Acute respiratory distress syndrome since 1967 and still going strong

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Since its formal description as an entity in 1967, acute respiratory distress syndrome (ARDS) has been a constant and unwelcome companion to the critical care physician. Despite significant advances in ventilation practices, there has been little change in mortality in the last two decades. This trend may in part be due to ARDS having significant heterogeneity with physiological and pathological phenotypes that are fundamentally different and which current definitions do not discriminate between. Without clinical trials taking this into consideration, and the application of precision therapies to a targeted phenotype, progress with this syndrome will remain elusive. This narrative explores some of the current concepts relating to ARDS, and includes a discussion around the pairing of airway pressure release ventilation (APRV) with a specific phenotype as an example of "phenotype-specific treatment" based on physiological suitability and emerging evidence that supports the concept.

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Introduction

Acute respiratory distress syndrome (ARDS) is a familiar and devastating inflammatory pulmonary condition, initiated by myriad insults, both local and systemic. Despite extensive research into treatment strategies, it has a frustratingly high mortality, relatively unchanged in the last two decades, and sadly remains underrecognised and undertreated.[1] As the name implies, ARDS is a syndrome rather than a distinctive disease entity, with marked aetiological and pathophysiological heterogeneity often not appreciated in the phenotype that presents clinically.[1,2] This is a fact that has been evident since Ashbaugh published his seminal work in 1967.[3]

Definition

While a number of definitions for ARDS have evolved over time, the current syndromic Berlin definition does little to acknowledge this heterogeneity, with the diagnosis based on: "the presence of new or evolving bilateral lung infiltrates within 7 days of the defined insult, resulting in altered oxygenation as measured by the ratio of arterial partial pressure of oxygen to the inspired oxygen fraction (PaO_2: FiO_2 ratio) less than 300 mmHg with application of at least 5 cmH_2O positive end expiratory pressure (PEEP). All the above should not be completely explained by cardiogenic pulmonary oedema".[4] It is unfortunate that this complex entity has been reduced to such a restrictive definition, providing only prognostic value with no diagnostic or therapeutic direction. Classification of patients using this definition will also tend to over-diagnose ARDS based on post-mortem specimen review and does not discriminate between ARDS and ARDS-mimics.[2]

What is increasingly evident is that there is no "typical" or "classic" ARDS.

Redefining acute respiratory distress syndrome

Histopathologically, it is recognised that early on, there are consistent findings of diffuse alveolar damage (DAD): alveolar epithelial and vascular endothelial injury, alveolar haemorrhage, leukocyte infiltration and a protein rich exudate within the alveoli; however, it is the very heterogenous and complex interaction between aetiological, biochemical and cellular pathways, influenced by individual patient biology, which dictates the clinical presentation and determines treatment response and outcome. Previous attempts at targeting these interactions have been disappointing due in part to this heterogeneity and the lack of individualised therapy during validation in clinical trials.[2,5]

Continually using these criteria for randomisation into interventional trials for ARDS, with its inability to discriminate, results in a very heterogenous population being subjected to homogenised therapies that are neither specific to, nor beneficial (and in some cases possibly harmful) to the differing phenotypes.[6] It is no surprise then that time and again, results show very modest or absent treatment effects across the study cohorts with trial-defined interventions. Acknowledgement of this heterogeneity and the implications for treatment within study populations has, in fact, given rise to the term "Heterogeneity of treatment effect" or HTE. While a treatment effect may be seen in one sub phenotype, it may not in another.[2]

This has been highlighted by the current SARS-CoV-2 pandemic, with continued debate raging over the varied presentations of COVID-19 pneumonia, its differing phenotypes and response to therapies. Conflicts around the "H type, L type, non-invasive

ventilation vs high flow nasal oxygen vs invasive ventilation, prone positioning, the hyperinflammatory phase, and whether or not this is really ARDS", exemplify the quandary.[7] This is a prime example of where the interplay between inciting pathogen, host biology, and the resulting pathophysiological presentation has been recognised and individualised treatment strategies have been directed to target each of the three contributing elements.

In the age of precision medicine, persistence with treating ARDS as a single entity is completely contrary.

Towards ARDS phenotypes

With recent, and past evidence, pointing to this heterogeneity, there is a strong push to individualise and personalise therapy.[5-9] This can only occur if we define that which we are treating. The European Respiratory Society proposals encourage recognition of the *Aetiological, Biological and Physiological* contributions to ARDS.[2,6] Research agendas incorporating these three tenets will allow interrogation of the heterogeneity within each of these realms and their contribution to the patients' presentation, with the intent of elucidating various ARDS sub-phenotypes. Focusing investigation on these sub, and eventually endo-types, will allow the recognition of "treatable traits", and hence more targeted therapy.[2,5,6,8,10]

While it is important for research purposes to consider these three elements separately, there is in reality a very complex interplay between them. The inciting pathogenic process is intimately linked to the host's biological response which in turn will impact on the severity of the disease. Importantly the same insult does not result in the same disease severity in all patients, and differing insults do not always result in the same disease presentation. Added to this, what we see clinically and physiologically is directly linked to the host response to the inciting event. This is the fundamental principle underlying the argument that treatment should be phenotype aware.

While the argument is scientifically sound and biologically and clinically relevant, the identification of defined phenotypes with specific treatable traits is still ongoing. However, there has been significant progress, and fascinating insights have been gained into potential phenotypes and there have been early signals of benefit with selected treatment. Identification of hyper and hypo-inflammatory ARDS phenotypes, with differing biomarker and mortality profiles, along with specific treatment effects have been identified. The hyperinflammatory phenotype appears to be more PEEP responsive, and an open lung ventilatory approach more beneficial in this cohort.[2,5,10-15] Similarly, from a pathophysiological standpoint, there is defined benefit in phenotypic presentations with lower PaO_2: FiO_2 ratios and non-focal (versus focal) ARDS in treatment response to PEEP, prone positioning and use of neuromuscular blockade.[16,17]

There is no one size fits all!

Since therapeutic trials have failed to show significant progress with regard to mortality reduction in ARDS, the mainstay of management remains supportive and relies heavily on ventilatory support modalities.

The mid-1970s saw the arrival of efficient mechanical ventilators with electronic servo controllers, allowing flow manipulation, new modes and the ability to provide PEEP. Fortuitously all of this occurred not long after Ashbaugh published his paper on ARDS in 1967. This technological advance proved to be revolutionary. It wasn't until the late 80s and early 90s, however, that there was acceptance of the fact that the ventilator was both friend and foe, and that mechanical ventilation could, in fact, produce significant harm capable of both inciting and amplifying lung injury and the concept of ventilator-induced lung injury (VILI)
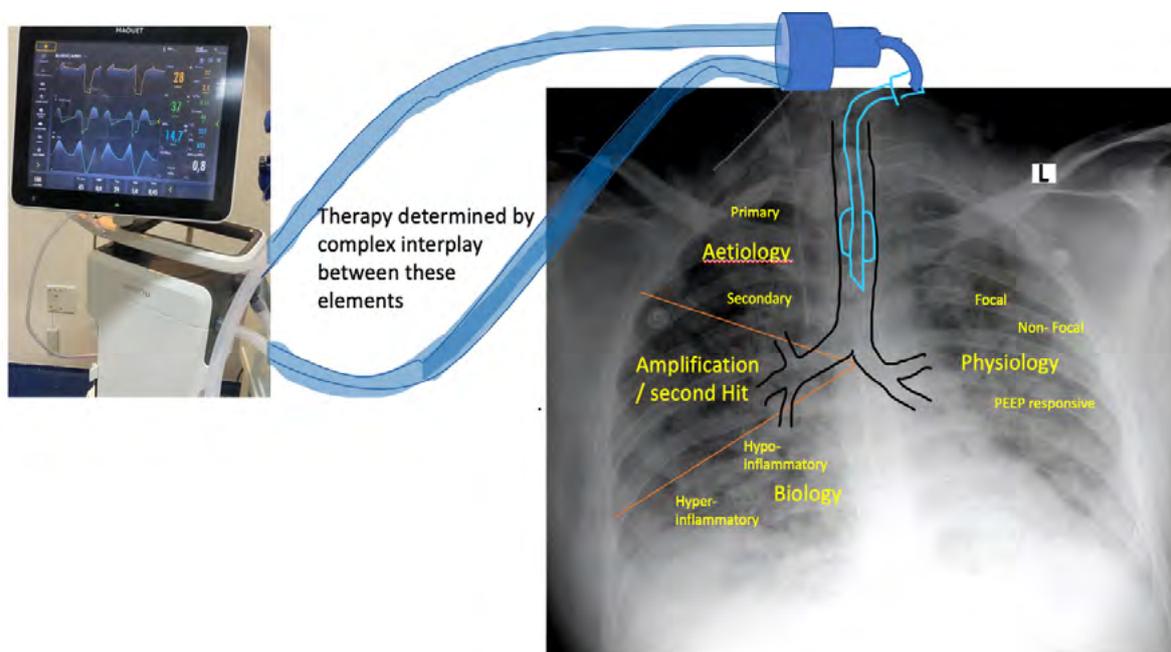

Figure 1: Infographic-interplay between aetiology, biology and physiology in ARDS

was born.[18] The years that followed saw significant interest in this topic, with introduction of the concepts of "lung protective ventilation" and "low tidal volume ventilation" (Amato and Brochard independently in 1998) and finally was thrust into the limelight with the publication of the Acute Respiratory Distress Syndrome Network paper in 2000.[19-21] This has led to the almost universal adoption of the low tidal volume (LTV) ventilation method.

Concepts that have evolved subsequently include Gattinoni's "baby lung", Amato's "driving pressure", how much PEEP is enough, recruitment manoeuvers, "the open lung concept" and more recently "mechanical power".[22-24] While all these concepts are highly valid, the lack of improvement in survival in the recent past, highlighted again by the LUNG SAFE investigators, is instructive.[1]

What every one of these concepts has in common, is that the ventilator exerts a force on the lung, creating stress and strain in an already compromised system. The magnitude of the stress and strain within the lung is, however, not uniform and is heavily influenced by the distribution of the affected tissue, and the biological milieu of the host.

The lung is an exceptional organ. A collection of approximately 400–600 million alveoli each a few microns thick, linked by an intricate network of airways, surrounded by a capillary network that accepts the entire cardiac output and wrapped in the pleura somewhat like two wizard's hats on either side of the heart. Its function is primarily to facilitate gas exchange, but in order to do this, alveolar structures must withstand significant mechanical forces throughout life with estimations at as high as 10^9 strain cycles.[25] By materials engineering standards, this would be considered impressive and indicating that structurally the lung is well designed to mitigate these forces. Structural integrity is ensured by two systems; a fibroelastic network of axial, peripheral and septal fibres referred to as tensegrity (most effective at high lung volumes), and the surfactant system (effective at low lung volumes). Both of these systems along with alveolar shape, very effectively reduce alveolar stress.

Alveolar shape, not spherical as previously thought, has flattened walls shared with adjacent alveoli conferring a polygonal configuration. These adjacent alveoli also communicate via the pores of Kohn. This is important as the alveoli are thus interdependent, and as such, collapse in one area results in increased wall tension and stress being transmitted to adjacent areas. Within collapsed areas, alveolar reopening reduces stress in adjacent alveoli and facilitates recruitment in a domino effect. Despite in-depth knowledge of lung structure, the true micromechanics at an alveolar level remain elusive due to the difficulty of visualising and examining their behaviour in vivo.[25] Much of the work looking at alveolar stress and strain at the extremes of volume and pressure is thus based on surrogates and computer modeling. Our best guesses then are derived from surrogate inflammatory markers, and histopathological specimens from both animal trials and patient necropsy.

Any force applied across the lung is distributed across all areas that are then open. The greater the surface area across which pressure is distributed, the lower the resultant stress and vice versa. This is relevant when considering force application and resultant stress with mechanical ventilation.

Forces experienced by the lung will also be in proportion to regional elastance since this is not homogeneous, even in healthy states. Application of positive pressure will thus likely result in regional over- and under-distention, depending on local elastance.

So how to ventilate?

Positive pressure ventilation (PPV) in patients with ARDS is then not a simple matter. Consider having to account for differing phenotypes with wide variation in pulmonary mechanics and non-uniform distribution of diseased/affected tissue with no real-time method of assessing the micromechanics of the alveolus to allow feedback. This is a familiar problem and is similar to the difficulties encountered when managing haemodynamics with access only to macrocirculatory parameters rather than having a window on the microcirculation. During PPV, we conscientiously monitor macro-ventilatory variables such as pressure, flow, dynamic and static compliance etc., without necessarily knowing the impact at a micro-mechanical or micro-ventilatory level.

There is a vast body of work published on how we should ventilate ARDS, and what adjuncts can be used. There is also disagreement between various key opinion leaders in the field. The purpose here is not to critique or rehash these sources and recommendations, but rather to introduce some inquisitive and scientific thinking. Can mechanical ventilation be personalised? Considering that this concept is relatively new, it is not yet accompanied by a vast amount of published evidence. However, there are some very encouraging signals to be found in published works, both recent and past.

A recent randomised control trial (RCT) looking at personalised ventilation vs current standard of care aimed at the pulmonary ARDS morphology was based on the above premise that there is HTE between diffuse and focal disease. While no mortality benefit was demonstrated in the intention to treat analysis between the two arms, there was a 21% misclassification of patients with focal vs diffuse disease. Post hoc analysis of data excluding these misclassified patients did show lower mortality in the personalised group. The patients who were misclassified and received inappropriate treatment according to the trial protocol, also had significantly higher mortality.[5] So alignment of ventilation strategy with phenotype may indeed show some benefit.

To explore this further, consider the airway pressure release ventilation (APRV) ventilatory mode. While APRV has been utilised since the late 1980s, there is a paucity of work on this mode in comparison to mainstream ventilation practice involving LTV and lung protective ventilation. It has also for

much of this time been considered only as a rescue mode. This has likely led to less acceptance, lower uptake and use late in the disease process when mortality is not likely to be easily altered.

Work from Maryland's R Adams Cowley Shock Trauma Centre has provided some very interesting insights. While admittedly single centre data, from a relatively homogeneous patient cohort (severely injured trauma patients), this group has continuous experience with APRV dating back to the 90s. Initially used as a rescue mode, observations by this group have been central to their changing practice and the work that followed with fascinating results. Having observed that many of their patients showed development or evolution of ARDS within the first 24 to 36 hours after admission, they questioned whether changing ventilator strategies early may impact outcome. This led to early initiation of APRV with a consequent reduction in the incidence of ARDS and mortality in their patient cohort.[26] A striking animal-based model and a later systematic review of 66 199 trauma patients in North America served to reinforce these findings.[27-29]

In a porcine model with induced sepsis via a two-hit method, APRV was compared to LTV, and both of those to a sham model with no sepsis ventilated at 10 ml/kg body weight. Both the LTV and APRV modes were only initiated once the porcine model had met the criteria for ARDS. While the APRV group performed significantly better than the LTV group with regard to oxygenation, haemodynamics and reduced interleukin 6 (IL-6) levels, the postmortem macroscopic specimens and histology of the lungs were the most impressive aspect of the study. Macroscopically the lungs from the APRV group looked well inflated and pink, while the other two showed significant congestion and collapse. On microscopic evaluation the following was evident:

"*APRV resulted in significantly reduced fibrinous exudates, capillary congestion, leukocyte infiltration, and alveolar wall thickness (p < 0.05 vs LTV and sham;). Sham animals exhibited more severe histological injury than LTV and APRV animals in the categories of atelectasis, fibrin deposits, leukocyte infiltration, and intra-alveolar haemorrhage.*"[29]

This reinforced their theory that tailored ventilation in the form of APRV could retard the development of ARDS in the inflammatory response type ARDS when initiated early.[27]

This trend was reinforced by the large retrospective review of outcomes of 66 199 trauma patients in Level 1 centres across North America, confirming that the early application of APRV in a single centre was accompanied by a significant reduction in ARDS incidence (14% vs 1.3%) and in hospital mortality (14.1% vs 3.9%). The patients in this study compared well with patients in other centres in terms of injury severity and the lung injury prediction score.[28]

While it is important to acknowledge that there are limitations when analysing retrospective data, what stands out is the homogeneity of the group as a whole (all ARDS following severe trauma) and managed in a system in which standards of care are otherwise similar. Despite this, an astonishing reduction in the incidence of ARDS in a single centre with a single difference in practice is demonstrated. In this case, selecting a specific therapy in a more homogeneous group may have identified a treatable trait.

In a more recent RCT, Zhou and colleagues, randomised 138 patients with ARDS, ventilated for less than 48 hours to either APRV or LTV according to the ARDSnet protocol with the primary outcome being ventilator free days at day 28. ARDS aetiologies were broad, and ventilation was not individualised based on these. There were, however, some interesting findings. The primary outcome, earlier extubation and shorter ICU duration of stay was met, with a significant difference in favour of the APRV group. Physiological variables of oxygenation, improved compliance, reduced need for sedation and lower vasopressor use also favoured the APRV group. While there was no statistically significant difference seen in ICU mortality between the two groups, as the study was not powered for this, there was a trend in favour of the APRV group.[9]

While there is already critique of the above study (there is no perfect trial… yet) and there will always be proponents and opponents of individual therapies, the work of the investigators sends a strong signal.

In its most simplistic form, APRV is a modification of continuous positive airway pressure (CPAP) with time cycled expiratory releases to a lower pressure. The higher pressure is designated pressure high (P high) and the lower pressure, pressure low (P low). Spontaneous breathing can also occur comfortably, independent of the ventilator cycle. The time cycled pressure releases to P low, are set to occur for very brief periods of time, the time low (T low) which is usually from 0.35–0.8 seconds in adult patients, (may be as short as 0.2s) depending on lung elastance. The rationale for this is twofold. Firstly, to allow release breaths to unload some of the metabolic burden of breathing at high CPAP pressures (CO_2 elimination) and secondly, the very short release time is designed to prevent de-recruitment and airway closure during this phase. The end-expiratory lung volume that results can thus be manipulated and is set based on the duration of the T low and with assistance of the expiratory flow pattern. Breath termination should be set to occur between 50% and 75% of peak expiratory flow rate (see Figure 2). Current expert opinion suggests that the target should be at least 75% for best effect.[8,30,31] This very short release prevents the pressure decrement from reaching the P low, and auto-PEEP is created. The setting of the P low is usually then at 0 cmH_2O to provide a better gradient for expiratory airflow. The auto-PEEP that results effectively means that the true driving pressure within the lung will be between the P high and the auto-peep generated.[8,27,28]

From this description, there are similarities to conventional ventilation: There is a driving pressure to a set upper inflation pressure, a PEEP that will be a consequence of the short release, and a machine mandated respiratory rate per minute that is a composite of the time high (T high) and the T low divided into

60 seconds. The obvious differences are the very long machine inverse inspiratory:expiratory ratios (I:E) that result, and the ability of the patient to breathe at any time during the cycle, the latter determining the total respiratory rate.

Herein lie the two greatest benefits and the rationale for its use.

The long "reverse" I:E ratios reported with APRV are based on the background machine rate with cycling from P high to P low. This is, however, not what the patient experiences, since the mode is a spontaneous one and the actual I:E is determined by the patient rather than the ventilator. The prolonged periods at P high do offer benefit. This is effectively a prolonged recruitment manoeuvre. In order to reopen atelectatic alveoli, a critical opening or threshold pressure must be attained, and since alveolar recruitment is a time-based phenomenon with each alveolus having a specific time constant, there must be sufficient pressure for a sufficient time. This allows both slow and effective recruitment, with redistribution of gas and volume within the lung according to the regional elastance differentials. The sustained nature of the pressure allows for maximal effect of alveolar interdependence on adjacent alveoli since there is no actual allowance for tidal de-recruitment as is seen with conventional PPV. To maximise these benefits, the time spent at T high should be in the order of 80–90% of the respiratory cycle.[8,30,31]

It is important to note that the recruitment seen with this mode occurs over a period of time, in the order of hours. It is not magic but relies on the correct application of pressure to the correct pathophysiological process. Again, this illustrates the linking of the correct therapy to the correct phenotype.

The other important benefit of this mode is the spontaneous respiration that occurs. Fundamentally, positive pressure in a passive respiratory system cannot give the same airflow distribution as spontaneous breathing. Inevitably, positive pressure on its own will tend to be distributed to non-dependant areas first. If the critical opening pressure of the dependant regions is not achieved, or maintained, over-distention and increased stress on the ventilated lung units will occur. Spontaneous breathing, on the other hand, by means of the force exerted by pleural pressure will tend to favour the dependant areas. The potential to expand and ventilate these areas is thus enhanced by the spontaneous breathing efforts at P high, rather than by application of additional positive pressure. Preservation of spontaneous breathing is then fundamental to the recruitment potential of APRV. The enhanced recruitment, with increased alveolar volume then should theoretically also improve the stress that the lung is subjected to since pressure is now distributed evenly over a greater area.[8,30,31]

While the spontaneous nature of this mode has oxygenation and lung kinetic advantages, they are not limited to these. The cardiovascular effects, despite concerns raised by opponents regarding the high mean airway pressures and venous return, seem to be less pronounced than expected. This is a common thread in the clinical and animal trials of APRV in which preserved haemodynamics, and or lower vasopressor requirements than in

the control cohort are observed. It is likely that the preservation of the cardiopulmonary interaction with spontaneous breathing, as well as the positive pressure effect on cardiac transmural pressures contribute to the observed benefit. Caution should, however, be exercised in the patient that has significant hypovolaemia. Focused ultrasound assessment at initiation of the APRV (and for that fact, any PPV in patients with ARDS) along with macrohaemodynamic monitoring should be standard-of-care anyway in our current critical care environments and will allow directed therapy to avoid any cardiovascular compromise.[8,26,28,30,31]

Care of patients requiring mechanical ventilation for ARDS, often involves the use of sedation, and not infrequently, neuromuscular blockade (NMB).[32] The use of these is primarily to facilitate patient ventilator synchrony, which in the more severe cases becomes essential. The spontaneous nature of this mode, even for those requiring significant support, reduces the need for sedation and obviates the need for NMB. This avoids the negative side-effects of these agents, allows for patients to be awake and interactive where suitable, and improves potential for mobilisation.

The spontaneous nature of the mode also facilitates the weaning process since there is no need to lighten sedation daily to assess patient-ventilator interaction and change to spontaneous modes. As recruitment progresses, there are active indicators evident on displayed ventilator scalars. Oxygen requirements are obviously weaned according to patient requirement, monitored saturation and PaO_2. As lung dynamics improve with recruitment, the release volumes will often increase, and at the same time, the gradient of the flow time slope from peak expiratory flow rate (PEFR) to the termination of expiration point (T-PEFR) will decrease (see Figure 2). This allows for a reduction of P high, extension of T low if required to maintain the 75% target for expiration, and lengthening the period of T high. This is the "drop and stretch" approach as described by Habashi.[8]

Physiologically then, APRV seems to have significant benefits that are well suited to the diffuse, hyperinflammatory, PEEP responsive phenotype, with some very convincing observational data for use in trauma patients, as well as emerging signals of benefit in other aetiologies with similar phenotypic presentation. This provides some credence to the arguments that more tailored management, which is phenotype-specific, will yield greater benefit.

It is beyond the scope of this discussion to cover every aspect of APRV, its implementation nuances and troubleshooting; however, the most important points have been mentioned in the text along with their physiological rationale. Figure 2, puts these in a visual perspective with the important points referred to above. Excellent information on the mode and its use, and cautions, can be found in the references.
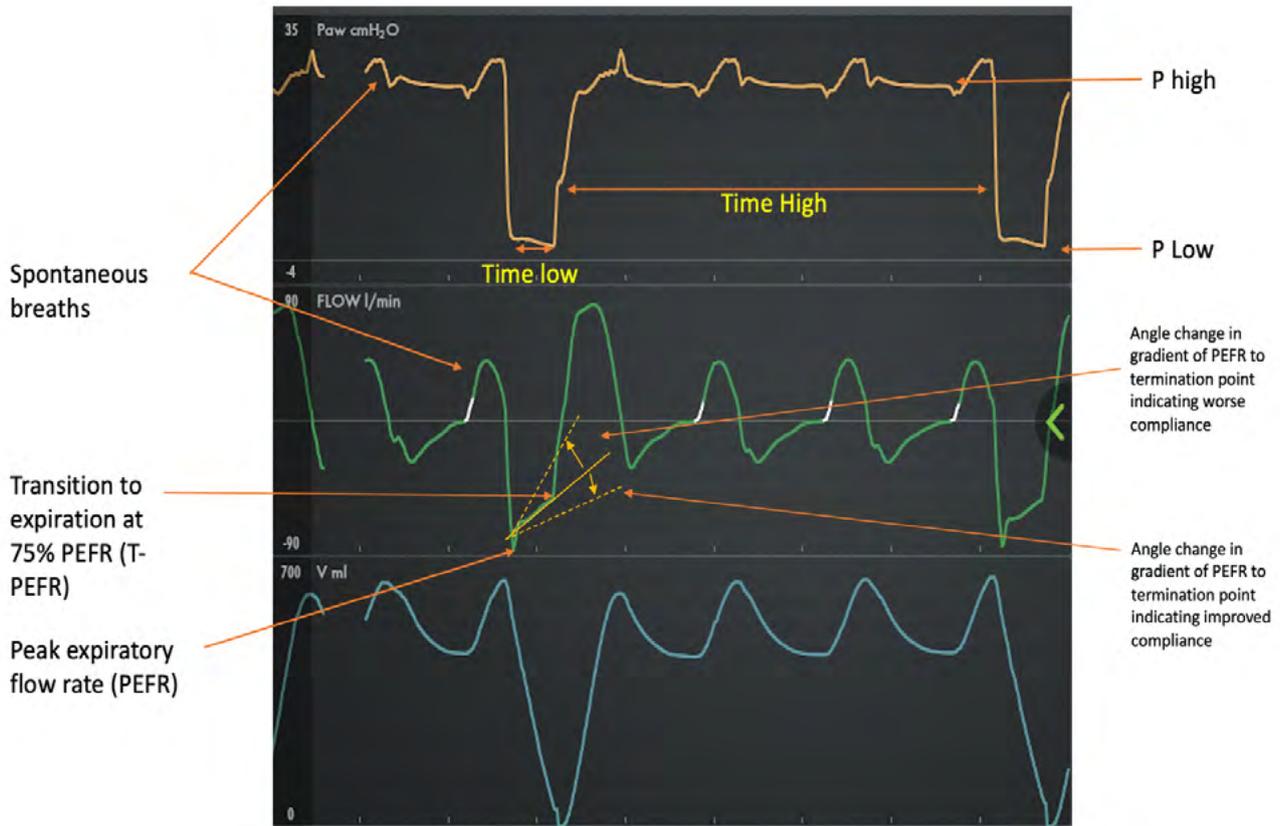
Figure 2: APRV pressure, flow and volume time scalars

Conclusion

While ARDS has a unifying syndromic definition, it remains a very heterogeneous entity, with a complex interplay between initiating event, host biology, amplifiers and the resultant pathophysiological presentation. It is only with recognition of this fact, and the impact it has on treatment choices, that we will see the emergence of treatable traits and hopefully phenotype aware treatments. The above discussion has by no means answered all the questions for the audience. The intended function is rather to highlight the heterogeneity of ARDS, future directions for research, and to illustrate where we already have some evidence as to how a supportive therapy such as APRV may have unique advantages over conventional ventilatory practice when aligned with certain phenotypic ARDS traits.

The onus is now on the reader to further explore the topic with some understanding of the pathology, physiological background and acceptance that PPV is not a "one size fits all" therapy but requires careful tailoring to the pathology at hand.

"Knowledge is an unending adventure at the edge of uncertainty."
Jacob Bronowski

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