure was < 5 cmH_2O just before the onset of inspiration.[17]

Reluctance to explore PEEP prior to 1967 was curious given publications in the late 1930s on the effectiveness of continuous positive pressure breathing in treating acute pulmonary edema.[18, 19] During World War II it was also effective in treating post-traumatic "wet lung" syndrome.[20] By 1959 PEEP was shown to increase functional residual capacity (FRC) and oxygenation during general anesthesia.[21] And a 1962 symposium reflecting upon the Cournand study[17] also pointed out that mean airway pressure rather than positive end-expiratory pressure was the primary factor in hemodynamic compromise.[22]

A crucial opportunity was missed in not re-assessing the need for large V_T ventilation once PEEP was found to be effective. In addition, the singular focus on PEEP in turn biased the interpretation of other early PEEP studies. Consideration was not given to both the initial rationale for using a large V_T and its singularly negative impact: the generation of both high peak intrathoracic pressures and prolonged positive pressure decay during expiration.[23] Thus, PEEP levels > 10 cmH_2O were largely interpreted as dangerous and generally avoided.

Yet, in 1978 Suter and colleagues[24] systematically examined the combined effects of V_T and PEEP on respiratory system compliance (C_{RS}). Increasing V_T from 10-20 mL/kg caused a precipitous decline in C_{RS} at relatively low PEEP levels (6-10 cmH_2O). In contrast, when V_T was limited to 5 and 7 mL/kg C_{RS} steadily increased even at PEEP of 15 cmH_2O; thus anticipating the era of lung-protective ventilation (LPV) (**Fig 1**). The curious lack of attention paid to this study likely reflected that, at the time, only two studies had suggested the possibility of VILI.[25, 26]

In addition, ventilators of the 1970s generally lacked a direct means of measuring end-inspiratory plateau pressure (P_{plat}) and C_{RS}; thus limiting the ability to assess lung stress. In order to measure P_{plat} the tubing powering the expiratory "mushroom valve" had to be manually occluded to create the end-inspiratory hold. This became virtually impossible with early intermittent mandatory ventilation (IMV) requiring an external source of continuous gas flow. Thus the impact of both PEEP and V_T on lung stress was functionally removed from clinical consideration.

Both the technical limitations and the absence of consideration to pulmonary mechanics during this period was best exemplified in the Super-PEEP approach to treat severe ARDS.[27-29] This strategy prioritized optimizing oxygenation by targeting a P_{aO2} of 60-100 mmHg on an $F_{IO2} \leq$

0.55, a V_T of 12-15 mL/kg with reported PEEP levels of 27-54 cmH_2O. In essence oxygenation goals took precedence over the risk of lung overdistension. Pulmonary mechanics were not reported and appeared not to have factored into decision making.

1980s: Chest Tomography and Ventilator-Induced Lung Injury Models

In the mid-to-late 1980s VILI emerged as topic of concern as computed tomography (CT) studies of ARDS revealed heterogeneously distributed injury of varying intensity (**Fig 2**).[30, 31] This led to the adult "baby lung" concept: "normal" (aerated) lung tissue at end-expiration in *severe* ARDS (200-500 g) is equivalent to that of a 5-year-old child.[32] In consequence, a commonly used V_T of ~15 mL/kg functionally became ~ 40 mL/kg: that used in the seminal VILI study from 1974.[26] These findings buttressed other preclinical VILI studies;[33-35] both re-affirming and expanding upon pioneering research done decades before.[25, 26] Shortly afterwards came the first clinical study[36] of LPV in ARDS incorporating permissive hypercapnia first used in treating status asthmaticus.[37] When applied to ARDS, LPV was associated with a mortality of ~19% (~50% less than predicted).[36]

Throughout the 1990s as VILI research increased, two separate international consensus conferences on mechanical ventilation and ARDS strongly recommended maintaining $P_{plat} \leq 30$ or 35 cmH_2O and not > 40 cmH_2O.[12, 38] These events coincided with the National Institutes of Health forming the ARDS Clinical Trials Network (ARDSNet) that in 2000 firmly established the efficacy of LPV in reducing ARDS-associated morbidity and mortality.[39]

Current Concepts in Protective Ventilation Strategies for ARDS

By the time the ARDSNet study was published in 2000 there already had been substantial progress in understanding the molecular biological mechanisms of inflammation and coagulation by which VILI develops.[40] Because of this research we came to understand the association between ARDS, VILI and multi-organ dysfunction syndrome (MODS) that results in multiorgan failure: the primary cause of ARDS-related mortality.[36, 41-44] And over the past 20 years "protective ventilation" has broadened from the initial three pillars of LPV (ie. minimizing strain, shear, and hyperoxic related lung injury) to include right-heart-protective ventilation, diaphragmatic protective ventilation, and most recently the possibility of patient self-inflicted lung injury (P-SILI).

Lung-Protective Ventilation

At its most fundamental LPV is about matching V_T to the existing FRC, which in ARDS averages 600-1800 mL depending upon severity.[45] Doing so largely prevents global and regional overdistension that causes cellular injury and exacerbates disease-associated inflammation. A V_T of 4-8 mL/kg is targeted to maintain $P_{plat} \leq 30$ cm H_2O and elastic driving pressure or P_{DR} (ie P_{plat}-PEEP) ≤ 15 cmH_2O. Both P_{plat} and P_{DR} are indirect signifiers for peak lung stress and the change in tidal lung stress respectively. Yet even in severe ARDS, when FRC is markedly reduced, substantial overdistension occurs in non-dependent regions despite achieving targeted V_T and P_{plat} (ie. 6 mL/kg and 28 cmH_2O respectively).[46] Emerging evidence suggests targeting P_{DR} to ≤ 13 cmH_2O may reduce mortality risk further,[47] along with improved pulmonary function in survivors.[48]

Shear injury occurs when obstructed/collapsed peripheral airways and alveoli are repeatedly forced open and then re-collapse during tidal ventilation. Because heterogeneously

injured lungs distribute stress unequally, most alveolar shear injury occurs at the interface between neighboring normal and injured structures. When PEEP stabilizes newly recruited alveoli shear injury is reduced and the impact of V_T-related strain injury also *might* decrease by providing a larger surface area to accommodate V_T without creating disproportionate stress. However, this would occur only when alveolar recruitment is greater than corresponding regional overexpansion of patent alveoli. Finally, intrapulmonary shunt and areas of low ventilation/perfusion also decreases, so that F_{IO2} can be reduced towards non-toxic levels (ie. $\leq$ 0.60).[9] The effects of Pplat and PEEP on recruitment and de-recruitment are discussed below.

Right Heart Protective Ventilation

The pulmonary vasculature is a low resistance, high capacitance system reflected in the thin muscular wall of the right ventricle (RV), thus making it particularly vulnerable to failure with sustained elevations in pulmonary vascular resistance. ARDS is characterized by pronounced pulmonary arterial and capillary endothelial injury resulting in arterial and microvascular thrombosis,[49] vascular constriction from hypoxemia, hypercapnia and acidosis,[50] vascular compression from pulmonary edema,[51] and alveolar hyperinflation.[52] Overtime, these acute changes evolve into a chronic phase characterized by vascular smooth muscle hypertrophy, fibrosis and capillary obliteration.[53]

Sustained pulmonary arterial hypertension causes RV dysfunction. In ARDS this often progresses to acute *cor pulmonale* (ACP) signifying right ventricular ischemia. If not reversed it eventually causes left ventricular failure and progressive systemic hypotension.[54] Prior to LPV the incidence of ACP in ARDS often reached 60%,[55] compared to 22-25% during LPV.[56,57-59] In severe ARDS however the incidence of ACP can still reach 50%.[60] Furthermore, patent foreman

ovale is relatively common in severe ARDS (~16-19%), wherein right-to-left intra-cardiac shunting further complicates ventilator management, particularly when P_{plat} and PEEP are highly elevated.[56, 61]

When neither high P_{plat} nor high PEEP are present, ACP does not appear to increase mortality risk in ARDS.[59, 62] Nonetheless, severe ACP carries significantly higher mortality in ARDS than its absence (57% vs. 42%, P = 0.03).[59] Severe ACP was one of four factors independently associated with mortality in ARDS, the others being: P_{aO2}/F_{IO2} < 150 mmHg, $P_{DR} \geq$ 18 cmH_2O, arterial carbon dioxide tension (P_{aCO2}) > 48 mmHg, and pneumonia as primary etiology.[59]

The primary features of RV protective ventilation are to keep P_{plat} < 27 cmH_2O, P_{DR} < 18 cmH_2O and PEEP $\leq$ 10 cmH_2O. Respiratory rate is titrated to keep P_{aCO2} < 48 mmHg unless intrinsic PEEP occurs (or worsens).[63] If these measures are insufficient (or unfeasible), ancillary therapies such as prone position, extracorporeal membrane oxygenation (ECMO) or extracorporeal CO_2 removal (ECCO2R), and inhaled vasodilators, are recommended.[63] Improved RV function and/or reduced pulmonary arterial pressure in ARDS also occurs with prone position,[60] and inhaled vasodilators.[64-67] In addition, the largest ECMO trial in ARDS reported substantial reductions in P_{plat}, PEEP, and P_{aCO2} with increased oxygenation suggesting corresponding improvements in RV function;[68] that previously had been observed in case reports.[69]

Power Transfer in VILI and the Role of Extracorporeal Support

During inspiration the lungs store energy needed to overcome tissue elastic recoil that in turn drives passive exhalation. This fact has modified the concept of VILI and LPV to propose that $V_{\dot{E}}$ demand plays a role because the *repetitiveness* of applied stain/stress represents power transferred from the ventilator to the lungs. This however involves 3 specific "preconditions" (caveats): 1) the relative size of the "baby lung" (ARDS severity) which determines tissue "capacity" to receive tidal energy pulses, 2) the relatively durability (or "fragility") of injured and non-injured tissue to endure repetitive energy pulses, and 3) the duration or cumulative power transfer following VILI onset.[70, 71] Mechanical power transfer to the lungs > 12 joules/min is associated with VILI in animal models,[72] and has been independently associated with mortality in ARDS.[47]

Elevated $V_{\dot{E}}$ demand in ARDS reflects both metabolic rate and physiologic dead-space fraction (V_D/V_T) that increases markedly from mild to severe ARDS; whereas C_{RS} correspondingly decreases.[73] Thus, the highest energy transfer potentially exacerbating VILI occurs in severe ARDS when lung injury (and tissue fragility) is most acute. Although power transfer can be lessened by inducing permissive hypercapnia, this too has inherent drawbacks. Hypercapnia-induced increases in respiratory drive evokes severe dyspnea and likely potentiates asynchrony,[74] the suppression of which requires generous use of sedatives and often the addition of neuromuscular blockade.

In this context, either ECMO or $ECCO_2R$ has substantial merit. Lung protection afforded by venovenus ECMO in ARDS primarily has focused upon oxygenating venous blood to reduce VILI risk by reducing F_{IO2} and PEEP requirements. In contrast venoarterial ECMO partially supports systemic O_2 delivery when cardiac output is impaired. ECMO has been used in severe

ARDS since the early 1970s.[75] However, because contemporaneous practices included large V_T ventilation the potential benefits of ECMO were not realized (mortality ≥ 90% with or without ECMO).[76]

By 1984 extracorporeal support in ARDS had incorporated the idea of combining $ECCO_2R$ with low frequency pressure control, inverse ratio ventilation (PC-IRV) limiting P_{plat} to 30-35 cmH_2O to promote "lung rest".[77] A small observational study reported a surprisingly low mortality of 23% (projected mortality > 90%) that was difficult to interpret given numerous methodological issues. In 1994 a randomized controlled trial of "lung-rest" that combined PC-IRV (P_{plat}/PEEP: 45/24 cmH_2O, V_T: 3 mL/kg, Rate: 3) with $ECCO_2R$ was compared to protocolized volume ventilation with high PEEP (16 cmH_2O) and moderate V_T (10 mL/kg). Mortality was not different (67% vs. 58% respectively, P=0.80).[78] The 2009 "CESAR" trial compared a "rest strategy" consisting of PCV (P_{plat}/PEEP: 20-25/10-15 cmH_2O, Rate: 10, F_{IO2}: 0.30) with venovenous ECMO to the ARDSNet lower-PEEP LPV strategy.[79] Mortality was substantially lower in the ECMO arm (37% vs. 49% respectively). However, among other methodological issues, there was no documentation of actual adherence to the ARDSNet protocol (ie. use of the protocol was only "encouraged"). This raised serious concerns over the study's internal validity.[80]

The most recent randomized controlled trials of ECMO[68] and $ECCO_2R$[81] for ARDS also found no mortality benefit compared to well-established protocolized LPV management used in the Express[82] and ARDSNet[39] trials. However, the results of the "EOLIA" trial[68] were intriguing given the clear trend towards improved mortality favoring ECMO (35% vs. 46%, P=0.09) and

significant improvement when analyzed according to treatment failure (ie. mortality in the ECMO arm vs. mortality and crossover to ECMO therapy in the LPV arm): 35% vs. 58%, P<0.001.

However, the crossover group had more severe lung injury at randomization and higher mortality compared to control arm subjects not requiring ECMO (57% vs. 41% respectively).[83] This "intention-to-treat" trial was terminated early for futility leaving the study's interpretation ambiguous. One plausible interpretation is that the higher mortality in the control arm was due to the sicker crossover subjects who did not appear to benefit from ECMO. Both treatment arms made very liberal use of the full array adjunctive therapies used in severe ARDS. Hence, continued deterioration in severe ARDS despite LPV with higher PEEP and multiple ancillary therapies suggests that the addition of ECMO is unlikely to be beneficial.

ECMO as rescue therapy in severe ARDS will likely continue. Slow enrollment in the EOLIA trial (6 years) suggests that ECMO is reasonably applicable only to a small fraction of ARDS cases. Furthermore, the clearly negative results of the "REST" trial,[81] and high incidence of serious adverse events (31%) renders routine use of $ECCO_2R$ in less severe ARDS unlikely.

Respiratory Muscle Physiology and Mechanical Ventilation

Respiratory muscle physiology research greatly informed our understanding of patient-ventilator interactions, ventilator dependence and the potential exacerbation of both VILI and MODS. Beginning in the mid-1970s loaded breathing and muscle fatigue became a focus of interest,[84-86] with studies relevant to assisted mechanical ventilation emerging a decade later.[87-91] These studies demonstrated that patient effort continues throughout most or all of mechanical inspiration. Prior to this there had been a pervasive lack of curiosity despite

decades long clinical encounters of patients "fighting the ventilator".[3] These studies flipped the narrative to the ventilator (and thus the clinician) "fighting the patient".

Diaphragmatic Protective Ventilation

That work of breathing often exceeded physiologic "resting levels" raised particular concern that patients with diaphragmatic fatigue/failure might receive inadequate support necessary to facilitate recovery. This prompted additional exploration into respiratory muscle injury during critical illness that distinguished two opposing mechanisms. "Use atrophy" describes respiratory muscle inflammation from exposure to excessive workloads,[92] both in healthy subjects and those with chronic lung disease. This occurs even following brief exposure to maximal loading.[93] Clinically the phenomenon of delayed diaphragmatic injury and inflammation (occurring 3 days after brief periods of intensive loading) produced diaphragmatic weakness;[94, 95] rendering the diaphragm more susceptible to further fatigue and injury. Thus, disallowing a period of full rest following either acute respiratory failure onset, or after a failed weaning trial, might induce chronic fatigue and paradoxically prolong ventilator dependence.

In addition sepsis causes diaphragmatic injury, wherein the diaphragm exhibits exaggerated proinflammatory gene expression and hence cytokine production.[96] Passive mechanical ventilation in sepsis substantially reduced muscle injury and improved diaphragmatic force generation.[97] At ICU admission the majority (64%) of subjects with acute respiratory failure exhibit diaphragmatic weakness associated with either sepsis or disease severity that carries a poorer prognosis.[98] Thus attributing diaphragmatic dysfunction primarily to mechanical ventilation practice can be misleading.

In contrast, ventilator induced diaphragmatic dysfunction (VIDD or "disuse atrophy") is the progressive loss of diaphragmatic force generating capacity (eg. ~40-50%) from prolonged periods of passive ventilation and loss of electromyographic stimulation; the duration of which appears species-dependent (eg. 1 day in rabbits vs. 11 days in baboons).[99] In critically ill subjects undergoing prolonged passive ventilation diaphragmatic strength progressively decreases by 32±6% over 6 days (becoming prominent at ~3-4 days).[100] These findings coincided with evidence of muscle fiber injury and muscle atrophy. Resumption of muscular contraction following disuse atrophy likely increases vulnerability to load-induced injury.[99]

Conversely, in animal models of spontaneously-triggered mechanical ventilation diaphragmatic weakness is ameliorated substantially compared to passive ventilation with strength reductions of 14% vs. 48% respectively over 3 days.[101] Other studies found periodic interruptions of passive ventilation with spontaneous breathing attenuated diaphragmatic mass and strength loss compared to passive ventilation. In a clinical study in which biopsies were obtained, subjects capable of generating spontaneous efforts ~36% of the time over an 8-day course had significantly less diaphragmatic injury compared to those with a 3-day course of passive ventilation.[102]

In summary the strategy of diaphragmatic protective ventilation involves a 2-pronged approach involving both sedation and ventilator settings.[103] First, is to limit the duration and incidences of passive ventilation and prevent excessive ventilatory support that needlessly suppresses patient effort. Second, is avoiding prolonged periods of highly loaded breathing, particularly early in the course of acute respiratory failure. Many of these patients present with

acute diaphragmatic weakness, muscle injury and fatigue; the resolution of which (depending upon several factors) may require from one to several days.[88, 98, 104]

The Concept of Patient Self-Induced Lung Injury in ARDS

Lung stress is trans-alveolar pressure generated either by positive airway pressure or negative pleural pressure from muscular contraction, and is the basis of the "push-pull" concept of assisted breathing.[105] Under normal lung physiology distending pressure across fluid-like structures transmits stress *relatively* evenly such that the risk of VILI or P-SILI is likely minimized except under extreme conditions (see below).[106]

By the late 1980s studies on healthy animals in whom hyperventilation was either chemically induced (rate: 69, V_T: 9 mL/kg),[107] or by negative pressure mechanical ventilation (rate: 25 V_T:44 mL/kg),[33] produced acute lung injury within a matter of minutes or hours (depending upon V_T size). Histological examination found diffuse alveolar damage, and altered permeability edema.[33]

Hydrostatic mechanisms also may have contributed because intense negative intrathoracic pressure increases both venous return and left ventricular afterload leading to pulmonary engorgement and pulmonary hypertension,[108] A similar mechanism appears responsible for transient acute lung injury in elite athletes due to pulmonary capillary stress failure.[109] When comparing positive vs. negative pressure ventilation one study found substantially greater pulmonary edema generated by negative intrapleural pressure versus positive pulmonary intravascular pressure despite the same V_T and relative driving pressure.[33]

The significance of initial pre-clinical research was not appreciated until clinical studies of early neuromuscular blockade in ARDS reported both significantly reduced mortality and mechanical ventilation duration.[110] A related study found significantly reduced proinflammatory mediators both in pulmonary edema fluid and serum.[111] Thus, combining evidence that $P_{DR} \leq 15$ cmH_2O reduces mortality risk in ARDS,[112] with aforementioned preclinical evidence, and clinical studies showing large esophageal pressure swings commonly occur during assisted ventilation in ARDS, raised the possibility that vigorous spontaneous breathing efforts may exacerbate lung injury and worsen outcomes.[113, 114] Concern over P-SILI is supported by anecdotal evidence of extreme esophageal pressures swings of 35 cmH_2O during LPV in severe ARDS;[115, 116] one study observing extraordinarily severe alveolar edema.[115]

Mean esophageal pressure swings of 14-17 cmH_2O are observed in sedated ARDS subjects during assisted LPV at ~7 mL/kg V_T.[117] Preclinical acute lung injury models of LPV (V_T: ~8 mL/kg, P_{plat}: 30 cmH_2O) found inspiratory esophageal pressures of only 5 cmH_2O produced transpulmonary pressures of 35 cmH_2O that exacerbated lung injury.[118]

However, the negative impact of spontaneous breathing may depend upon the underlying severity of acute lung injury.[119] In the aforementioned preclinical model, spontaneous breathing during mild lung injury occurred at both a lower P_{plat} and lower effort causing dorsal lung recruitment with improved oxygenation and little histological impact (compared to passive ventilation). In contrast, severe lung injury stimulated greater spontaneous effort at a higher baseline P_{plat} that (paradoxically) promoted cyclical derecruitment worsening both oxygenation and lung injury compared passive ventilation (see below). Preclinical models also observed “occult Pendelluft” motion wherein diaphragmatic

contraction redistributes alveolar volume away from non-dependent to dependent lung regions causing paradoxical overdistension of dependent lung without changing delivered V_T.[120]

Another aspect of P-SILI is that excessive breathing efforts in the acute phase of ARDS foments fluid transudation worsening pulmonary edema, gas exchange and C_{RS}.[115] This is further exacerbated by compensatory expiratory muscle recruitment during loaded breathing that promotes derecruitment by creating a counterforce to applied PEEP.[121] In contrast, during passive ventilation PEEP facilitates pulmonary edema clearance,[122, 123] that in ARDS already is markedly depressed.[124] Moreover, the inability to clear pulmonary edema in ARDS is associated with increased mortality.[125]

It's important to recognize we are in the very early stages of understanding the potential clinical significance of P-SILI. The extent of lung injury induced by negative pleural pressure swings when the resulting global strain is limited to 5-8 mL/kg vs. 12-15 mL/kg is likely substantial and clinically relevant in terms of balancing risk factors affecting outcomes. These issues must be better understood before altering sedation practices as "prophylaxis" against P-SILI (see below).

The Implications of Spontaneous Breathing during Critical Illness

Prior to the advent of IMV all weaning was done by spontaneous breathing trials (SBT) reflecting the limitations of ventilator technology.[126] The advantages afforded by IMV during this period were: 1) avoidance of hypocarbia during assisted ventilation with elevated respiratory drive, 2) countering cardiac output depression associated with high PEEP and 3)

providing partial $V_{\dot{E}}$ support in difficult to wean patients by allowing longer periods of exercise reconditioning without excessive discomfort.[127]

IMV emerged partly as a byproduct of critical care practices that successfully stabilized patients with catastrophic illness or injury, that in turn promoted survival to the recovery phase, albeit often in a severely debilitated state. This preceded our awareness of critical illness related myopathies and neuropathies,[128] as well as providing appropriate nutritional support.[129] Thus clinicians increasingly encountered "some patients" who were "difficult to wean"; for which IMV provided a reasonable solution.[130]

What began as a recovery phase strategy transformed into a popular primary ventilation mode. At the time the rationale supporting IMV met with criticism,[127, 131] along with evidence that it did not improve weaning efficacy.[132, 133] Later on it was demonstrated that as IMV rate decreased respiratory drive increased, so that mandatory breaths did not reduce patient work of breathing (**Fig 3**).[91] This likely increased the risk for acute diaphragmatic injury as well as chronic diaphragmatic fatigue.

Although early SBT attempts in debilitated patients were poorly tolerated, the unappreciated advantage was clinicians could intervene quickly to provide appropriate periods of diaphragmatic rest and rapid recovery (ie. avoidance of chronic diaphragmatic fatigue).[134-136] In contrast, IMV proponents recommended progressively reducing the mandatory rate "as long as spontaneous respiratory efforts occurred and arterial pH remained > 7.30 *regardless of the other measurements*."[emphasis added].[137]

The rationale for IMV as a primary mode of ventilation was based upon misperceptions involving both of the frequency of difficult weaning and the nature of its origins.[135, 138] What followed was a positive feedback loop: as IMV gained popularity, so too did the illusion that most patients were likely "difficult to wean"; requiring a gentle transition to unassisted breathing.[131] The philosophy of gradual weaning seamlessly transferred over to PSV in the 1980s. The tendency to always initiate PSV at elevated levels was dubiously interpreted as "actively weaning".

Gradual weaning as standard practice was discredited by large prospective trials in the mid-to-late 1990s. Regardless of weaning modality, the strategy of gradual withdrawal actually increased mechanical ventilation duration by 6-9 days.[139] In addition, a once daily SBT was found superior to both IMV and PSV in reducing weaning duration.[140] Most telling, a major study examining weaning techniques in acute respiratory failure found 89% of potentially eligible subjects passed their initial screening SBT and therefore could not be enrolled.[140] This affirmed previous observations that more than 70% of mechanically ventilated patients resume unassisted breathing without difficulty.[138] In addition, protocolized daily screening for weaning readiness followed by an SBT significantly reduced mechanical ventilation duration.[141] In ARDS the combination of daily screening, SBT and conservative sedation practices reduced both median duration of mechanical ventilation and ICU length of stay by 5 days.[142]

Recruitment and Derecruitment in ARDS

The Legacy of "Congestive Atelectasis"

"Contrary to widespread belief, true anatomic atelectasis is not greatly contributory to the observed pathophysiology and response to treatment; specifically the severity, duration and potential reversibility of increased pulmonary capillary endothelial permeability and the resultant magnitude and persistence of transcapillary leakage of both fluid and particularly serum protein are major determinants for a wide variation in clinical course."[emphasis added]

Carl Teplitz[143]

A lingering problem in understanding how best to ventilate patients with ARDS was inherited from the 1950s. "Congestive atelectasis" was coined by Jenkins and colleagues[144] to describe pathologic findings from post-operative respiratory failure that became commonplace, particularly in trauma patients during both World War II,[20] and the Vietnam war.[145, 146] However, the original case series by Jenkins et al. consisted mostly of subjects with abdominal infection or trauma who developed hemodynamic instability and fever; suggesting septic shock.[144] The primary pathology findings were pronounced capillary congestion and alveolar hemorrhage with atelectasis being a prominent finding only in a minority of subjects.[144]

The term congestive atelectasis also was used by Ashbaugh and colleagues in describing ARDS, but their vague wording suggested atelectasis, interstitial-alveolar hemorrhage and pulmonary edema were equally prevalent findings.[11] In contrast, both contemporaneous[15, 147] and subsequent pathologic studies found alveolar filling (not atelectasis) was the primary abnormality during the early exudative phase of ARDS.[143, 148-152] After 1967 the modifier "congestive" was dropped, while curiously the descriptor atelectasis persisted.

This had an unintended consequence wherein atelectasis has been misinterpreted to imply acutely injured lungs can potentially be "fully recruited" and thus (at least subliminally) implying a return to a normal state. This in turn facilitated the idea that patient outcomes might improve with open lung-oriented strategies favoring higher PEEP and recruitment maneuvers, PC-IRV, APRV and high-frequency oscillatory ventilation (HFOV). Yet, when eventually tested in large randomized controlled trials (if ever seriously attempted) the results have been disappointing.[153-155]

Although recruitment and derecruitment were implicitly discussed since the beginning of ICU mechanical ventilation,[7, 14, 156] it wasn't until the early 1990s with the advent of open lung ventilation,[157] that the discussion became explicit and a focal point of attention. The idea of alveolar recruitment and derecruitment in ARDS met with skepticism and has highlighted the ambiguous nature of what actually occurs when we attempt to "open up" the lungs. In particular the "overly liberal usage" of atelectasis when alveolar flooding is the primary lesion has been problematic.[158] With certain exceptions (eg. obstructive lobar collapse, abdominal compartment syndrome) *profound* tidal collapse in ARDS is unlikely. Moreover, equating "derecruitment" with "nonaerated" tissue is also problematic because its usage confuses fundamentally different lesions: degassed/collapsed alveoli versus alveolar filling.[158]

In oleic acid models of acute lung injury (which closely mimics the exudative phase of ARDS),[159] decreased gas volume in dependent zones does not cause collapse because of alveolar filling.[160, 161] This created considerable problems interpreting the lower inflection point in pressure-volume curves. At first believed to signifying "full alveolar recruitment", it was later interpreted as the "beginning of recruitment" in the non-dependent injured lung.[162] Yet, a

lower inflection point may represent the initial impedance to inflation of an edematous, non-collapsed lung, the transition from liquid-filled to gas filled airspaces by displacing edema,[158] or overcoming intrinsic PEEP.[162]

This is not to suggest compressive atelectasis plays no role in ARDS. Rather, it is to *re-emphasize* and redirect our attention to the key role played by peripheral airway obstruction/collapse and alveolar filling in ARDS. Most importantly, "full lung recruitment" in ARDS is neither plausible nor necessary. CT studies examining lung recruitment (whatever that actually signifies) estimated that tissue consolidation accounts for ~25% of the lung in ARDS.[163] Moreover, improved oxygenation in ARDS has not translated into clinically meaningful outcomes.[39, 153] Mortality in ARDS is caused primarily by the presence or development of MODS, which is intimately associated with VILI and not severe refractory hypoxemia (see below).[41, 42, 164, 165]

Infant Respiratory Distress Syndrome and Open Lung Ventilation

The theoretical basis for open lung ventilation (upon which HFOV, PC-IRV and APRV are conceptually associated), originated in treating infant acute respiratory distress syndrome.[166, 167] Studying the effects of mechanical ventilation in hyaline membrane disease used *non-injurious* surfactant washout models that largely produce homogenous lung collapse as well as homogenous recruitment/reinflation.[168-170] These models deviated fundamentally from the mechanics and pathology of ARDS, and therefore tended to facilitate misleading generalizations about the potential effectiveness of open lung strategies for treating ARDS. It is not coincidental

that prior to introducing the concept of open lung ventilation in 1991,[157] much of Dr. Lachman's prior work focused on the treatment of hyaline membrane disease.[171-173]

Fast vs. Slow Pulmonary Compartments

An underappreciated aspect of ARDS is the presence of fast and slow pulmonary compartments reflecting the distribution and severity of lung injury. This has shaped our perceptions of recruitment potential as well as derecruitment; that in turn influenced how we interpreted the effectiveness of recruitment at any setting of P_{plat} and PEEP.[174] Furthermore, historically we assessed the effectiveness of PEEP on oxygenation between 10-15 minutes.[175] Perhaps valid during the fibrotic end-stage of ARDS,[176] it is highly questionable in the exudative phase of moderate to severe ARDS.

The presence of slow compartments have been observed during PC-IRV in infants, [167] in response to PEEP,[176-179] PC-IRV in adults,[180] and prone positioning.[181] Prospective studies that carefully examined the presence and time course of pulmonary compartments in ARDS observed time periods ranging from several minutes to several hours.[177, 178, 182]

What was being described likely reflected the effects of reopening collapsed or obstructed peripheral airways/alveolar ducts and redistribution of pulmonary edema; the time course of which is determined by several factors (eg. the amount and viscosity of edema, airway film surface tension, radial traction supporting peripheral airways, physical obstruction by fluid plugs, presence and amount of functional surfactant, and the presence of inflammatory cells and cellular debris).[174] These in turn determine how the interplay of applied airway pressure and maneuver duration impacts the potential effectiveness of recruitment maneuvers

and recruitment enhancing modes. Furthermore, the time course for recruitment within a single breath is very limited (ie. ~85% occurring within 2 seconds).[183]

Two clinical implications issue from this. First, radical time inversions during PC-IRV or APRV (eg. 2:1 and beyond) have little effectiveness in terms of recruitment. More importantly, oxygenation improvements in these approaches likely reflects the effects of intrinsic PEEP, the distribution of which is uncertain and perhaps higher in less-injured or normal tissue.[184] In contrast, the negative consequence of sustained high intrathoracic pressure includes perpetuating strain injury in non-dependent regions, increased risk of *cor pulmonale*, and compromised hemodynamics;[160] thus increasing the risk of hypoperfusion and ischemia to vital exchange organs that may perpetuate systemic inflammation (see below).

An initial rationale for IRV in ARDS was the hypothesis that as expiration proceeds, underinflated alveoli become increasingly susceptible to hydrostatic compressive forces. Therefore shortening expiratory time in order to "catch the lung at a critical volume on its way down" would reduce the risk of collapse.[185, 186] However, derecruitment in dependent lung regions generally begins at PEEP < 15 cmH_2O and infrequently < 20 cmH_2O,[174] thus obviating the need for time inversion in managing ARDS.

Second, the observed response of the slow pulmonary compartment, as evidenced by progressive recruitment over time, suggests that recruitment of obstructed and collapsed peripheral airspaces requires repetitive application of pressure during tidal ventilation over an extended time period. And because recruitment maneuvers are applied for only a few minutes the actual or "optimal" efficacy of any tested pressure levels remains unknown.

Finally, the theoretical attractiveness of HFOV was that it prevented VILI by avoiding convective gas flow and the effects of regional time constant differences in causing regional lung overdistension.[187] But these very problems likely occurred during HFOV because regional time constant abnormalities probably resulted in regional "static over-inflation".[170, 188, 189] This was apparent in one trial by both higher vasopressor requirements and incidences of barotrauma.[155]

Current Understanding and Implications of Recruitment and Derecruitment in ARDS

CT studies observed that *maximal recruitment* in the middle lung regions occurs between a P_{plat} of 20-30 cmH_2O; whereas dorsal zones begin to recruit at a P_{plat} of ~20 cmH_2O with the largest incremental change in dorsal aeration also occurring at a P_{plat} of 30 cmH_2O.[190, 191] In ARDS, derecruitment is a continuous process that usually becomes prominent at PEEP < 15 cmH_2O,[191] and is both pronounced and rapid dorsally when PEEP falls below 10 cmH_2O.[191,192,193]

These findings imply that in the absence of pronounced extrathoracic compressive forces, PEEP levels of ~10-15 cmH_2O at a V_T producing a P_{plat} of 25-30 cmH_2O is likely sufficient to achieve adequate oxygenation at a relatively non-toxic F_{IO2}. This has been repeatedly confirmed in several major LPV studies (**Table 1**).[39, 82, 194, 195]

PEEP: Curative vs. Supportive Therapy

An intriguing aspects of recruitment-oriented ventilation strategies in ARDS (ie. IMV-Super-PEEP, PC-IRV and APRV) has been its advocacy in trauma care.[29, 196, 197] Trauma-associated ARDS often involves large volume resuscitation with fluids and blood products that

augment lung injury through indirect pathways (ie. transfusion-related acute lung injury or TRALI).[198, 199] Trauma-induced capillary leak syndrome (TICS) commonly results from severe injury exacerbated by crystalloid solutions in a condition known as transfusion-associated circulatory overload (TACO). The persistence of TICS following injury is complex and variable, [200] whereas the clinical presentation of TACO often overlaps with and mimics TRALI.[198]

TICS may cause further complications (ie. anasarca, ascites, and abdominal compartment syndrome) that often require recruitment-oriented ventilation strategies. PEEP counters intra-parenchymal hydrostatic forces promoting pulmonary edema formation, and compressive forces associated with decreased chest wall compliance.

In addition, a prominent feature of TICS is severe hypoproteinemia.[200] In ARDS alveolar edema has a protein concentration similar to plasma (ie. $\geq$ 75%),[201] so that TICS-induced hypoproteinemia lowers edema viscosity; thereby reducing the "yield pressure" and time needed to recruit obstructed peripheral airways and redistribute edema from the alveolar space.[174] This likely enhances the efficacy of recruitment to a greater extent than what otherwise occurs in ARDS without overhydration (eg. pneumonia). Ashbaugh and colleagues suggested as much observing that PEEP appeared to "reverse the syndrome" in fluid-overloaded trauma subjects.[11] This gave rise to the illusion of PEEP as "curative". In contrast, Ashbaugh and colleagues observed that in ARDS associated with pneumonia or aspiration "the illness was likely to be prolonged and refractory to treatment".[14]

The misconception that PEEP is "curative" was long embraced by IMV/Super-PEEP proponents, even suggesting PEEP or CPAP might prevent ARDS.[202] The illusion of PEEP as curative reflected the fact that early onset (eg. ~4 days) trauma-associated ARDS is associated

with lower mortality among patients who generally are younger and healthier than other ARDS etiologies.[164, 203-205] Moreover, trauma-induced ARDS is associated with significantly less endothelial and epithelial injury; supporting the impression that it may be self-limiting in nature.[203, 205] The pro-curative PEEP argument preceded our understanding of systemic inflammatory response syndrome, wherein ARDS often represents "the pulmonary manifestation of multiple failing organs".[206]

VILI, Organ Cross-Talk, ARDS Phenotypes and Multiorgan Dysfunction Syndrome

VILI and diaphragmatic injury contribute to systemic inflammation leading to MODS and eventually multi-organ failure: the primary determinant of ARDS mortality.[41-44, 164, 165, 207] This occurs via "organ cross-talk" by which capillary endothelial injury in one organ (generating proinflammatory, procoagulant, chemoattractant mediators) spills over into the systemic circulation activating an inflammatory response in the endothelium of distant organs.[165, 206, 208, 209] Highly vascularized exchange organs (eg. kidneys, intestines, liver) tend to be the initial and most vulnerable organs; in turn instigating a self-perpetuating injury pattern. In ARDS, pulmonary-renal dysfunction is an early manifestation of MODS,[210] with profound consequences as secondary renal failure in ARDS increases mortality (ie. ~60-80%).[208]

Despite decades of research most therapies used in ARDS (particularly pharmacologic) have been ineffective. Thus, it has become increasingly apparent that clinical criteria used to define syndromes such as ARDS and sepsis are inherently inadequate in understanding the underlying biology necessary for developing effective drug treatments, as well as more refined approaches to mechanical ventilation.[211, 212] Particular to ARDS is the variety of injurious agents

fomenting acute lung injury, the wide range of physiologic abnormalities it produces, the related biological pathways and gene expression involved, and how the syndrome evolves or resolves over time.

Current trends in ARDS research involve devising strategies based upon recent advances in our understanding. This includes varied clinical presentations such as lobar vs. diffuse lung injury, severity of hypoxemia, and most recently the interactions between proinflammatory mediators with markers of endothelial dysfunction that distinguish early resolution from persistent hypoxemia.[213] Newer still is examining specific gene expression governing inflammation that might provide a more comprehensive understanding of ARDS, and also the possibility for highly specific novel drug therapies for certain ARDS phenotypes, or perhaps targeting current therapies more effectively. Research in this area already has discerned ARDS subphenotypes associated with the spectrum of inflammatory response (ie. uninflamed, reactive, hyporeactive and hyperreactive) suggesting the existence of "treatable traits" with implications beyond ARDS.[214] The hoped-for result is developing more "personalized medicine" for the treatment of ARDS and other critical illnesses.

"Wither Goest Thou?": Integration of Ventilator and ICU Monitoring Data with Other Health Systems Data, ARDS Phenotypes, Computational Intelligence and Closed-Loop Ventilation

The 60-year history of ICU mechanical ventilation witnessed enormous growth in our understanding of ARDS and critical illness generally, as well as the breathtaking advances in technology. These have vastly improved the quality of care delivered compared to that received in 1961. However, misperceptions, misconceptions, and missed opportunities occurred along

the way that negatively impacted patient outcomes; some of which have taken generations to overcome or still persist. To some degree this was inevitable as our comprehension of ARDS came from integrating accrued knowledge in a process akin to creating a mosaic: the image cannot be recognized until a sufficient number of pieces are identified and placed in proper relationship to one another.

Unfortunately, that only represents part of the problem. The other problem has been an all too human propensity to resist abandoning long held practices that are no longer relevant. All ventilator modes and associated practices were created during a specific historical period reflecting the limitations of our understanding at that moment (eg. IMV, PC-IRV, APRV). The broader implications of this reluctance was recently commented on, that "despite strong evidence and explicit guidelines for delivering state of the art care, adoption of current best practices for using LPV to treat ARDS have lagged".[215]

Resistance to change, I believe, is partly explained by certain innate perceptual limitations. An example is the 22% relative mortality reduction found in the ARDSNet low V_T study.[39] This finding projected a "number to treat" whereby for every 11 ARDS patients treated with a 6 mL/kg V_T one additional life is saved. Hence, the reality that injurious ventilation increased mortality was too subtle to be perceived in clinical practice. The legacy of our ~200,000-year-old nervous system was its primary orientation towards interpreting "real time" phenomena that promoted our survival in a radically different environment.[216] Therefore, our ability to *fully comprehend* complex phenomena such as ARDS mortality can only be discovered by the latent potential our nervous system afforded us: the capacity for highly abstract thought

and computational skills. However, the complex reality of ARDS is too often obscured by the potency and immediacy of our impressions formed in an emotional charged environment that is the ICU. And this brings us to the threshold of "whither goest thou?"

Further progress towards improved outcomes in ARDS will require "machine learning" (artificial neural networks) for understanding biologically discreet clusters of phenotypes using multiple protein biomarkers that might lead to highly targeted therapies.[212] Moreover, this potential will expand considerably with the integration of ARDS genomics. The "transcriptomics" of nucleic acid-based arrays has already broadened the scope of exploration to "tens of thousands of genes", providing a more comprehensive overview for understanding the pathophysiology ARDS and the potential for creating personalized medicine.[212]

And whereas molecular biology and genomics suggest potential breakthroughs in the decades to come, near-term advances in care might be closer. We can now collect massive amounts of moment-by-moment data from ventilators, monitors and other devices in the ICU that can be filtered, uploaded, and integrated with much larger data bases containing laboratory, demographics, comorbidities, and other information to create much grander mosaics of what occurs dynamically during the course of critical illnesses.

Such "computational intelligence" generated by artificial neural networks perform tasks such as pattern association and pattern recognition including algorithms oriented to biostatistical multivariable analyses.[217] Discovered patterns then can predict future data (eg. model development and testing) or perform "other kinds of decision making under uncertainty" (eg. perhaps closed loop ventilation). One such method (ie. "radial basis functions") was

developed over 40 years ago by visionaries who created computerized geometric displays of cardiorespiratory and metabolic variables. These were plotted as a wheel and graded according to mean ± 4 standard deviations using "normalized" control subjects.[218, 219] This computerized schema was used at first to identify and then to chart the movement of individual patients over time and their response to discreet therapeutic interventions in the ICU (**Fig 4**).

Given current and future advances in super-computing similar schemas applied to much broader data capture might be used to study ARDS, sepsis, and other critical illnesses to better understand pathophysiology dynamically and its response to contemporary therapies. This could be accomplished on a time scale far beyond our cognitive capacity. And once integrated with biomarkers and genomics these findings might shed light on potential therapies tailored and timed to specific ARDS phenotypes which then could be assessed for efficacy.

Scaled down versions of similar temporal plots potentially could be developed for ventilator management and integrated with other monitoring devices. In consequence, it may be possible for computational intelligence to assess and assist (eg. through advisories) ventilator management or perhaps direct closed loop interventions in response to numerous other inputs (eg. blood pressure, stress index, volumetric capnography etc.). The possibilities for how mechanical ventilation might be adjusted in treating ARDS 20 years from now is as unimaginable today, as it was for us 50 years ago to imagine current practices when the Bennett MA-1 ventilator represented the forefront of technology.

The practice of performing hand-gathered ventilator and gas exchange data and entering it into a computer for "snapshot" status assessments will soon vanish (at least in

countries with advanced health care delivery). It is unlikely that we will see new ventilator modes and more likely that automated adjustments based on more sophisticated monitoring will utilize existing volume, pressure, or dual control mode technology.

Respiratory therapists are (and I believe will continue to be) indispensable members of the critical care team. That was very apparent during the first technological boom of the mid-1980s, when both ventilator modes and associated monitoring achieved a level of sophistication exceeding the practical limitations (or inclinations) of other critical care practitioners.[220] However, our cognitive skill set will need to keep pace in order to remain relevant. Most importantly, as our understanding of ARDS and the role of mechanical ventilation advances, we need to avoid the all too human tendency to hold on to beliefs instilled in us at earlier points in our career. Such attitudes are counterproductive to improving patient outcomes. And so, it is only fitting to give the last word to our colleague, mentor and dear friend Bob Kacmarek who many years ago famously challenged our profession with the command: Carpe Diem![221]

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Figure Legends

Fig 1. The inter-relationship between end-expiratory pressure and tidal volume on quasi-static chest compliance (C_{Tstat})resulting in patients with acute respiratory failure (Suter et al. 1978, Reference 24, with permission)

Fig 2. Comparison of frontal chest radiograph (A) to chest tomography images at the carinal (B) and juxta diaphragmatic (C) levels showing both the heterogenous distribution and intensity of lung injury along with areas of relatively preserved, aerated lung tissue. (San Francisco General Hospital ARDS Registry, IRB# 268589).

Fig 3. Differences in patient work of breathing (WOBpt) between patient-triggered manual breaths during synchronized intermittent mandatory ventilation (SIMV-triggered) and corresponding unsupported spontaneous breathing (Spon) as the mandatory rate is reduced from 100% (ie. all efforts resulting in a triggered mandatory breath) to 0% (ie. breathing on continuous positive airway pressure through the ventilator). Note that as mandatory breaths are reduced, the resulting increase in respiratory drive and work of breathing performed during spontaneous efforts continues during mandatory breaths as well. Thus reducing the effectiveness of mandatory breaths to off-load the inspiratory muscles. The graph was generated from tabular data (Marini et al. 1988 reference 91).

Fig 4. An early example of computational intelligence using “radial basis functions” to plot cardiorespiratory variables in a surgical patient. The center plot representing the physiologic response to an unspecified therapy. The four surrounding reference plots represent archetypal patterns expressing different physiologic states. From upper left moving clockwise: A State

represents a balanced or healthy physiologic response to surgical stress, whereas States B through D represent an increasingly unbalanced pathological trajectory towards the development of multi-organ failure (MOF) and a pre-moribund state. The computer program could calculate the characteristics of any current state and the relative "distance" and movement towards or away from other states over time and/or in response to interventions (Cerra et al 1979 Reference 218 with permission).

Table 1. Lung protective ventilation characteristics over the first 3 study days in major trials

Trial	Variable	Day-1	Day-3
ARMA (lower PEEP)[39]	P_{plat} (cmH_2O)	25	26
	PEEP (cmH_2O)	9	9
	F_{IO2}	0.56	0.54
	P_{aO2} (mmHg)	76	77
ALVEOLI (lower PEEP)[194]	P_{plat} (cmH_2O)	24	24
	PEEP (cmH_2O)	9	9
	F_{IO2}	0.54	0.52
	P_{aO2} (mmHg)	78	77
ALVEOLI (Higher PEEP)	P_{plat} (cmH_2O)	27	26
	PEEP (cmH_2O)	15	13
	F_{IO2}	0.44	0.40
	P_{aO2} (mmHg)	85	74
Express (lower PEEP)[82]	P_{plat} (cmH_2O)	21	21
	PEEP (cmH_2O)	7	7
	F_{IO2}	0.66	0.58
	P_{aO2} (mmHg)	89	91
Express (higher PEEP)	P_{plat} (cmH_2O)	28	27
	PEEP (cmH_2O)	15	13
	F_{IO2}	0.55	0.46
	P_{aO2} (mmHg)	108	102
LOVS (lower PEEP)[195]	P_{plat} (cmH_2O)	25	25
	PEEP (cmH_2O)	10	9
	F_{IO2}	0.58	0.52

	P_{aO2} (mmHg)	80	76
LOVS (higher PEEP)	P_{plat} (cmH_2O)	30	29
	PEEP (cmH_2O)	16	12
	F_{IO2}	0.50	0.41
	P_{aO2} (mmHg)	88	75

Key: F_{IO2} = inspired oxygen fraction, PEEP = positive end-expiratory pressure, P_{aO2} = arterial oxygen tension, P_{plat} = plateau pressure.

Fig 1

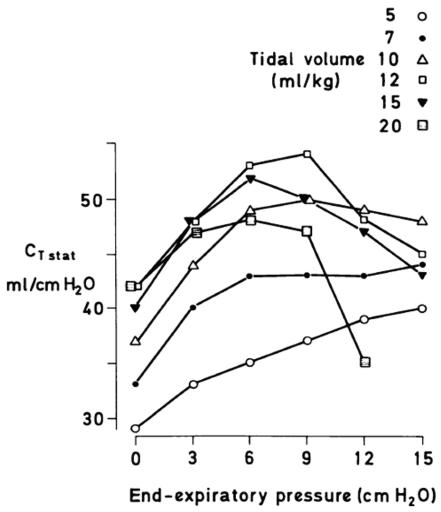

Fig 2

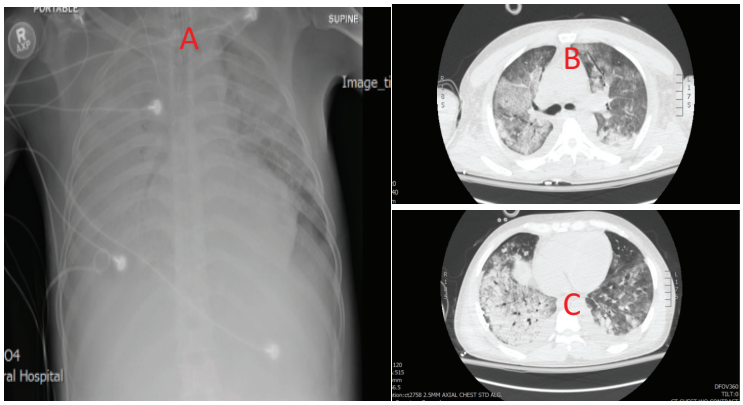

Fig 3

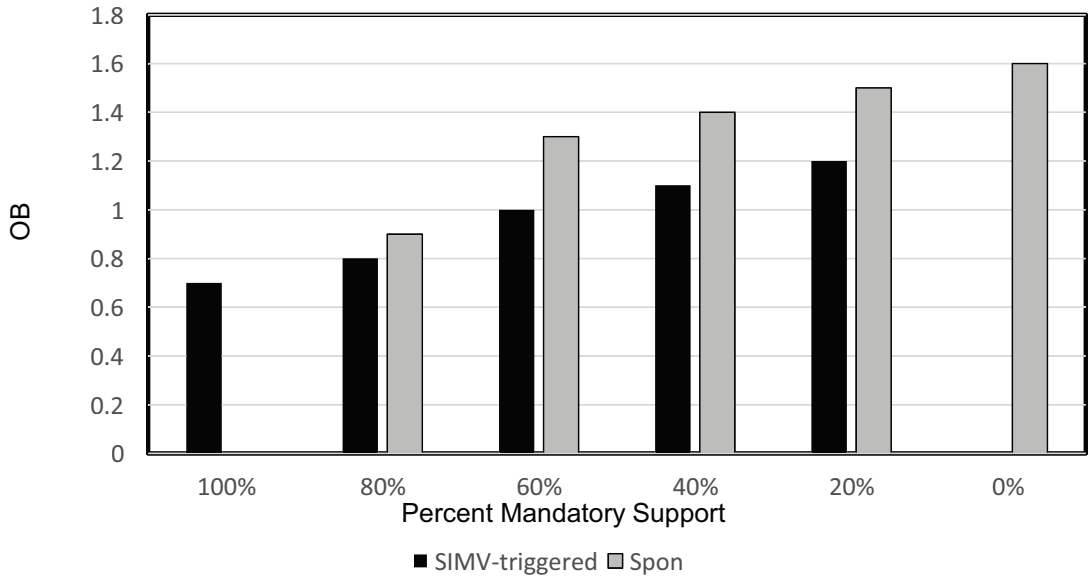

Fig 4