Austin Journal of Pulmonary & Respiratory Medicine

Open Access

Austin Publishing Group

Special Issue - Acute Respiratory Distress Syndrome

Commentary: Spontaneous Ventilation in the Setting of Early Severe Stabilized ARDS: Heresy?

Pichot C, Petitjeans F, Ghignone M and Quintin L*

JF Kennedy Hospital North Shore Campus, WPalm Beach, Fl and Physiology, France

***Corresponding author:** L Quintin, MD, PhD, 29 Rue R Brechan, 69003 Lyon, France

Received: August 10, 2016; **Accepted:** December 15, 2016; **Published:** December 21, 2016

Abstract

After 50 years of research in the field of severe Acute Respiratory Distress Syndrome (ARDS) (PaO2/FiO2<100), according to Villar, et al., only 3 interventions stand out: low tidal volume (Vt), muscle relaxants and prone positioning. Nevertheless, some authors have proposed various modalities of spontaneous ventilation in the setting of early severe ARDS. We surmise that immediately after stabilization of acute cardio-ventilatory distress, an "analytical" management of early severe ARDS should include the following: reduced ventilatory demands (i.e. minimized O2 consumption: normothermia, etc.); improved cardiac output; upright positioning; minimized work of breathing, defined by a normalized tidal volume and respiratory rate; normalized acidosis; minimal hypercapnia; high positive end-expiratory pressure (PEEP: 10-24 cm H2O); low-level pressure support; and sedation without respiratory depression or cognitive side effects evoked by alpha-2 agonists. Such an analytical bundle requires evidence-based demonstration.

Keywords: Acute respiratory distress syndrome; Severe acute respiratory distress syndrome; ARDS; PaO2/FiO2 <100; Controlled mechanical ventilation; Muscle relaxant; Prone position; Spontaneous ventilation; Pressure support; Low PvO2 effect; Upright position; Sedation ; Alpha-2 adrenergic agonists; Alpha-2 agonists; Dexmedetomidine; Clonidine; Respiratory depression; Cognition; Side effects

Abbreviations

APRV: Airway Pressure Release Ventilation; ARDS: Acute Respiratory Distress Syndrome; CCU: Critical Care Unit; CMV: Controlled Mechanical Ventilation; CO, Q: Cardiac Output; COPD: Chronic Obstructive Pulmonary Disease; CT: Computed Tomography; ECMO: Extracorporeal Membrane Oxygenation; ERR: Extra-Renal Replacement; FRC: Functional Residual Capacity; H+: Acidosis; IAP: Intra-Abdominal Pressure; LV: Left Ventricle; NIH: National Institutes of Health; NIV: Non-Invasive Ventilation; NMB: Neuromuscular Blockers; PaO_2/FiO_2=P/F: Oxygenation Index; PEEP: Positive End Expiratory Pressure; Pflex: Pressure measured at inflexion of inspiratory or expiratory pressure-volume curve; Pplat: Plateau Pressure; PS: Pressure Support; P-V curve: Pressure-Volume curve; MOF: Multiple Organ Failure; RASS: Richmond Agitation-Sedation Scale; RR: Respiratory Rate; RV: Right Ventricle; SV: Spontaneous Ventilation; $SsvcO_2$: O_2 Saturation in the Superior Vena Cava; TAPSE: Tricuspid Annular Plane Systolic Excursion; "upright" position: 60° head up reverse Trendelenburg position with legs down; VA: Alveolar Ventilation; VO_2: Whole-Body O_2 Consumption; Vt: Tidal Volume; WOB: Work of Breathing, respiratory work

Introduction

After 50 years of research in the field of Acute Respiratory Distress Syndrome (ARDS), Villar, et al. [1] state that only 3 interventions stand out: low tidal volume (Vt), paralysis (muscle relaxants, Neuromuscular Blockers (NMB)) and prone positioning [1]. The success of proning is remarkable (28-day mortality, prone: 16%; supine: 32% [2]). Thus, campaigning for early Spontaneous Ventilation (SV) in the setting of severe ARDS (PaO_2/FiO_2=P/F<100) borders on heresy. Here, early spontaneous ventilation in the setting of severe ARDS will make use of Pressure Support (PS), as early as possible once the acute cardio-ventilatory distress has been controlled. Three intervals should be delineated in the setting of ARDS: a) acute cardio-ventilatory distress ("Friday night ventilation" in the setting of "shock state" not considered here [3], observed immediately upon arrival to the critical care unit: CCU; <6-12 h) [3]; b) early stabilized ARDS, up to 3-7 days after the beginning of the symptoms, the only time interval considered in this commentary; c) late ARDS not considered here. Our proposition [4] emphasizes spontaneous ventilation ("adapt the ventilator to the patient" [5]) which is largely ignored. Thus our proposition is at variance with the conventional view: general anesthesia (GA, renamed "analog-sedation") with or without NMB to lower VO_2 and synchronize the patient to the ventilator, proning and if possible, preservation of spontaneous breathing efforts. Therefore, can SV be used early in the setting of early severe stabilized ARDS? Some, including a proponent of short-term paralysis [6], have proposed various modalities of SV [5,7-15] in the setting of early severe ARDS.

ARDS is, operationally, a disease of oxygenation imposing to generate a high transpulmonary pressure to reopen at end-inspiration alveoli closed during expiration (airway closure); this imposes a high metabolic demand on ventilatory muscles and ultimately acidosis and possible ventilatory arrest. ARDS is not a disease of respiratory genesis nor of ventilatory muscles: these muscles need assistance only to the extent that the valves, circuit and tracheal tube impose a non-physiologic load, in addition to re-opening closed alveoli. To

Citation: Pichot C, Petitjeans F, Ghignone M and Quintin L. Commentary: Spontaneous Ventilation in the Setting of Early Severe Stabilized ARDS: Heresy?. Austin J Pulm Respir Med 2016; 3(2): 1046.

put it differently, the limiting factor of life, especially in the setting of ARDS, is the surface available for the diffusion of O_2, irrespective of the setting ("focal" or "diffuse" ARDS), but not the CO_2 excretion. Indeed, the use of high $PaCO_2$ is reported for limited periods, purportedly [16,17] or inadvertently [18,19]. Once the acute cardio-ventilatory distress is controlled, the use of Controlled Mechanical Ventilation (CMV), with or without paralysis, to stop or impede spontaneous breathing makes no sense:

a) SV lowers the intrathoracic pressure and Pplat and increases venous return, thus Cardiac Output (CO).

b) The diaphragm unfolds the "zone 3" alveoli (i.e. converting more alveoli from zone 1 and 2 into zone 3 and optimizing the VA/Q), given al lung in the upright position (figure 11 in [32] increases alveolar ventilation (VA) and squeezes the hepato-splanchnic sphere, enhancing venous return [20].

c) In the conscious, spontaneously breathing upright patient, the elastic recoil of the rib cage maintains a high Functional Residual Capacity (FRC) and tension in the diaphragm ("spring-out force"), as opposed to a loss of muscle tone under deep sedation/GA with/without paralysis [21-23].

Therefore, the VA/Q ratio is better preserved by SV than by CMV. Furthermore, as spontaneous ventilation lowers the intrathoracic pressure, increasing the surface available for O_2 diffusion with a high positive end-expiratory pressure (PEEP i.e. >10-24 cm H_2O [24]) is possible with acceptable Pplat (≤25-35 cm H_2O). Unfortunately, this straightforward schema is not applicable because a) respiratory muscle fatigue ("fatigue") occurs after hours of respiratory distress, leading to metabolic acidosis (H+) and possibly, respiratory arrest; b) ARDS occurs most often as a consequence of sepsis or other pathologies that generate Multiple-Organ Failure (MOF), but only rarely single-organ failure; and c) ARDS may occur in an obstructive lung, adding restriction to obstruction. To take into account the complexity of single organ failure (ARDS proper as O_2 defect) within the setting of MOF, we hypothesized [4] that early stabilized ARDS should be managed by improving analytically the following items in the following order: CO, reduced O_2 consumption (VO_2), upright positioning, minimized work of breathing (WOB, tidal volume: Vt, respiratory rate: RR, controlled acidosis and CO_2), high PEEP, low pressure support and sedation without respiratory depression and cognitive side-effects.

Heart

The Right Ventricle (RV), lung and Left Ventricle (LV) are pumps in series, which implies that a "maximally aerated lung without any circulation is a useless organ" [25]. Therefore, given an iterative echo-cardiographic assessment [26], the heart should be assessed at least twice daily during early severe ARDS to normalize LV ejection back to adequacy (low "CO_2 gap"<5-6 mm Hg, $SsvcO_2$>70-75%, adequate lactates toward <2 mM) by any mean (volume, pulmonary arterial dilators, inotropes, increased right coronary perfusion with pressors [27], etc.). Then, the PEEP should be increased to increase FRC, step by step, while RV dilatation or more accurately septal bulging [28] or Tricuspid Annular Systolic Excursion (TAPSE) are observed iteratively, at each PEEP level.

Addressing the circulation first is also a consequence of the dependency of the P/F index upon the circulation [29]:

a) A "low PvO_2 effect" decreases arterial oxygenation and overestimates lung injury: correcting CO improves PvO_2 and P/F. Presumably, increased VO_2 (fever, etc.) is observed together with an inadequate cardiac output (hypovolemia, etc.), leading to low $SsvcO_2$. Conversely, a "normal" VO_2 is observed with depressed CO (cardiac failure, hypovolemia, etc.) and reduced peripheral arterial oxygenation.

b) By contrast, a low cardiac output lowers the shunt, increases P/F and underestimates the lung injury [30]. Presumably, the lowered CO de-recruits pulmonary capillaries, amongst other explanations [31]: West's zone 3 [32] is being transformed into zone 1 (figure 11 in [32]).

c) RV overload re-opens a foramen ovale and increases shunt [33].

Therefore the clinician should address circulation first before curing the lung.

Position

Prone positioning generates remarkable results [2] due to an increase in VA to well-perfused areas [34]. However, we hypothesize that, for bipeds, the "upright" position (60° head up reverse Trendelenburg position with legs down [35,36]) should be preferred, preferred especially when obesity or increased Intra-Abdominal Pressure (IAP) are present. This requires tedious iterative nursing. Just moving from the supine to the upright position increases the P/F in 32% of ARDS patients, "especially for …severe ARDS" [37]. In healthy volunteers with a closed glottis that are moved from a standing to a supine position, the intra-thoracic pressure increases by approximately 9 cm H_2O [38]; conversely, can one infer that the upright position will reduce intrathoracic pressure? Furthermore, 25-80% (mean 50%) of the increased Intra-Abdominal Pressure (IAP) is transmitted into the thorax [39]. Therefore, transitioning from CMV to SV and from the supine to an upright position in an obese patient or a patient presenting with increased IAP will presumably lower the intra-thoracic pressure. Given a Pplat of ≤30 cm H_2O [40], this allows one to further increase the PEEP.

Work of Breathing (WOB)

1) O_2 Consumption (VO_2): "Reducing metabolic and ventilator demand [may] be among the most important of the unproven rules that guide management…..with the judicious use of sedative agents/anxiolytics/antipyretics" [41]. In stable patients, the following apply: a) lowering the temperature (39.7 to 37.0 °C) reduces the VO_2 (-18%) [42] and b) paralysis lowers the VO_2 during the early phase of ARDS (CMV+NMB *vs.* CPAP, -18%) [43]. Thus, in the setting of acute cardio-ventilatory distress, paralysis and normothermia (≈35.5-37 °C, e.g. by surface cooling) will enlarge this reduction in VO_2 for a few hours, increasing a precarious cardio-ventilatory reserve.

2) Circulation: In the setting of acute tamponade in SV dogs, 23% of the CO is routed to the ventilatory muscles. In contrast, when the dogs are paralyzed, only 3% of the CO is routed to the ventilatory muscles [44]. These data should not be over-interpreted because a)

during acute cardio-ventilatory distress immediately upon arrival to the CCU, suppressing the WOB with NMB for a few hours makes sense to lower VO_2 and b) when early severe ARDS is considered, the WOB should be fully minimized (see below) to allow one switching to SV, as early as possible.

3) Tidal volume: low pressure support?

First, inspiratory work: in the presence of basal atelectasis (focal ARDS) or diffuse alveolar damage (diffuse ARDS), a high transpulmonary pressure is necessary to generate sufficient tidal volume and re-open the terminal airways closed at some point during expiration. Just setting the PEEP at an appropriately high level should limit closing-reopening of the alveoli (atelectrauma, inflammation) and lower the inspiratory work [45]. Given an appropriately high PEEP, the lung will function on the highest slope of the Pressure-Volume (P-V) curve ("best" compliance [46,47]): when placed on its highest slope, the diseased lung needs lower inspiratory assistance [48-51] and lower PS [52-54].

Second, an acidotic patient in acute cardio-ventilatory distress generates a high transpulmonary pressure, a large Vt and a high RR before fatigue and ventilatory arrest. Carteaux observed Vt≈8-14 ml.kg (mean=10.6 ml.kg) with RR≈30-40 (mean=36) in ARDS patients in which Non-Invasive Ventilation (NIV) failed [55]: this is the *only* rationale to paralyze the respiratory muscles during the stabilization of acute cardioventilatory distress to get immediate reduction of VO_2.

Third, in the setting of early severe stabilized ARDS, active contraction of the diaphragm combined with high PS may generate a large transpulmonary pressure [53,54] and Vt [56]. Conventional weaning after ARDS uses high PS and low PEEP. By contrast, a) after control of acidosis, a normalization of Vt and RR is observed: this lowers WOB. b) we surmise that, after control of acute cardio-ventilatory distress, but during the early phase of severe ARDS, "inverted" settings [57] are appropriate: high PEEP (see below), low PS set stringently (low inspiratory trigger; "expiratory trigger" set at <5-10% in severe restrictive disease as ARDS [58] at variance with >50% in obstructive disease [59]; automatic tube compensation [60]: "adapt the ventilator, not the patient" [5]). This will overcome the load generated by the valves, circuits (3-5 cm H_2O) [61] and the tracheal tube [62] and unload the respiratory muscles (as shown by a minimized activity of the sternocleidomastoid muscle [63]). As ARDS is a restrictive disease ("baby lung" [64]), a Vt<6 ml·kg-1 leads to minimal over distension [48]. This is to be qualified as such a Vt exposes ≈30% of patients to hyperinflation [65]. Indeed, the objectives of protective ventilation under CMV (low driving pressure [66]/Vt [67]) apply equally to SV (low transpulmonary pressure; figure 1 of [52]).

4) Respiratory Rate (RR): A high RR is associated with failure of PS during weaning of ARDS patients [68] and during failure of NIV before intubation [55]. Therefore, a high RR should be stringently controlled: high VO_2, acidosis, CO_2 and agitation. Second, during weaning from ARDS, a high PO_2 is associated with a low RR [69]. Therefore, the use of a FiO_2 just sufficient for a SaO_2 ≥85-90 or 88-92%, is adequate under SV a) recovery from acute hypercapnic respiratory failure in the setting of established Chronic Obstructive Pulmonary Disease (COPD), b) CMV in the setting of early severe stabilized ARDS [24,70]. However the use of a FiO_2 just sufficient for a SaO_2 ≥85-90 or 88-92% is inadequate under SV, in the setting of early severe ARDS. Given SV, the hypoxic drive should be thoroughly suppressed, with a FiO_2 aimed at a high SaO_2 (≈98-100%) [69]. Under SV, the use of high PEEP (see below) will allow one to achieve high SaO_2, firstly with a high FiO_2 and later, *after* perennial alveolar recruitment, with a low FiO_2.

5) Acidosis (H+): Severe metabolic acidosis leads to a high RR and large Vt. Therefore, acidosis should be thoroughly controlled (presumably pH >7.20-7.30 with a favorable trend in lactate concentration and CO_2 gap) by any mean, such as lowering the VO_2, adequate CO, improved microcirculation, surface cooling and/or Early Extrarenal Replacement (ERR), before switching to SV [71].

6) Capnia: Permissive hypercapnia used in the setting of status asthmaticus [16] has completely changed the goal of mechanical ventilation to oxygenation itself, with CO_2 being partially neglected [64]. Nevertheless, high CO_2 levels increase pulmonary impedance [72] in a setting where the incidence of RV failure is ≈25% despite "protective" ventilation [73]. In addition, hypercapnia increases the RR. Therefore, given the drawbacks of high $PaCO_2$ [72], in the setting of early severe stabilized ARDS, $PaCO_2$ should be maintained <60 mm Hg. Normothermia (35.5-37°C) helps. Furthermore, extracorporeal CO_2 removal set on ERR [74] allows one to combine a low VO_2, ultra-low Vt and near-normocapnia, making analytical management much easier (spontaneous ventilation: high PEEP-low PS; CMV: high PEEP-low driving pressure).

Peep

From an operational point of view, ARDS was very schematically viewed above as an oxygenation restricted to oxygenation disease. As O_2 is 22 times less diffusible than CO_2, high CO_2 is rarely encountered [75]. Conversely, proning the patient is associated with a reduced $PaCO_2$ in favorable cases. What does this imply? Atelectasis redistributes itself within minutes following proning [64]. Thus, atelectasis is not a fixed phenomenon. PEEP will improve oxygenation, irrespective of the mechanism in early ARDS (atelectasis *vs.* increased lung water *vs.* inflammation). Edema is of importance in non-survivors [76], making fluid restriction an additional tool at later intervals, *after* control of the acute cardio-ventilatory distress. Then, what is an appropriate PEEP? Given a low Vt under SV [53,56] or CMV [77], a "higher PEEP associated with low Vt is beneficial in severely hypoxemic ARDS patients when administered early in the course of ARDS and when ARDS is diffuse" [77]. A PEEP=22-24 cm H_2O is used when a FiO_2=1 is needed [24]. This view needs to be qualified because a) emphasis on high PEEP in the setting of high FiO_2 [24] was to suggest increased PEEP rather than relying on high FiO_2 for extended intervals b) "focal" ARDS (basal atelectasis alone, acute hypoxemic non hypercapnic respiratory failure) requires a low PEEP, while diffuse ARDS requires a high PEEP [78] and c) in obese patients, focal ARDS requires a high PEEP to counteract the effect of the IAP on basal atelectasis [39,51] and to achieve adequate end-expiratory transpulmonary pressure and suppress cyclical collapse (airway closure).

1) Esophageal catheter: The esophageal balloon catheter

("balloon") was described in spontaneously breathing upright volunteers [79]. Given the absence of the weight of the mediastinal organs, is trans-pulmonary pressure more readily usable in the "upright" spontaneously breathing ARDS patient [23]? If the PEEP is to be set using a balloon [80], one goal is to separate chest wall mechanics *vs.* lung i.e. optimize functional residual capacity of the lung itself (FRC; lung re-expansion) without over distension of the lung itself.

To avoid end-inspiratory over distension, the first option leads to an end-inspiratory transpulmonary pressure of ≈27 cm H_2O (young spontaneously breathing healthy volunteers) [81]. Given an end-inspiratory transpulmonary limit of 25 cm H_2O, this allows one to increase the PEEP to the highest possible level (from 18 to 22 cm H_2O [82]) in a sub-group of patients presenting for Extracorporeal Membrane Oxygenation (ECMO), improve the P/F over 30 min and skip ECMO in 50% of the patients [82]. However, older subjects may only tolerate levels of transpulmonary pressure lower than 27 cm H_2O, if reference [81] applies.

To suppress end-expiratory cyclic alveolar collapse, the second option sets end-expiratory transpulmonary pressure to 10 cm H_2O (FiO_2=1) and improves the oxygenation over 72 h as well as the outcome [83]. Finally, the ventilator generates pressure and volume data and allows one to calculate lung compliance and transpulmonary pressure during changes in PEEP without the balloon [84]: will this information allow the selection of the lowest PEEP with the highest compliance without a balloon?

2) Numbers: When the balloon is unavailable, "magic" numbers are the second best option. Specifically, before a CT scan, or when the Pflex cannot be determined on a P-V curve, the investigators use a high PEEP [78,85] of 10-16 cm H_2O [86,87]. This level should be carefully adjusted as soon as possible (trial PEEP) to the lowest level. First, the PEEP is adjusted to the highest level tolerated by the RV (increasing PEEP, see § heart). Second, the trial PEEP should, at its lowest level (decreasing PEEP), generate a SaO_2 of ≈98-100% to avoid hypoxic drive and increased RR in the setting of spontaneous ventilation [69]. The issue is not to fully reopen the lung [17,88] but rather to reduce a "penumbra" area around the atelectatic areas to increase the P/F from below 100 to above 150-200. This will allow one to extubate the trachea as soon as possible, i.e. infection and overall clinical status permitting. If, following recruitment maneuvers, a high PEEP reverts the derecruitment [89], how long should the PEEP remain high to improve P/F perennially? There are no published data on this issue: "Modification of respiratory system mechanics required a long time and, the changes likely reflect a progressive modification of the underlying pulmonary pathology, rather than the achievement of a steady state » [90]. Thus, this is a function of the extent of the disease: when the PEEP is lowered too early, de-recruitment occurs. Furthermore, in our hands, derecruitment is very difficult to revert, even if the PEEP is set back to high levels (PEEP≥15-20 cm H_2O) without recruitment maneuvers. When CMV is used [40], a high PEEP should be set with a Pplat <25-35 cm H_2O, leading to a simultaneous improvement of the P/F, lowering of the Pplat and finally a lowering of the PEEP over 12-72 h [83,87]. When high PEEP-low PS is used, improved P/F is observed with similar kinetics.

c) Intrinsic PEEP: The PEEP should be set according to possible pre-existing obstructive disease. In-deed, a high intrinsic PEEP (PEEPi) is observed in supine ARDS patients (up to 8 cm H_2O [91]). Under SV, this generates a high expiratory work in addition to the high inspiratory work considered above. Therefore, under SV, the setting of the extrinsic PEEP should take into account the PEEPi of the considered patient, measured before switching to SV.

Which mode of ventilation is most suitable? While airway pressure release ventilation (APRV)+SV appears physiologically superior to PS [15,92,93], evidence-based epidemiology is lacking (https://clinicaltrials.gov/ct2/show/NCT01862016?term=richard+jcm&rank=1). Regardless, our limited experience with APRV makes PS our present choice.

Sedation

In the setting of early severe ARDS, the stringent provision made for short (i.e. 48 h) [94,95] paralysis is too often by-passed. General anesthesia suppresses respiratory rhythm genesis, evokes deep sedation [96], delayed emergence, emergence delirium and, when combined with paralysis, myoneuropathy [97]. However,

1) Sedation can be almost entirely withdrawn with minimal side-effects [98]; and

2) Only indifference to the tracheal tube and to the CCU environment (ataraxia, medical patient) and nociceptive stimuli (analgognosia, surgical patient) are required ("cooperative sedation"). Alpha-2 agonists evoke indifference to the environment in volunteers [99] and CCU patients [100] as well as an indifference to pain [101,102]. Therefore, midazolam/propofol and opiates, to be interrupted daily, are now irrelevant. Alpha-2 agonists should be considered, not during weaning, but as first-line sedative agents [103] during early severe ARDS [50,51], as soon as the acute cardio-ventilatory distress is controlled. Alpha-2 agonists evoke no respiratory depression [104] in volunteers [105, 106], no delayed emergence nor delirium. This explains the reduced length of intubation in a setting different from ARDS [107]. Under PS, provided the elevated WOB is analytically controlled (§ WOB), in the presence of a low threshold for inspiratory trigger, a high RR due to excessive triggering is not observed when alpha-2 agonists evoke -3<RASS<-1. Finally, in contrast to anesthetics that suppress the elastic recoil of the rib cage [21,22], the intact ventilatory mechanics observed in ambulatory hypertensive patients administered clonidine for decades shows that alpha-2 agonists do not suppress this recoil: may we speculate that sedation evoked by alpha-2 agonists does not suppress elastic recoil, does not lower the FRC and, thus, keeps the lung inflated ?

3) A "ceiling" effect is observed with high-dose dexmedetomidine/clonidine, to be supplemented with neuroleptics, if needed [103,108]. Such a deep sedation evokes no respiratory depression. As soon as the P/F improves from below 100 to above 150-200, sedation will be easily lightened. Given an im-proved overall clinical status, this will lead to early extubation without the interruption of alpha-2 agonists, ease the tolerance to Non-Invasive Ventilation (NIV) [109,110] and early physiotherapy.

4) Alpha-2 agonists lower the hypothalamic set point for shivering [111], the VO_2 [112] during weaning [113] and increase the mixed venous saturation [114] ("avoid the low PvO_2 effect"), presumably increasing the margin of safety when very low PaO_2 is

present. Therefore, normothermia (35.5-37°C) is easily achieved.

5) Alpha-2 agonists increase the levels of anti-inflammatory cytokines [115] and decrease the levels of pro-inflammatory cytokines [116], of possible relevance.

Conclusion

Our hypothesis is that CMV with paralysis is necessary in the setting of acute cardio-ventilatory distress or severe metabolic acidosis *only* [71]. Should the patient be switched from CMV to SV at 3, 6, 12, 24 [6] or 48 h [94,95] after arrival to the CCU? The answer is "as soon as some improvement [is] observed, pressure support ventilation [is] started" [117]. In the setting of early, severe, diffuse ARDS, analytical management (circulation, position, normothermia, acidosis, CO_2, high PEEP: 10-24 cm H_2O range, low PS) should not be considered as absurd. With alpha-2 agonists as first-line sedatives [103], improved oxygenation can be observed over 12-72 h, as reported previously [4,50,51,71,118]. By applying our analysis to ≈30 severe ARDS patients, we observed a mortality of ≈5% and extubation within 3-6 days after arrival at the CCU. As this non-randomized recruitment is presumably skewed, evidence-based documentation is necessary. Our analytical bundle implies an overal organ-by-organ and case-by-case approach and if serial assessments dictate, returning to the accepted practice (1) (CMV, paralysis [95] and (2) proning).

Conflict of Interest

Note added in proof : During the review process, Pellegrini et al, Am J Resp Crit Care Med, 2016, dec 6, in press, published data showing that during spontaneous ventilation in the setting of mild ARDS in pigs, the diaphragm acts a an expiratory brake preventing atelectasis. The phenomenom is detectable already half-way down the expiration. Conversely, muscle paralysis promotes end-expiratory lung collapse. Therefore elastic recoil is of key importance during inspiration as explained in the core of the present ms. But active expiration must be considered to heal the lung, adding rationale to the present commentary.

L Quintin holds US patent 8 703 697 B2 for the treatment of early severe diffuse acute respiratory distress syndrome. The other authors declare no conflict of interest.

Funding

Block grants from U of Lyon to EA 4612.

References

1. Villar J, Kacmarek RM, Guerin C. Clinical trials in patients with the acute respiratory distress syndrome: Burn after reading. Intensive Care Med. 2014; 40: 900-902.
2. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013; 368: 2159-2168.
3. Gattinoni L, Carlesso E, Brazzi L, Cressoni M, Rosseau S, Kluge S, et al. Friday night ventilation: a safety starting tool kit for mechanically ventilated patients. Minerva Anestesiol. 2014; 80: 1046-1057.
4. Pichot C, Petitjeans F, Ghignone M, Quintin L. Is there a place for pressure support ventilation and high end-expiratory pressure combined to alpha-2 agonists early in severe diffuse acute respiratory distress syndrome? Med Hypotheses. 2013; 80: 732-737.
5. Wrigge H, Reske AW. Patient-ventilator asynchrony: adapt the ventilator, not the patient! Crit Care Med. 2013; 41: 2240-2241.
6. Yoshida T, Papazian L. When to promote spontaneous respiratory activity in acute respiratory distress patients? Anesthesiology. 2014; 120: 1313-1315.
7. Marini JJ. Spontaneously regulated *vs.* controlled ventilation of acute lung injury/acute respiratory distress syndrome. Curr Opin Crit Care. 2011; 17: 24-29.
8. Yoshida T, Rinka H, Kaji A, Yoshimoto A, Arimoto H, Miyaichi T, et al. The impact of spontaneous ventilation on distribution of lung aeration in patients with acute respiratory distress syndrome: airway pressure release ventilation versus pressure support ventilation. Anesth Analg. 2009; 109: 1892-1900.
9. Patroniti N, Foti G, Cortinovis B, Maggioni E, Bigatello LM, Cereda M, et al. Sigh improves gas exchange and lung volume in patients with acute respiratory distress syndrome undergoing pressure support ventilation. Anesthesiology. 2002; 96: 788-794.
10. Zakynthinos SG, Vassilakopoulos T, Daniil Z, Zakynthinos E, Koutsoukos E, Katsouyianni K, et al. Pressure support ventilation in adult respiratory distress syndrome: short-term effects of a servocontrolled mode. J Crit Care. 1997; 12: 161-172.
11. Sydow M, Burchardi H, Ephraim E, Zielmann S, Crozier TA. Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. Am J Respir Crit Care Med. 1994; 149: 1550-1556.
12. Wrigge H, Downs JB, Hedenstierna G, Putensen C. Paralysis during mechanical ventilation in acute respiratory distress syndrome: back to the future? Crit Care Med. 2004; 32: 1628-1629.
13. Chiumello D. Spontaneous breathing during mechanical ventilation. Crit Care Med. 2005; 33: 1170-1171.
14. Zeravik J, Borg U, Pfeiffer UJ. Efficacy of pressure support ventilation dependent on extravascular lung water. Chest. 1990; 97: 1412-1419.
15. Putensen C, Mutz NJ, Putensen-Himmer G, Zinserling J. Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999; 159: 1241-1248.
16. Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis. 1984; 129: 385-387.
17. Borges JB, Okamoto VN, Matos GF, Caramez MP, Arantes PR, Barros F, et al. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. Am J Respir Crit Care Med. 2006; 174: 268-278.
18. Prys-Roberts C, Smith WD, Nunn JF. Accidental severe hypercapnia during anaesthesia. A case report and review of some physiological effects. Br J Anaesth. 1967; 39: 257-267.
19. Slinger P, Blundell PE, Metcalf IR. Management of massive grain aspiration. Anesthesiology. 1997; 87: 993-995.
20. Permutt S. Circulatory effects of weaning from mechanical ventilation: the importance of transdiaphragmatic pressure. Anesthesiology. 1988; 69: 157-160.
21. Westbrook PR, Stubbs SE, Sessler AD, Rehder K, Hyatt RE. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J Appl Physiol. 1973; 34: 81-86.
22. Hedenstierna G, Edmark L. The effects of anesthesia and muscle paralysis on the respiratory system. Intensive Care Med. 2005; 31: 1327-1335.
23. Hedenstierna G. Esophageal pressure: benefit and limitations. Minerva Anestesiol. 2012; 78: 959-966.
24. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004; 351: 327-336.
25. Jardin F. Acute leftward septal shift by lung recruitment maneuver. Intensive Care Med. 2005; 31: 1148-1149.
26. Vieillard-Baron A, Slama M, Mayo P, Charron C, Amiel JB, Esterez C, et al.

A pilot study on safety and clinical utility of a single-use 72-hour indwelling transesophageal echocardiography probe. Intensive Care Med. 2013; 39: 629-635.

27. Prewitt RM, Matthay MA, Ghignone M. Hemodynamic management in the adult respiratory distress syndrome. Clin Chest Med. 1983; 4: 251-268.

28. Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP. Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med. 1981; 304: 387-392.

29. Repesse X, Aubry A, Vieillard-Baron A. On the complexity of scoring acute respiratory distress syndrome: do not forget hemodynamics! J Thorac Dis. 2016; 8: E758-E764.

30. Dantzker DR, Wagner PD, West JB. Instability of lung units with low VA/Q ratios during O_2 breathing. J Appl Physiol. 1975; 38: 886-895.

31. Dantzker DR, Lynch JP, Weg JG. Depression of cardiac output is a mechanism of shunt reduction in the therapy of acute respiratory failure. Chest. 1980; 77: 636-642.

32. West JB, Dollery CT, Naimark A. Distribution of Blood Flow in Isolated Lung; Relation to Vascular and Alveolar Pressures. J Appl Physiol. 1964; 19: 713-724.

33. Mekontso Dessap A, Boissier F, Leon R, Carreira S, Campo FR, Lemaire F, et al. Prevalence and prognosis of shunting across patent foramen ovale during acute respiratory distress syndrome. Crit Care Med. 2010; 38: 1786-1792.

34. Guerin C, Baboi L, Richard JC. Mechanisms of the effects of prone positioning in acute respiratory distress syndrome. Intensive Care Med. 2014; 40: 1634-1642.

35. Burns SM, Egloff MB, Ryan B, Carpenter R, Burns JE. Effect of body position on spontaneous respiratory rate and tidal volume in patients with obesity, abdominal distension and ascites. Am J Crit Care. 1994; 3: 102-106.

36. Richard JC, Maggiore SM, Mancebo J, Lemaire F, Jonson B, Brochard L. Effects of vertical positioning on gas exchange and lung volumes in acute respiratory distress syndrome. Intensive Care Med. 2006; 32: 1623-1626.

37. Dellamonica J, Lerolle N, Sargentini C, Hubert S, Beduneau G, Di Marco F, et al. Effect of different seated positions on lung volume and oxygenation in acute respiratory distress syndrome. Intensive Care Med. 2013; 39: 1121-1127.

38. Rahn H, Otis AB. The pressure-volume diagram of the thorax and lung. Am J Physiol. 1946; 146: 161-178.

39. Pelosi P, Quintel M, Malbrain ML. Effect of intra-abdominal pressure on respiratory mechanics. Acta Clin Belg Suppl. 2007: 78-88.

40. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008; 299: 646-655.

41. Marini JJ. Unproven clinical evidence in mechanical ventilation. Curr Opin Crit Care. 2012; 18: 1-7.

42. Manthous CA, Hall JB, Olson D, Singh M, Chatila W, Pohlman A, et al. Effect of cooling on oxygen consumption in febrile critically ill patients. Am J Respir Crit Care Med. 1995; 151: 10-14.

43. Manthous CA, Hall JB, Kushner R, Schmidt GA, Russo G, Wood LD. The effect of mechanical ventilation on oxygen consumption in critically ill patients. Am J Respir Crit Care Med. 1995; 151: 210-214.

44. Viires N, Sillye G, Aubier M, Rassidakis A, Roussos C. Regional blood flow distribution in dog during induced hypotension and low cardiac output. Spontaneous breathing versus artificial ventilation. J Clin Invest. 1983; 72: 935-947.

45. Katz JA, Marks JD. Inspiratory work with and without continuous positive airway pressure in patients with acute respiratory failure. Anesthesiology. 1985; 63: 598-607.

46. Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med. 1975; 292: 284-289.

47. Kirby RR. Continuous positive airway pressure: to breathe or not to breathe. Anesthesiology. 1985; 63: 578-580.

48. Roupie E, Dambrosio M, Servillo G, Mentec H, el Atrous S, Beydon L, et al. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. Am J Respir Crit Care Med. 1995; 152: 121-128.

49. Froese AB. High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time! Crit Care Med. 1997; 25: 906-908.

50. Pichot C, Picoche A, Saboya-Steinbach M, Rousseau R, de Guys J, Lahmar M, et al. Combination of clonidine sedation and spontaneous breathing-pressure support upon acute respiratory distress syndrome: a feasability study in four patients. Acta Anaesthesiol Belg. 2012; 63: 127-133.

51. Galland C, Ferrand FX, Cividjian A, Sergent A, Pichot C, Ghignone M, et al. Swift recovery of severe hypoxemic pneumonia upon morbid obesity. Acta Anaesthesiol Belg. 2014; 65: 109-117.

52. Guldner A, Pelosi P, Gama de Abreu M. Spontaneous breathing in mild and moderate versus severe acute respiratory distress syndrome. Curr Opin Crit Care. 2014; 20: 69-76.

53. Freebairn R, Hickling KG. Spontaneous breathing during mechanical ventilation in ARDS. Crit Care Shock. 2005; 8: 61-66.

54. Rittayamai N, Brochard L. Recent advances in mechanical ventilation in patients with acute respiratory distress syndrome. European respiratory review: an official journal of the European Respiratory Society. 2015; 24: 132-140.

55. Carteaux G, Millan-Guilarte T, De Prost N, Razazi K, Abid S, Thille AW, et al. Failure of Noninvasive Ventilation for De Novo Acute Hypoxemic Respiratory Failure: Role of Tidal Volume. Crit Care Med. 2016; 44: 282-290.

56. Leray V, Bourdin G, Flandreau G, Bayle F, Wallet F, Richard JC, et al. A case of pneumomediastinum in a patient with acute respiratory distress syndrome on pressure support ventilation. Respir Care. 2010; 55: 770-773.

57. Petitjeans F, Quintin L. Non-invasive Failure in de novo acute hypoxemic respiratory failure: high positive end-expiratory pressure-low PS, i.e. "inverted" settings? Crit Care Med. 2016.

58. Mauri T, Bellani G, Grasselli G, Confalonieri A, Rona R, Patroniti N, et al. Patient-ventilator interaction in ARDS patients with extremely low compliance undergoing ECMO: a novel approach based on diaphragm electrical activity. Intensive Care Med. 2013; 39: 282-291.

59. Tassaux D, Gainnier M, Battisti A, Jolliet P. Impact of expiratory trigger setting on delayed cycling and inspiratory muscle workload. Am J Respir Crit Care Med. 2005; 172: 1283-1289.

60. Wrigge H, Zinserling J, Hering R, Schwalfenberg N, Stuber F, von Spiegel T, et al. Cardiorespiratory effects of automatic tube compensation during airway pressure release ventilation in patients with acute lung injury. Anesthesiology. 2001; 95: 382-389.

61. L'Her E, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, et al. Physiologic effects of noninvasive ventilation during acute lung injury. Am J Respir Crit Care Med. 2005; 172: 1112-1118.

62. Brochard L, Rua F, Lorino H, Lemaire F, Harf A. Inspiratory pressure support compensates for the additional work of breathing caused by the endotracheal tube. Anesthesiology. 1991; 75: 739-745.

63. Brochard L, Harf A, Lorino H, Lemaire F. Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. Am Rev Respir Dis. 1989; 139: 513-521.

64. Gattinoni L, Pesenti A. The concept of "baby lung". Intensive Care Med. 2005; 31: 776-784.

65. Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2007; 175: 160-166.

66. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld

DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015; 372: 747-755.

67. Network ARDS. Ventilation with lower tidal volume as compared with traditional tidal volume for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000; 342: 1301-1308.

68. Cereda M, Foti G, Marcora B, Gili M, Giacomini M, Sparacino ME, et al. Pressure support ventilation in patients with acute lung injury. Crit Care Med. 2000; 28: 1269-1275.

69. Pesenti A, Rossi N, Calori A, Foti G, Rossi GP. Effects of short-term oxygenation changes on acute lung injury patients undergoing pressure support ventilation. Chest. 1993; 103: 1185-1189.

70. Aggarwal NR, Brower RG. Targeting normoxemia in acute respiratory distress syndrome may cause worse short-term outcomes because of oxygen toxicity. Annals of the American Thoracic Society. 2014; 11: 1449-1453.

71. Pichot C, Petitjeans F, Ghignone G, Quintin L. Spontaneous ventilation-high PEEP upon severe ARDS: an erratum to further the analysis. Med Hypotheses. 2013; 81: 966-967.

72. Mekontso DA, Charron C, Devaquet J, Aboab J, Jardin F, Brochard L, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. Intensive Care Med. 2009; 35: 1850-1808.

73. Vieillard-Baron A, Schmitt JM, Augarde R, Fellahi JL, Prin S, Page B, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. Crit Care Med. 2001; 29: 1551-1555.

74. Terragni PP, Birocco A, Faggiano C, Ranieri VM. Extracorporeal CO2 removal. Contrib Nephrol. 2010; 165: 185-196.

75. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med. 2002; 346: 1281-1286.

76. Jozwiak M, Silva S, Persichini R, Anguel N, Osman D, Richard C, et al. Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. Crit Care Med. 2013; 41: 472-480.

77. Guerin C. The preventive role of higher PEEP in treating severely hypoxemic ARDS. Minerva Anestesiol. 2011; 77: 835-845.

78. Rouby JJ, Lu Q, Goldstein I. Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2002; 165: 1182-1186.

79. Milic-Emili J, Mead J, Turner JM, Glauser EM. Improved Technique for Estimating Pleural Pressure from Esophageal Balloons. J Appl Physiol. 1964; 19: 207-211.

80. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, et al. The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med. 2014; 189: 520-531.

81. Colebatch HJ, Greaves IA, Ng CK. Exponential analysis of elastic recoil and aging in healthy males and females. J Appl Physiol Respir Environ Exerc Physiol. 1979; 47: 683-691.

82. Grasso S, Terragni P, Birocco A, Urbino R, Del Sorbo L, Filippini C, et al. ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure. Intensive Care Med. 2012; 38: 395-403.

83. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med. 2008; 359: 2095-2104.

84. Lundin S, Stenqvist O. Transpulmonary can be determined without esophageal pressure measurements. Minerva Anestesiol. 2015.

85. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med. 2006; 354: 1775-1786.

86. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998; 338: 347-354.

87. Villar J, Perez-Mendez L, Lopez J, Belda J, Blanco J, Saralegui I, et al. An early PEEP/FIO2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2007; 176: 795-804.

88. Kirby RR, Downs JB, Civetta JM, Modell JH, Dannemiller FJ, Klein EF, et al. High level positive end expiratory pressure (PEEP) in acute respiratory insufficiency. Chest. 1975; 67: 156-163.

89. Villar J, Kacmarek RM. What is new in refractory hypoxemia? Intensive Care Med. 2013; 39: 1207-1210.

90. Chiumello D, Coppola S, Froio S, Mietto C, Brazzi L, Carlesso E, et al. Time to reach a new steady state after changes of positive end expiratory pressure. Intensive Care Med. 2013; 39: 1377-1385.

91. Koutsoukou A, Armaganidis A, Stavrakaki-Kallergi C, Vassilakopoulos T, Lymberis A, Roussos C, et al. Expiratory flow limitation and intrinsic positive end-expiratory pressure at zero positive end-expiratory pressure in patients with adult respiratory distress syndrome. Am J Respir Crit Care Med. 2000; 161: 1590-1596.

92. Putensen C, Hering R, Muders T, Wrigge H. Assisted breathing is better in acute respiratory failure. Curr Opin Crit Care. 2005; 11: 63-68.

93. Richard JC, Lyazidi A, Akoumianaki E, Mortaza S, Cordioli RL, Lefebvre JC, et al. Potentially harmful effects of inspiratory synchronization during pressure preset ventilation. Intensive Care Med. 2013; 39: 2003-2010.

94. Gainnier M, Papazian L. Paralysis during mechanical ventilation in acute respiratory distress syndrome: back to the future ? a reply. Crit Care Med. 2004; 32: 1629-1630.

95. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010; 363: 1107-1116.

96. Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MA, et al. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med. 2013; 39: 910-918.

97. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med. 2011; 183: 364-371.

98. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010; 375: 475-480.

99. Davies DS, Wing LMH, Reid JL, Neill E, Tipett P, Dollery CT. Pharmacokinetics and concentration-effect relationships of intravenous and oral clonidine. Clin Pharmacol Ther. 1977; 21: 593-601.

100. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. Br J Anaesth. 2001; 87: 684-690.

101. Hood DD, Mallak KA, Eisenach JC, Tong C. Interaction between intrathecal neostigmine and epidural clonidine in human volunteers. Anesthesiology. 1996; 85: 315-325.

102. Kauppila T, Kemppainen P, Tanila H, Pertovaara A. Effect of systemic medetomidine, an alpha-2 adrenoceptor agonist, on experimental pain in humans. Anesthesiology. 1991; 74: 3-8.

103. Pichot C, Ghignone M, Quintin L. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting? J Intensive Care Med. 2012; 27: 219-237.

104. Voituron N, Hilaire G, Quintin L. Dexmedetomidine and clonidine induce long-lasting activation of the respiratory rhythm generator of neonatal mice: possible implication for critical care. Respir Physiol Neurobiol. 2012; 180: 132-140.

105. Bailey PL, Sperry RJ, Johnson GK, Eldredge SJ, East KA, East TD, et al. Respiratory effects of clonidine alone and combined with morphine, in

humans. Anesthesiology. 1991; 74: 43-48.

106. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. Anesthesiology. 1992; 77: 1125-1133.

107. Ruokonen E, Parviainen I, Jakob SM, Nunes S, Kaukonen M, Shepherd ST, et al. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med. 2009; 35: 282-290.

108. Shehabi Y, Botha JA, Ernest D, Freebairn RC, Reade M, Roberts BL, et al. Clinical application, the use of dexmedetomidine in intensive care sedation. Crit Care Shock. 2010; 13: 40-50.

109. Akada S, Takeda S, Yoshida Y, Nakazato K, Mori M, Hongo T, et al. The efficacy of dexmedetomidine in patients with noninvasive ventilation: a preliminary study. Anesth Analg. 2008; 107: 167-170.

110. Huang Z, Chen YS, Yang ZL, Liu JY. Dexmedetomidine versus midazolam for the sedation of patients with non-invasive ventilation failure. Intern Med. 2012; 51: 2299-2305.

111. Myers RD, Beleslin DB, Rezvani AH. Hypothermia: role of alpha 1- and alpha 2-noradrenergic receptors in the hypothalamus of the cat. Pharmacol Biochem Behav. 1987; 26: 373-379.

112. Quintin L, Viale JP, Annat G, Hoen JP, Butin E, Cottet-Emard JM, et al. Oxygen uptake after major abdominal surgery: effect of clonidine. Anesthesiology. 1991; 74: 236-241.

113. Liatsi D, Tsapas B, Pampori S, Tsagourias M, Pneumatikos I, Matamis D. Respiratory, metabolic and hemodynamic effects of clonidine in ventilated patients presenting with withdrawal syndrome. Intensive Care Med. 2009; 35: 275-281.

114. Flacke JW. Alpha-2 adrenergic agonists in cardiovascular anesthesia. J Cardiothorac Vasc Anesth. 1992; 6: 344-359.

115. Xu B, Makris A, Thornton C, Ogle R, Horvath JS, Hennessy A. Antihypertensive drugs clonidine, diazoxide, hydralazine and furosemide regulate the production of cytokines by placentas and peripheral blood mononuclear cells in normal pregnancy. J Hypertens. 2006; 24: 915-922.

116. Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. Br J Anaesth. 2001; 86: 650-656.

117. Page B, Vieillard-Baron A, Beauchet A, Aegerter P, Prin S, Jardin F. Low stretch ventilation strategy in acute respiratory distress syndrome: eight years of clinical experience in a single center. Crit Care Med. 2003; 31: 765-769.

118. Pichot C, Petitjeans F, Ghignone M, Quintin L. Swift recovery of severe acute hypoxemic respiratory failure under non-invasive ventilation. Anaesthesiol Intensive Ther. 2015; 47: 138-142.

Austin J Pulm Respir Med - Volume 3 Issue 2 - 2016
ISSN : 2381-9022 | www.austinpublishinggroup.com

Citation: Pichot C, Petitjeans F, Ghignone M and Quintin L. Commentary: Spontaneous Ventilation in the Setting of Early Severe Stabilized ARDS: Heresy?. Austin J Pulm Respir Med 2016; 3(2): 1046.