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Please cite as:

Jaber, S, Bellani, G, Blanch, L, Demoule, A, Esteban, A, Gattinoni, L, Guérin, C, Hill, N, et al. (2017). The intensive care medicine research agenda for airways, invasive and noninvasive mechanical ventilation. INTENSIVE CARE MEDICINE, vol. 43, p. 1352-1365, ISSN: 0342-4642,

doi: 10.1007/s00134-017-4896-8

# The ICM Research Agenda on "Airways, Invasive and Noninvasive Mechanical Ventilation"

05 Feb 2017

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**Total word count: n= 5486**

**References: n= 106**

**Tables: n= 3**

**Figures: n= 3**

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**Conflict of interest statement**

Dr Blanch is inventor of a US patent owned by Corporació Sanitaria Parc Taulí: “Method and system for managing related patient parameters provided by a monitoring device,” US Patent No. 12/538,940. LB owns stock options in BetterCare S.L., a research and development start-up of Corporació Sanitària Parc Taulí (Spain).

Dr. Jaber reports receiving consulting fees from Drager, Hamilton, Maquet, and Fisher & Paykel

Dr. Navalesi’s research laboratory has received equipment and grants from Maquet Critical Care. He also received honoraria/speaking fees from Maquet Critical Care.

CG, JJM and JLV declare no conflict of interest.

## Introduction

In an important sense, support of the respiratory system has been a defining characteristic of intensive care since its earliest inception. The pace of basic and clinical research in this field has escalated over the past two decades, resulting in palpable improvement at the bedside in both efficacy and outcome [1]. As in all medical research, however, novel ideas built upon prior observations are continually proposed, tested and retained or discarded based on the persuasiveness of consensus and evidence. What follows are summary descriptions of the current standards of management practice in respiratory support, the areas of present-day uncertainty, and our suggested agenda for the near future of research aimed at testing current assumptions, probing uncertainties, and solidifying our foundation for progressing to the next level.

**1/ What is the current standard of care for delivering the best possible critical care in your field?**

### ***1.a/ Artificial Airway Management***

Airway management in the intensive care unit (ICU) has advanced rapidly in the last decade. Delivering the best possible care involves addressing four key components to mitigate the risk to the patient: preparation, tube placement, oxygenation, and human factors. Certain granular aspects of these components are still controversial; however, these four components must be addressed to optimize safety of intubation in the ICU.

Critically ill patients have physiologic disturbances that increase their risk with even one attempt at intubation [2]. Repeated attempts increase the hazard [3]. Optimization of hemodynamics with fluid resuscitation and vasopressor support should be performed, as over one-third will decompensate after intubation, especially in patients with a high shock index (HR/SBP >0.8) [4]. Patients with hypoxemic acute

respiratory failure (ARF) have a reduced functional residual capacity and shunt physiology, which make preoxygenation more difficult and increase the procedural hazard [5]. Noninvasive ventilation (NIV) [6], heated and humidified nasal oxygen [7-9] and flush rate oxygen by facemask improve preoxygenation compared to traditional facemask alone [5]. Intubation in the head-up position can reduce the risk of aspiration, and prior visualization of the gastric compartment by ultrasound can identify patients likely to benefit from gastric decompression [10].

Considerations regarding endotracheal tube placement include drug and device selection to maximize the chances of successful intubation without a complication [11]. Ideal drug selection depends on the patient's physiology and the operator's assessment of the potential difficulty with laryngoscopy, rescue oxygenation, or a surgical airway. Options include graded sedation with short acting drugs like propofol [12], induction with hemodynamically neutral sedatives (ketamine or etomidate)[11], and use of a neuromuscular blocking agent after sedation [11, 13]. If an awake endoscopic approach is planned, nasal high flow oxygen (HFNC) or NIV can be useful for maintaining oxygen saturation during the procedure. Jaber et al. [14] reported that applying HFNC plus NIV before orotracheal intubation was superior to apneic pre-oxygenation with NIV alone. Instrument selection is more controversial. Most studies report video laryngoscopy to be superior to direct laryngoscopy [15]; however, the results of some studies indicate no difference in first attempt success [16, 17]. If one performs direct laryngoscopy, a video laryngoscope should be available for use in the event of a first attempt failure [15].

Oxygenation during laryngoscopy is potentially useful to extend apnea time and avert desaturation. Despite mixed evidence, apneic oxygenation should be performed, as it is a low cost, low-risk, high reward intervention [5]. In the event of a 'cannot intubate-cannot oxygenate (CICO)' scenario, a supraglottic device can provide temporary rescue oxygenation if facemask ventilation proves inadequate; if CICO persists, airway access should be secured surgically and without delay using an open technique.

Human factors must be addressed to improve safety [18, 19]. A team-based approach and simulation training using an algorithm should be instituted to standardize

airway management as much as possible in the unpredictable context of ICU airway management. Finally, carts appropriately stocked for laryngoscopy, rescue oxygenation, and readiness to perform the surgical airway access needed for the difficult airway should be present and immediately available.

### **1.b. Non-invasive ventilation (NIV)**

NIV is administration of mechanical ventilation without an artificial airway. In its broadest meaning, NIV includes both noninvasive CPAP and positive pressure ventilation (NPPV). While the latter requires a ventilator, the former is preferentially applied by means of an adjustable flow-meter and a PEEP valve. While often providing the same physiological benefits regarding inspiratory effort and gas exchange, NIV offers several major advantages over invasive ventilation: 1) better comfort, reducing the need for analgesic and/or sedative drugs; 2) easier application and removal of the interface than with an endotracheal tube, allowing greater flexibility of use; and 3) preserved ability to cough, swallow and verbally communicate. Furthermore, because NIV interferes minimally with airway protection and defenses, the risk of ventilator-associated pneumonia and other infectious complications is reduced [20], which makes this technique particularly appealing for immunosuppressed patients. However, NIV is not suitable for all patients and is contraindicated in those requiring cardio-respiratory resuscitation or who are hemodynamically unstable, are unable to protect the airway or manage airway secretions, or require high levels of airway pressure. NIV is not appropriate for those who manifest agitation, lack of cooperation or non-hypercapnic coma. NIV outcome depends on the patient's characteristics, *i.e.*, etiology, severity and reversibility of ARF and co-morbidities. Success often hinges on logistic factors, such as location of treatment and team expertise, as well as on specific technical features related to ventilators and interfaces. These latter are of fundamental importance. Air-leaks are ubiquitous and, if excessive, can promote NIV failure by contributing to patient-ventilator asynchrony and discomfort [21]. They can be contained by properly



choosing and applying the interface and by using ventilators equipped with dedicated NIV software capable of detecting and compensating for leaks [21]. The interface has to be comfortable enough to make NIV well tolerated. ARF severity, facial characteristics, tendency for claustrophobia and duration of NIV application should all be considered when choosing the interface. As patients with ARF are generally mouth-breathers, full face masks are preferred initially [22]. However, there is no perfect interface for all patients and the choice must be individualized. Also, when prolonged, near-continuous NIV application is necessary, a rotational interface strategy should be considered [23]. The timing of NIV administration is also important. Early NIV may be used to prevent the occurrence of frank ARF and avert the need for endotracheal intubation as other measures address the precipitating cause [24]. Patient selection is crucial, aiming to avoid patients at excessive risk of NIV failure. NIV is strongly recommended for patients with hypercapnic ARF, especially in those with a COPD exacerbation [25], and ARF secondary to cardiogenic pulmonary edema [26]. NIV can facilitate the extubation of COPD patients intubated for hypercapnic ARF; however, as for all instances where NIV is used in alternative to invasive ventilation, this application requires an ICU team highly experienced with this technique [27]. In patients at high risk of extubation failure, NIV soon after planned extubation reduces the rate of reintubation and improves overall outcomes [28]. For many patients, HFNC, a methodology that reduces breathing frequency, provides some deadspace washout, applies low level airway pressure and may improve distribution of ventilation, appears to offer an appropriate alternative for this specific indication [29]. NIV reduces the rate of respiratory complications including reintubation in patients after high risk surgeries [30] and chest trauma [31]. Although some patients might benefit, widespread use of NIV in *de novo* hypoxemic ARF, in particular those with ARDS, is presently not advisable [32].

The emergence of NIV has clearly been of value for patients with hypercapnic respiratory failure and cardiogenic pulmonary edema, but it must be administered to selected patients using appropriate equipment in the right location by skilled and experienced staff.

### **1.c. Invasive ventilation**

A primary focus of research and recommendations on invasive ventilation recently has been centered on ARDS, in which ventilation settings have been shown able to affect patient outcome (figure 1). The cornerstone for lung protective ventilation, deriving from the ARDS Network (ARMA) trial, remains the use of a tidal volume of 6-8 ml/kg (Predicted Body Weight) while limiting plateau pressure below 30 cmH<sub>2</sub>O [33]. More recent data suggest that a higher “driving pressure” (i.e. the difference between plateau pressure and PEEP) is the variable most strongly associated with adverse outcomes [34, 35], underlining the importance of monitoring this parameter. Adoption of protective tidal volumes in clinical practice remains suboptimal and, of greater concern, plateau pressure is measured in less than half of all patients [36]. Clinical trials concerning the setting of PEEP have been less conclusive [37-39], but meta-analyses suggest that “higher PEEP” might benefit patients with moderate/severe acute respiratory distress syndrome (ARDS) [40]. The panel of experts of the “ARDS definition task force”, also recommended the use of “low” PEEP in mild ARDS and “higher PEEP” in moderate to severe ARDS [41]. LUNG SAFE data, on one hand confirm that higher PEEP is associated with improved outcome [35], but on the other also show the reluctance of clinicians to increase PEEP and a tendency to favor raising the inspired oxygen fraction to correct hypoxemia [36]. The use of maneuvers to maximize alveolar recruitment has also been shown to be safe and effective in improving oxygenation when followed by an upward revision of PEEP, but their impact on outcome is unclear [42]. No convincing evidence favors either volume- or pressure-cycled ventilatory modes over the alternative [43]. Because two large randomized controlled trials (RCT) showed no benefit and possible harm from high-frequency oscillatory ventilation [44, 45], its use in ARDS is not recommended.

Certain ventilatory adjuncts may confer important benefits in well selected patients. Prone positioning favors recruitment of dorsal lung regions, improved oxygenation and decreased ventilator induced lung injury. The positive influence of prone positioning on survival from ARDS were recently shown [46, 47] in patients with a PaO<sub>2</sub>/FiO<sub>2</sub> <150 mmHg. The same subset of ARDS patients also benefit from continuous infusion of

neuromuscular blocking agents in the first 48 hours on invasive ventilation, with improved survival and decreased incidence of barotrauma [48]. Although gentle spontaneous efforts may improve the distribution and efficiency of ventilation, vigorous spontaneous breathing, which acts together with airway pressure to increase transpulmonary inspiratory pressure, is discouraged.

Following resolution of acute respiratory failure, guidelines recommend to attempt liberation from mechanical ventilation by performing a spontaneous breathing trial in patients with cardiovascular stability (none or minimal vasopressors), no continuous sedation and a PaO<sub>2</sub>/FiO<sub>2</sub> of  $\geq 150$  mmHg with a PEEP  $\leq 8$  cmH<sub>2</sub>O [49]. While the most commonly used classification divided patients into simple, prolonged and difficult weaning [49], a novel categorization of patients has recently been proposed, based on pragmatic definitions of separation attempts and weaning success [50]. Finally, recently published guidelines, recommend weakly to use inspiratory pressure augmentation in the initial spontaneous breathing trial, and to use protocols to minimize sedation. A strong recommendation was made to use preventative non-invasive ventilation (NIV) for high-risk patients immediately after extubation [51].

## **2/ What have been the major recent advances in the field? (Table 1)**

### ***2.a/ Airways and noninvasive mechanical ventilation***

Useful options and improved interfaces have been developed and deployed. The mechanisms of benefit and indications for HFNC oxygen and conventional NIV in acute hypoxemic non-hypercapnic respiratory failure have been refined in recent years. In one RCT, intubation rates were similar in patients managed with HFNC, NIV administered by facemask and standard oxygen therapy; however, mortality rates were lower with HFNC than with NIV or standard oxygen therapy, and HFNC was associated with improved comfort and less dyspnea [52]. In patients with ARDS randomized to receive NIV through helmets or face masks, the helmet group had lower intubation rates, more

ventilator-free days, shorter ICU stays, and lower mortality [53]. Studies in immunocompromised patients with hypoxemic respiratory failure showed that early HFNC [54] or NIV [55] did not reduce intubation rates, duration of mechanical ventilation, hospital stay, or mortality compared with oxygen therapy alone, but another study using propensity-score matching in similar patients reported that HFNC was associated with lower intubation rates, shorter ICU stays, and lower mortality rates than NIV [56]. Among postoperative patients with hypoxemic respiratory failure following abdominal surgery, use of NIV compared with standard oxygen therapy reduced the risk of tracheal reintubation within 7 days as well as the incidence of nosocomial infection [30].

Indications for non-invasive support have been better defined. Compared with conventional oxygen therapy, post-extubation HFNC reduced reintubation rates in patients at low risk of reintubation [57]. In another study of patients at high risk for reintubation, the same authors reported that although reintubation rates were similar with HFNC and NIV, HFNC was associated with reduced postextubation respiratory failure and shorter ICU stays while causing no major complications [29]. Jaber et al. [14] reported that applying HFNC plus NIV before orotracheal intubation was superior to apneic pre-oxygenation with NIV alone. The bulk of current evidence, therefore, suggests that HFNC is a promising approach for multiple stages and indications in acute respiratory failure.

## ***2.b/ Invasive Mechanical ventilation***

Recent years have seen better appreciation and understanding of the hazards tied to mechanical ventilation. Ventilatory strategies using low end-inspiratory plateau airway pressure, low tidal volume ( $V_T$ ), and high PEEP improve survival in ARDS (figure 1). The driving pressure is the strongest predictor of death in ARDS, although limited epidemiologic information is available. The observational “Lung Safe” study, which assessed how clinicians ventilate ARDS patients, reported that less than two-thirds of

patients received  $V_T \leq 8$  mL/kg of predicted body weight and 82.6% received PEEP < 12 cmH<sub>2</sub>O. Factors associated with improved survival were higher PEEP, lower peak, plateau, and driving pressures, and lower respiratory rate [35]. All these factors, together with  $V_T$ , interact to increase/decrease the mechanical power transferred to lung parenchyma (figure 2) [58]. Recent studies conclude that lung-protective MV principles should be applied regardless of the risk of ARDS. Though intriguing, such recommendations remain controversial at the present time. Furthermore, vigorous spontaneous breathing with assisted mechanical ventilation may increase the risk of lung damage [59]; however, most patients switched to proportional assist ventilation maintain driving pressures within a range currently considered safe during controlled mechanical ventilation [60].

Patient-ventilator asynchronies occur commonly during mechanical ventilation and have been linked statistically to adverse outcomes [61]. Clusters of ineffective inspiratory efforts occurring between prolonged uneventful periods during pressure support and proportional-assist ventilation are associated with longer duration of MV and higher rates of hospital mortality. Clusters appear to predict outcomes better than the proportion of asynchronies occurring during the MV period, suggesting the need to continuously monitor machine response and neural breathing rhythm [62]. Low-dose sedatives may reduce respiratory drive and impair triggering synchrony, although dexmedetomidine causes fewer asynchronies than propofol at similar levels of consciousness [63].

### **3/ What are the common beliefs that have been contradicted by recent trials?**

Over the past few years, some large trials have provided results that were in contradiction with prevailing belief in the fields of airways, NIV and invasive mechanical ventilation. Here, we discuss three specific topics: corticosteroids in acute exacerbations of COPD, NIV for ARF in immunocompromised hosts, and HFOV in ARDS.

In addition to bronchodilators, corticosteroids are recommended during COPD exacerbations to decrease local bronchial inflammation and airway obstruction [64]. Studies supporting corticosteroid treatment in these patients, however, have been conducted outside the ICU or in patients with disease of mild-to-moderate severity who do not require mechanical ventilation. In addition, previous meta-analyses indicate that corticosteroids, while decreasing treatment failure rate and the length of hospital stay, have little effect on mortality [65]. Two RCTs were performed in patients with severe exacerbations requiring ICU admission. Both studies were underpowered. The first one [66] showed that intravenous methylprednisolone (0.5 mg/kg) was associated with a reduction in the duration of mechanical ventilation (3 vs 4 days) and in the NIV failure rate (0% vs 37%). On the contrary, the second trial [67] failed to demonstrate any beneficial effect of oral prednisone (1 mg/kg) on ICU mortality, duration of mechanical ventilation, and ICU length of stay, but did indicate that steroids increased the number of hyperglycemic episodes. A meta-analysis [68], pooling studies performed in non-critically ill and critically ill patients, showed benefit from corticosteroids on treatment success rate in non-critically ill patients, whereas there was no benefit in critically ill patients.

NIV has been proven effective to reduce intubation and mortality rates, mainly in acute in chronic respiratory failure and in acute cardiogenic pulmonary edema and, to a lesser extent, in *de novo* ARF [69]. In the early 2000's, two single-center studies reported clear benefit from NIV for ARF in immunocompromised hosts, both in patients with hematological diseases [70] and in patients with solid organ transplants [71]. These results had a strong influence on guidelines and on clinical practice. Recently, a large multicenter trial was performed [55] in patients with various causes of immunosuppression (mostly hematologic malignancies and solid tumors) to compare the effects of NIV versus oxygen alone on clinical outcomes. In this study, NIV did not reduce intubation rate, mortality or length of stay. The generally improved prognosis of immunocompromised patients treated in the ICU may help to explain these findings. Although these results do not contraindicate NIV in immunocompromised patients with ARF, they suggest that the benefit of NIV in this population is less dramatic than previously observed.

HFOV delivers small VT at high respiratory rates and at high mean airway pressure, with the aim to protect the lungs from overdistension and derecruitment [72]. The idea behind this approach is that targeting an “open lung” and ventilating with very low tidal volumes may enhance lung protection as compared to conventional strategies. Preliminary data in ARDS patients were encouraging [73]. Two recent studies, however, have contradicted this belief. The OSCILLATE trial [74] was prematurely aborted after 548 patients had been randomized because of excess hospital mortality in the HFOV group as compared to the control group treated with conventional ventilation (47% vs 35%,  $p < 0.005$ ). Doses of sedatives were higher and there was a trend for more barotrauma in the HFOV group (18% vs 13%). Finally, mean airway pressure was higher with HFOV compared to controls (31 cmH<sub>2</sub>O vs 24 cmH<sub>2</sub>O), a characteristic that likely caused hemodynamic compromise. (Indeed HFOV patients received vasoactive/inotropic drugs more frequently and in higher doses.) Together, these shortcomings may explain the increased mortality. The OSCAR trial [75], mainly conducted in centers with limited or no experience with the HFOV technique and treating patients with ARDS of lower severity, did not show differences in 30-days mortality between HFOV and usual care (42% vs. 41%). Why HFOV did not work in these trials potentially can be attributed to numerous factors. One is ineffective “recruitment” (as much as 24% of the ARDS lung remains non-recruitable even at pressures of 45 cm H<sub>2</sub>O [76]). High mean airway pressures resulted in sustained overdistension of healthy lung parenchyma, afterloading the right ventricle and impeding venous return by elevating intrathoracic pressure. Other possibilities include the high amount of “energy” dissipated in heterogeneous ARDS lungs (due to the extremely high respiratory rates during HFOV), and the difficulties presented by managing a ventilator mode with unusual settings and lack of conventional alarms. These data remind us that providing optimal ventilator settings in ARDS is not an easy task and suggest that conventional treatment (with moderate to high PEEP levels, low tidal volumes and moderate driving airway pressures, as happened in the OSCILLATE usual care group) is currently a reasonable approach to lung protection. Today one could argue that prone position would be strongly recommended in this scenario. Tomorrow, one could speculate that prone position will be implemented with extracorporeal gas exchange

techniques to further improve lung protection while maintaining adequate gas exchange and minimizing the physical and hemodynamic impact of mechanical ventilation.

#### **4/ What are remaining areas of uncertainty?**

Uncertainty might, in the area of medicine and research, describe a state in which the medical community is not able to provide clear evidence that a treatment, intervention, or the knowledge base upon which they rest, is adequately proven. Such uncertainty might pertain to established beliefs and practices, as well as to those we newly propose or discover and try to apply. In the field of intensive care medicine the primacy of “nihil nocere” and superiority of treatment outcome should guide the quest for certainty. In respiratory medicine, a field in which more uncertainties and beliefs than certainties and proofs might exist, the areas selected by the authors for discussion are therefore biased and subjective. In general, however, we believe that most uncertainties in the field of respiratory support arise as to how to individually tailor treatment in such a way that a patient has the best possible chance to survive at the lowest human cost. Selected examples of our current uncertainties are provided regarding artificial airways, invasive and non-invasive ventilation.

#### **Artificial Airways**

Development and wide spread use of percutaneous tracheostomy (PDT) has led to recent increases in the numbers of tracheostomies performed and of the published studies dealing with this procedure [76-78]. The belief that early tracheostomy might reduce the rate of pneumonias and consequently improve outcome for invasively ventilated patients has been contradicted. In contrast, it has been demonstrated that some patients treated with an “early” tracheostomy receive this intervention unnecessarily, imposing additional risk without benefit for the individual patient [79]. Long term outcome of tracheostomized patients is extremely poor, raising the troubling question of whether the performance of a tracheostomy often acts more as a tool for directing patients in the medical system than as an indicated measure for the individual



patient [80, 81]. The optimal airway and care for the individual patient in need of respiratory support remains an open issue that definitively requires a better answer than we can give today.

### **Natural Airways**

Corticosteroids are recommended during COPD exacerbations to decrease local bronchial inflammation and airway obstruction [64]. Yet optimal dosing and timing remain unclear for the gravely ill patient; studies supporting corticosteroid use have not been directed toward those requiring invasive mechanical ventilation. Indeed, a recent meta-analysis [68], indicated benefit of corticosteroids on treatment success rate in non-critically ill patients, whereas no consistent benefit accrued in critically ill patients. Given such inconsistent results, whether steroids should be used in which doses and for what duration remain open-ended questions.

### **Invasive Mechanical ventilation**

Reduction or avoidance of ventilator-induced injury (VILI) has become a leading focus of respiratory support [80, 82]. Success and assertiveness of this directive has two primary bases: first, a plausible theory in which the key determinants of mechanical ventilation (pressures, volume, PEEP) play defined and reproducible roles, and second, the demonstration by a large RCT that limiting one of the determinants (tidal volume: TV) reduces mortality in mechanically ventilated patients [33]. The VT-associated delta ('driving') pressure has been shown predictive for mortality in a retrospective analysis [34]. However, factors other than the characteristics of the individual tidal cycle determine the occurrence and severity of VILI. Recently, it was suggested that an inclusive single variable, the mechanical power, might summarize all mechanical stressors shown experimentally and by observation to injure the lungs during mechanical ventilation [58]. Uncertainty remains regarding whether mechanical power, though measurable, should help guide machine settings. Moreover in weighing relative risks and benefits of medications and procedures for the individual, the value and timing of implementing neuromuscular paralysis or extracorporeal gas exchange so as to reduce transmission of power to the lungs remains undetermined. Although

extracorporeal gas exchange (ECMO) techniques are still undergoing safety testing and refinement, one could speculate that they might be implemented together with prone positioning to further improve lung protection and maintain adequate gas exchange while minimizing the demands that intensify the physical and hemodynamic impacts of mechanical ventilation.

HFOV delivers small VT at high respiratory rates and high mean airway pressures, with the aim to protect the lungs from tidal over-distension and de-recruitment [72]. Targeting an “open lung” and ventilating with very low tidal volumes theoretically should enhance lung protection as compared to conventional strategies. Whether HFOV holds value for selected patients or should be never used remains open to question.

### **Noninvasive ventilation (NIV)**

The clear role of NIV in avoiding an artificial airway for COPD and cardiogenic pulmonary edema [83] has extended its use to states, diseases and entities in which beneficial effects are questionable [84, 85]. NIV uses a different interface but does, as MV, transmit mechanical power to the lungs and can evoke asynchrony. Moreover, the pressure targeted nature of NIV leave trans-pulmonary pressure and tidal volume unregulated. Such drawbacks of NIV, as well as its relative limitations and advantages for treating severe acute respiratory support, raise the question of which role extracorporeal gas exchange can, will and should play in this setting [86, 87].

**5/ What the international group of experts recommend as the top 10 studies/trials to be done in the next 10 years and what are expected outcomes/results of these trials.**

### **Recommended Studies for the Next Decade**

Important lessons have been learned in constructing the research base for present-day management of ARF. Foremost among these is that the populations we treat are diverse and that the definitions with which we identify our patients and select subjects for trials are imprecise. Moreover, complexity of the syndromes we confront as well as interactions among the co-interventions we apply weaken traditional reductionist approaches that focus on single (sometimes inappropriate) target variables while too often ignoring important confounders and applying patient inclusion and exclusion criteria of questionable validity. Understanding the etiologic cause of acute illness and potential consequences of intervention should ideally precede the implementation of such symptomatic treatments as mechanical ventilation and/or hemodynamic optimization. Heterogeneity, non-individualized dosing, and uncertain duration of application bedevil standardized responses and degrade the power of the study to discriminate between treatment effects. In this ICU context of patient diversity, imprecise definitions and multiple dynamically interactive variables reductionist thinking takes us only so far; so-called 'emergent' phenomena often yield surprising and even misleading results [88]. Consequently, admirable efforts have frequently given rise to costly, slowly completed and inconclusive RCT studies, even as they generated interesting questions and observations that helped refocus the process. Innovative approaches, such as the adaptive trial designs shown helpful in other medical disciplines [89], will likely improve and expedite RCT execution. Yet, whatever the contribution of these newer study architectures and analytic methods might be, direct application of population-based results to the individual are liable to remain problematic in such a complex, ill defined and heterogeneous setting for all but the most obvious

questions of interest; therefore, the recent emphasis on precision medicine and personalization of care is especially relevant to our currently syndrome-based discipline [90].

Treatment timing and intensity as well as condition severity often determine the value or peril of the tested intervention. Several important examples pertain to ventilation: The level of PEEP applied to a given patient may help or harm, depending on recruitability, driving pressure, and pressure baseline [34]. Paralytics maybe life preserving during the earliest stage of severe ARDS [48] but lead to disability and diaphragmatic weakness (VIDD) if unnecessarily sustained [91]. Prone positioning, a key adjunct to ventilating severe ARDS, is a potentially life-saving intervention [92] whose utility is stage, duration, and perhaps recruitability dependent [93, 94].

Focusing on the static characteristics of the individual tidal cycle (i.e., PEEP, plateau and VT) is clearly a restrictive approach toward intervening in a complex VILI process that has been shown by laboratory experimentation to be strongly influenced by cycling frequency, flow rate, flow contour, and vascular pressure [95]. Therefore, future studies may need to take into account various dynamic as well as static mechanical elements as well as non-mechanical co-factors that modulate the straining effect.

Investigators, educators and clinicians tend to skip logical steps and unwisely extrapolate as we hasten to apply the results of the latest RCT or meta-analyses that indicate what to do without clear biologic plausibility. It is sobering that uncorroborated RCTs sometimes produce unanticipated but convincing results that have strong but temporary impact as they are overturned by subsequent contradictory RCTs or meta-analyses. While there is an unquestioned association between high-pressure ventilation strategies and mortality, for example the ARMA study [33], we do not have incontrovertible evidence that a less favored approach actually retards lung healing or inflicts VILI. If it does, how do such consequences for lung functioning lead to death? Adequate gas exchange, the lung's primary function, can nearly always be accomplished and maintained. Mechanistic linkage is even less clear for adverse outcomes associated with patient-ventilator asynchrony [61] and for the putative benefits of intraoperative lung protection applied to patients without overt lung disease

so as to avoid undesired outcomes that occur days later [96]. The wisdom of attempting to apply population-based data to a specific individual without understanding the circumstances and mechanisms that drove the study results can be misguided. In the field of respiratory support it is reasonable to question whether RCTs should be undertaken without a design underpinned by a strong mechanistic rationale [97]. Prediction of expected outcomes from clinical trials is hazardous unless underpinned by such a foundation or by an already convincing body of observational studies, biological plausibility and clinical experience.

In the near future, progress toward improved RCTs maybe aided by recently developed tools that help in patient selection, personalization, and study conduct (Table 2) [90]. Such innovations include “big data” analysis to determine key interactive variables and to refine appropriate phenotypes (Figure 3) [98], biomarkers of individual responsiveness and hazard (proteomics, metabolomics, etc.), whole genome profiling [99] and innovative trial designs (e.g, the aforementioned adaptive approach) [89] and analytics (e.g., recursive partitioning). These newer tools may allow us eventually to address vitally important but understudied questions relevant to respiratory support, such as innate adaptability and resilience to critical illness, respiratory muscle conditioning, VIDD avoidance [82] and rehabilitation [100]. The causative impact of current ventilator approaches on chronic critical illness is likely to be profound, but with few exceptions ideal management approaches currently remain undefined. It is unclear, for example whether our traditional focus upon achieving stability remains in the best interest of the patient after the initial period of rescue has passed. Maintaining normal physiologic targets, e.g., for oxygen saturation, may obligate use of noxious therapies [101]. Could it be that we need to monitor patient progress and capability more closely to encourage reconditioning at an earlier stage of illness, rather than to support too much for too long? [102]

Unlike laboratory investigations, RCTs seldom define disease mechanisms but can potentially contribute to our understanding of them. Conversely, comprehending underlying mechanisms and taking thoughtful account of solid experimental and observational data is often key to developing effective trial design. Although the number

of unanswered and important questions is boundless, intriguing recent observations and RCT results help set the near-term direction for our research efforts (Table 3). Over the next decade, important areas of investigation, addressed either in the laboratory or at the bedside, should include defining the roles of spontaneous breathing efforts in preventing or exacerbating VILI [59], discovering the true basis for the association of asynchrony and adverse patient outcome [61, 103], and determining the contributions of flow contour, breathing pattern and minute ventilation to the hazard safety that accrues to mechanical ventilation [95]. The vexing question of how best to set PEEP may eventually yield to the mechanism-defined design of the RCT that explores it. The need to record trans-pulmonary pressure for PEEP selection and lung strain assessment should be settled [104]. Whether and how ventilator support itself encourages chronic critical illness urgently deserves attention [105]. Both basic and clinical studies need to be performed in order to test competing hypotheses regarding observable and modifiable variables that may act as the proximate mechanical impetus to VILI, such as transpulmonary driving pressure [104, 106], power delivery [58], and strain intensity [95]. Further studies are needed to confirm the *causative* influence of driving pressure and the value of pharmacoparalysis, as well as to resolve questions regarding their mechanisms of harm and benefit. Finally, the full potential for extracorporeal techniques coupled to NIV or HFNC to avert the need for intubation should be explored as these newer technologies are refined.

## **Conclusion**

Effects of interventions depend on timing and individual predispositions to response and hazard [18, 19]. Well executed clinical trials designed without appropriate selection criteria in mind may be relevant to the population studied but are open to misinterpretation and misapplication in practice. Powerful new tools for conducting sophisticated RCTS and implementing precise, personalized medicine, such as 'big data' analysis, whole genome testing, and closed loop decision support hold immense

potential to reshape and reform both our research efforts and our daily practice. Whatever the sophistication of decision supports, however, the ICU practitioner, primed by guidance of the research base and alert to the integrating feedback that only the individual patient's bedside response can provide, will remain instrumental to the delivery of high quality respiratory system support.

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**Table 1. Advances of the Past Decade in the Field of Ventilation**

<b>Preoxygenation, intubation, airways management</b>
- Optimization of preoxygenation using HFNC oxygen and/or NIV - Use of videolaryngoscope devices
<b>Healthy lungs (or Non-ARDS)</b>
- Prevention ARDS occurrence - Improved operative and peri-operative ventilator management
<b>ARDS</b>
- Early prone positioning for ARDS - Selective use of muscle relaxants for oxygenation failure - Evolution & deployment of extracorporeal gas exchange - Esophageal pressure monitoring for selected clinical applications - Re-focusing VILI on driving pressure and energetics of ventilation - Widespread awareness of need for lung protection
<b>Weaning-extubation, sedation</b>
- Asynchrony detection, prioritization, and therapy - Extension of esophageal pressure monitoring to clinical applications - Avoidance of excessive sedation and protracted controlled ventilation - Recognition and prevention of ventilator induced diaphragm dysfunction (VIDD)
<b>NIV and Oxygenation</b>
- Development of improved NIV interfaces and HFNC - Dedicated NIV software and ventilators

**Abbreviations:** HFNC: High-Flow Nasal Cannulae; ARDS: acute respiratory distress syndrome; NIV: noninvasive ventilation



**Table 2. Tools for Personalizing and Improving Efficiency of Clinical Studies**

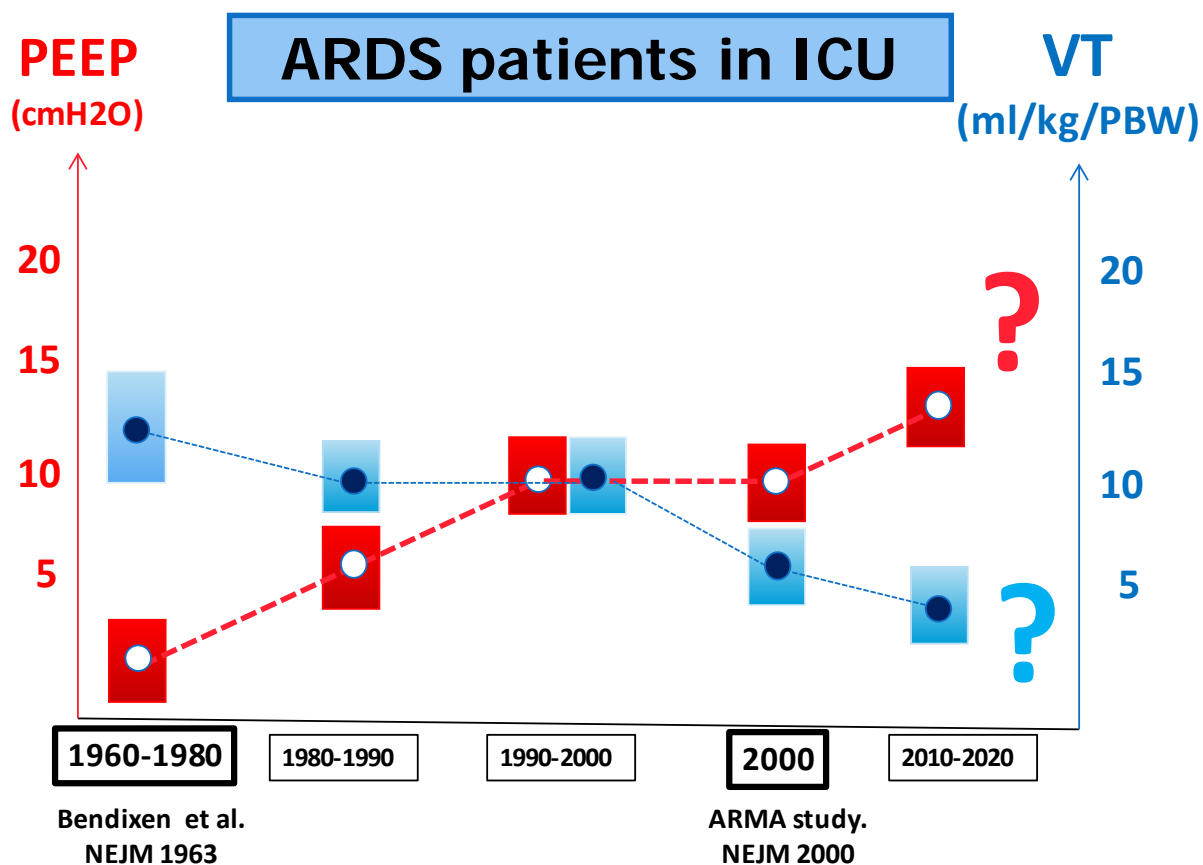
• Detailed Phenotyping
• Whole Genome Characterization
• “Big Data” Analysis
• Quantitative Biomarkers
• Mechanism-Driven Protocols
• Innovative Trial Designs and Analyses
• Education – simulation

**Table 3. Suggested Study Topics For the Next Decade**

<b>Study</b>	<b>Topic Area</b>
1	<ul style="list-style-type: none"> <li>- Value and limitations of transpulmonary pressure</li> <li>- Energetics of ventilation: Roles of PEEP, plateau, driving pressure, power</li> <li>- Relative hazards of increased PEEP vs. increased FiO<sub>2</sub></li> <li>- Imaging guided ventilatory management (CT scan at bedside and/or ultrasound)</li> </ul>
2	<ul style="list-style-type: none"> <li>- Indications and contraindications for spontaneous breathing</li> <li>- Timing the transition from full to partial ventilator support</li> </ul>
3	<ul style="list-style-type: none"> <li>- Mechanisms of benefit from pharmaco-paralytic agents</li> <li>- Evaluation new specific drugs</li> </ul>
4	<ul style="list-style-type: none"> <li>- Prevention and exacerbation of VIDD</li> <li>- Impact of ventilatory pattern, monotony and variation</li> <li>- Prevention ARDS occurrence in healthy lung patients</li> </ul>
5	<ul style="list-style-type: none"> <li>- When and who should receive lung protective ventilation?</li> </ul>
6	<ul style="list-style-type: none"> <li>- Hazards and mechanisms of synchrony</li> </ul>
7	<ul style="list-style-type: none"> <li>- Extra-pulmonary gas exchange in avoiding and weaning from invasive ventilation</li> </ul>
8	<ul style="list-style-type: none"> <li>- Defining the relative values of NIV and high flow nasal O<sub>2</sub></li> </ul>
9	<ul style="list-style-type: none"> <li>- Impact of monitoring lung biomarkers in selected populations</li> </ul>
10	<ul style="list-style-type: none"> <li>- Impact of auto-adjusting ventilatory modes</li> </ul>

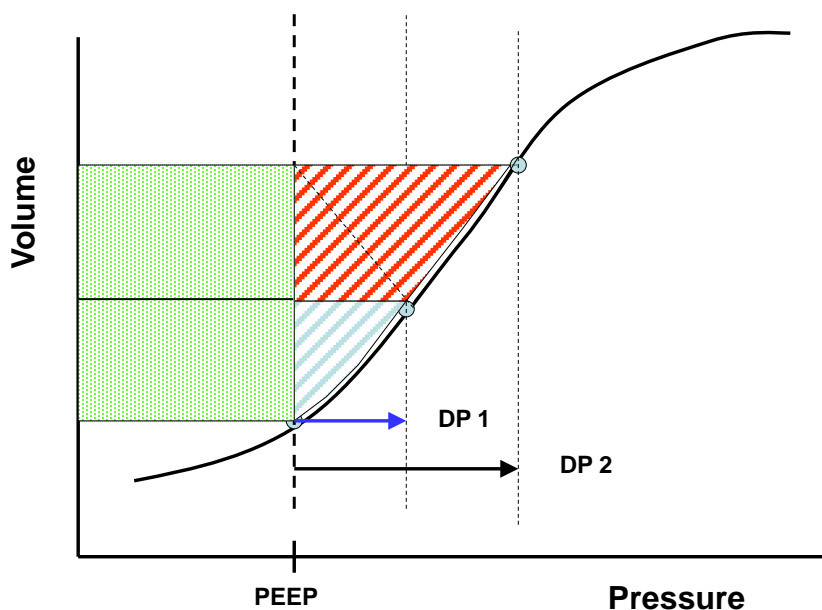
Figure 1.

Evolution of Tidal Volume (VT) expressed in predicted body weight (PBW) and Positive End Expiratory Pressure (PEEP) in cmH<sub>2</sub>O in the last 50 years in ARDS patients.



**Figure 2.**

Schematic relationship depicting the non-resistive components of the equation of motion that determine the energy delivered to the lung during the tidal breath.



Total non-resistive ('quasi-elastic') energy imparted per cycle is the sum of the pressure-volume areas enclosed by PEEP (green shading), and by the tidal driving pressures associated with a small tidal volume (DP 1) and with a tidal volume twice as large (DP 2). Note that the tidal elastic energy area for the larger tidal volume (sum of red and blue areas) is more than twice that of the smaller tidal volume (blue hatched area). The inspiratory power exerted by the machine on the lung parenchyma (energy units per minute) is the product of cycling frequency and the respective colored energy areas. A portion of the total potential energy stored during inspiration is recovered during expiration. [Modified from Marini & Jaber, *Int Care Med* 2016 [95]]

**Figure 3**

'Big database' collection in an ICU environment. Phenotypes determined from analyses of such data could theoretically facilitate personalization of care and improve selection of subjects for research trials. (From Ghassemi [98])

