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Early severe acute respiratory distress syndrome: What's going on? Part II: controlled vs. spontaneous ventilation?

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Abstract

The second part of this overview on early severe ARDS delineates the pros and cons of the following: a) controlled mechanical ventilation (CMV: lowered oxygen consumption and perfect patient-to-ventilator synchrony), to be used during acute cardio-ventilatory distress in order to "buy time" and correct circulatory insufficiency and metabolic defects (acidosis, etc.); b) spontaneous ventilation (SV: improved venous return, lowered intrathoracic pressure, absence of muscle atrophy). Given a stabilized early severe ARDS, as soon as the overall clinical situation improves, spontaneous ventilation will be used with the following stringent conditionalities: upfront circulatory optimization, upright positioning, lowered VO_2, lowered acidotic and hypercapnic drives, sedation without ventilatory depression and without lowered muscular tone, as well as high PEEP (titrated on transpulmonary pressure, or as a second best: "trial"-PEEP) with spontaneous ventilation + pressure support (or newer modes of ventilation). As these propositions require evidence-based demonstration, the reader is reminded that the accepted practice remains, in 2016, controlled mechanical ventilation, muscle relaxation and prone position.

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Key words: acute respiratory distress syndrome, ARDS, severe ARDS; acute hypoxic non-hypercapnic respiratory failure; driving pressure; tidal volume, Vt, low tidal volume, ultra-low tidal volume; positive end-expiratory pressure, PEEP; transpulmonary pressure; controlled mechanical ventilation; spontaneous ventilation; spontaneous breathing; pressure support, airway pressure release ventilation; sedation, cooperative sedation; alpha-2 adrenergic agonist, clonidine, dexmedetomidine

The previous chapter overviewed, for residents rotating through the critical care unit (CCU), basic pathophysiology required to *analyze* early severe acute respiratory distress syndrome (ARDS). An emphasis was placed on spontaneous ventilation both in the setting of the healthy volunteer and of severe ARDS. This chapter will address the pros and cons of controlled mechanical ventilation, with the help of muscle relaxation, as opposed to the putative advantages of spontaneous ventilation. So far, spontaneous ventilation has *not* achieved evidence-based demonstration: thus, as in part I, conjectures are within [➞….➞], following [1].

I. MUSCLE RELAXATION VERSUS SPONTANEOUS VENTILATION?

When muscle relaxation is considered, the overall picture appears to be simplified with 48 h of muscle relaxation [2]. A sober interpretation may be considered.

A. MUSCLE RELAXATION

In *severe* ARDS (P/F < 120), muscle relaxation [2] lowered the mortality (45 to 31%; difference of −32%; $P = 0.04$), multiple organ failure (MOF), and barotrauma and led to more ventilator-free days and identical CCU-acquired paresis. Muscle relaxation was hypothesized to minimize excessive transpulmonary pressure, patient-to-ventilator asynchrony [2], ventilator-induced lung injury (VILI), atelectrauma, overdistension, the release of mediators [3], and lowered inflammation [4]. This trial [2] demonstrates *only* that *perfect ventilator–patient synchrony* (pneumothorax: placebo: 11.7%; muscle relaxant : 4%; $P = 0.01$) *and lowered oxygen consumption (VO_2)* lower mortality in the setting of *early* ARDS. [➞Nothing more: this excellent paper [2] does not demonstrate that muscle relaxants are the only way to achieve ventilator-to-patient synchrony nor lowered VO_2➞]. Most commentators overlook setting up PS

as soon as possible after 24 h [5] or 48 h of muscle relaxation [2, 6]. This design [2] is in line with the optimized circulation/cardiological strategy: "*As soon as some improvement was observed, pressure support ventilation was started* " [7]. Indeed, a muscle relaxant lowered the VO_2 during the early phase of ARDS (controlled mechanical ventilation: CMV vs. CMV+muscle relaxation: VO_2 reduced by –8%; CMV+muscle relaxation vs. continuous positive airway pressure: CPAP: –18% [8]).

In brain-dead patients, 18–69 h of diaphragmatic inactivity combined with CMV resulted in marked atrophy in the diaphragm myofibers [9]. The functional consequence was demonstrated in patients undergoing CMV for at least 5 days; a time-related decrease in diaphragmatic function was observed as early as day 0–1 and dropped to 32% of the baseline value after 6 days of CMV [10]. Does a 48 h time course of controlled mechanical ventilation, with or without paralysis, generate ventilator-induced diaphragmatic dysfunction?

[➞Although most would agree that acute cardio-ventilatory distress (11) requires lowered VO_2 and WOB, including *transient* muscle relaxation, switching to spontaneous ventilation is too often not adhered to, as emphasized earlier [6, 7, 12]. In our daily practice, we observe that overlooking this *early* transition from muscle relaxation to PS prolongs muscle relaxation, sedation (i.e. *de facto* general anesthesia), CMV and leads to CCU-acquired diseases (e.g., ventilator-induced diaphragmatic dysfunction, sepsis, delirium, and MOF). Thus, after 48 h or more of muscle relaxation the patient cannot be weaned from the muscle relaxant, sedation and/or ventilatory support: a vicious cycle has been created (iatrogenic disease), generating late ARDS and late MOF. Fibrosis superimposes itself on atelectasis, inflammation and increased lung water. The reduction in work of breathing (WOB) has not been *analytically* addressed upfront. Sedation is inappropriate (Table I part II), thereby evoking respiratory depression and/or emergence delirium. Borrowing general anaesthesia from the operating room in the CCU, revamped as "analgo-sedation", is inappropriate: the patient needs only indifference both to the CCU environment and to pain (ataraxia and analgognosia i.e. "cooperative sedation") [13, 14]. In a setting different from severe ARDS, minimal sedation appears suitable [15]. Our argument is not against the *transient* [16] use of muscle relaxation in the setting of acute cardio-ventilatory distress in order to buy time and correct analytically (Table 1 part II) this "shock state" but against any *prolonged* use of analgo-sedation combined with muscle relaxation leading to a descent into MOF and CCU-acquired diseases. Indeed, [➞*use of [muscle relaxation] remains a last resort* [17], i.e. after a thorough *analysis* of the VO_2, respiratory rate (RR), tidal volume (Vt), acidosis (H+), CO_2, and O_2.

If muscle relaxation is selected in order to handle the acute cardio-ventilatory distress, the shorter it is, the better [6, 9, 10, 12].

B. SPONTANEOUS VENTILATION

Because pressure support (PS) allows the selection of fixed driving pressure but *not* transpulmonary pressure and Vt, all of the parameters interact with one another. We will first cover transpulmonary pressure, then the respiratory rate (RR).

1. PRESSURE SUPPORT

During the weaning of chronic obstructive pulmonary disease (COPD) patients, suppressed sternocleidomastoid (SCM) electrical activity suggests suppressed diaphragmatic fatigue. In *COPD* patients, a PS = 10 cm H_2O suppressed SCM activity in 5/8 patients while a PS = 20 cm H_2O eliminated diaphragmatic fatigue in the remaining patients (Fig. 3 in [18]). The optimal PS was associated with a Vt = 5–9 mL kg^{-1} and an RR = 20–35 breaths per min [18]. Increasing the PS from 0 to 20 cm H_2O decreased the VO_2 (288 ± 49 to 213 ± 54 mL min^{-1}; –26%) [18]. As the electrical activity of the SCM muscle is greater when diaphragmatic fatigue is present [18], the adequacy of the PS driving pressure may be approached through *palpation* of the SCM muscle. The PS should be diminished step by step from a high value (e.g. 15–20 cm H_2O) until phasic SCM activity re-appears. Then PS is increased immediately above this level to avoid diaphragmatic fatigue, overdistension and apnea. The PS would allow minimal diaphragmatic activity without fatigue, at least in COPD patients [18]. During weaning, PS reduced the weaning duration and CCU stay [19].

PS vs. APRV: Firstly, APRV appeared superior to volume-controlled ventilation (inverse inspiratory to expiratory ratio) in mild ARDS [20]. Under APRV, several indices improved over a 16 h period (Ppeak, decreased shunt, and improved ventilation/perfusion ratio: VA/Q). In this respect, after 24 h, SV accounted for 34 ± 14% of the total ventilation [20].

Secondly, APRV+SV led to a lower Ppeak, lower RR and higher PaO_2/FiO_2 (P/F) compared with pressure-controlled ventilation [21]. Importantly, by day 1, patients with a similar P/F (~250) at inclusion worsened back to moderate ARDS (P/F < 200) in the pressure-controlled group. In contrast, the P/F improved to above P/F >300 in the SV+APRV group [21], and was associated with a reduced CCU stay (APRV+SV: 23 days; pressure controlled ventilation: PCV: 30 days) [21]. Moreover, a higher cardiac index and lower requirements for vasopressor, inotrope and sedative drugs were observed in the APRV+SV group [21]. Hence, *SV preserves the VA/Q better than CMV* because a higher P/F was observed when the SV accounted for ~10% of the total ventilation [21].

Table 1. An alternative strategy in early severe diffuse ARDS [27, 28, 30, 71]?

[→I Working hypothesis [27, 30]:

a) to minimize the alveolar "penumbra area" (i.e. increase the size of the baby lung [102]) next to the true atelectatic areas without RV afterloading as opposed to re-expanding all atelectatic areas at once (Fig. 1 in [103])

b) b) given an *overall* improved clinical status, the objective is to increase P/F from < 100 with high PEEP (15–24 cm H_2O) to PF > 150–200 with PEEP = = 10 cm H_2O and switch to extubation+non-invasive ventilation (NIV)+physiotherapy, as early as possible

II. Summary:

1) Ascertain severe ARDS: P/F < 100 after 30 min (Vt ~7 mL kg^{-1}, PEEP = 10 cm H_2O, FiO_2 = 1) [60]

2) Optimize circulation (cardiological strategy):

a) rule out patent foramen ovale, especially if no oxygenation response to PEEP elevation (Dessap 2010 in part I)

b) avoid a "low PvO_2 effect" [7] and RV dysfunction

3) Use an upright position [81] and lower intra-abdominal pressure (gastric, bladder and colonic drainage: *early* facilitation of bowel movements)

4) Normalize the temperature (≈36°C) to lower the VO_2 [16, 45, 70] and VCO_2, leading to a low Vt (≤ 5 mL kg^{-1}; consider veno-venous CO_2 removal

5) Normalize acidosis (optimized cardiac output: CO_2 gap < 5–6 mm Hg; $SscvO_2$ > 70–75%; early EER therapy to lower lactates ≤ 2; infection control; rare administration of buffer) in order to lower the RR. This is the pathophysiological cornerstone of this alternative strategy because ARDS occurs rarely as single-organ failure but most often within the context of septic shock and early MOF

6) CO_2: avoid major hypercapnia [55] in order to lower the risk of RV failure and increased RR

7) O_2: a high FiO_2 will lower RR in SV [40]

8) SV should be set stringently only following control of ventilatory demands and metabolic demands

Measure the PEEPi prior to switching to SV and consider bronchodilators

High PEEP to suppress cyclical end-expiratory collapse, atelectrauma and WOB early on.

Select a low PS to avoid large transpulmonary pressure and volotrauma [35]

Set low inspiratory trigger, high pressure rise time [57], low expiratory trigger [59], automatic tube compensation = 100% [56]

9) Sedation: an absence of respiratory depression [94] should be considered as the pharmacological cornerstone of all of the cardio-ventilatory physiology discussed throughout ms. If necessary, alpha-2 agonists should be combined with neuroleptics, to −3 < RASS < −2 [13]

a) all the optimization of the cardio-ventilatory physiology, delineated in these two chapters, is *useless* if the respiratory generator is not free of any depressing influence [94]

b) conversely, alpha-2 agonists, without optimized cardio-ventilatory physiology, are useless.

10) revert to proning, muscle relaxants and CMV would this alternative strategy fail

III. Limitations*:*

This alternative strategy does not apply to the patient with:

1) acute cardiopulmonary distress ("shock" state): an ultra-short course of controlled mechanical ventilation combined to muscle relaxation (e.g., 1–6 h) allows one address pre-arrest emergency, re-oxygenate the patient, optimize circulatory function, lower oxygen consumption, insert the lines, perform echocardiography, CT scan, fiberoptic bronchoscopy, and initiate extra-renal replacement at once, as neatly summarized [11]

2) severe metabolic/lactic acidosis [28]: a strong H^+ stimulus requires muscle relaxation to lower RR and CO_2 production. Accordingly, a pH > 7.23–7.29 is needed to switch to SIMV [83]. Early extra-renal replacement therapy should be considered aggressively. SV should pick up as soon as H^+ is controlled (e.g., pH ≥ 7.30?)

3) severe denutrition or acquired myoneuropathy following prolonged CCU stay or use of sedative agents: ventilatory muscle failure and delirium should be addressed upfront, before heading to SV

IV. Position*:*

To lower Pplat, changes in intra-thoracic pressure from the upright to the supine position [104] should be kept in mind. Abdominal pressure [105] is lowered (gastric, bladder and colonic drainage, early facilitation of bowel movements). Thus, to *us*, "upright" position (reverse Trendelenburg, 60° head-up position, 45° legs down) appears for *bipeds* the most appropriate position to allow for adequate gas exchange [79–81], especially when high chest wall elastance (obesity, increased IAP, etc.) requires high PEEP to achieve the appropriate transpulmonary pressure. There is *no short cut* to improve the VA/Q ratio: the reader should be aware that an upright position needs tedious repositioning. The upright position will restore a functional "zone 3" (Fig. 11 in [96]). Given a high PEEP, an active diaphragm will unfold the collapsed alveoli while the gravity will fill up the capillaries with blood, optimizing the VA/Q ratio

V. Lowering VO_2 (Fig. 1 in [16]; Fig. 1 in [82]):

As stated in the introduction, the intensivist should deal, analytically and therapeutically, in a differentiated manner high ventilatory *ventilatory* demands (large Vt, high RR : "*soif d'air*") as opposed to high *metabolic* demands (fever, agitation, sympathetic activation, etc.). These 2 types of demands are inter-related. An anti-infectious strategy should be considered upfront. Next, the respiratory muscles capture some 21% of the cardiac output in spontaneously breathing dogs experiencing cardiac tamponade [106, 107]. Thus, RR should remain low [39]. By extension WOB is the limiting factor. To lower RR and VO_2, minimizing the hypercapnic [55] and acidotic drives, and normothermia (36°C), are mandatory, especially in the presence of *septic* shock (hypoxic drive: see below). As lowering the temperature by ≈2.4°C lowers VO_2 by 18% [70], normothermia increases the cardioventilatory reserve [45] and allows one to lower Vt and RR (≈36°C via extrarenal replacement therapy or a cooling device and/or pharmacology: paracetamol/ /alpha-2 agonists [82, 108, 109]). Muscle relaxants are of great value [8], *transiently,* only during acute cardio-ventilatory distress [16]

Table 1. (cont'd). An alternative strategy in early severe diffuse ARDS [27, 28, 30, 71]?

VI. Circulation:

Upfront circulatory improvement will:

a) rule out a patent foramen ovale: when a low PvO_2 effect has been ruled out, an absence of oxygenation response to PEEP elevation requires looking for PFO then perform a CT scan (responders vs. non-responders: Table 6, part I, § trial-PEEP)

b) correct a much-overlooked "*low PvO_2 effect*" [7, 110]: the cardiac output should return to adequacy ($SsvcO_2$ > 70–75% or a difference in arterial-central venous O_2 saturation < 30%, CO_2 gap < 5–6 mm Hg, adequate trend in lactate heading < 2 mmol L^{-1})

c) avoid RV dysfunction (septal bulging) caused by high PEEP [111] or hypercapnia [55]

Given the difficulty in assessing micro-circulation, circulatory optimization implies adequate urine output, in the absence of extra renal replacement therapy. Repeated echocardiographies look for septal leftward bulging or reduced LV preload in the setting of high PEEP

VII. *Analysis* of the blood gases:

Each laboratory value of the arterial *and* central venous blood gases results should be scrutinized, step by step (pH, $PaCO_2$, PaO_2, CO_2 gap, SaO_2, $SsvcO_2$, lactates) and confronted with the clinical picture i.e. literarily facing the patient (e.g., high RR, large Vt vs. H^+, CO_2, temperature, etc.) given the period considered (acute cardio-ventilatory distress vs. stabilized early severe ARDS vs. weaning). For example, switching to SV is based on H+ [28 , 83]. The method to differentially lower FiO_2 and PEEP is based on PaO_2 (Table 4, part I; Table 1, part II)

H^+: see above

CO_2: hypercapnia ($PaCO_2$ > 60 mm Hg) [55] is to be avoided (risk of RV failure, increased RR), before switching to SV. Putensen 2001 [21] keeps 45 < $PaCO_2$ < 55 mm Hg

Oxygen: see weaning

VIII. Ventilatory settings: *Expiration vs. inspiratory assistance* (§ I B 2)

1) Expiration:

This strategy bases itself on repeated RV echocardiographic assessments (no leftward septal bulging), physiological measurements (P–V curve [112] or esophageal balloon: end-expiratory [48] transpulmonary pressure) or, if the balloon is unavailable, (SaO_2 > 88–92% in the setting of CMV [41, 42] as opposed to SaO_2 > 95–100% in the setting of SV [40]). This high stretch strategy regarding recruitment (balloon or P–V curve or trial-PEEP) wil suppress cyclical alveolar collapse and optimize ventilation (high numerator in VA/Q ratio). Once high PEEP resets lung volume to higher FRC, changing CMV to SV allows one to lower Pplat, reduce circulatory [113] and muscular [9, 10] effects of positive pressure ventilation. Moreover, a lowered Pplat evoked by an upright position and PS will allow one to implement higher PEEP levels (15–24 cm H_2O), generating a swifter resolution to alveolar collapse. A 12 h trial of high PEEP segregate responders vs. non-responders (Table 6, part I)

2) Inspiration:

One explanation for low PS (5–10 cm H_2O) or very low PS (3–5 cm H_20; "Smart Care" on Drager Evita XL/Infinity V500) [29, 30] is:

a) if adequate (Fig. 2 in [114]; Fig. 1 in [115]) PEEP is used, the lung is constantly above the closing volume, thus set on the highest slope of the P–V curve [114]. High PEEP, when adequate [76], allows the lung to operate on the part of the P–V curve (incremental limb [116]; decremental [49]) with the highest slope [114] (Fig. 2 in [114]: "best compliance" [117] in "safe window": Figure 1 in [115]). Given this high slope, a small increment in pressure generated by low PS generates in turn a large change in volume. *The higher the PEEP needed to keep the lung above closing volume, the smaller the tidal volume needs to be* [51, 115] (Fig. 2 in [114]). Indeed, a sigh (i.e., twice the Vt) leads rarely to Pplat = 40 cm H_2O when a high "optimal" PEEP is used [53]. Presumably keeping the diseased lung above FRC minimizes pressure injury [50], despite repetitive sighs and high PEEP [53]. This applies to either high frequency ventilation (HFV), or protective ventilation (Vt ≤ 5 mL kg^{-1}), or a very low level of PS

b) the diaphragm generates negative intrapleural pressure which adds on mechanical support (for limitations: see PS and transpulmonary pressure; Figs 1 and 2 in [33]).

c) to overcome the WOB generated by the valves and tubing in healthy volunteers, PS = 3–5 cm H_2O is needed [118]. The implication is that the baby lung has a normal compliance. Nevertheless, the accessory muscles should be at rest all the time: automatic tube compensation [56] will perform nearly all WOB: no sternal notch retraction, no use of accessory muscles, etc. Therefore, PS had to be set to a surprisingly low level (3–10 cm H_2O, low inspiratory trigger, low expiratory trigger [59], high pressure rise time, automatic tube compensation 100%) in patients presenting with early severe ARDS undergoing moderate permissive hypercapnia ($PaCO_2$ ≤ 60 mm Hg) [55] under high PEEP (15–24 cm H_2O) [30, 71]. These observations agree with earlier findings [18, 35, 36]. Negative intrapleural pressure (generated by an active diaphragm) and a high slope *above* closing volume lead to a low PS and small Vt sufficient to maintain acceptable $PaCO_2$. PEEP set in order to achieve the highest slope of the deflation limb of the P–V curve combines with minimal transpulmonary pressure. Trial-PEEP based on oxygenation [54] may be easier to set up. *This technique contrasts with the accepted view that PS should be set high (e.g., 15–25 cm H_2O) when weaning begins*

Surprisingly, following *control of ventilatory and metabolic demands, under alpha-2 agonists* (see below), we observed virtually no ventilator asynchronies in those spontaneously breathing patients under PS

3) Weaning:

a) PS level: The PS level is progressively lowered from 10 cm to lower values (≈5 cm H_2O), as long as the patient presents no discomfort, no sternal notch retraction, no use of the sternocleido-mastoid muscle. To our surprise, high PEEP combined to "Smart Care" software (Evita 4 XL/Infinity V500, Drager) allows one to achieve early and easy weaning in the setting of severe acute hypoxemic failure in a morbidly obese patient [30]

b) FiO_2 (Table 4, part I): The goal is to achieve

SaO_2 > 98–100% on high PEEP+FiO_2 = 1

then SaO_2 = 98–100% or ≥ 95–100% on FiO_2 = 0.4+high PEEP (15–24 cm H_2O): lower FiO_2 by 0.2 at the time

then SaO_2 = 98–100% on FiO_2 = 0.4+PEEP = 10 cm H20 (lower PEEP from 15–24 cm H_2O progressively to 10 cm H_2O while keeping SaO_2 > 95–100% to minimize hypoxic drive; lower PEEP by 2–5 cm H_2O at the time). This requires 12–120 h in our hands (low PS-high PEEP), as observed earlier [48, 64, 92]

c) extubation: Given an adequate overall condition (temperature, inflammation, circulation, etc.), extubation is followed immediately by continuous non–invasive ventilation (FiO_2 = 0.4, PEEP = 10, 24/24 h) then discontinued (18/24 h, then 12/24, then 6/24) while PEEP is lowered accordingly after a few days. Fiberoptic bronchoscopy is performed with the help of a physiotherapist immediately before extubation in order to clear out secretions as much as possible (Quenot, personal communication)

Table 1. (cont'd). An alternative strategy in early severe diffuse ARDS [27, 28, 30, 71]?

a) PS against newer modes of ventilation: Neurally Adjusted Ventilatory Assist (NAVA) is more appealing to further ventilator-to-patient synchrony and maintain breathing variability [119]. Accordingly, APRV with spontaneous ventilation [24] is more efficacious than PS [88], based on the distribution of blood flow to unventilated areas [23, 120]. Epidemiologic data are lacking to select the best ventilatory mode under spontaneous ventilation (BIRDS: https://clinicaltrials.gov/ct2/show/NCT01862016)

IX. Sedation:

At variance with current practice, treatment of early severe ARDS should not rely only on stringent cardio-ventilatory physiology but also on stringent brain stem neurophysiology [94]. A *sedation devoid of circulatory and ventilatory side-effects is* the key pharmacological issue: alpha-2 agonists, devoid of respiratory depressant effects [94, 121] are to be administered to −3 < RASS < −2 [13]. If high-dose alpha-2 agonists do not generate enough quietness, neuroleptics are to be added: loxapine, haloperidol [13, 122, 123]). Alpha-2 agonists generate no emergence delirium and prolonged elimination, and alter the hypothalamic set-point [124] thus causing slight hypothermia (≈ 35,5°C) [108, 109, 125] and lower VO_2 during weaning [82]. Thus, "cooperative" sedation [13, 126], or little/no sedation [15, 127] in non-combative patients, are to be considered [27, 30, 71]. Then, new ventilator modes (PS, APRV, etc.) will be used within the most appropriate pharmacological setting

Provided that volemia is optimized (little or no ventilator-evoked variations in vena cava, little or no increase in cardiac output or BP following passive leg rising), sympathetic de-activation through the use of alpha-2 agonists warrants interest:

a) increased pressor response to noradrenaline in the setting of septic shock [128, 129] or experimental sepsis [130, 131]

b) reduced pulmonary hypertension [132]

c) increased diastolic compliance [133]

d) reduced intraabdominal pressure [134]

e) reduced microvascular permeability [135], of interest as high pulmonary water content is considered [136]. In this respect, the reader should note that alpha-adrenergic blockade decreases pulmonary extravascular leakage in the setting of experimental haemorrhage [137]

f) diuresis [138] in the setting of ascites [139–141], cardiac failure [142] and critical care [143]

g) lowered pro-inflammatory IL6 [144], increased anti-inflammatory IL10 [145]

The use of SV in the setting of early severe diffuse ARDS remains seldom used [39, 40]. This lack of enthusiasm may be related to the absence of epidemiological data:

a) clearly, the mode of ventilation was selected appropriately, e.g., [21], with a reduction in CCU stay. Accordingly, the present BIRD trial (clinicaltrials.gov/ct2/show/NCT01862016) uses a combination of APRV+SV

b) thus we surmise that conventional sedative agents were selected *inappropriately:* alpha-2 agonists [13, 122] do not suppress the respiratory drive [94], but suppress the emergence delirium. *Non-conventional sedation with alpha-2 agonists is by itself unlikely to modify outcome* [146, 147]: by contrast, the combination of stringent spontaneous ventilation and alpha-2 agonists is mandatory in order to achieve superiority [148]

Two final observations are required, namely: a) would this alternative strategy be a failure (tachypnea, high or low Vt, acidosis, absence of improvement of P/F, etc.), reverting early to proning+CMV+muscle relaxation [2, 63] is strongly advised; and b) this strategy requires evidence--based demonstration ←]

This result could be due to an *active* diaphragmatic contraction, throughout inspiration, the recruitment of previously unventilated alveoli, or to a redistribution of the flow towards previously ventilated lung units. Additionally, PS appears to be superior to CMV but inferior to APRV+SV [22, 23]. Accordingly, when P/F < 300, APRV appears to be superior compared to PS. Unfortunately, the analysis does not further segregate P/F < 100 vs. P/F < 200. Similar favourable results were observed in 8 moderate/severe ARDS under APRV [24].

Third, lung aeration appears to be superior upon APRV+SV as opposed to PS in patients with a high proportion of severe ARDS (aerated lung from 29 to 43% as opposed to 39 to 44%, respectively). Given a *similar airway pressure, a greater increase in the P/F was observed with APRV compared to PS* (APRV: 79 to 398; PS: 96 to 249). A higher MAP was observed under APRV+SV than under PS and was presumably linked to an active compression of blood from the viscerae by the diaphragm [25]. The reader should note that, presumably, very low P/F values [40–66] were handled with spontaneous ventilation [26].

Despite these physiological data, an epidemiological study ("BIRDS" trial: clinicaltrials.gov/ct2/show/NCT01862016) is required to assess the CMV vs. APRV+SV comparison and to determine which SV mode should be used. At present, *given stringent [27–30] conditions, spontaneous ventilation improves gas exchange upon ARDS* [21].

2. TRANSPULMONARY PRESSURE AND TIDAL VOLUME: "NAÏVE" PRESSURE SUPPORT?

Large transalveolar pressure and tidal pressure excursions (≈Pplat) are the determinants of tissue damage [31]. A transpulmonary pressure of PL = 15 cm H_2O generates a Vt of ~2500 mL (i.e., 2/3 of the total lung capacity) [32]. While marathon runners can withstand a Vt >25 mL kg^{-1} for 2–3 hours [31], it does not follow that a "baby lung" may withstand a Vt >5 mL kg^{-1} for weeks. The transpulmonary

pressure under CMV (PL = PAW [generated by the respirator]-Ppleural) becomes, under SV-PS, PL = PAW (amplitude of PS)+Pmuscles (generated by the respiratory muscles) (Figs 1 and 2 in [33]). PS evokes the smallest PL compared to APRV and synchronized intermittent mandatory ventilation (IMV) [34]. Switching from CMV to PS leads to a lower Ppeak, identical Vt [35], increased synchrony and a higher chest wall (CW) compliance. However, the diaphragm generates a higher end-inspiratory transpulmonary pressure (Figs 1 and 2 in [33]). Thus, the transpulmonary pressure may *increase* to a very high level (Table in [35]: +51 cm H_2O) if PS is not appropriately reduced (Figs 1 and 2 in [33]) and/or the Vt is not adequately monitored and reduced (36). This may create overdistension [35], making a high PS *potentially* detrimental [35] (Figs 1 and 2 in [33]). The spontaneous engagement of the diaphragm may lead to regional variation in the transpulmonary pressure (greatest in dependent regions) with greater recruitment of the lung volume and possibly further VILI in a "baby lung". The transpulmonary pressure may still be high with the danger of a large Vt while the low airway pressure may look deceptively safe (Figs 1 and 2 in [33]). In this respect, inflation of the dependent regions at the expense of the non-dependent regions has been observed at identical tidal and lung volumes i.e. *pendel-luft* [37] (Figs 1 and 2 in [37]). This *pendelluft* may inflate the atelectatic regions and improve lung recruitment. Conversely, the *pendelluft* may worsen local lung injury when associated with the intrinsic positive end-expiratory pressure (PEEP) or a triggering delay [37] (Fig. 1 in [37]). These data [37] were only partially conclusive because the patient was acidotic (pH = 7.28, BE = −8 mmol L^{-1}, Vt = 7.8 mL kg^{-1}, possibly associated with high inspiratory efforts). Nevertheless, they [37] point out that a "naïve" [35] use of SV may worsen lung injury.

To summarize, *spontaneous ventilation should not generate a high transpulmonary pressure* [35, 36] (Figs 1 and 2 in [33]; Fig. 1 in [37[). Both "early" (§ I B 1) and "late" inspiration are to be checked: under PS, setting the Pplat ≤ 26–32 cm H_2O does *not* automatically protect against VILI unless the Vt [36] or esophageal pressure are monitored.

3. PRESSURE SUPPORT AND RESPIRATORY RATE

Late vs. early ARDS: *In transitioning to SV, swiftness is mandatory.* The use of PS was successful in early ARDS as opposed to its failure in late ARDS [38]. Indeed, patients successfully transitioned to PS presented a shorter duration of CMV (success ~10 d of CMV; failure ~20 d, presumably due to fibrosis during late ARDS; inclusion: 48 patients with > 7 days of intubation, P/F = 210 ± 69, PaO_2 > 80 mm Hg, PEEP >15 cm H_2O, and any FiO_2) [39]. Immediately following the transition to PS, the P/F was unchanged, the $PaCO_2$ and mean airway pressure (~15 cm H_2O to ~13) were decreased, and the pH, minute ventilation and RR were increased. PS failure occurred at a later interval (≈20 ± 8 h) and was correlated with a longer duration of intubation, increased RR, higher $PaCO_2$, lower P/F, higher Vd, Vd/Vt, Ppeak and pulmonary pressure and similar or lower Vt (similar PEEP ~9 cm H_2O irrespective of success or failure). Thus, success comprised: 79% of the 48 patients, PS ~14 cm H_2O over 48 h; and a minimal increase in RR: 15 ± 4 to 22 ± 6, while failure comprised: PS≈22 cm H_2O; major increase in RR: 19 ± 4 to 36 ± 13 cycles per min (cpm); increased $PaCO_2$; decreased PaO_2; and circulatory instability) [39]. The "naïve" [35] use of SV may be detrimental when the patient is unable to select an appropriate RR by himself.

Hypoxic drive (Table 4, part I and Table 2, part II): An ill-quoted paper beautifully demonstrated that ARDS patients under PS ventilation experienced a decrease in RR from 34 to 25 cpm when the PaO_2 was increased from 55 to 158 mm Hg [40] (Table 4B, part I). [→Therefore, a SaO_2 level close to 95–100% should be the goal during the weaning period of severe ARDS under SV in order to lower the RR and WOB, thus allowing early transition to SV. This practice (SaO_2 = 95–100% under spontaneous ventilation-PS) [40] contrasts with weaning COPD patients who tolerate a SaO_2≈85–90% and the extension of this COPD practice to stabilized early severe ARDS under CMV (target: SaO_2 = 88–92% to avoid O_2 toxicity [41, 42]. The use of SV in early severe ARDS implies stringent conditions (e.g., high SaO_2 to lower the RR)←].

Acidosis: Experimentally, injection of sodium salicylate into the cisterna magna generate threefold increases in Vt, RR and minute ventilation. Some animals died. By contrast, following barbiturates and muscle relaxants no changes and no death occurred [43]. Indeed, the clinician is well aware of hyperventilation and increased RR in the setting of head injury, diabetic ketoacidosis, high altitude edema, severe haemorrhage and drug intoxication, as well as in ARDS [44].

If *SV is considered, lowered* VO_2 [45] *and minimized RR* [40] *are mandatory*. Briefly, all the factors influencing Vt and RR are to be minimized (temperature, H^+, CO_2, central noradrenergic-peripheral sympathetic activity, agitation) to handle the oxygenation defect itself.

Setting up CMV vs. SV:

a) In the setting of CMV, the Vt/driving pressure should be set first, prior to increasing the PEEP to an acceptable Pplat [46]. When the CMV is considered with a fixed Vt ≤ 5–6 mL kg^{-1}, setting the PEEP is based on either lung mechanics (Pplat [46], or end-inspiratory transpulmonary pressure [47]), or oxygenation combined with lung mechanics (end-expiratory transpulmonary pressure [48]), or the decremental [49]

Table 2. Pending questions (see also [101])

[➞To consider a few of the issues at stake:

I. Setting PEEP:

Irrespective of any "open lung" approach, leftward septal bulging is to be avoided: the right ventricle is a low-pressure generator.

Is volu- or barotrauma (Table 5, part I) linked to a high PEEP and/or to the amplitude of the absolute Pplat? to the transpulmonary end-inspiratory pressure?

Is volu- or barotrauma linked to the total duration of the mechanical ventilation? The literature (7, 62) does not provide clear-cut answers (Table 5, part I). Amato states: lung "*damages are more closely related to the amplitude of cyclic stretch than to the maximal level of stretch*" [50]. Stated differently,

1) does Figure 2 in [67] (Mortality = f [as Plat observed on day 1]) hold true when *short* periods of ventilation are considered?

2) given an identical area under the Pplat = f(time) curve, is a high PEEP (e.g., 20–24 cm H_2O), or a high Pplat, for a short period of time (6–12 h up to 72 h) followed by early extubation less detrimental than lower levels of PEEP for extended periods of mechanical ventilation («low stretch strategy») [7]?

How should PEEP be set up?

1) end-inspiratory pressure to the limit?

Can strategy [47] using end-inspiratory transpulmonary pressure up to ≈ 25 cm H_2O, be extended to the upper limit measured in healthy volunteers at maximal inspiration, i.e., ≈37–44 cm H_2O [149, 150] for a *few* hours? or to a upper limit somewhere between 27 and 37–44 cm H_2O? Grasso points in this direction : he increases PplatRS from 31 to 38 cm H_2O with PplatL increasing from 17 to 25 cm H_2O [47]. Presumably,: a) this question pertains primarily to the use of CMV as opposed to SV; and b) older patients, because of loss of elastic tissue, may tolerate lower end-inspiratory pressure i.e. < 27 cm H_2O.

2) end-expiratory pressure to the limit?

End-*expiratory* transpulmonary pressure is set slightly positive (0–10 cm H_2O: Fig. 2E in [48]) to avoid cyclical alveolar end-expiratory collapse (end-inspiratory limit: 25 cm H_2O). The use of a high end-expiratory transpulmonary pressure = 10 cm H_2O is restricted to FIO_2 = 1.0 according to the NIH Table [48]: Table 4A, part I. Could a higher end-*expiratory* transpulmonary pressure be used? Presumably this pertains to the use of SV: PS, APRV, etc. as opposed to CMV?

3) end-inspiratory pressure to the limit combined to end-expiratory pressure to the limit? How may the esophageal catheter be used in the setting of high PEEP-low PS?

As long as the end-inspiratory transpulmonary pressure does not exceed 27–44 cm H_2O for a very limited period of time to be defined, could a high end-inspiratory pressure be used *combined* to a high transpulmonary end-expiratory pressure (e.g., 10 cm H_2O [48] or more?) be used until the FIO_2 is ≤ 0.4, then PEEP lowered?

4) is the PEEP necessary to maintain acceptable oxygenation (SaO_2 = 88–92% under CMV [42] identical or different from the PEEP necessary to avoid cyclical end-expiratory alveolar collapse (see [48])?

II. Maintaining PEEP:

How long should an adequately high level of PEEP be maintained to counteract atelectasis (strictly speaking: the loss of aeration/collapse) or inflammation or increased lung water? accordingly how long should the intervals between PEEP lowering be: 6 h? 12 h? more? Some indications may be found in the ART trial [151].

Improvement of oxygenation presents 2 different time courses (minutes/hours vs. 12 to 72 h):

1) Kirby [90], Borges [91], and Grasso [47] showed an improvement over a few *hours*, as they use high PEEP [90] vs. recruitment maneuvers [91] vs. PEEP tailored to end-inspiratory transpulmonary pressure [47].

2) other studies show an improvement over a few *days* (3–5 d) as they use either spontaneous ventilation-assisted breathing [20, 21] vs. a low stretch strategy [64] vs. medium-high PEEP [92] (Table 7, part I) vs. end-expiratory transpulmonary pressure [48]. Accordingly, an increase in PEEP from 5 to 15 cm H_20 does not lead to an equilibrium in oxygenation even after 60 min in the setting of ARDS (P/F = 177 ± 71) and may "*reflect a progressive modification of the underlying pulmonary pathology, rather than the achievement of a new steady state*" [152]: the unfolding of collapsed alveoli? decreased lung water? decreased inflammation?

The NIH table (Table 4A, part I [42]) implies that the FiO_2 and PEEP should be lowered *simultaneously*. Our observations [28, 30, 71] do not fit with this proposition [42]. Our observations fit with the second group: P/F increased from ≈50 to ≥ 150–200 over 12–72 h. This implies that PEEP is *not* to be lowered simultaneously with FiO_2, *contrary* to the suggestion of the NIH table (Tables 4A, part I and 1, part II).

Decreased muscle tone of inspiratory muscles affects FRC unfavourably [95]. Accordingly, does a preserved muscle tone (i.e., no anaesthetics/opioid analgesics/conventional sedatives but "cooperative" sedation with alpha-2 agonists [13]) affect FRC favourably, once an acceptable P/F is observed?

III. Extubation:

When should extubation be considered? Presumably, this is a function primarily of the overall status of the patient him/herself (i.e. circulation, kidney injury, infection, inflammation, tissue edema/weight), secondly of the ventilatory status and lastly, of the follow-up: intensive physiotherapy/ /rehabilitation and non-invasive ventilation, up to discharge from the CCU?

a) P/F > 150 with PEEP ≤ 10 cm H_2O: the criteria to switch from non-invasive ventilation to tracheal intubation-invasive ventilation uses a P/F < 150 as a cut-off point. Does *reverse* thinking apply? Although this has been accepted throughout this article, this requires evidence-based demonstration, irrespective of the use of CMV vs. SV.

b) P/F > 200 with PEEP ≤ 10 cm H2O?➞]

limb of the P–V curve (above the critical *closing* pressure, Figs 1 and 4 in [49]) or the trial-PEEP. Basically, as long as "Friday night ventilation" [11] handles acute cardioventilatory distress, a driving pressure ≤ 15 cm H_2O (50) is set (Vt ≤ 5 mL kg^{-1} [51]); this implies lowering the VO_2. Then, the PEEP is increased to Pplat = 30 cm H_20. Next, the "trial" PEEP is set to SaO_2 = 88–92% under CMV [41, 52, 53] using the high PEEP-low FiO_2 table [42] (Table 4, part I). The next morning, sophisticated investigations (e.g., CT scan, electrical impedance tomography, balloon, or trial-PEEP [54]) will allow the titration of an individualized PEEP.

b) SV is considered as soon as the acute cardio-ventilatory distress improves [7]. Because the Vt cannot be fixed under PS, the rationale for setting the PEEP before the Vt holds in reverse. First, the PEEP is set to avoid end-expiratory collapse above the critical *closing* pressure and to target the end-*expiratory* transpulmonary pressure, the decremental limb of the P–V curve or a higher pre-defined SaO_2 (trial PEEP; SaO_2 ≥ 98–100%; Table 4, part I). [➞Then, a minimized VO_2 (Table 2, part II), an acceptable hypercapnia [55], a relatively high PO_2 evoking a low RR [40], and a PS set to the minimum [30] will generate the lowest Vt (≤ 5––6 mL kg^{-1}) and minimize firstly: i) the use of respiratory muscles (palpation of SCM; Fig. 3 in [18]) with a low inspiratory trigger, automatic tube compensation [56], rapid pressure rise time [57, 58]; and ii) the inspiratory transpulmonary pressure (low expiratory trigger [59]; Figs 1 and 2 in [33]; Fig. 1 in [37])←].

II. PERSPECTIVES

A. STRATEGIES TO HANDLE EARLY SEVERE ARDS:

1. REQUIREMENTS

Irrespective of any preference for controlled vs. spontaneous ventilation, the oxygenation defect should be *analytically* corrected (§I) (i.e., up-front circulatory optimization, position, normothermia in order to minimize VO_2, CT scan, fiberoptic aspiration, anti-infectious strategy, ERR, itemized assessment of CO_2 vs. H^+ drive, and sympathetic de-activation). To ascertain ARDS, the P/F should be re-assessed after 30 min of standardized ventilation [60] (Vt≈7 mL kg^{-1}, PEEP = 10 cm H_2O, and FiO_2 = 1.0). The reader should be aware that the PEEP = 10 cm H_2O suggested by Ferguson (60) is higher than the PEEP = 5 cm H_2O required by the Berlin definition [61], biasing the selection towards more severe ARDS. Both a low driving pressure [50] and a high PEEP [62] appear to be mandatory in early diffuse ARDS. The Pplat should be based on the end-inspiratory PL (up to 25 cm H_2O) [47] while the PEEP should be based on the end-expiratory PL (0–10 cm H_2O) [48]. *Swiftness* is mandatory due to comorbidities and CCU-acquired diseases; minimizing muscle relaxation (≈5 d) and sedation (≈10 d) is key, irrespective of the assignment in the prone vs. supine position [63], in order to improve the outcome. This swiftness is at odd with a "low stretch" strategy that relies on prolonged intubation [7] (CMV up to improvement followed by PS as quickly as possible; low PEEP < 10 cm H_2O with a Pplat < 29 cm H_2O combined with inotropic/vasopressor support if necessary; historic group ~14 d of CMV; recent group ~17 d) [64].

2. CONTROLLED MECHANICAL VENTILATION: "PROTECTIVE" VENTILATION

"Protective" ventilation (Fig. 1 in [65]) is now optimized and includes a high PEEP [62, 66], a Pplat that is as low as possible [51, 67] (Fig. 2 in [51]) or < 25–30 cm H_2O [46, 68], with an adequate $PaCO_2$/pH [55], time-limited muscle relaxation (24 h [5] or 48 h [2]), and a prone position [63]. An ultra-low Vt may be achieved through veno-venous CO_2 removal [69]. [➞Because lowering the temperature by ~2.4°C lowers the VO_2 by 18% [70], normothermia (≈36 °C) is a non-invasive option to lower the Vt [27, 45, 71]←].

When the Pflex cannot be determined, a PEEP = 15 cm H_2O [72, 73] or 16 cm H_2O [74] or a PEEP ≥ 15 cm H_2O or < 10 cm H_2O can be used in highly or poorly recruitable lungs, respectively. "Magic" numbers (PEEP up to Pplat < 30 cm H_2O, driving pressure ≤ 15 cm H_2O or Vt ≈ 6 mL kg^{-1}) lead to a high PEEP and low driving pressure *only* for the time necessary to stabilize a sick patient ("Friday night ventilation" [11]) and to differentiate focal vs. diffuse ARDS [75, 76]. However, these "magic" numbers expose ~30% of patients to hyperinflation [68]. Therefore, an individualized approach to optimize the end-inspiratory [47] vs. end-expiratory transpulmonary pressure [48] should be adopted as early as possible; this end-expiratory approach will improve oxygenation in severe ARDS [47, 48] and reduce mortality (P = 0.049 on 28 d mortality, n = 30 vs. 31 [48]).

Individualized Vt and individualized PEEP during muscle relaxation combined with proning remains the accepted practice in 2016 [2, 63]. *Indeed, the only interventions to withstand the test of outcome* [77] *are, so far, low Vt/driving pressure [50], muscle relaxants, and the prone position* [2, 63, 77, 78].

3. CMV FOLLOWED BY EARLY TRANSITION TO SV

[➞When severe acute hypoxemic respiratory failure is observed alone i.e. within the setting of single organ failure [27, 28, 30, 71], SV with high PEEP appears to be suitable within 3–12 h following normothermia, controlled H^+ status, intubation, the insertion of lines, imaging, fibre optic bronchoscopy, and a CT scan. In contrast, when uncontrolled infection and severe metabolic acidosis evoke early MOF, an anti-infectious strategy, extrarenal replacement and normothermia should aggressively control the VO_2 and H^+ prior to the initiation of SV [28].

Given these caveats (II A 1), in the setting of single-organ failure, a high PEEP (typically ≥ 15–20 cm H_2O) combined with prone positioning early in severe ARDS dramatically improves the P/F over ~24 h with *only* one session of prone positioning (Quintin, unpublished data). Thus, the CMV may be switched to PS as soon as the SV has recovered after the interruption of muscle relaxants. This schema (III-A 3) is halfway between the schema § II A 2 (muscle relaxant for 24 [5] or 48 h followed by SV [2, 6]) and the schema § II B (early high PEEP-low PS under alpha-2 agonists [27, 28, 30, 71]); "*as soon as some improvement [is] observed, pressure support ventilation [is] started*" [7]. Thus, a "one-size-fits-all" strategy gives way to a patient-by-patient approach←].

B. ANYTHING NEW UNDER THE SUN? YES: ANALYTICAL MANAGEMENT!

[→So, what is new in early severe ARDS? The understanding that has emerged from the ARDS conundrum over the last 50 years currently allows, at this moment, ARDS to be *analytically* addressed. Thus, circulation (venous return, RV afterload, and LV preload [7]), ventilation (H^+, CO_2, O_2, RR, and Vt), position ("upright" position [79–81]), VO_2 [45, 70, 82], temperature [45], intact respiratory neurogenesis, sympathetic de-activation, inflammation, and reduced lung water should be disentangled, one after the other, analyzed and normalized as early as possible to allow for early spontaneous ventilation.

Two different time intervals should be separated:

1) Acute cardio-ventilatory distress ("shock" state): what should be done immediately when a severe ARDS patient arrives at 10 pm in the CCU? Reference [11] delineates a neat step-by-step approach for the management of acute cardio-ventilatory distress. The consensus [2, 11, 63] works nicely as long as the acute cardio-ventilatory distress is considered [11]. Given the remarkable achievements of CMV + muscle relaxation + proning [63], campaigning for SV (Table 2, part II) calls for unremitting rigor.
2) The next morning, given a patient with early severe *stabilized* ARDS, all of the *pathophysiology outlined above points to a direction at odds with the present consensus* (CMV ± muscle relaxation ± prone position) [2, 63]. Indeed, *the intensivist should envision the ARDS patient as an "upright"/sitting individual who is spontaneously breathing, presenting to the emergency department or CCU, and suffering from an oxygenation defect: why should this spontaneously-breathing sitting or supine patient be transformed into a supine anesthetized paralyzed patient, such as one emerging from the operating room?* What is applicable at 10 pm [11] is not applicable the next morning [27, 30, 71] when all investigations (i.e., CT scan and bronchoscopy), physiological measurements (i.e., pressure-volume curve: P-V curve, esophageal catheter: "balloon", and trial-PEEP), and expertise are available. Indeed, a) the use of synchronized IMV in an early trial led to a mortality rate of 16% [83] using synchronized IMV; b) a total of 79% of the patients using synchronized IMV; a total of 79% of the patients (P/F < 300) were managed with PS as long as the RR did not increase disproportionately [39]. These results favour SV [5, 12, 20, 26, 38, 84–89] or APRV+SV [21, 24].

All groups [5–7, 12] emphasize the necessity to switch to SV as early as possible. Irrespective of the CMV vs. SV strategy, achieving a P/F ≥ 150–200 *swiftly* should be the concern (~30 min [47] vs. a few hours [90, 91] vs. a few days [28, 30, 48, 71, 92]). The take-home message remains: "*avoid tracheal tubes, minimize sedation, prevent ventilator-induced lung injury and nosocomial infections*" [69]. Thus, we [27, 28, 30, 71, 93] capitalize on previous approaches to move faster in the same direction. *Stringent physiological principles are to be met analytically*, irrespective of an emphasis on early SV [27, 28, 30, 71, 93] as opposed to CMV ± proning [2, 63]. Preserved respiratory neurogenesis [94], preserved respiratory muscle power and tone [95], the West schema drawn in an *upright* position (Fig. 11 in [96]) and adequate diaphragmatic mechanics (Fig. 1 in [97]) are to be kept in mind: therefore, general anaesthesia (hypnotics, opioid analgesics, muscle relaxant i.e., "analgo-sedation") combined with CMV and/ /or proning makes little sense [95] in a patient with early severe *stabilized* ARDS. Some argue that "*the evidence for beneficial effects of spontaneous breathing has been gathered in less severe… ARDS with modest ventilatory demands*" [98]. Thus, as argued iteratively throughout the present review, analysis is key: in early severe ARDS, the *temperature, Vt, RR, CO_2 and H^+ drives should be fully normalized to lower ventilatory and metabolic demands* [45] *before heading to spontaneous ventilation*. SV and CMV are in a continuum rather as opposed to the two sides of the Great Wall of China. Furthermore, is there any reason [98] to separate moderate and severe ARDS? This distinction [98] does not hold (Fig. 1 in [29]) as the same overall principles apply irrespective of mild vs. moderate vs. severe ARDS [29]. Accordingly, a trial is presently underway using APRV + SV in early ARDS (BIRDS trial: clinicaltrials.gov/ct2/show/ NCT01862016).

Lowering the mortality in severe ARDS (~16% in the best series) [63, 83] implies going *back to physiology* (Table 1, part II)←].

III. CONCLUSION

Early severe ARDS is neither a failure of the ventilatory pump nor of respiratory neurogenesis. Instead, ARDS is caused by a reduction in the surface for O_2 diffusion in the

early stage (restrictive disease) and an *iatrogenic* disease in the later stages [75, 95, 99, 100]. The early management of severe ARDS should be thoroughly *analytical*. Early recruitment [62] without overdistension [68] aims toward swift extubation in order to avoid CCU-acquired diseases. Under stringent conditions (circulation, upright position, VO_2/temperature, acidosis, $PaCO_2$, work of breathing, tidal volume, respiratory rate, absence of respiratory depression, sympathetic de-activation, suppressed agitation: Table 1, part II), spontaneous ventilation [5, 12, 20, 21, 26–28, 30, 38, 71, 84–89] requires an evidence-based demonstration. *Controlled mechanical ventilation with muscle relaxants* [2] *and proning* [63] *remain, in 2016, the accepted practice* [11]. Ongoing research ([101] and Table 2, part II) on the pathophysiology of ARDS will simplify its management and reduce mortality.

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This review is for residents. Thus, the readers should write directly to the corresponding author to pinpoint any error, to generate an erratum if necessary.

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