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THE YEAR IN REVIEW: MECHANICAL VENTILATION DURING THE FIRST YEAR OF THE COVID-19 PANDEMIC

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Abstract

Corona virus disease 2019 (COVID-19) represents the greatest medical crisis encountered in the young history of critical care and respiratory care. During the early months of the pandemic, when little was known about the virus, the acute hypoxemic respiratory failure it caused did not appear to fit conveniently or consistently into our classification of acute respiratory distress syndrome (ARDS). This not only re-ignited a half-century's long simmering debate over taxonomy, but also fueled similar debates over how PEEP and lung-protective ventilation should be titrated, as well as the appropriate role of non-invasive ventilation in ARDS. Furthermore, COVID-19 ignited other debates on emerging concepts such as ARDS phenotypes and patient self-inflicted lung injury from vigorous spontaneous breathing. Over a year later these early perplexities have receded into the background without having been reviewed or resolved. With a full year of evidence having been published this narrative review systematically analyzes whether or not COVID-19 associated respiratory failure is essentially ARDS, with perhaps a somewhat different course of presentation. This includes a review of the severity of hypoxemia and derangements in pulmonary mechanics, PEEP requirements, recruitment potential, the ability to achieve lung-protective ventilation goals, duration of mechanical ventilation, associated mortality, and response to non-invasive ventilation. It also reviews the concepts of ARDS phenotypes and patient self-inflicted lung injury as these are crucial to understanding the contentious debate over the nature and management of COVID-19.

Introduction

"Que sçais-je?" ("What do I know?")

Michel de Montaigne

With the exception of acquired immune deficiency syndrome (AIDS), corona virus disease 2019 (COVID-19) represents the greatest medical crisis the world has confronted since the "Great Influenza" pandemic of 1918. And certainly it is the most profound crisis in the young history of critical care and respiratory care. Even the AIDS epidemic did not remotely resemble the enormous strain on critical care capacity, healthcare provider staffing and mechanical ventilators. However, this review of mechanical ventilation during the first year of the pandemic is not concerned with issues such as the lack of ventilators that captivated both mainstream and social media. Rather its focus is the more interesting and deeper issue that animated the first months of pandemic and has lingered afterwards, perhaps forgotten or dismissed by many, but nonetheless one without definitive resolution or consensus.

At the pandemic's onset there seemed to be a collective moment of self-doubt amidst the terrifying chaos of COVID-19. Its *apparent* unusual presentation questioned how we apply the term ARDS and its ramifications on our approach to treatment. This uncertainty vaguely resembled controversies from the 1970s when the very idea of ARDS was considered by some "a distinctive non-entity" that "serves no useful purposes".[1] This is not to insinuate that in 2020 the validity of ARDS as an entity was being challenged, but rather the *validity of what is encompassed by the definition*. The specific characteristics of ARDS presentation have always engendered debate. The pandemic simply brought these long simmering issues to the forefront yet again. The basis for this was established in 2003 when the term "severe acute respiratory syndrome" (SARS) was coined rather than an alternative name in which ARDS was a salient feature.[2] Naming has consequences.

Now with the perspective of time, the accruement of experience, data, and waning emotions, this narrative review is focused on our current understanding of COVID-19 associated respiratory failure and its response to mechanical ventilation. It also explores the controversies that arose in the early months of the pandemic as well. During this time frame interesting opinions regarding both ARDS and COVID-19 were expressed, most based upon clinical impressions and interpretation of the scientific literature that deserve further exploration. These topics are consigned to supplementary materials for those interested. For the primary topics of interest the critique presented in this review focuses on how COVID-19 resembles or differs from our current understanding of ARDS. The intention is that we might answer the question the great Renaissance philosopher posed to himself every day: what do I know?[3]

To Intubate or Not?

Two inter-related clinical management controversies arose almost immediately after the pandemic reached Europe and the United States. The first was whether or not patients with respiratory insufficiency should be intubated before exhibiting signs of overt failure.[4, 5] The second was whether an apparently unusual presentation of COVID-19 respiratory failure was indeed ARDS; thereby raising questions whether the approach to invasive ventilation should be modified in response.[6-8] These controversies influenced how respiratory care was practiced over the first year of the pandemic.

The rationale for early invasive ventilation was based upon three factors. First, fear regarding potential aerosolization from managing patients either with non-invasive invasive ventilation (NIV) or high flow nasal oxygen.[9-11] Clinicians involved with aerosol-generating procedures have approximately 3 times the infection risk compared to other healthcare professionals.[12] Early on the infection rate among healthcare workers was ~4% in China (the majority in Wuhan) and 14% in Italy.[13, 14] Second, was concern for potential development of patient self-inflicted lung injury (P-SILI) from spontaneous breathing at a supranormal V_T generated by high trans-alveolar pressures (> -15 cmH_2O) from a combination of high

respiratory drive, preserved respiratory muscle strength and near-normal lung volumes.[7] Hypothetically, early intubation and control of the ventilatory pattern might mitigate the severity of respiratory failure.[15, 16] Third, early reports from China described sudden, acute respiratory destabilization in 46-65% of COVID-19 patients in the ICU,[17, 18] raising apprehension of delayed detection in overwhelmed hospitals.[15, 19, 20] Thus pre-emptive intubation appeared reasonable from a safety perspective.

The counterargument, colloquially referred to as "avoid intubation at all costs",[21] was largely driven by the following rationale. Early on invasive ventilation was associated with extraordinarily high mortality (~70-100%).[22-25] Also, severely hypoxemic patients initially appeared stable, with relatively intact pulmonary mechanics and respiratory muscle reserve, often without apparent respiratory distress ("silent hypoxemia").[5, 26] Again, in the context of overwhelmed clinicians and a looming (sometimes actual) shortage of ventilators, forestalling intubation with non-invasive respiratory therapies appeared and rational and pragmatic.[8] And in terms of infection control the evidence, as it existed, strongly suggested that the primary risk for clinician infection was not NIV or high flow nasal oxygen, but rather intubation and associated periods of bag-mask ventilation.[27]

Is This Really ARDS?

"Taxonomy is described sometimes as a science, sometimes as an art, but really it's a battleground."

Bill Bryson[28]

The second controversy was that COVID-19 induced respiratory failure differed substantially from ARDS. This raised questions whether invasive ventilation practices should deviate from current evidence-based lung-protective ventilation (LPV) guidelines and protocols. The controversy ranged from circumspect, well-reasoned, tentative opinions (based upon decades of ARDS research),[7, 8] to skewed interpretations regarding the Berlin Definition criteria for syndrome onset,[29] to ill-informed conjecture

such as COVID-19 resembling high-altitude (ie, "hydrostatic") pulmonary edema rather than altered permeability pulmonary edema (the quintessential feature of ARDS).[30]

Whether COVID-19 respiratory failure differs from ARDS should, as a first step, refer back to the definitions of *taxonomy* and *syndrome*. Taxonomy refers to how phenomena are organized or classified according to *common attributes*. By its nature taxonomy is rule-based which to some degree is unavoidably arbitrary and thus prone to controversy. Syndrome, derived from the Greek word for "*concurrence*", refers to a set of *co-related signs and symptoms* associated with a particular disease or disorder. ARDS represents *an effect* emanating from a multitude of potential initiating sources causing acute pulmonary tissue injury and an inflammatory response. These result in varying degrees of severity in both epithelial and endothelial injury, altered permeability pulmonary edema, altered lung mechanics and hypoxemia.

As such, the definition of ARDS requires that it be based upon *common attributes* for making a classification when numerous pathogenic agents can initiate lung injury. These being: 1) a specific threshold of oxygenation dysfunction using the ratio arterial oxygen tension to inspired oxygen fraction (P_{aO2}/F_{IO2}) ≤ 300 mmHg (ie, an approximation of the traditional hypoxemia threshold of P_{aO2} ~ 60 mmHg on room air), 2) radiographic presentation of bilateral lung opacities *suggestive of disseminated alveolar injury*, and 3) an inciting mechanism (etiology) known or suspected to cause acute lung injury.

Although the definition of ARDS has evolved since 1967 (albeit with controversy), these defining characteristics fundamentally have not. Most relevant to COVID-19 is that viral pneumonia accounted for 33% of subjects in the seminal 1967 paper first describing ARDS.[31] And evidence suggests that ARDS was the primary cause of early mortality during the 1918 H1N1 pandemic.[32] Since 1967 multiple viruses have been associated with the syndrome including influenza, adenovirus, varicella, hantavirus and

coronavirus.[2] In early reports from China between 65-85% of COVID-19 patients admitted to the ICU met ARDS criteria.[33, 34]

Part of the controversy rests with the fact that radiographic evidence of ARDS has always been the most vulnerable criterion given the high degree of interobserver variability (even among experts).[35] In addition, a telling observation was that radiologically "COVID-19 lung involvement is unique having a *pneumonia pattern* rather than a typical ARDS pattern *at least in the initial phase during the first days after intubation"* [italics added].[36] Implicit in this statement is that severe hypoxemia was associated with initial lobar pneumonia. In addition, the speed of acute lung injury progression in viral ARDS is dependent upon *the speed of viral replication* which differs between viruses (eg, H1N1 vs. SARS CoV-1),[32] and perhaps between SARS CoV-2 variants as well. And an underlying contributing factor has been the tendency towards under-recognition of ARDS in clinical practice.[37]

Finally, a misreading of Berlin Definition criteria likely played a role. A review paper cited 3 early studies from China in which the median time from symptom onset to ARDS was 8-12 days.[29] Although the time frame exceeds the criterion established by the Berlin Definition Taskforce,[38] the authors did not use the full description which included *"or new or worsening respiratory symptoms"* (ie, underlying disease progression as alluded to above). Interestingly, the "7 day-from-onset" criterion was based on a single center study of 182 subjects with risk factors who subsequently developed ARDS, but excluded pneumonia as a risk factor.[39] Between 35-56% of subjects enrolled into large prospective ARDS treatment trials had pneumonia as primary etiology; thus limiting the external validity upon which the 7-day criterion was initially based.[40-44]

The Theory of ARDS Phenotypes

Phenotypes are the *observable characteristics* of an organism (eg, physical, morphologic, biochemical), whereas *genotype* refers to an organism's entire catalogue of genes available for potential

expression. Phenotypes represent an *interaction* between the organism's genotype and *the environment* it encounters. Specific to ARDS this would include infectious or other injurious agents and the therapies used to treat it (eg, invasive ventilation, hyperoxia, pharmacologic agents, etc.). In COVID-19 associated ARDS use of the term phenotypes created more controversy than clarity.[45-50] Regardless of etiology individual responses to acute lung injury exist along a spectrum ranging from mild to severe that involves the interplay of several factors.

In ARDS, phenotypic expression would encompass either the propensity or disinclination for developing a hyperimmune response to acute lung injury ("cytokine storm syndrome").[51, 52] An individual's *genetic susceptibility* would also apply to the propensity for developing hyperoxic acute lung injury,[53] and ventilator-induced lung injury.[54] Prior to COVID-19, interest in ARDS phenotypes focused on apparent hypo- or hyper-inflammatory ("reactive") responses to acute lung injury. Hyperinflammatory phenotypes are thought to occur in ~33% of ARDS cases, are associated with severe ARDS, and perhaps more responsive to PEEP, certain pharmacologic therapies, and conservative fluid management.[55-57]

However, it is difficult to disentangle an individual's response to COVID-19 induced lung injury from numerous inter-related factors such as: 1) the magnitude of infectious insult (including the potential impact of SARS CoV-2 variants), 2) the usual stages of pneumonia progression,[50] 3) the presence of comorbidities, 4) abnormal body habitus (ie, the extent to which it exaggerates hydrostatic forces that worsen chest mechanics, gas exchange and radiographic findings), and 5) the intensity and duration of exposures to hyperoxia and injurious ventilation patterns. There also exists the inherent problems of conducting physiologic research in the critical care setting (eg, selection bias, small sample sizes) that are magnified under pandemic conditions.

The most succinct criticism of phenotyping COVID-19 was that it was premature.[46] First and foremost it preceded systematic, unbiased data collection that ultimately leads to "a phenotypic signature

specific to high gene expression".[46] Second, the attempt was based upon single center data and "anchored' on only one or two clinically apparent variables".[46]

COVID-19 Phenotypes

The COVID-19 phenotypes hypothesis was raised early on in editorials based upon observations made in an undisclosed number of subjects, and subsequently reported as being made in 150 subjects.[7, 8] The basis was severe hypoxemia dissociated from corresponding reductions in respiratory system compliance (C_{RS}) usually observed in ARDS. Consequently it was proposed that COVID-19 associated respiratory failure be classified as non-ARDS ("Type 1") and ARDS ("Type 2").[8] Of note, the term "non-ARDS" was quickly modified to "atypical ARDS".[58]

In Type 1, computerized tomography (CT) imaging showed essentially normal gas volume and *minimal* (~8%) non-aerated lung tissue associated with normal C_{RS} (80 mL/cmH_2O), and disproportionately elevated venous admixture (56%). This was attributed to severe ventilation-perfusion mismatching caused by loss of compensatory hypoxemic vasoconstriction (from viral injury of the pulmonary vascular endothelium), rather than intrapulmonary shunt from large amounts of non-aerated tisssue.[7] In contrast, Type 2 exhibited a classic ARDS profile with markedly reduced lung volume (~60% of normal) with 39% non-aerated lung tissue and both venous admixture and C_{RS} typically found in ARDS (49% and 43 mL/cmH_2O respectively).

The proposed phenotypes were later renamed from Type 1 to Type L (ie, low lung elastance or high, "preserved" lung compliance) and from Type 2 to Type H (ie, high lung elastance or low lung compliance) based on data culled from 150 subjects.[7] In addition to describing these archetypal presentations of COVID-19 respiratory failure the authors (as well as others) suggested a modified approach to ventilator management (**Table 1**).[7, 20, 59]

COVID-19 Phenotypes and Lung Protective Ventilation

The ensuing controversy over modifying LPV for COVID-19 focused primarily on liberalizing V_T in steps from 6 mL/kg to 7, 8 and perhaps 9 mL/kg when hypercapnia or severe dyspnea were present, and *only in* those patients presenting as Type L.[7, 8] In other words, those in whom lung volume is well preserved so that the risk of developing ventilator-induced lung injury (VILI) would be relatively minor and a reasonable trade-off to balance other risk factors (see below).

Liberalized V_T within accepted LPV parameters has been a consistent feature of European studies for decades.[60-68] In addition, the 2016 LUNG SAFE international survey also used 8 mL/kg as the upper threshold for LPV.[64] Moreover, the Surviving Sepsis Campaign Guidelines for COVID-19 recommended a V_T between 4-8 mL/kg.[69] Hence, the insinuation that these circumscribed guidelines deviated from accepted LPV norms was highly misleading.[46, 70] Furthermore, these recommendations are in stark contrast to others who suggested COVID-19 can be managed safely with a $V_T \leq 11$ mL/kg (assuming that plateau pressure was ≤ 32 cmH_2O).[6, 71]

Reasonable liberalizing of V_T from 6 to 7-8 mL/kg was based upon observations that it "often attenuates dyspnea"[8] and is supported indirectly by studies on V_T demand during LPV (see **Supplementary Materials: Part 1**).[72] A peculiar aspect of arguments against liberalizing V_T,[73, 74] is that it conveniently ignored discussing the reliance upon sedation to control dyspnea and asynchrony which also carries substantial risk of harm.[75-77] A decade ago evidence suggested patient-ventilator asynchrony was associated with worse outcomes,[78] and more recent evidence suggests that *persistent*, *severe* patient-ventilator asynchrony may be particularly harmful.[79] In this context the issue of whether P-SILI is a factor in COVID-19 progression (and its potential exacerbation by dyspnea frequently associated with V_T -mismatching during LPV), raises legitimate cause for concern (see below).

The second controversy focused on how PEEP should be applied. The Surviving Sepsis Guidelines for COVID-19 "suggesting a higher PEEP strategy over a lower PEEP strategy" (ie, PEEP > 10 cmH_2O) drew

particular criticism.[69] In response, an editorial[80] pointing out the vague nature of the criticism replied that "higher PEEP does not necessarily imply very high levels of PEEP". That statement was made in the context of remarking upon a small PEEP study for which it was written.[81] In that study borderline super-PEEP (18 cmH_2O) applied in Type L subjects with relatively preserved C_{RS} (58 mL/cmH_2O) markedly improved oxygenation and end-expiratory lung volume (EELV), but predictably came at the expense of overdistension and hemodynamic impairment.[81] Similarly, investigators in Greece also observed relatively preserved C_{RS} (50-65 mL/cmH_2O) with median "best PEEP" levels of only 8 cmH_2O. This led them and others to criticize use of "pre-defined" PEEP such as the ARDSNet PEEP/F_{IO2} tables and recommended their "abandonment" in "most" COVID cases.[6, 36, 82]

Phenotypes vs. Disease Evolution in COVID-19

Early reports regarding COVID-19 phenotypes were limited by the lack of specific data despite claims it was based upon "detailed observation of several patients and discussions with colleagues" and "more than 50% of the 150 patients measured by the authors and confirmed by several colleagues in Northern Italy".[7] This initial description was quickly followed by specific data from 16 subjects showing that mean C_{RS} of 50±14 coincided with mean Q_S/Q_T of 0.50±0.11.[58] Yet he first detailed mechanical ventilation study from Italy on COVID-19 phenotypes did not appear until October 2020 and included data from only 32 subjects.[68]

A striking comment was that COVID-19 associated ARDS "as the same disease presents itself with "impressive non-uniformity" and that "such a wide discrepancy [between magnitude of hypoxemia and corresponding severity in reduced C_{RS}] "is almost never seen in severe ARDS".[7, 58] These observations were accompanied by proforma statements listing potential confounding factors such as: 1) the combined effects of infection severity and host response, 2) variability in individual responses to hypoxemia, and

(particularly crucial to their hypothesis), 3) that the duration between disease onset and observation would lead to a time-related disease spectrum with two primary "phenotypes."[7]

In other words COVID-19 ARDS likely evolves over time and "transitions" from a mild to severe phenotype which, based on the "timing of presentation" (scientific observation) may present "insurmountable methodological challenges" to study.[7, 83] But liberalizing the definition of ARDS phenotypes from hypo- vs. hyperimmune response, to one suggesting that apparent variations in COVID-19 expression somehow fundamentally differs from the non-uniformity observed in ARDS (irrespective of etiology) is highly suspect in its reasoning (see **Supplementary Materials Part 2)**.

Conflicting Evidence Regarding COVID-19 Phenotypes

Last September data published from 38 COVID-19 subjects with ARDS contradicted the idea of phenotypes.[84] In these subjects chest CT imaging (using "non-quantitative analysis") was done directly after intubation revealing that only ~35% met either Type L or Type H criteria. The majority represented discordant results regarding the lack of association between C_{RS} and the amount of poorly or non-aerated tissue suggesting wide overlap in presentations.

The following month COVID-19 phenotype proponents published an in-depth study on the gas exchange, pulmonary mechanics and CT findings alluded to in their early editorials.[68] In this case-controlled comparison subjects with confirmed COVID-19 ARDS were matched 1:1 with two separate non-COVID ARDS cohorts by P_{aO2}/F_{IO2} and by C_{RS}. CT quantitative analysis of lung tissue was performed at a standardized of PEEP of 5 cmH_2O (ie. removing the confounding effects of therapeutic lung recruitment from assessing baseline pathophysiology). COVID-19 ARDS subjects shared similar amounts of poorly aerated lung tissue with the P_{aO2}/F_{IO2} -matched ARDS cohort, but in almost every other aspect they more closely resembled the C_{RS}-matched ARDS cohort ("(see **Supplementary Materials Part 3**).

The discrepancies between these studies reflects the inevitable limitations imposed by small sample sizes. Possible differences between the studies likely included timing of measurements relatively to disease onset. This is particularly relevant given radiographic reports that rapid progression of lesions was sometimes observed.[85, 86] Also the lack of standardization of ventilator settings in one trial,[84] and differences between non-quantitative vs. quantitative analysis of CT scans between the studies may have influenced their interpretation.

Pathologic and Radiologic Features of COVID-19

Finally, the existence of proposed COVID-19 phenotypes is inextricably tied to the declaration that they represent a "time related disease spectrum".[7] Such statement requires reviewing both the pathologic and radiologic evidence on COVID-19 associated respiratory failure. A brief letter describing 6 post-mortem exams observed that COVID-19 associated lung injury progressed over time.[87] Findings in subjects who died 5 days following symptom onset revealed lymphocytic pneumonia with both interstitial and alveolar infiltration consistent with a Type-L presentation. The 5 other subjects who died at ~20 days all presented with acute fibrinous organizing pneumonia and extensive intra-alveolar and bronchiolar involvement, as well as endothelial injury consistent with Type H presentation.

A subsequent study of 41 subjects compared histopathologic findings between subjects who died at varying time points.[88] Similar findings were observed among subjects who died within the first 8 days in contrast to those who died afterwards. The first cohort exhibited a predominantly exudative pattern with interstitial and intra-alveolar edema and varying degrees of alveolar hemorrhage, fibroblastic proliferation, and hyaline membrane formation. Subjects who died between 17-40 days largely presented with fibroblastic proliferation with densely fibrotic areas. And across study time frames pulmonary microthrombosis was frequently found. The histopathologic pattern and *time-dependent evolution* of diffuse alveolar damage found in subjects with COVID-19 associated ARDS was "stereotypical" of that

observed in non-COVID ARDS.[88] Another study observed an early stage characterized by "neutrophilic, exudative capillaritis with microthrombosis" in contrast to a later stage with a classic ARDS presentation of "diffuse alveolar damage and ongoing intravascular thrombosis in small to medium sized vessels".[89]

Radiologic findings regarding COVID-19 progression were consistent with those found at autopsy. CT imaging in 63 subjects was compared between initial examination and reexamination between Days 3-14.[86] Initial examination found 30% of subjects had only single lobe involvement, whereas ~55% had 4-5 lobes with patchy/punctate ground glass opacities as the primary characteristic. Re-examination found variable (sometimes rapid) disease progression with diffuse lesions of increasingly dense ground glass opacities as well tissue consolidation ("white lung"). The general impression of investigators was that CT imaging of COVID-19 were "similar to common viral pneumonia."[86]

The Renin-Angiotensin-System and Hypoxemia in COVID-19

Dysregulation of compensatory hypoxemic pulmonary vasoconstriction in Type L phenotype aligns with the fact that SARS CoV-2 pulmonary infection primarily targets angiotensin converting enzyme (ACE II) receptors of the pulmonary endothelium.[90] In brief, ACE II receptors are part of the renin-angiotensin-system in which the hormone angiotensin produces vasoconstriction. ACE is abundantly produced by the capillary endothelium and plays a major role in maintaining ventilation-perfusion balance in response to hypoxemia.[91] ACE-II receptors also are found in both airway and alveolar epithelial cells, with emerging evidence that angiotensin plays a prominent (albeit complicated) role in the inflammatory response to both ARDS and ventilator-induced lung injury.[91]

An alternative explanation is that infected alveolar epithelial cells downregulate ACE-2 activity causing unopposed ACE-1 activity in neighboring endothelial cells. Although this would effect a disproportionate release of endothelin-1 (a potent pulmonary vasoconstrictor) causing recruitment of

pulmonary capillary beds,[50] the end result would be similar: severe hypoxemia from ventilation-perfusion mismatching.

Observation and Interpretation during a Global Medical Crisis

Thus, both pathologic and radiographic findings suggest that what initially was interpreted as COVID-19 phenotypes appears to be disease progression. This is likely attributable to a confluence of factors including the relative timing of study to a variable disease progression. More importantly, scientific inquiry normally affords the luxury of open-ended contemplation prior to publication. The COVID-19 pandemic afforded no such luxury. Enormous pressure likely was felt by preeminent ARDS researchers to quickly make some sense of their preliminary observations and convey them to a global audience struggling to understand (let alone) manage a novel viral pandemic. These observations appear concordant with those penned by Dr. Gattinoni and colleagues towards the end of 2020.[92]

The Theory of Patient Self-Inflicted Lung Injury (P-SILI)

The earliest description of COVID-19 ARDS pathogenesis posited that a minority (20-30%) of patients who either initially presented as (or later transitioned to) Type H phenotypes may have had their disease course exacerbated by P-SILI from spontaneous breathing at a supranormal V_T and high trans-alveolar pressures.[7] Prolonged inspiratory efforts resulting in both excessive pleural pressure swings $\geq$ 15 cmH_2O and V_T ($\geq$ 15 mL/kg) was proposed to cause or perpetuate acute lung injury.[7] And as severe SARS CoV-2 infection involves the vascular endothelium, it was further suggested that the carotid bodies may become hypersensitive to hypoxemia, causing abnormally heightened respiratory drive (disproportionate to the severity of hypoxemia) and thus contributing to P-SILI.[93]

First, strenuous diaphragmatic contractions would normally cause high negative pleural pressures to be transmitted homogenously across healthy lungs (“fluid behavior”) thus minimizing abnormal strain-stress development. But heterogeneously injured lungs dissipate pressure unevenly, so that stress

becomes amplified at the interfaces between collapsed/consolidated tissue and surrounding normally aerated tissue ("solid behavior"); thus resulting in greater inflammation and edema formation (particularly in dependent lung regions).[94]

Pre-clinical evidence has demonstrated that high V_T ventilation generated by negative transpulmonary pressure induces acute lung injury in normal lungs.[95, 96] In acutely injured lungs undergoing assisted ventilation, doxapram-induced inspiratory efforts resulting in only a moderate V_T (~ 8mL/kg) but transpulmonary pressures $\geq$ 30 cmH_2O produced the greatest degree of lung collapse, hyperinflation and histologic injury with a matter of only 4h.[97]

Clinical evidence supporting P-SILI remains speculative. First, in both COVID-19 and non-COVID-19 ARDS alike, P-SILI would likely follow the "2-hit" theory of lung injury, whereby the initial insult would prime the immune system, with subsequent high stress-strain ventilation further intensifying inflammation.[98, 99] Second, a "relatively safe" plateau pressure (Pplat) of $\leq$ 30 cmH_2O traditionally advocated for LPV assumed normal chest wall compliance, so that the projected *peak trans-alveolar stress* would not exceed 20 cmH_2O.[100] In addition, *tidal stress change* (ie, Pplat-PEEP > 15 cmH_2O has been shown to increase mortality risk.[101] But when examining figure 2 from that study it is apparent that the inflection point for mortality risk becomes pronounced only at ~ 20 cmH_2O (which was associated with a median V_T of 8 mL/kg).[101]

Finally, the *plausibility* of P-SILI has been documented in acute lung injury. Spontaneous breathing efforts during assisted ventilation in pneumonia or non-pulmonary sepsis produced median (IQR) transpulmonary pressures of 18 (14-23) cmH_2O.[102] Likewise, median (IQR) negative esophageal pressure swings of 17 (12-22) cmH_2O have been reported during unassisted breathing in ARDS, with individual measurements as high as 31 cmH_2O.[103] Also subjects recovering from COVID-19 ARDS were observed generating large negative intrathoracic pressures during weaning. Of particular interest, subjects who

developed relapse respiratory failure *24h after a weaning trial* generated greater negative pressure swings than those who did not: 18 (15-26) vs. 15 (7-18) cmH_2O; several of whom generated pressure swings ≥ 30 cmH_2O.[104] And in subjects with acute hypoxemic respiratory failure (78% with ARDS) generating a spontaneous V_T > 9.5 mL/kg was independently associated with NIV failure.[105] Moreover, it was observed that maintaining a V_T of 6-8 mL/kg was possible in only 23% of subjects despite pressure support levels used in spontaneous breathing trials (ie, 7 cmH_2O). This underscores the general difficulty in maintaining LPV goals in critically ill patients with heightened respiratory drive.

Invasive Ventilation Usage and Associated Mortality

Concern during the first months of the pandemic focused on extraordinarily high mortality associated with invasive ventilation. This was based largely upon 4 studies totally less than 500 cases.[22-25] That Chen and colleagues[25] reported all 17 invasively ventilated subjects died may have garnered disproportionate attention.

By the end of 2020 a large number of studies that included data on invasive ventilation had been published (**Supplementary Table 1**).[22-25, 34, 106-128] Regarding the need for invasive ventilation 32 observational studies with over 15,000 subjects reported median (IQR) usage of 23% (13-54%) with a corresponding mortality of 49% (31-70%). Some of the highest mortality rates (≥ 80%) were reported early on from countries and regions ravaged by the pandemic.[24, 25, 34, 106, 127] These represented the least prepared and also prior to discovering effective pharmacologic therapies.[129]

Because it was imperative to disseminate even preliminary information during the crisis, over half of these studies ceased data collection prior to hospital discharge and before establishing definitive outcome data. An international meta-analysis attempted to compensate for this by estimating both the lowest and highest possible mortality rates (ie, assuming all outstanding cases either survived or succumbed to COVID-19).[130] These estimates ranged from lowest 43% (95% CI, 36-51%) to highest 64%

(95%CI, 56-72%) mortality. When restricted to completed outcome data, the mortality was 49.5%. Another international study focused on hospital mortality differences based upon "organ support".[131] Among hospitalized subjects not requiring either invasive ventilation, renal replacement therapy or vasopressor therapy the mortality was only 8%. In contrast, mortality was 40.8% in those requiring only mechanical ventilation and increased to71.6% in those requiring dialysis and vasopressor support (ie, multi-organ dysfunction syndrome or MODS).

For perspective, observational studies of ARDS in the LPV era have reported 95% confidence intervals for mortality of 31-39% (mild), 37-43% (moderate). and 42-50% (severe).[64] And similar to COVID-19, when ARDS was associated with renal failure mortality risk increased to 80% in some studies.[132] COVID-19 mortality associated with invasive ventilation is similar to that observed during the SARS CoV-1 pandemic (45-48%),[133, 134] and lower than that observed with the Middle East Respiratory Syndrome corona virus (MERS CoV) epidemic (60-74%).[135-137]

Invasive Ventilation Duration

Prolonged invasive ventilation also has been observed with COVID-19.[111] In the aforementioned studies 16 reported duration as it pertained to survivors, time to first successful extubation trial, or based upon the presence of MODS. With one exception central tendency exceeded a week.[118] Another study reported duration was not appreciably different between survivors and non-survivors; moreover in those intubated following NIV failure mean duration increased by 2 days (15 to 17).[126]

Acute kidney injury and the need for renal replacement therapy had a variable impact on invasive ventilation duration depending upon outcome.[138] Acute kidney injury alone increased median duration for all subjects versus survivors by 2.5 and 3.5 days, respectively. Among those also requiring dialysis overall median duration was unaltered (14 days), but increased substantially between survivors who

required dialysis therapy compared to survivors not requiring dialysis: 28.6 (21.1-37.2) vs. 15.0 (9.1-19.6) days.

This exemplifies the problem with collecting data during a pandemic. The urgent need for information virtually compels reporting incomplete outcome data distinct from established norms (eg. status at hospital discharge or Day 90). In consequence the interpretation of invasive ventilation duration (or associated mortality) can be misleading. In one study 35% of subjects successfully extubated had a median duration of 10 (6-15) days, whereas 65% remained ventilator dependent with median duration of 18 (14-24) days when data collection stopped. [111]

For perspective, randomized controlled trials of lung protective ventilation in ARDS (wherein comorbidities are largely removed as a factor) the mean or median duration of invasive ventilation for lower versus higher PEEP strategies was similar to those reported for COVID-19, respectively: 13.5 and 14.2 days,[40] 21 and 25 days,[44] 10 days each,[43] and 22 and 17 days.[139] In addition, a large observational study of weaning ARDS subjects either by spontaneous breathing trials/daily sedation interruptions or usual care practices produced findings within the range reported in COVID-19: median (IQR) of 9 (4-17) and 14 (6-29) days respectively.[140]

PEEP and Tidal Volume Parameters

Twenty-four reviewed studies provided initial ventilator data (**Table 3**).[84, 107, 108, 111, 114, 116, 117, 121, 128, 141-154] In 22 of these mean/median PEEP requirements were 10-16 cmH_2O **(Table 3, Fig 1)**. A crude approach for determining the need for particularly high PEEP levels (ie, approaching the "super-PEEP" threshold of 20 cmH_2O) are values demarcating 1 standard deviation (SD) above the mean, or the 75th percentile. In only 4 (18%) studies did these demarcation thresholds exceed 16 cmH_2O and only one reached 20 cmH_2O.[128, 144, 148, 150] By comparison, lower range PEEP requirements (ie. demarcated by 1 SD below the mean or 25th percentile) were twice as frequent with 36% of studies reported values < 10

cmH_2O. For perspective, general PEEP requirements in ARDS during LPV are 10-18 cmH_2O for the vast majority of patients.[155] These findings suggest that PEEP requirements in COVID-19 associated ARDS are not different from the general ARDS population.

Among 18 reviewed studies reporting V_T in mL/Kg, 94% found mean/median values < 8 mL/kg and 78% at < 7 mL/kg (**Table 3, Fig 2**). Again, using the demarcation points described above violation of LPV V_T parameters (> 8 mL/kg) was reported in only 17% of studies;[68, 111] suggesting that COVID-19 V_T management was largely achieved within accepted LPV guidelines and liberalization was not widely practiced.

Respiratory System Compliance

Type L COVID-19 ("atypical ARDS") was observed in ~70-80% of ventilated subjects in Italy during the first months of the pandemic. The salient characteristic being relatively preserved C_{RS} (ie. > 50 mL/cmH_2O) versus Type H ("typical ARDS") demarcated by C_{RS} < 40 cmH_2O observed in only ~20-30% of subjects.[8, 58] Given that context, studies with timeline data accompanying invasive ventilation characteristics reported intubation occurred from 0-7 days after hospital admission with baseline observations proceeding soon afterwards (ie, mostly subjects with early ARDS).[108, 116, 121, 142, 147, 153, 154, 156]

In 68% of reviewed studies the central tendency for C_{RS} was $\leq$40 mL/cmH_2O and in only 9% did it reach 50 cmH_2O.[68, 70, 107, 108, 111, 114, 116, 121, 128, 142, 144-153, 157, 158] This was similar to non-COVID ARDS managed with LPV (32-38 mL/cmH_2O),[40, 44, 159-161] but higher than ARDS studies preceding LPV (30-34 mL/cmH_2O).[162] C_{RS} values at 1 SD above the mean or the 75th percentile $\geq$ 50 mL/cmH_2O were reported in 43% of studies (**Fig 3**).[68, 70, 107, 145, 147, 148, 153] However, with one exception,[68] the corresponding PEEP levels were 12-20 cmH_2O; thus the relevance of higher C_{RS} in assessing Type-L prevalance remains uncertain. In the largest study focused on COVID-19 lung mechanics C_{RS} decreased over 14 days from 38±11 to 31±14 mL/cmH_2O.[151] This was consistent with COVID-19 pathologic patterns wherein early on (hospitalization

Days 0-8) diffuse exudative patterns were prominent; replaced by pronounced fibroproliferative patterns afterwards.[88]

Thus, contrary to initial reports from Italy, C_{RS} was not well preserved. Even the higher dispersion of C_{RS} values mostly corresponded to higher PEEP (14-20 cmH_2O); that likely improved C_{RS} relative to what was measured preceding PEEP titration (eg, conventional initial PEEP of 5 cmH_2O).[68] Nonetheless, the puzzling observations of preserved C_{RS} reported in Italy also were reported anecdotally in nearby Greece.[36, 82] This raises an interesting question that perhaps a since-displaced CoV-2 variant circulating early on in Southern Europe might have had relatively slower replication, and thus slower progression of lung injury.

Lung and Chest Wall Compliance

Prior to the advent of LPV pathologic alterations in lung and chest wall compliance were measured in numerous studies. In studies reporting mean C_{RS} of 30-34 mL/cmH_2O, corresponding mean lung and chest wall compliances were 32-72 mL/cmH_2O and 59-147 mL/cmH_2O respectively: reductions of ~40-60% and 50-80% from normal respectively.[162]

Only 2 studies have reported lung and chest wall compliance in COVID-19. One study in which median (IQR) PEEP was 14 (12-15) cmH_2O, corresponding median values for C_{RS}, lung and chest wall compliance on the first day of invasive ventilation were 32, 41 and 154 mL/cmH_2O respectively, and were consistent with historical values reported in ARDS.[153] The other study collected data within 48hr of intubation at a median (IQR) PEEP of 10 (8-12) cmH_2O.[147] Although the median C_{RS} (44 mL/cmH_2O) was higher than historical values, both median lung and chest wall compliances (59 and 144 mL/cmH_2O respectively) were consistent with corresponding historical values. Although based upon limited data pathologic alterations in both lung and chest wall compliance in COVID-19 were similar to that reported in non-COVID ARDS.

The Interplay of Oxygenation, PEEP, and Compliance

In the early phase of COVID-19 ARDS oxygenation fell within the Berlin Definition boundaries of moderate ARDS with P_{aO2}/F_{IO2} central tendencies across most studies of 101-198 mmHg.[68, 70, 107, 108, 111, 114, 116, 117, 121, 128, 141, 142, 145, 149-151, 153, 154, 158] Using the previously described lower and upper demarcation criteria 40% of studies had P_{aO2}/F_{IO2} of $\leq$ 100 mmHg whereas 55% had P_{aO2}/F_{IO2} > 200 mmHg (**Fig 4**).

The relevance of this data obviously is limited by the corresponding PEEP at these demarcated boundaries. For 16 studies that also reported PEEP data, 6 in which lower P_{aO2}/F_{IO2} boundaries represented severe ARDS the corresponding PEEP boundaries were 7-11 cmH_2O; 5 of which were < 10 cmH_2O.[70, 108, 111, 147, 149, 151] In 9 studies reporting upper P_{aO2}/F_{IO2} boundaries representing mild ARDS the corresponding PEEP boundaries were 12-18 cmH_2O, and in 8 studies was $\geq$ 14 cmH_2O.[107, 114, 116, 117, 123, 128, 142, 145, 150] The relationship between central tendencies of P_{aO2}/F_{IO2} and PEEP across these studies showed a moderately high correlation (R = 0.77 [95% CI:0.56-0.88] P < 0.001). This suggests initial oxygenation defects reported in COVID-19 mostly reflected how PEEP was being used rather than providing an accurate assessment of the underlying oxygenation defect. Moreover, it appears that PEEP levels required to stabilize oxygenation in COVID-19 ARDS are not different from that used in non-COVID ARDS.

Lung Recruitment Potential

Lung recruitment potential in ARDS is multifactorial with both limited application and variable efficacy. Efficacy depends more upon both the timing of recruitment relative to ARDS evolution (ie, early exudative vs. later fibroproliferative phase) and the severity and distribution of lung injury (ie, diffuse vs. lobar patterns), than it does to lung injury etiology.[163] Five studies assessed recruitment potential in COVID-19 associated ARDS using a 10 cmH_2O increment or decrement in PEEP (**Supplementary Table 2**).[81, 147, 154, 164, 165]

Four studies used the recruitment-to-inflation ratio (R/I) to assess recruitment potential. Briefly, immediately following the sudden application or withdrawal of PEEP expired V_T will decrease or increase respectively compared to prior breaths. This is because gas is either "trapped" by increased PEEP or "released" by decreased PEEP. The trapped or released volume represents changes in EELV, so that "recruitment compliance" is calculated as expired $\Delta V \div \Delta PEEP$. This value is compared to C_{RS} measured at a PEEP of 5 cmH_2O (ie, compliance of the "baby lung"); based on the assumption of linear C_{RS} without changes in aerated lung units.[166] The R/I validation study determined that values $\geq$ 0.5 were indicative of high recruitment potential whereas values below 0.5 indicated poor recruitment potential.[166]

Four studies assessing R/I in COVID-19 presented evenly divided results, each reporting either poor or good recruitment potential. Yet most studies noted a wide range of individual R/I values.[147, 154, 165] Those with the lowest recruitment potential were studied in the fibroproliferative stage of ARDS and had extremely low mean C_{RS} (20 cmH_2O).[164] Similarly, Beloncle et al.[154] found that when R/I was repeated 5 days later, 30% of those initially classified as having high recruitment potential had transitioned to low recruitment potential with a corresponding decline in C_{RS}.

Two of 5 studies that recorded C_{RS} at each PEEP level observed that oxygenation and EELV increased markedly at higher PEEP levels despite exhibiting both declining C_{RS} and elevated stress index.[81, 165] This suggested recruitment occurred simultaneously with regional overdistension. Overall, the findings of recruitment potential in COVID-19 associated ARDS are consistent with those in non-COVID ARDS; specifically the timing of recruitment relative to ARDS onset.[163]

The Role of NIV in ARDS and Viral-Induced ARDS

Managing ARDS with NIV is controversial as the syndrome itself independently predicts therapeutic failure,[167] with overall intubation rates of 30-61% in some studies.[105, 167-173] In other studies, NIV failure rises with increasing ARDS severity from 19-22% (mild), 42-73% (moderate) and 47-84%

(severe).[167, 170, 171] In addition, specific P_{aO2}/F_{IO2} nodal points of < 150 mmHg,[105, 167, 168, 171, 173] < 175 mmHg,[169] and ≤ 179 mmHg)[170] are associated with NIV failure. NIV failure is strongly associated with MODS reflected in elevated illness severity scores and septic shock.[167-174] ARDS associated with viral pneumonia has produced mixed results. NIV failure in SARS CoV-1 was markedly lower (30-33%)[175-177] compared to Influenza A/B (44%),[174] H1N1 (59-85%),[178-181] and MERS (92%).[182] During COVID-19 a national database study reported NIV failure of 49%.[126]

The Role of NIV in COVID-19

In China where the initial treatment approach to COVID-19 favored NIV,[11] an early nationwide study reported that NIV accounted for 87% of all mechanical ventilation with a substantially lower failure rate of 25%, and associated mortality of 17% (compared to 50% in those requiring invasive ventilation).[122] A similar study from Wuhan also reported higher initial NIV usage (57%) with associated mortality of 41% versus 92% in those requiring invasive ventilation.[24]

Specific NIV studies in COVID-19 largely focused on the use of CPAP in the non-ICU setting (**Table 3**). [183-196] Unfortunately 46% of these were research letters often lacking pertinent data.[183-188] Nonetheless, 71% of all studies reported relatively low failure rates of 11-28%; and relatively low associated mortality among those without care limitations (≤ 30%).[154, 183-185, 187, 191, 193] This was accomplished mostly with moderate CPAP (≤ 12 cmH_2O). However, these results often were accompanied either by low, vague thresholds for escalating care from low-level oxygen therapy (eg, supplemental O_2 > 6L/min to maintain S_{pO2} > 92%),[183, 186] or provided no documentation whatsoever.[185, 188, 196]

In 8 traditional observational studies, failure rates were 17-57% with associated mortality of 22-97%.[189-196] In some studies substantially higher mortality was reported in subjects in which the pre-NIV P_{aO2}/F_{IO2} was < 150 mmHg (53%),[189] or had care limitations in place (55-72%).[187, 190, 195]

NIV duration was reported in 50% of studies with median values of 5-6 days.[183, 190] In some studies median duration was 3-8 days when therapy was successful compared to 0.7-8 days in those requiring intubation, and 1.8 days in those with care limitations in place.[185]

Risk factors associated with NIV failure included increased age,[186, 189, 190, 195, 196] admission Sequential Organ Failure Assessment (SOFA) score,[185, 193, 196] Severe Acute Physiology Score (SAPS-III),[196] vasopressor use,[196] renal replacement therapy,[196] and number of comorbidities.[190, 193] Likewise, increased levels of C-reactive protein,[187, 189, 195] Interleukin-6,[187] lactate dehydrogenase,[190] d-dimers,[186] and decreased platelet levels,[189] also were associated with NIV failure. Together these signify marked inflammation often observed in MODS, endothelial dysfunction, pulmonary hypertension and a procoagulant state.

Pulmonary related variables associated with NIV failure included severity of pneumonia at hospital admission,[187] decreased time to oxygen therapy failure (particularly when it resulted in P_{aO2}/F_{IO2} < 150 mmHg),[190] and hyperpnea (ie, median minute ventilation of 15.8 L/min corresponding with median P_{aCO2} of 41.5 mmHg).[186] Despite the general association between low P_{aO2}/F_{IO2} and NIV failure, some studies found that neither baseline P_{aO2}/F_{IO2} values,[186] nor a cut-off of < 150 mmHg were predictive.[184] Nonetheless, larger studies affirmed the predictive value when P_{aO2}/F_{IO2} was < 150 mmHg.[189, 190] Successful NIV therapy was characterized by marked improvement in P_{aO2}/F_{IO2} and decreased respiratory *f* after initiation (particularly a *f* < 30) along with sustained P_{aO2}/F_{IO2} > 150 mmHg over the course of therapy.[190]

The characteristics of NIV use and outcomes in COVID-19 associated ARDS appear similar to those in non-COVID ARDS in terms of the main drivers of therapeutic failure: 1) poor baseline oxygenation (and absence of sustained improvement with therapy), 2) co-morbidities and 3) illness severity and the presence of MODS. That several of these factors also drive mortality during invasive ventilation should be considered when judging the relative efficacy of either therapy.

The Risk of Healthcare Provider Cross Infection during NIV

Only a few studies reported healthcare provider infection data.[183, 184, 186, 194] Two studies reported no infections when healthcare providers had access to the full range of personal protective equipment and when environmental controls were in place.[184, 186] Another study reported only that COVID-19 infection rates among healthcare providers increased from 6 to 10% after implementing NIV (the only detail provided was that bacterial filters were placed on the expiratory limb of the circuit).[183] The most detailed information was provided by a study from Lombardy Italy during the initial wave when hospital resources were extremely limited. Despite the availability of personal protective equipment, healthcare provider infection rate was high (11.5%) and corresponded to a lack of negative pressure rooms for conducting NIV therapy.[194]

During the 2003 SARS Co-V-1 pandemic healthcare provider infection primarily occurred prior to identification of the highly contagious virus as the source and therefore, prior to instituting protective measures.[27, 133, 197, 198] When healthcare providers were given access to the full range of personal protective equipment (along with stringent environmental controls) there was no further incidence of cross infection.[175, 199]

Summary Observations

It was perhaps inevitable that COVID-19 would rekindle the long, contentious debate over what constitutes ARDS and its management. This issue dates back to the mid-1970s with Dr. Petty's "confessions of a lumper",[1] and has continued throughout the history of ARDS reflected in the need to develop a lung injury score,[200] the American European Consensus Conference definition,[201] and the Berlin Definition.[38] It is quite possible that in the aftermath of COVID-19, the definition of ARDS will be re-examined, and perhaps modified to adjust for how specific viral pathogens might alter the progression of acute lung injury. The unanticipated pathophysiologic effects from SARS Co-V utilization of the ACE-2

receptor to infect pulmonary tissue stands as an important lesson to be incorporated into our understanding of ARDS.

And in answer to the controversies that animated the early months of the pandemic, the vast majority of patients with COVID-19 requiring invasive ventilation ultimately presented with ARDS. This is supported by its viral etiology, its histopathologic pattern and evolution, radiographic presentation and evolution, PEEP requirements, severity of hypoxemia, compliance, recruitment potential, duration of invasive ventilation, and responsiveness to NIV. All of these characteristics are uniformly consistent with non-COVID ARDS. As regards mortality associated with invasive ventilation in COVID-19, the majority of studies found it to be within or below that reported in the general ARDS population.

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Figure Legends

Fig 1. Distribution of baseline PEEP requirements during invasive ventilation ordered from lowest to highest mean or median values (S denotes only the study order) Dispersion of values as either 1 standard deviation above/below the mean or the $25^{th}/75^{th}$ percentile.

Fig 2. Distribution of baseline tidal volume (V_T) during invasive ventilation ordered from lowest to highest mean or median values (S denotes only the study order) Dispersion of values as either 1 standard deviation above/below the mean or the $25^{th}/75^{th}$ percentile.

Fig 3. Distribution of baseline respiratory system compliance (C_{RS}) during invasive ventilation ordered from lowest to highest mean or median values (S denotes only the study order) Dispersion of values as either 1 standard deviation above/below the mean or the $25^{th}/75^{th}$ percentile.

Fig 4. Distribution of baseline P_{aO2}/F_{IO2} (arterial oxygen tension-to inspired oxygen fraction) during invasive ventilation ordered from lowest to highest mean or median values (S denotes only the study order) Dispersion of values as either 1 standard deviation above/below the mean or the $25^{th}/75^{th}$ percentile.

Table 1. Proposed COVID-19 phenotypes of respiratory failure and early management recommendations*

	Type L	Type H
Original designation	Type 1	Type 2
Time course	Early	Late
Defining characteristic	~preserved lung compliance (low lung elastance)	decreased lung compliance (high lung elastance)
C_{RS} demarcation	$\geq$ 50 mL/cmH_2O	< 40 mL/cmH_2O
Chest CT findings	• preserved lung volume • ↓% non-aerated lung tissue • ↑lung weight	• ↓ lung volume • ↑% non-aerated lung tissue • ↑↑ lung weight
Most salient gas exchange characteristic	Severe hypoxemia disproportionate to % non-aerated lung tissue	Severe hypoxemia proportionate to % non-aerated lung tissue
Primary source of severe hypoxemia	↓V/Q	↑Q_S/Q_T
LPV settings		
V_T (mL/kg)	6-9[†]	$\leq$ 6
f	15-20	— [‡]
PEEP (cmH_2O)	8-10	$\geq$ 14
Prone Positioning	"Rescue therapy": ↑ V/Q Prolonged duration not advised: marginal benefit at best (ie. minimal lung recruitment potential)	Prolonged course (16-20h/d) to facilitate lung recruitment. Substantial benefit likely as in non-COVID-19 ARDS
Inhaled Vasodilators	Questionable benefit due to loss of apparent "vasoplegia" (ie. loss of vasomotor tone).	Potential benefit as pulmonary hypertension is associated with severe non-COVID-19 ARDS. Suggests speculation that partial resolution of vasoplegia might occur over disease course.

Key: ARDS = acute respiratory distress syndrome, COVID-19 = corona virus disease 2019, C_{RS} = respiratory system compliance, CT = computer tomography, *f* = respiratory frequency, LPV = lung protective ventilation, PEEP = positive end-expiratory pressure, Q_S/Q_T = intrapulmonary shunt fraction, V/Q = ventilation-to-perfusion ratio, V_T =- tidal volume. *based on references 7 and 8. [†]increases > 6 only for hypercapnia or attempting to reduce dyspnea (rather than increasing f) [‡]not specified.

Table 2 Mechanical ventilation characteristics

Study	Setting/N	P_{aO2}/F_{IO2} (mmHg)	C_{RS} (mL/cmH_2O)	PEEP (cmH_2O)	V_T (mL/kg) or mL
Chiumello[68]*	SC, N = 32	107±60	50±15	NR	7.7±0.9
Chiumello[68]†	SC, N = 32	160±62	50±16	NR	8.4±1.9
Bos[70]	SC, N = 38	132±48	49±24	10 (9-12)	424±73
Grasselli[123]	MC, N = 1,150	160 (114-220)	NR	14 (12-16)	NR
Liu[153]	SC, N=8	230±49	34±8	10±1	7.5±0.6
Botta[116]	MC, N = 553	159 (129-201)	32 (26-40)	14 (11-15)	6.3 (5.7-7.1)
COVID Crit Care Group[117]	MC, N = 4,643	154 (103-222)	33 (26-42)	12 (10-14)	6.1 (5.8-6.7)
Ziehr[142]	SC, N = 66	182 (135-245)	35 (30-43)	10 (8-12)	NR
Hernandez-Romieu[121]	SC, N = 231	148 (111-205)	34 (27-47)	NR	NR
Haudebourg[147]	SC, N = 30	111 (96-128)	44 (35-51)	10 (8-12)	6.0 (5.9-6.7)
Zangrillo[143]	SC, N = 73	NR	NR	12 (10-14)	6.7 (6.0-7.5)
Bhatraju[144]	MC, N =24	NR	29 (25-36)	13 (11-17)	NR
Mitra[114]	SC, N = 117	180 (148-216)	35 (31-44)	12 (10-14)	400 (350-450)
Schenck[111]	SC, N = 267	103 (82-134)	28 (23-38)	10 (8-12)	7.0 (6.1-8.1)
Rojatta[145]	SC, N = 41	183±69	42±19	13±2	NR
Barbeta[107]	SC, N = 50	174 (128-232)	40 (33-52)	13 (11-14)	6.8 (6.3-7.3)
Ferrando[108]	MC, N = 742	120 (83-177)	35 (27-45)	12 (11-14)	6.9 (6.3-7.8)
Sjoding[146]	SC, N = 130	NR	35 (27-43)	12 (8-14)	5.9 (5.2-6.9)
Zangrillo[143]	SC, N =73	NR	NR	12 (10-14)	6.7 (6.0-7.5)
Lenka[148]	SC, N = 32	NR	44 (31-59)	16 (14-20)	NR
Brault[149]	SC, N = 24	101 (81-126)	33 (26-41)	12 (7-15)	6.1 (5.4-6.8
Cummings[128]	MC, N = 203	129 (80-203)	27 (26-36)	15 (12-18)	6.2 (5.9-7.2)
Diehl[150]	SC, N = 13	198 (167-298)	40 (33-45)	16 (15-17)	6.0 (5.2-6.2)
Vanderbunder[151]	IMC, N = 372	132 ± 53‡	38 ± 11	12 ± 3‡	6.3 ± 0.8‡

Kassis[153]	SC, N =40	150 (123-182)	41 (34-50)	14 (12-15)	6.2 (5.8-6.7)
Beloncle[154]	SC, N = 25	135 (119-195)	NR	12 (10-15)	6.0 (5.9-6.1)
Auld[158]	SC, N = 165	132 (100-178)	34 (28-46)	NR	NR

Key: C_{RS} = respiratory system compliance, IMC = international multicenter study, MC = multicenter study, NR = not reported, P_{aO2}/F_{IO2} = ratio of arterial oxygen tension to inspired oxygen fraction, PEEP = positive end-expiratory pressure, SC = single medical center, V_T = tidal volume, *matched cases to non-COVID ARDS by P_{aO2}/F_{IO2}, †matched cases to non-COVID ARDS by C_{RS}, ‡Study reported mean C_{RS} for the entire sample and then subdivided into cohorts by a cut-off of 35.4 mL/cmH_2O. As there was little distinction between cohorts in terms of P_{aO2}/F_{IO2}, PEEP and V_T, values of the higher compliance cohort are reported.

Table 3 Non-invasive ventilation usage and outcomes

Study, Setting N	NIV Evaluation • Initial O_2 Rx • Hypoxemia Criteria • Baseline P_{aO2}/F_{IO2}	NIV Failure ETI Associated Mortality	NIPPV/CPAP: Parameters Treatment Duration Time to NIV Failure
Brusasco[184] SC, GW/SCU N=64	• VM (F_{IO2} 0.50) • P_{aO2}/F_{IO2} < 200 • P_{aO2}/F_{IO2}: 119 (99-153)	ETI: 11% Mortality: 6%	CPAP: 10 cmH_2O Treatment Duration: NR
Di Domenico[195] SC, GW/SCU N=90	• O_2 Mask 12L/min • S_{pO2} < 90% • 248±17 • 186±20(DNR/DNI)	Unrestricted Care: ETI: 57% Mortality:47% DNR/DNI Care: Mortality 89%	Parameters:NR Treatment Duration: NR Time to NIV Failure: ≤ 1d
Gaulton[188*†] MC, ICU N=59	• NR • NR • NR	ETI: 18% Mortality: NR	CPAP: 11±2 cmH_2O Treatment Duration: NR
Oranger[183] SC, GW/SCU N=38	• NR • O_2 > 6L/m to keep S_{pO2} > 92% • NR	ETI: 24% Mortality: 0%	CPAP: 10(8-12) cmH_2O Treatment Duration: 5 (2-8)d; 8(4-11)h/d
Sivaloganathan[185] SC, ICU, GW/SCU N=58	• NR • NR • NR	ICU ETI: 47% Mortality:14% DNR/DNI Care: Mortality 83%	CPAP: NR Treatment Duration No ETI:72 (41-132) h Time to ETI: 17 (4-31) h 55% failure ≤ 24h DNI: 44 (8-103) h

Avdeev[186] MC, GW/SCU N=61	• NR • O_2> 6L/min O_2 to keep S_{pO2} > 92% • P_{aO2}/F_{IO2}: 164 (131-200)	ETI: 28% Mortality: 88%	CPAP (74%): 10(10-12) cmH_2O ΔPS/PEEP (26%): 10 (8-12) /10(10-13) cmH_2O Treatment Duration No ETI: 8(6-11) d Time to ETI: 3(3-8) d
Aliberti[187*] MC, GW/SCU N=157	• VM $F_{IO2} \geq 0.50$ or NRM • $P_{aO2}/F_{IO2} < 300$ • P_{aO2}/F_{IO2}: 143 (97-203)	ETI:22% Mortality: 26% DNI/DNR Care Mortality: 55%	CPAP: 11±2 cmH_2O F_{IO2}: 0.6(0.5-0.6) Treatment Duration Success: 7(4-12) d Failure: 7 (1-8) d Time to ETI: 3(2-5) d
Bellani[189*] MC, GW/SCU and ICU N=798	• NR • NR • P_{aO2}/F_{IO2}: 168±98	ETI: 17% Mortality without ETI: 22% Mortality when initial $P_{aO2}/F_{IO2} <$ 150: 53%	85%CPAP: 11±3 cmH_2O 10% NIPPV (data NR) Treatment Duration NR Admit to NIV: 1 (0-4) d Time to ETI: 8 (5-13) d
Coppadoro[190*] MC, GW/SCU N=303	• NRM • NR • P_{aO2}/F_{IO2}: 103 (79-176)	Unrestricted Care: ETI: 31% Mortality: 41% DNI/DNR Care Mortality:72%	CPAP: 10 (7-10) Treatment Duration 6 (3-9) d; 21h/d Admit to NIV: 1 (0-2) d
Menzella[193] SC, GW/SCU N=79	• VM • P_{aO2}/F_{IO2}: 100-199 on VM F_{IO2} 0.60 • P_{aO2}/F_{IO2}: 120±42	ETI: 27% Mortality: 25%	BiPAP: 18±2/9±2 cmH_2O Treatment Duration All: 7±5 d Success: 9±4 d

			Death: 6±4 d Time to ETI: 3±3 d
Franco[194‡] SC, GW/SCU N= 507	• NRM 10-15 L/m • S_{aO2} < 94% • P_{aO2}/F_{IO2}: 150±90 (CPAP) and 138±66 (PS)	ETI: 25% (CPAP), 28% (PS) Mortality: 30%,30%	CPAP: 10±2 cmH_2O PS Δ17±3 / PEEP 10±2 cmH_2O Treatment Duration: NR
Baqi[192] SC, ICU N=100	• Basic O_2 Rx to keep S_{pO2} > 92% • P_{aO2}/F_{IO2}: ≤ 300 • Baseline: NR	ETI: 40% Mortality: 97%	Parameters: NR Treatment Duration: 4 (2-6) d
Grieco[191*] MC-RCT, ICU N=109	• VM F_{IO2} 0.24-0.60 • P_{aO2}/F_{IO2}: ≤ 200 • P_{aO2}/F_{IO2}: 102 (82-125)	ETI: 28% ETI Mortality: 24%	ΔPS/PEEP: 10(10-12)/12(10-12) Treatment Duration: NR Initial Rx: 48h continuous NIPPV
Kurtz[196] MC N=4188	• NR • NR • P_{aO2}/F_{IO2}: 216 (89-329)	ETI: 52%	NR NR NR

Key: BiPAP = bi-level positive airway pressure, DNI/DNR = do not intubate/do not resuscitate, ETI = endotracheal intubation, GW/SCU: general ward or COVID-19special care unit, MC = multicenter study, NA= not applicable, ND = national database, NIPPV = non-invasive positive pressure ventilation, NIV = noninvasive ventilation, NR = not reported, NRM = non-rebreather mask, P_{aO2}/F_{IO2} = arterial oxygen tension-to-inspired oxygen fraction ratio, PS = pressure support, RCT = randomized controlled trial, Rx = therapy, S_{aO2} = arterial oxygen saturation, S_{pO2} =oxygen saturation by pulse oximetry, SC = single medical center, VM = venti mask, *helmet interface only, †Enrolled subjects with body mass index > 25kg/M^2. ‡mixed helmet and facemask use (helmet: 99% during CPAP and facemask 79% during NIPPV))

Supplementary Table 1. Invasive mechanical ventilation usage and outcomes in hospitalized subjects

	Study Period	Data Source	%MV	Duration (d)	MV-Mortality
Karagiannidis[126]	2-4/2020	NDR. N = 10,021	14.6%*	15.1±12.1	53%
Almazeedi[125]	2-4/2020	NDR N = 1,096	2.8%	NR	62%†
Haase[124]	3-5/2020	NDR, N 323	82%	13 (7-21)	41%†
Grasselli[141]	2-3/2020	MC, N = 1,1,50	88%	NR	26%†‡
Botta[116]	3/2020	MC, N = 553	NR	13.5 (7.5-22.5)	42%
Zhou[23]	12/2019-1/2020	MC, N = 191	17%	NR	97%
Wang[122]	12/2019-1/2020	MC, N = 1,590	3.1%	NR	50%†
Yang[34]	12/2019-1/2020	SC, N = 710	3.1%	NR	86%
Yang[110]	3-5/2020	SC, N = 106	61.3%	12 (8-18)	18.5%
Hua[24]	2-3/2020	MC, N = 469	24%	NR	92%
Auld[158]	3-5/2020	MC, N = 231	75%	9 (5-14)	36%†
Khamis[120]	2-4/2020	MC, N = 63	25%	NR	31%
Richardson[106]	3-4/2020	MC, N = 1,500	12.2%	NR	88.1%
Israelsen[119]	3-4/2020	SC, N=175	15.4%	NR	59.3%†
Regina[118]	3/2020	SC, N = 145	24.8%	6.0 (5.0-11.0)	9.7%†
COVID Crit Care Group[117]	2-5/2020	MC, N = 4,643	80%	13 (8-18)	31%
Ferguson[115]	3-4/2020	MC, N = 72	18.1%	17 (13-29)	__§
Mitra[114]	2-4/2020	SC, N = 117	63.2%	13.5 (8-22)	15.4%†
Salacup[113]	3-4/2020	SC, N = 242	22%	NR	70%
Suleyman[112]	3/2020	MC, N = 355	32%	NR	50%
Bahl[22]	3/2020	MC, N = 1461	21.1%	NR	71%

Chen[25]	1-2/2020	SC, N = 799	2.1%	NR	100%
Schenck[111]	3-4/2020	SC, N = 267	NR	10 (6-15) [ll]	34.8%[†]
Barbeta[107]	3/2020	SC, N = 50	NR	NR	34%
Ferrando[108]	3-6/2020	MC, N=742	NR	14 (7-24)	32%[†]
Sjoding[146]	3-6/2020	SC, N =130	NR	NR	30%[†]
Fominskiy[138]	2-4/2020	SC, N= 112		13 (10-16)	16.7%[¶]
				17 (11-28)	38.9%[**]
Argenziano[109]	3-4/2020	SC, N = 850	26%	9 (7-32)	49%[†]
Giacomelli[127]	2-3/2020	SC, N = 233	3.4%	NR	88%[†]
Cummings[128]	3/2020	MC, N = 1150	17.6%	18 (9-28) [††]	41%[†]

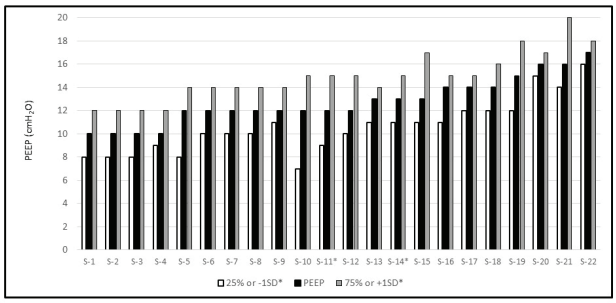
Key: MV = mechanical ventilation, MC = multicenter study, NA = not applicable (data not collected based on study design), NDR = national data registry, NR = not reported, MN = multinational study, *includes those failing trial of non-invasive ventilation [†]mortality at study closure, [‡]intensive care unit mortality as approximate invasive MV mortality, [§]Mortality associated with MV not reported. [ll]MV duration in 77 subjects successfully extubated and 18 (14-24) days in 141 under MV at time data collected ceased. [¶]without acute kidney injury, [**]acute kidney injury, [††]27(15-32) days among survivors.

Supplementary Table 2. Recruitment potential in COVID-19 associated ARDS.

Study /N	Timing from ARDS Onset/ETI	Characteristics	R/I PEEP increment and directional Δ	Results
Pan[164]	9±6 days	P_{aO2}/F_{IO2}: 128±53 mmHg	10	R/I: 0.21±0.14
N=12	42%: < 5 days		15 to 5	83%poor recruit
	42%: 10-21 days	C_{RS}: 20±8 mL/cmH_2O		6% daily R/I > 0.5
Mauri[165]	5 (1-11) days	PEEP: 12(12-15) cmH_2O	10	R/I: 0.79 (0.53-1.08)*
N=10	60%:< 5 days			Range: 0.16 to 1.40*
	30% > 10 days	P_{aO2}/F_{IO2}: 99 (69-145) mmHg	5 to 15 or 15 to 5	EELV: 0.80 (0.62-0.99) L*
				EELV rec: 0.31(0.26-0.49)L*
				ΔPplat/ΔPEEP: 1.2/1
				C_{RS}: ↓10%
				P_{aCO2} : ↑5 mmHg
				% Δ Dorsal V:↑30%*
				% Δ global inhomogeneity index:↓16%*
				P_{aO2}/F_{IO2}: ↑58%
Grasso[81]	2 days	C_{RS} 58±8 mL/cmH_2O	10	EELV: ↑0.45±0.1L
N=8		P_{aO2}/F_{IO2}:131±22 mmHg	9 to 19	C_{RS}: ↓19%
				P_{aO2}/F_{IO2}: ↑58%
				SI: ↑0.97 to 1.22
				CI: ↓19%
Haudebourg[147]	2 days	C_{RS}: 44 (35-51) mL/cmH_2O	10	0.40 (0.23-0.50)
N=30		P_{aO2}/F_{IO2}:119 (97-163) mmHg	15 to 5	
Beloncle[154]	1.5 days	PEEP: 12cmH_2O	10	R/I: 0.55 (0.47-0.77)
N=26	Repeated on day 5	P_{aO2}/F_{IO2}: 135 (119-195) mmHg	15 to 5	<u>Day1 recruitment potential:</u>
				64% median R/I 0.70 (high)
				36% median R/I 0.41 (poor)
				<u>Day 5</u>: (10 highly recruitable subjects still intubated): 30% transitioned to poor recruitment potential.
				EELV: ↑0.28 (0.22-0.42)L
				C_{RS}: ↓10%

Key: CI = cardiac index, C_{RS} = respiratory system compliance, EELV = end-expiratory lung volume, EELVrec = change in end-expiratory lung volume attributed to lung recruitment, ETI = endotracheal intubation, P_{aO2}/F_{IO2} = arterial oxygen tension to inspired oxygen fraction ratio, P_{aCO2} = arterial carbon dioxide partial pressure, PEEP = positive end-expiratory pressure, Pplat = plateau pressure, R/I = recruitment to inflation ratio, *measurements made by electrical impedance tomography.

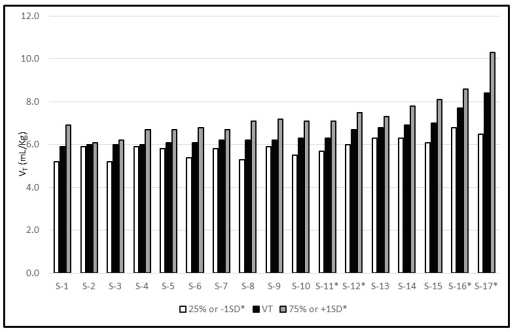
Fig 1



Distribution of baseline PEEP

338x190mm (96 x 96 DPI)

Fig 2



Distribution of baseline tidal volume

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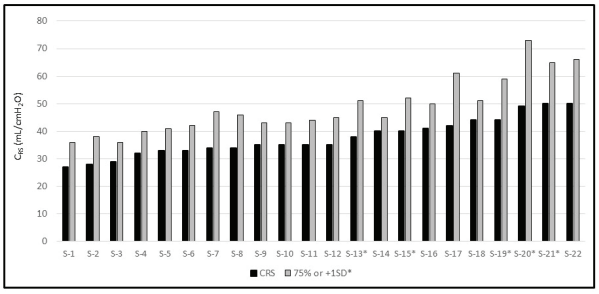
Fig 3



Distribution of baseline respiratory system compliance

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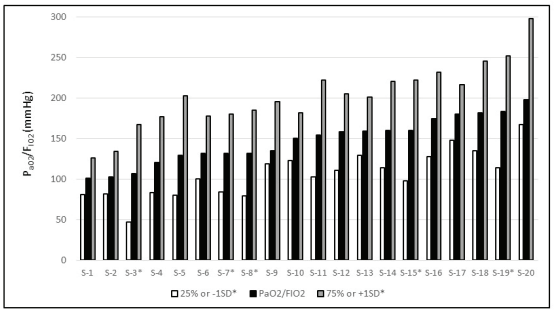
Fig 4



Distribution of baseline PaO2/FIO2

338x190mm (96 x 96 DPI)