

Early severe acute respiratory distress syndrome: What's going on? Part I: pathophysiology

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"What we know is the biggest impediment to acquiring new knowledge"

Claude Bernard

To Jean-Marc Bernard, MD, PhD, anesthesiologist, clinician-scientist and friend, who died from pulmonary fibrosis following ARDS contracted while caring for a patient, in the critical care unit

Abstract

Severe acute respiratory distress syndrome (ARDS, $\text{PaO}_2/\text{FiO}_2 < 100$ on $\text{PEEP} \geq 5$ cm H₂O) is treated using controlled mechanical ventilation (CMV), recently combined with muscle relaxation for 48 h and prone positioning. While the amplitude of tidal volume appears set ≤ 6 mL kg⁻¹, the level of positive end-expiratory pressure (PEEP) remains controversial. This overview summarizes several salient points, namely: a) ARDS is an oxygenation defect: consolidation/difuse alveolar damage is reversed by PEEP and/or prone positioning, at least during the early phase of ARDS b) ARDS is a dynamic disease and partially iatrogenic. This implies that the management of the ventilator may be a life-saver by reducing the duration of mechanical ventilation, or detrimental by extending this duration, leading into critical care-acquired diseases. Indeed, a high PEEP (10–24 cm H₂O) appears to be a life-saver in the context of early severe diffuse ARDS; c) tidal volume and plateau pressure cannot be identical for all patients; d) the only remaining rationale for CMV and muscle relaxation is to suppress patient-ventilator asynchrony and to lower VO_2 , during the acute cardio-ventilatory distress. Therefore, in early severe diffuse ARDS, this review argues for a combination of a high PEEP (preferably titrated on transpulmonary pressure) with spontaneous ventilation + pressure support (or newer modes of ventilation). However, conditionalities are stringent: upfront circulatory optimization, upright positioning, lowered VO_2 , lowered acidotic and hypercapnic drives, sedation without ventilatory depression and without lowered muscular tone. As these propositions require evidence-based demonstration, 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, V_t , 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

This overview is for residents heading to the critical care unit (CCU): it a) reviews the pathophysiology of early severe acute respiratory distress syndrome (ARDS; Tables 1–3; b) provides conjectures applicable to therapy; and c) highlights salient figures from the *early* literature (glossary, figures quoted in text available at https://www.researchgate.net/profile/Luc_Quintin/contributions).

There are no clear-cut definitions of early vs. late ARDS (thought to lead to fibrosis). With respect to early ARDS, the interval proposed may last for < 3–4 days (d) [1, 2] up to 1–7 d [3] after the beginning of symptoms or intubation. This manuscript restricts itself to:

- a) early ARDS: it makes minimal references to late ARDS, fluid overload, malnutrition or multiple organ failure (MOF).
- b) *operational* considerations: which level of positive-end expiratory pressure (PEEP) [4], which tidal volume (Vt), controlled vs. spontaneous ventilation? Therefore, the involvement of atelectasis vs. inflammation vs. increased lung water [5] in the genesis of ARDS will be considered cursorily. For simplicity, ARDS will be primarily analyzed as a single-organ failure pertaining to oxygenation. Real-life ARDS within the setting of early MOF will be considered in chapter II (perspectives paragraph; Table 1, part II). Non-ventilator strategies (i.e., prone position, nitric oxide and extra corporeal membrane oxygenation [ECMO]) will be mentioned briefly.

To stay within evidence-based medicine, facts will be separated from conjectures noted between [→.....←] as borrowed from [6]. [→Thus, the biases of this review (spontaneous ventilation: SV in treatment of early severe ARDS) are delineated in the perspectives paragraph and Table 1, part II:

- a) The work of breathing (WOB) should be thoroughly *minimized* using spontaneous ventilation (SV). Thus, the ventilator should be adapted to the patient instead of adapting the patient to the ventilator [7]. Clinically, WOB takes into account the transpulmonary pressure and respiratory rate (RR), which are increased as a function of the lung disease itself and generate high ventilatory demands (Table 1, part I: definition of severe ARDS). These high *ventilatory* demands (Vt, RR) should be differentiated, analytically and therapeutically, with concurring high *metabolic* demands (temperature, agitation, sympathetic activation, etc.).

- b) High positive-end expiratory pressure (i.e. PEEP ≥ 10–24 cm H₂O according to the NIH table; Table 4, part I) should be set early [8]. PEEP should be guided first by echocardiography [9], then, ideally by an esophageal catheter (“balloon”) [10–12], or as a second-best by “trial” PEEP to minimize the effects of overdistension and PEEP (i.e., right ventricular (RV) failure, hypotension, positive fluid balance [13, 14], and baro-trauma: Table 5, part I)←].

ARDS is a very heterogeneous syndrome which combines an acute onset of cyanosis that is refractory to O₂, tachypnea, dyspnea/polypnea (i.e., increased ventilatory demands [15]), reduced compliance, diffuse alveolar infiltration (which becomes more or less severe as a function of the progression or regression of the disease) and an improvement with PEEP = 5–10 cm H₂O [16]. This early description [16] observed swift clinical and radiological improvements in some patients: this suggested, early on, to “buy time”, allowing pneumonia or sepsis to improve, and the lung to heal itself. At that early time, given the incipient [16]

Table 1. Berlin definition of acute respiratory distress syndrome (ARDS) [19]

1) Timing: within 1 week of a known clinical insult or new/worsening respiratory symptoms
2) Chest imaging. ^a bilateral opacities — not fully explained by effusions, lobar/lung collapse, or nodules
3) Origin of Edema: respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
4) Oxygenation ^b
Mild: $200 < \text{PaO}_2/\text{FiO}_2 \leq 300$ with PEEP or CPAP ≥ 5 cm H ₂ O ^c
Moderate: $100 < \text{PaO}_2/\text{FiO}_2 \leq 200$ with PEEP ≥ 5 cm H ₂ O
Severe: $\text{PaO}_2/\text{FiO}_2 \leq 100$ with PEEP ≥ 5 cm H ₂ O
Hospital or 90 days mortality is 45% (42–48%) in the severe ARDS group. Within the severe ARDS group exists a subgroup (15% of all ARDS patients) with a 52% mortality (48–56%) with: P/F < 100, compliance of the respiratory system: $\text{Cr}_s < 20 \text{ mL cm H}_2\text{O}^{-1}$, or standardized minute ventilation at $\text{PaCO}_2 = 40$ ($\text{VE}_{\text{corr}} = \text{minute ventilation} * \text{PaCO}_2/40$) > 13 L min ⁻¹
Refractory hypoxia is defined as $\text{PaO}_2 < 70 \text{ mm Hg}$ on $\text{FiO}_2 = 0.8$ –1 (P/F: 70–87), PEEP > 10 cm H ₂ O for > 12–24 h [30]. Surprisingly, this is an infrequent cause of death: only 15% of all ARDS deaths are caused by refractory hypoxia [30]

^aChest X-ray or CT scan; note that the Berlin definition *excludes* “focal” ARDS caused by atelectasis [87]

^bIf altitude higher than 1000 m, correction factor should be made as follows: $\text{PaO}_2/\text{FiO}_2 * (\text{barometric pressure}/760)$

^cThis may be delivered non-invasively in the mild ARDS group

Note: 1) to adjust Vt, the formula to calculate predicted body weight (PBW) is: Male: ideal body weight = $50 + 0.91 (\text{height [cm]} - 152.4)$; example 186 cm: 81 kg. Female: $45.5 + 0.91 (\text{height [cm]} - 152.4)$; 165 cm: 57 kg²) a better survival is observed when driving pressure is adjusted < 15 cm H₂O [17], rather than Vt considered *per se* (see text). 3) the early template of the Berlin definition considered minute ventilation standardized at $\text{PaCO}_2 = 40 \text{ mm Hg}$ ($\text{VE}_{\text{corrected}} = \text{minute ventilation} * \text{PaCO}_2/40$). Indeed, when severe ARDS is considered, a P/F < 100 with a $\text{VE}_{\text{corrected}} > 13 \text{ L min}^{-1}$ segregate 15% of the ARDS patients with a 52% mortality [19]. [→Thus every effort should be made to normalize temperature, acidosis, hypocalcemia to move on as early as possible to spontaneous ventilation so as to handle the oxygenation defect separately (Table 1, part II)←]

Table 2. Ten clinical entities that may be mistaken for ARDS (Guerin, Intens Care Med 2015, 41: 1099–1102)

	Typical time course for symptoms to develop	Associated symptoms and signs	Characteristic radiographic findings	Bronchoalveolar lavage findings
ARDS Cough, tachypnea with inflammation in the setting of aspiration, severe infection, trauma	Up to 7 days Bilateral opacifications (interstitial or alveolar); CT: ground glass and denser opacifications	Increased neutrophils, especially on early stage		
Congestive heart failure, pulmonary edema	Variable from acute (hour) to chronic (months) depending on type of heart disease	Peripheral edema, dyspnea, orthopnea, chest pain	Interstitial or alveolar opacification, usually central but may be diffuse or asymmetric; pleural effusions (right > left), cardiomegaly, vascular congestion	Pink, frothy fluid without acute or chronic cellular inflammation
Idiopathic pulmonary fibrosis (usual interstitial pneumonitis)	Variable: usually many weeks, months, few years	Dry cough, “Velcro” crackles, dyspnea on exertion and rest in advanced stages	Diffuse interstitial markings, traction bronchiectasis, honeycombing, predominantly in bases, scattered ground glass opacification	Increased neutrophils
Cryptogenic organizing pneumonia (bronchiolitis obliterans with organizing pneumonia)	Variable but usually over weeks-months	Cough, fever, dyspnea, malaise	Bilateral, frequently peripheral opacifications. CT: diffuse or patchy ground glass opacifications, patchy air-space opacification, small nodules	Increased cells, predominantly lymphocytes, but also increased neutrophils and eosinophils
Non specific interstitial pneumonitis	Variable: usually over weeks-months	Dry cough, dyspnea, fatigue, may be associated with connective tissue disease	Patchy ground glass opacification, interstitial opacifications, symmetric, peripheral, subpleural	Increased lymphocytes
Granulomatosis with polyangiitis (Wegener’s granulomatosis)	Variable, but usually over weeks-months	Cough, dyspnea, malaise, hemoptysis; may present with sinusitis or glomerulonephritis	Diffuse alveolar and interstitial opacifications; multiple nodules diameter 2–8 cm frequently with cavitation, air space consolidation; diffuse alveolar opacifications if pulmonary hemorrhage	Variable depending on activity of disease and treatment: increased neutrophils, eosinophils and lymphocytes may be seen; increased Ig G/ /albumin compared with serum
Diffuse alveolar hemorrhage	Days-few weeks	Cough, hemoptysis, dyspnea; may present with granulomatosis with polyangiitis or systemic lupus erythematosus, bone marrow transplantation or exposure to cytotoxic drugs	Diffuse alveolar infiltrates, usually bilateral but may be asymmetric and associated with nodules if granulomatosis with polyangiitis, some of which may cavitate	Increasingly bloody lavage return with multiple aliquots
Goodpasture’s syndrome	Variable, usually progresses over days-weeks	Cough, hemoptysis, hypoxemia; may present with acute kidney failure	Bilateral predominantly alveolar opacifications, nonspecific	Increasingly bloody lavage return with multiple aliquots
Acute hypersensitivity pneumonitis	Within several hours of exposure to offending antigen	Cough, dyspnea, fatigue	Diffuse interstitial opacifications; CT: ground glass	Increased lymphocytes
Acute eosinophilic pneumonia	Usually < 10 days	Cough, dyspnea, chest pain, crackles, hypoxemia	Diffuse interstitial opacifications, alveolar when more advanced; small pleural effusions; CT: ground glass and dense opacifications	Eosinophilia
Drug-induced lung disease	Variable, usually over several months	Cough, dyspnea, hypoxemia after exposure to amiodarone, bleomycin, etc.	Variable, may present as interstitial (more likely) or alveolar opacifications	Variable; amiodarone toxicity may involve alveolar proteinosis, acute and chronic inflammation

Table 3. Studies most often used in this review

Author	Year	Setting	Primary end-point	n	Ventilatory mode	Ppeak/Plat (cm H ₂ O)	PEEP (cm H ₂ O)	Vt (mL kg ⁻¹)	FiO ₂	Sedation	Main result	Mortality (%)
Kirby	1975	Acute respiratory insufficiency	Effect of increasing PEEP following failure of low PEEP level (up to 20 cm H ₂ O) to lower QS/Qt		IMV		Up to 32 cm H ₂ O	12			Pneumothorax: 14%. High incidence of subcutaneous emphysema. PEEP as a "fundamental mean of aborting/reverting" ARDS	39%
Suter	1975	Acute respiratory failure	Delineate optimal PEEP according to maximal compliance		Volume controlled on assist mode	N/a	6–18 up to a decrease in cardiac output	13–15	0.21–0.75		At "best" PEEP, optimum values are observed for O ₂ transport, compliance, lowest dead space, SvO ₂	
Darioli	1984	Status asthmaticus	Evaluate an approach set to oxygenation and lowering airway pressure	n = 26	Volume controlled	Ppeak ≤ 50		8 to 12 adjusted to Ppeak ≤ 50 or PaCO ₂ < 90 mm Hg	FiO ₂ set to normal PaO ₂	Diazepam	Correction of hypoxemia with manual ventilation using 6 to 8 breaths per min. Hypoventilation up to 4 d i.e. liquefaction of secretions; barotrauma: 3 out of 26; 12%	Mortality: 0%
Hickling	1990	P/F < 150; lung injury score > 2.5	Evaluate mortality in ARDS patients with Ppeak < 40 cm H ₂ O	n = 50	Synchronized intermittent mandatory ventilation	Ppeak < 40 cm H ₂ O	PEEP = 9 (range: 0–25 cm H ₂ O)	Vt as low as 5 mL kg ⁻¹ with PaCO ₂ < 70 mm Hg			Tachypnea; hypercapnia in 16 patients (32%); pH = 7.02 in one patient	Actual mortality: 16%; predicted mortality on Apache II: 40%
Amato	1998	P/F: protective: 112; conventional: 134	Mortality and complications upon protective vs. conventional ventilation	24 (conventional) vs. 29 (protective)	Pressure controlled or PS mostly	Driving pressure < 20 cm H ₂ O; protective: 32; conventional: 34	PEEP = Pflex+2 cm H ₂ O or empirical: 16 cm H ₂ O; protective: 16 cm H ₂ O; conventional: 7 cm H ₂ O (first hour)	6 vs. 12		Fentanyl/diazepam	Barotrauma: 42% (conventional) vs. 7% (protective); improvement P/F within 24–48 h in protective group; stagnation of P/F in conventional group	71% death (conventional) vs. 38% (protective); P < 0.001
Brower	2000	P/F < 300 (ALI; ARDS)	Outcome upon low Vt	432 (low) vs. 429 (traditional)	Volume-assist-control	Day 1: low: 25; traditional: 33	Use of PEEP/FiO ₂ table; day 1: low: 9.4; traditional: 8.6	6 vs 12	Low: 0.56; conventional: 0.51		Barotrauma: similar	Low Vt: 32%; traditional: 40%; P = 0.007

Table 3. (cont'd.). Studies most often used in this review

Author	Year	Setting	Primary end-point	n	Ventilatory mode	Ppeak/Plat (cm H ₂ O)	PEEP (cm H ₂ O)	Vt (mL kg ⁻¹)	FiO ₂	Sedation	Main result	Mortality (%)
Mercat	2008	P/F < 300	Outcome upon high PEEP compatible with Pplat ≤ 28–30 regardless of effect on oxygenation	Low: 382; high: 385	Volume-assist-control	< 30	Low: external+intrinsic PEEP < 9; high: titration up to Pplat ≤ 30	6			The high PEEP group had higher ventilator-free days and organ failure free days	Low: 31%; high: 28%
Meade	2008	P/F < 250	Outcome on low Vt vs. low Vt; recruitment maneuvers, and high PEEP	Low: 475; high: 508		< 30	PEEP according to FiO ₂ /PEEP; day 1 high: 15; low: 10	6	Table		The high PEEP group had lower rate of refractory hypoxemia	Low: 40%; high: 36%
Ferguson	2004	P/F < 200	Impact of screening process using standardized ventilator settings on ARDS prevalence	n = 41	Volume-controlled	Ppeak < 35	10	7–8	1		Persistent ARDS: 41% of the patients; P/F = 92 to 94 after 30 min of standardized ventilation; Transient ARDS: 58%, P/F = 136 to 310	Persistent ARDS: mortality: 53%; Transient ARDS: 12%
Villar	2007	P/F < 300 or < 200	Identification of persistent ARDS following standardized setting; outcome according to P/F < 300 or 200	n = 170	Volume assist-control mode	5 to 10 according to protocol	5 to 10 according to protocol	7 to PBW	0.5 to 1 according to protocol		58% of the patients met criteria for established ARDS after day 1 is observed on PEEP ≥ 10 and FiO ₂ ≥ 0.5; mortality: 45%	Hospital mortality = 45% (P/F < 200); 20% mild ARDS (P/F < 300); 6% P/F > 300
Villar	2006	P/F < 200 after 24 h on standardized setting;	PEEP = Pflex+2 and low Vt should improve outcome	n = 50 (Pflex+low Vt) vs. 45 (control)	Volume assist-control	Control group: PEEP ≥ 5; Pflex group: PEEP = Pflex+ 2 cm H ₂ O	Control: Vt = 9–11 PBW; low Vt = 5–8; PCO ₂ = 35–50 by adjusting RR	Control: FiO ₂ to SaO ₂ > 90% and PaO ₂ = 70–100			Lower number of ventilator free days and additional organ failure in Pflex-low Vt group	Control: hospital mortality 55% vs. Pflex-low Vt = 34%, P = 0.04

Table 3. (cont'd.). Studies most often used in this review

Author	Year	Setting	Primary end-point	n	Ventilatory mode	Ppeak/Plat (cm H ₂ O)	PEEP (cm H ₂ O)	Vt (mL kg ⁻¹)	FIO ₂	Sedation	Main result	Mortality (%)
Talmor	2009	P/F < 300	Oxygenation can be improved by adjusting PEEP to maintain positive transpulmonary pressure (P/F after 72 h)	n = 30 (balloon) vs. n = 31 (conventional)			Balloon: PEEP = 0–10 according to table Both groups: 6 mL kg ⁻¹ to PBW (balloon group: end inspiratory transpulmonary pressure < 25 cm H ₂ O; conventional: as Brower 2000 low Vt), 40 < PaCO ₂ < 60 mm Hg		FIO ₂ to PaO ₂ ; 55–120 mm Hg or SaO ₂ > 88%		P/F higher by 133 after 72 h in the balloon group (balloon: 147 to 280; conventional: 145 to 191)	Mortality (28 d) lower in balloon group (P = 0.049)
Grasso	2012	P/F < 100 presenting for ECMO	Would use of end expiratory transpulmonary pressure ≥ 25 cm H ₂ O lead to reduce the incidence of ECMO?	n = 7 (ECMO) vs. 7 (non-ECMO)	ARDS network protocol	PplatRS = 31 cm H ₂ O	PEEP: ECMO group: 17 cm H ₂ O; non ECMO: 17 increased to 22				Increasing end-inspiratory transpulmonary pressure of the lung from 17 to 25 led to increase P/F from 67 to 180 over 20–30 min and no ECMO	
Cereda	2000	P/F < 300	Success rate of transitioning from CMV to PS in mild ARDS	n = 48	Continuous positive pressure ventilation (volume-controlled) then pressure support		PEEP < 15	PS level to totally unload the elastic work of breathing			Success: n = 38 (79%); PS = 15, PEEP = 9, duration of intubation: 9 d; failure: 10 patients, PS = 22, PEEP = 9, duration of intubation: 20 d, major cause of failure: high respiratory rate, increased PaCO ₂ , decreased PaO ₂ , hypotension, decreased cardiac output	
Putensen	2001	severe multiple trauma; P/F < 300 or P/F < 200	Would spontaneous breathing with APRV prevent deterioration of gas exchange or allow's faster recovery than controlled mechanical ventilation	APRV: n = 15; PCV: n = 15	Airway pressure release ventilation vs pressure controlled ventilation		PEEP > Pflex+2	Vt < 7 mL kg ⁻¹ to 45 < PaCO ₂ < 55 mm Hg	FIO ₂ adjusted to PaO ₂ < 60 mm Hg	Midazolam-sufentanil to Ramsay 3	APRV: increases in compliance, PaO ₂ , P/F, cardiac index, lower requirements in noradrenaline, dobutamine, midazolam-sufentanil	
Guerin	2013	P/F < 150	Would early prone positioning improve outcome upon severe ARDS?	Prone: 237; supine: 229	Volume controlled mode	Pplat ≥ 30 cm H ₂ O, PEEP according to table	Vt = 6 mL kg ⁻¹ PBW		Table		Number of prone sessions: 4 ± 4, duration: 17 ± 3 h	Mortality: prone: 16%; supine: 33%; lowered incidence of rescue therapy in the prone group

Table 4. O₂ toxicity and absorption atelectasis in the setting of high FiO₂
A: High PEEP/lowFiO₂ table generated by the ARDS network (“NIH table”) [141]

FiO ₂	0.3	0.3	0.4	0.4	0.5	0.5–0.8	0.8	0.9	1.0
PEEP (cm H ₂ O)	12	14	14	16	18	20	22	22	22–24

This table is referred to by most groups, despite its shortcomings (experts’ consensus [141]). Nevertheless, during a recent international seminar (Paris international conference, June 2016, held by the Francophone Society of Critical Care), all experts reported the use of high PEEP (≥ 15–20 cm H₂O) very close to the ones proposed in the NIH table.

Protocol changes [141] allowed one to use higher levels of PEEP (up to 18–24 cm H₂O) in both low and high PEEP groups when high O₂ concentration was needed to withstand poor oxygenation (Vt = 6 mL kg⁻¹, Pplat ≤ 30 cm H₂O). The reader should note that:

- a) high PEEP levels are to be considered *before* heading to high FiO₂ in strong contrast to what is observed in daily practice, bearing in mind absorption atelectasis and O₂ toxicity.
- b) target SaO₂ was set to 88–95% or PaO₂ = 55–80 mm Hg under CMV [141]. For memory, the knee on the O₂ saturation curve (~90%) roughly corresponds to PaO₂ ≈ 60 mm Hg. SaO₂ ≈ 50% corresponds to PaO₂ ≈ 25 mm Hg [1].
- c) the NIH table (Table 4A) is much more stringent than the practice we observe in most French CCUs and even our present practice biased toward high high PEEP (FiO₂ = 0.4, PEEP = 10): indeed a PEEP = 12 cm H₂O corresponds to an FiO₂ = 0.3 in the NIH table.

[- Three different time intervals are to be managed differently:

- a) acute cardio-ventilatory distress (“shock” state): using FiO₂ = 1 appears reasonable for a limited period of time [158], given O₂ toxicity and re-absorption atelectasis.
- b) early stabilized severe ARDS proper: following stabilization, a relatively low SaO₂ (88–95%) [141] is acceptable during the acute phase of stabilized severe ARDS, under CMV, outside the shock state [158]. Indeed, severe hypoxia is not lethal in fit climbers [159]. Given these premises [159], low SaO₂ (88–92%) [160] is acceptable in early stabilized severe ARDS under CMV + PEEP: oxygenation is achieved with high PEEP despite relatively low FiO₂.
- c) weaning: does this applies during the weaning phase under PS? When CMV + high PEEP is considered [141], weaning is initiated when acceptable arterial oxygenation is achieved at the same PEEP and FiO₂. This implies that PEEP and FiO₂ are lowered *simultaneously* under CMV+high PEEP [-].

B: Effect of high FiO₂ on respiratory rate under spontaneous ventilation [161]

	H1	I	L	H2
PaO ₂ (mm Hg)	158 ± 68	75 ± 12	55 ± 6	152 ± 68
SaO ₂ (%)	96.5 ± 1.6	92.6 ± 2.7	86.3 ± 3.1	96.2 ± 1.5
PaCO ₂ (mm Hg)	45.1 ± 8.0	42.9 ± 6.8	41.1 ± 6.4	45.1 ± 11.0
pH (arterial)	7.43 ± 0.04	7.45 ± 0.04	7.46 ± 0.04	7.43 ± 0.05
RR (1 min ⁻¹)	25 ± 5.5	30.6 ± 7.5	34.0 ± 7.6	25.5 ± 6.3

High (H): minimum FiO₂ at which 95 < SaO₂ < 100; Intermediate (I): idem with 90 < SaO₂ < 95; Low (L): idem with 85 < SaO₂ < 90.

Unfortunately, in the setting of ARDS, relative hypoxia, as tolerated during the weaning of COPD patients (SaO₂ > 85%), leads to high RR in spontaneously breathing patients (Table 4B) [161]. Conversely a high PaO₂ is followed by a low RR, under SV-PS. Therefore, during weaning under SV, lowering at the same time FiO₂ and PEEP if using the NIH table may not be applicable, as a low RR is the main goal [119]. In stabilized early severe ARDS under SV, PEEP is kept high while lowering FiO₂ as rapidly as possible to avoid O₂ toxicity. Thus, our approach [121, 162–166] is delineated in Table 1, part II

C: Absorption atelectasis (Figs 21, 74, 80–1 in [83])

“[T]he increase rate of collapse of a closed pocket when air is replaced by O₂ has been known since 1879 [Lichtheim]” [45]. Accordingly, alveoli (“lung unit”) with a low inspired VA/Q ratio collapse upon breathing at high FiO₂ [45]. This explains shunt and radiological atelectasis following the breathing at FiO₂ = 1. The outflow of gas from the alveolus through the alveolar-capillary membrane result in a condition of absent expired ventilation, leading to shunt without airway closure due to atelectasis of the unit. Furthermore, in the setting of high FiO₂, when PvO₂ decreases (exercise, heart failure, VA/Q inequalities, shunting), more alveoli become vulnerable to collapse. Conversely, all things equal, increases in PvO₂ tend to reduce the amount of atelectasis [45]

Absorption atelectasis explains that the shunt measured in the setting of FiO₂ = 1 overestimates the shunt present during breathing air: “the Pa O₂/FiO₂ ratio is influenced not only by ventilator settings and PEEP but also by FiO₂. First, changes in FiO₂ influence the intrapulmonary shunt fraction, which equals the true shunt plus ventilation-perfusion mismatching. At FiO₂ 1.0, the effects of ventilation-perfusion mismatch are eliminated and true intrapulmonary shunt is measured. Thus, the estimated shunt fraction may decrease as FiO₂ increases if V/Q mismatch is a major component in inducing hypoxemia (e.g., chronic obstructive lung disease and asthma). Second, at an FiO₂ of 1.0 absorption atelectasis may occur, increasing true shunt. Thus, at high FiO₂ levels (> 0.6) true shunt may progressively increase but be reversible by recruitment maneuvers.” [22]

knowledge, alveolar “recruitment” could not be delineated from overdistension. Recruitment involves the PEEP level, low end-expiratory transpulmonary pressure causing cyclical alveolar opening and collapse, and atelectrauma; by contrast *overdistension* involves dynamic lung distension, Vt or better driving pressure [17], and alveolar hyperinflation caused by end-inspiratory transpulmonary pressure such as volutrauma at end-inspiration.

Changes in the PEEP and FiO₂ modify the PaO₂/FiO₂ (P/F) ratio (normal > 350) [18]. P/F is a convenient index in order to classify ARDS severity (PEEP ≥ 5 cm H₂O; Table 1, part I) [19]. However, P/F presents with shortcomings: it a) lumps together the true shunt (perfusion of unventilated alveoli) and absorption atelectasis [20–22] (Table 4, part I); and

b) is affected by hemoglobin concentration and changes in A-VDO₂ secondary to cardiogenic shock (enlarged), septic shock (reduced) or intra-cardiac shunt [23–26] (detail in § cardiopulmonary interactions).

The mortality of severe ARDS (P/F < 100) is 45% [19]. A 16% mortality has been reported in the best series (P/F < 150) [27]. Indeed, the low mortality achieved in 1990 [28] was achieved again in 2013 [27] in sicker patients by proning. Mortality should be broken down as follows:

- a) early on, few deaths were linked to terminal respiratory failure [29] and only 16% of patients die from irreversible respiratory failure. A recent paper confirms infrequent deaths following refractory hypoxia (15% of all ARDS deaths) [30]. A 2% mortality from respiratory

Table 5. Barotrauma

The evolution of Pplat under low vs. high Vt and low vs. high PEEP is to be considered. Amato [131] observed that Plat *decreased* from 32 ± 1 cm H₂O (control) to 24 ± 1 cm H₂O (day 2–7) in the protective group and *increased* from 29 ± 1 cm H₂O to 38 ± 1 cm H₂O in the conventional group; (protective group: PEEP > Pflex + 2 cm H₂O, Vt < 6 mL kg⁻¹, driving pressure < 20 cm above PEEP, permissive hypercapnia, pressure-controlled ventilation; PEEP: protective group: 16 ± 1 cm H₂O; conventional group: normocapnia, Vt = 12 mL kg⁻¹, lowest PEEP to acceptable oxygenation = 9 ± 1 cm H₂O) [131]. *The conventional group was not healing*: high initial PEEP appeared beneficial, even if Pplat was increased, as long as the driving pressure did not change disproportionately [131]. These investigators [17, 40, 131] insisted, early on, on low driving pressure ≤ 15 cm H₂O. In this trial, the benefit of higher PEEP (≤ 24 cm H₂O) are evident regarding mortality (28 days (d) mortality: 38 vs. 71%, $P < 0.001$; hospital mortality: ns) but also regarding barotraumas (7% vs. 42%; $\hat{P} = 0.02$). Therefore, *the data show no link between early high PEEP and barotrauma, quite the contrary* [131]. The observation is: the stiffness of the lung observed in *late* ARDS (fibrosis) leads to pneumothoraces (see § driving pressure and Table 6); by contrast pneumothoraces are observed less often in the setting of *early* ARDS: at this time the stiffness of the lung is relatively low and stay low provided the driving pressure is low [17]

A similar observation is made when PEEP is set to the highest level compatible with an acceptable Pplat ≤ 28 –30 cm H₂O [125]: Pplat stays to 21 ± 5 cm H₂O in the minimal distension group (i.e. low PEEP) to day 7, while Pplat decreases from 27 ± 2 to 24 ± 6 cm H₂O in the setting of high PEEP. When PEEP is considered, it stays identical in the minimal distension group (7 ± 2 cm H₂O vs. 6 ± 2 cm H₂O). By contrast, high PEEP is lowered from 15 ± 3 to 9 ± 5 cm H₂O between day 1 and 7 [125]. The implication is clear: high PEEP is followed by reduced driving pressure, as opposed to what in observation in the low PEEP group: *the lung stiffens in the low PEEP group and regains elasticity in the high PEEP group*. This observation was confirmed [31, 105, 141, 167]. Additionally, P/F does not change over 7 days [141]. High PEEP combined to low driving pressure (low Vt and acceptable Pplat) recruits alveoli but allows Pplat/Ppeak to be lowered *faster* (i.e., more recruitment, less overdistension). Secondly, the incidence of barotrauma was much *lower* in the high PEEP group with PEEP set up to 24 cm H₂O (7 vs. 42%; $P = 0.02$) [131] but similar between low and high PEEP in other large trials with similar mortality [125, 141, 167]

Higher PEEP were observed in the low Vt group at early intervals (presumably due to lower Pplat) [105]. [→ Thus, higher PEEP may be viewed as having recruited more alveoli and cured *earlier* the oxygenation defect in the low Vt group. By contrast, *higher* PEEP levels were necessary at *later* intervals in the high Vt group: *the high Vt group was not healing but getting worse over time*←]. This trial was criticized as a) sicker patients were randomized to the low Vt with slightly higher PEEP group (P/F = 158 ± 73 vs. 176 ± 76), thus negating possible favorable outcome b) some groups insist on low driving pressure (< 15–20 cm H₂O) rather low Vt *per se* [40]. This latter view [17, 40, 131] fits with an end-*inspiratory* transpulmonary pressure limit ≈ 27 cm H₂O at partial inspiration in young healthy volunteers [132]

The combination of recruitment maneuvers (PEEP = 45 cm H₂O, driving pressure = 15 cm H₂O, i.e., Pplat up to 60 cm H₂O total) followed by a high PEEP course (20 ± 5 cm H₂O) led to an 8% incidence of barotrauma [40]. When Vt is considered, barotrauma was similar between Vt = 6 mL kg⁻¹ and 12 mL kg⁻¹ groups. In meta-analyses, high PEEP did not lead to an increased incidence of barotrauma (168, 169). A reduction of barotrauma was observed when low Vt + high PEEP as opposed to high Vt + high PEEP [170]. In a retrospective analysis, a similar observation is made when “low stretch” + high Vt is opposed to “low stretch” + low Vt: fewer pneumothoraces were observed in the low stretch + low Vt group (3% vs. 21%) [32]. Thus barotrauma is more closely associated with unsatisfactory strategies (e.g., high Vt or descent into late ARDS) than with a level of PEEP *per se* (high vs. low PEEP or “cardiological approach” [24] vs. “open lung approach”). Taken together, a high PEEP is not by itself linked to barotrauma. Are high PEEP linked to earlier recovery, less cyclical end expiratory collapse, less fibrosis and less barotrauma, as long as the driving pressure is low [17]?

- failure is observed ($n = 50$) following the introduction of spontaneous ventilation (synchronized intermittent ventilation, SIMV) with permissive hypercapnia [28]. Accordingly, when protective vs. conventional ventilation was compared, few deaths were linked to refractory respiratory failure (protective: Vt = 5–8 mL kg⁻¹, PEEP = Pflex + 2 cm H₂O, death = 12.5%; conventional: Vt = 9–11 mL kg⁻¹ PBW, PEEP ≥ 5 cm H₂O, death = 25%) [31].
- b) The bulk of the mortality is linked to circulatory or multiple organ failure (MOF). Most deaths in ARDS patients are related to sepsis, cardiac failure or MOF (overall mortality = 68%) [29, 31]. Early death was linked to early circulatory failure (i.e., refractory septic shock) [24]. Late deaths were related to refractory respiratory failure (presumably late ARDS) or MOF and were uncommon in the recent group (i.e., protective ventilation and proning; “historic” group = 64%; recent group = 32%) [24, 32].

[→ Therefore, is the core remaining mortality (~16–45%) related to comorbidities or critical care-acquired diseases? The answer to this question would explain why ARDS was postulated to be partially generated by mechanical ventila-

tion [33–36] irrespective of the progression of the disease (iatrogenic disease or ventilator-induced lung injury (VILI)). This hypothesis implies *swift* therapy (“avoid tracheal tubes, minimize sedation, prevent ventilator-induced lung injury and nosocomial infections” [37]) and led to the biases exposed above←].

I. PATHOPHYSIOLOGY: EVOLUTION OF THE IDEAS REGARDING ARDS

First, the management of early severe ARDS is at odds with the management of the acute exacerbation of chronic obstructive pulmonary disease (COPD) (e.g., in the setting of COPD, the necessity to rest the respiratory muscles for ≥ 12 –24 h with CMV and the relative hypoxia to SaO₂ = 88–92% during weaning). Secondly, ARDS is a “confusing and difficult problem” (i.e., a *conundrum*) that requires the deconstruction of a puzzle; then, the pieces of the puzzle are to be re-assembled to deduce the therapy. [→ Four issues should be *analytically* differentiated: the absence of failure of respiratory neurogenesis; the absence of respiratory muscle failure (at variance with poliomyelitis or the acute exacerbation of COPD); a ventilation/perfusion mismatch

leading to a VA/Q defect (Fig. 1 in [38]); and increased ventilatory demands (increased WOB: increased V_t [15] and/or RR caused by lung disease itself, opposed to metabolic demands: temperature, sepsis, metabolic acidosis, hypercapnia, sympathetic activation, respiratory generator activation). *Hypoxia can be handled efficiently only when all of these factors have been analytically separated* [41]. Two views are at odds in order to handle hypoxia: a) opening and keeping the alveoli open (“open lung approach”) [33, 39, 40] bearing in mind the primarily beneficial ventilatory consequences (recruitment); and b) optimizing circulation (“cardiological” approach) and avoiding RV dilatation [41] while bearing in mind the primarily detrimental circulatory consequences of high PEEP (RV “afterloading”). [→Thus, optimized circulation [24] combined with the recruitment of a “penumbra” area next to the atelectasis should increase the P/F > 150–200 with PEEP ≤ 10 cm H₂O as swiftly as possible. In the present review, based on the definition of severe ARDS (P/F < 100), on the criteria for intubation (P/F < 150), and an overall improved condition, the operational definition of “cured” ARDS will be a P/F > 150–200 with a PEEP ≤ 10 cm H₂O, which allows for extubation, continuous non-invasive ventilation (NIV) (Table 2, part II) [41]. Irrespective of the PEEP, this recruitment should neither enlarge the RV nor encroach on the LV (leftward septal bulging, reduced venous return within an unstretchable pericardium) to avoid reduced cardiac output and a “low PO_2 effect” [24]. Given that circulatory optimization is the key to stabilizing ARDS [24] and that circulation is too often ignored in the setting of ARDS, circulation will be considered first.

A. CARDIOPULMONARY INTERACTIONS

The heart-lung apparatus is a gas/blood exchanger in series. Thus, managing an oxygenation defect requires increasing the flow to the alveoli [24, 42, 43] together with an increase in the O₂ diffusion surface, to the alveolar recruitment [33]: to handle early severe ARDS, *circulatory improvement comes first* [24, 42–44]. Indeed, the oxygenation index P/F is affected by circulation [26]: a) a “low PvO₂ effect” decreases oxygenation and overestimates lung injury b) by contrast, a low cardiac output lowers the shunt, increases P/F and underestimates the lung injury [45] c) RV overload re-opens a foramen ovale and increases shunt [46].

1. CARDIAC OUTPUT

Cardiogenic shock: Under CMV, dogs following cardiac tamponade were alive 3 h after the onset of cardiogenic shock; in contrast, the SV animals died after ~2.3 h during the onset of severe lactic acidosis [47]. Lactates remained lower under CMV than under SV [48]. The reader should note that this animal model [48] investigates changes that occurred over several hours and is at odds with the induction

of anesthesia under SV in patients presenting with cardiac tamponade, which lasts for a few minutes from the induction to pericardiocentesis. The respiratory muscles received 21% (SV) vs. 3% (CMV) of the CO. [→Because CMV modifies the distribution of CO to the respiratory muscles [48], muscle relaxation combined with CMV is only one [49, 50] of several solutions. This result [47, 48] does not necessarily imply that SV is intrinsically detrimental in ARDS patients. A sober, more analytical, interpretation is:

- Time interval: acute cardio-ventilatory distress (“shock” state) is different from early stabilized severe ARDS. Therefore, two different time intervals require two different strategies (CMV + paralysis (1) opposed to SV).
- Synchrony: perfect synchrony of the ventilator to the patient is required [7] irrespective of the time interval (acute cardio-ventilatory distress vs. early severe ARDS) and how synchrony is achieved.
- Ventilatory demands: if every cause of increased WOB is dealt with, *analytically*, minimizing the WOB appears to be relevant from acute cardio-ventilatory distress [1, 47, 48] to weaning [51], irrespective of the use of CMV + muscle relaxation as opposed to recent modes (i.e., airway pressure release ventilation: APRV, or inspiratory flow assistance [52] i.e. pressure support [PS]) [41].

Oxygen consumption (VO₂): In stable postoperative patients without ARDS, a PS = 15 cm H₂O preserves diaphragmatic contraction while suppressing WOB [53]. WOB accounts for 11% of the VO₂ (6–15%) during spontaneous ventilation-continuous positive airway pressure (CPAP) [53]. By contrast, WOB is lowered in a similar manner during CMV and PS = 15 cm H₂O [53]. When weaning is considered in stable COPD patients, the difference in VO₂ between SV and CMV during unsuccessful weaning may increase from 2–3% to 10–59% (SV volunteers vs. COPD patients; mean = 27% of VO₂; increased RR from 19 ± 1 breaths per min to 31 ± 8) [51]. Accordingly, lowering the VO₂ allows smoother weaning [54] (Figs 1 in [49] and [54]). To our knowledge, no data are available that directly relate VO₂ or CO to WOB and the lactate concentrations in early ARDS.

In the setting of early acute non-hypercapnic respiratory failure (AHRF), increased V_t (successful NIV: 8 mL kg⁻¹; unsuccessful NIV: 12 mL kg⁻¹) and RR (successful NIV: 33 cpm; unsuccessful NIV: 36 cpm) were observed [15]. These high V_t should be opposed to the observation of smaller V_t (“rapid shallow breathing”) in the setting of “mostly... chronic... lung injury” (late ARDS) [2, 55]. Thus, intact ventilatory muscles and increased respiratory drive are inferred in early AHRF [15]. Therefore, VO₂ may be lowered by 32% by muscle relaxation when vigorous respiratory efforts are present [49] (Fig. 1 in [49]). Lowering the temperature from 39.4 to 37.0°C reduces the VO₂ by 18% and the VCO₂ by 20% [56]. As ARDS rarely presents itself as a “pure” oxygenation disease

(single-organ failure presenting with high ventilatory demands only), an elevated temperature is often present due to increased metabolic demands: a) sepsis; b) major metabolic acidosis; c) increased WOB; or d) sympathetic hyperactivity. [→ Thus, normothermia ($\sim 36^\circ\text{C}$) has a place in the armamentarium, especially when combined with minimized WOB under SV. Nevertheless, too few experts insist on the importance of lowering the VO_2 when oxygenation is the concern: “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” [57]. Accordingly, reducing the VCO_2 allows for the selection of very low Vt , minimizes hypercapnia, and alleviates its consequences on the RV [58]. In patients with septic shock, early normothermia lowers the vasopressor requirements and 14 d mortality [59]. Thus, lowering the VO_2 [56, 57] should be considered throughout early severe ARDS from acute cardio-ventilatory distress well into stabilization and weaning. This recommendation contrasts with the observation that a high fever in ARDS patients is associated with higher survival [60]. Possibly, patients with elevated temperatures [60] present with a high sympathetic activity and withstand major sickness ←].

Shunt vs. cardiac output (Fig. 5 in [23]): The shunt is a function of the cardiac output [23]. When increasing the PEEP does not result in decreased CO, decrements in the shunt are small [23]: newly recruited alveoli are presumably not perfused (increased VA and constant Q). Thus, any change in the P/F should be interpreted at a constant CO: indeed, the oxygenation increase induced by PEEP may not be due to the alveolar recruitment but to the decreased CO and decreased shunt and possibly capillary de-recruitment [1]. Accordingly, the CO and shunt decrease simultaneously in the presence of PEEP = 20 cm H_2O [44]. Moreover, increased CO and constant shunt occur when the recruited alveoli are perfused by the increased flow (increased VA and increased Q). [→ The goal of the treatment is to combine optimized circulation with alveolar recruitment of a “penumbra” area ←].

2. CARDIAC FUNCTION

Pulmonary hypertension [61] is associated with death [62] because it impedes RV ejection in $\sim 20\%$ of ARDS patients. Therefore, this vascular disease needs to be considered. Pulmonary hypertension was observed in patients with ARDS irrespective of the presence of hypoxemia or the pulmonary blood flow. This phenomenon was related to active vasoconstriction, decreased lung volume, increased interstitial pressure and edema, diffuse microemboli/thrombosis, and microvascular obstruction by fibrosis [61]. During late ARDS (2–5 days after tracheal intubation or 7–9 days from the beginning of respiratory symptoms), pulmonary artery filling defects (PAFD) were observed more often in patients presenting severe “acute respiratory failure” (ARF),

especially when disseminated intravascular coagulation was present. The mortality rate was higher when PAFD were present (PAFD present, mortality: 79%; normal angiogram, mortality: 39%) [63]. However, elevated pulmonary pressure was observed irrespective of the presence or absence of PAFD: more than one causative factor may be responsible for pulmonary hypertension [63]. This vascular disease may be permanently “vaso-destructive” and associated with death; conversely it may be “vaso-reactive” and reversible [63] either spontaneously or following treatment. The alveoli are unperfused because of this vascular disease but ventilated (i.e., large numerator and small denominator in the VA/Q ratio), with increased dead space and decreased CO_2 elimination [64].

Acute cor pulmonale: PEEP affects the cardiac output in 3 ways [65]. First, the direct reduction in the venous return is secondary to an increase in pleural pressure. However, this effect is minimal because the transmission of airway pressure to the pleural cavity may be trivial due to reduced lung compliance. Accordingly, the transmural central venous pressure is marginally affected by a high PEEP when compliance is low [66]. Secondly, in dogs, the pericardium lowers the RV distensibility and reduces diastolic filling [67]. Thirdly, an increased RV afterload occurs when excessive PEEP is used [68]: during tidal delivery, the distal airway pressure is usually higher than the PEEP, resulting in cyclical RV afterloading; this effect is the main cause of cardiac output reduction in mechanically ventilated patients [65].

Acute cor pulmonale (ACP) is defined as elevated pulmonary pressure and right ventricle (RV) dilatation associated with a leftward shift of the interventricular septum (systolic septal dyskinesia) without a reduction in the RV ejection fraction [41, 69]. A “moderate RV dilation does not necessarily mean RV dysfunction. However, when RV dilation is associated with septal dyskinesia, it reflects RV pressure overload” [70]. RV failure is defined as an enlarged RV dimension without, necessarily, a change in the fractional area contraction [70]. When a large Vt generates normocapnia [62], the incidence of ACP is high and is associated with high mortality (with ACP, 100%; without ACP, 33%) [62]. On day 3 of ARDS, 25% of patients present with RV failure (protective ventilation: $\text{Pplat} \leq 30$ cm H_2O , $\text{Vt} < 6\text{--}9$ mL kg^{-1} , RR = 12–16 breaths per min, permissive hypercapnia, PEEP = 7 ± 3 cm H_2O [3–15]; lowest P/F = 87 ± 24 and highest $\text{PaCO}_2 = 64 \pm 12$) [70]. However, if aggressive respiratory support does not worsen the ACP, the presence of ACP does not influence mortality [41]. The issue is: how is the ventilator set up? Accordingly, mortality decreases when the Pplat decreases over time (“historical” group: mortality: 56% with $\text{Pplat} > 35$ cm H_2O ; “recent” group: 13% with $\text{Pplat} < 27$ cm H_2O) [41]. Indeed, a $\text{Pplat} > 26$ cm H_2O is

associated with increased mortality and incidence of ACP. An additive effect is observed with a $P_{plat} > 35$ cm H₂O and ACP [41]. Finally, given a constant P_{plat} , very low V_t set to increase PEEP to higher levels leads to RV dilatation (hypercapnia, acidosis, increased RV afterload, and pulmonary vasoconstriction) [58].

Venous return: In addition to lowering pleural pressure and increasing transpulmonary pressure, diaphragmatic activity increases intraabdominal pressure (IAP) thereby increasing the venous return from the highly compliant splanchnic compartment into the thorax. This process presents consequences as a function of the pre-existing IAP [71] that are: a) favorable in patients with hypovolemia in which an increased IAP favors venous return; and b) unfavorable in patients with bowel obstruction, ileus, or excessive weight gain in which an increased venous return may overload the RV.

Circulatory optimization: A “maximally aerated lung without any circulation is a useless organ” [43]. First, a patent foramen ovale (PFO) should be ruled out: a) when PFO is prevalent, lowering PEEP from 11 to 5 cm H₂O suppresses PFO (13% of patients); b) when PFO is not observed, increasing PEEP from 9 to 14 cm H₂O evoked PFO in 9% of the patients; c) without PFO, increasing PEEP (5–15 cm H₂O) increases P/F (112 to 174); d) with PFO, an identical increase in PEEP does not increase P/F (114 to 117). *When a low P_{vO_2} effect has been ruled out, an absence of oxygenation response to PEEP elevation suggests looking for PFO* [46]. Next, a patient presenting with ARDS should be optimized to avoid a “low P_{vO_2} effect” [24, 42]. The left ventricular (LV) systolic area is reduced when the PEEP is increased above 15 cm H₂O [9]. Therefore, an adequate LV pre-load is even more relevant in the setting of a high PEEP. Ventilation-evoked variations observed in the vena cava should be minimized. Volemia, urine output, rhythm, contractility [44], right coronary perfusion pressure [72], an arterio-venous CO₂ gradient < 5 [73] or 6 mm Hg [74, 75] (“CO₂ gap”), venous saturation (the difference between the arterial and superior vena cava saturation [S_{svO_2}] $< 30\%$ or $S_{svO_2} > 70–75\%$ [1, 76]), trend for lactates towards < 2 mmol L⁻¹, and the absence of leftward septal bulging/RV dilatation [9, 24] should be optimized *upfront* as early as possible in the setting of severe ARDS. [→Then, the PEEP should be increased stepwise and the RV observed [9] iteratively. As soon as the RV enlarges or the tricuspid annular plane systolic excursion (TAPSE) decreases over several ventilator cycles, the PEEP is decreased to the previous level. Given the unknown lag time necessary for the RV to adapt to a higher PEEP, the echocardiographic assessment should be repeated ~1 h after the PEEP increase [58] or V_t change, and the arterial and venous blood gases verified←].

Handling early severe ARDS implies up-front circulatory optimization [24, 42, 44]. [→Provocatively: “saline, dobutamine and paracetamol” (Mercat, personal communication)←].

B. VENTILATORY DISEASE

1. LUNG VS. CHEST WALL MECHANICS

CO₂: During early severe ARDS, increasing the PEEP or proning the patient is associated with a lowered or stable PaCO₂. This result indicates an improved alveolar ventilation and outcome [77]. During late ARDS, unperfused but ventilated alveoli generate elevated dead space fractions. This elevated dead space is associated with poor outcomes and presumably reflects the extent of the pulmonary vascular injury [64]. Increased CO₂ is a sign of poor prognosis upon increasing PEEP or proning (Table 6, part I).

O₂ diffusion and shunt: O₂ is 22 times less diffusible than CO₂. Thus, the primary goal of therapy is increased surface for O₂ diffusion: indeed the limiting factor is not normocapnia anymore (“permissive hypercapnia”). Because expiration is slower than inspiration (typically inspiratory time/expiratory time = 1/2 under CMV) and PEEP acts at the end-expiration, this diffusion primarily occurs during expiration, without small airway closure. [→Schematically, at a zero end-expiratory pressure (ZEEP) the surface necessary for O₂ diffusion is reduced from the surface of a soccer field (healthy volunteer) to the penalty area (severe ARDS)←]. The part of the lung that is still functional is the “baby lung” (“restrictive” disease) [78]. The end-expiratory O₂ diffusion surface is defective due to the massive *loss of aeration*, increased extravascular lung water (linked to initial insult or volume loading during resuscitation), epithelial or endothelial injury to the alveolar-capillary membrane, or inflammation. As a result, the alveoli are not adequately perfused (low CO: presumably capillary de-recruitment), the hypoxic vasoconstriction is impaired in the unventilated dependent areas: this is due to a massive loss of aeration, surfactant injury, or high permeability type edema (flooded alveoli with high water content up to pulmonary edema). Extravascular lung water is associated with an outcome independent of the P/F changes [13]. Circulatory optimization requires volume infusion to generate ventilatory stabilization in early ARDS, especially when septic shock is present. As this review addresses only early ARDS, late ARDS in inflated patients [13, 14] is not considered. Obviously, following the stabilization of the acute cardio-ventilatory distress, early extra renal replacement (EER) [24] or diuretics will lower the weight and/or extra vascular lung water towards normal levels.

Alveolar collapse: Strictly speaking, atelectasis refers to lung tissue that has never become aerated. Therefore, acquired de-aeration is more correctly termed “collapse” [79]. Nevertheless, atelectasis is widely used in the ARDS literature. Condensation is presumably different from lung water accumulation [13]. Furthermore, compression and re-absorption atelectasis are different [80]:

Table 6. PEEP and tidal volume strategies

Before delineating the various ways of recruiting alveoli, the reader should keep in mind the cardiological approach, i.e., cardiac output optimization to suppress any "low PvO_2 effect" [24]. Although this group [24] bundles together cardiac output optimization with low stretch strategy, *the 2 issues are 2 separate issues*: a circulatory optimization may well be combined with recruitment of alveoli and high PEEP [40, 149, 162, 163, 171]

Each group has its own definition of the "best", "optimal", "right" PEEP, etc. Briefly, the titration of PEEP was based on lowest intrapulmonary shunt [39], "best" compliance and O_2 transport [126], physiological measurements (Pflex on the incremental [127] vs. decremental [3] limb of the P-V curve), trial PEEP, end-expiratory transpulmonary pressure [10], and lastly end-inspiratory transpulmonary pressure [11]

1) Open-lung approach:

- a) Kirby: "Optimal" [39] PEEP (25–42 cm H_2O) minimizes shunt without reduction of CO (intermittent mandatory ventilation: IMV, $V_t = 12$ mL kg^{-1} , low RR to normocapnia). A bimodal distribution was observed: some patients improve with PEEP < 28 cm H_2O whereas other patients improve with PEEP > 33 cm H_2O

Resetting PEEP from 0 up to 30 cm H_2O increased P/F from 48 ± 14 (severe ARDS) to 220 ± 98 (mild ARDS). [→ Thus, very high PEEP "cured" the oxygenation defect over a ≈ 3 h challenge (i.e., arbitrarily P/F > 150, irrespective of PEEP: see Table 2, part II)←]. Several observations were apparent [39]: a) from the group report [39], presumably early ARDS was considered; b) most often, a swift improvement in the pulmonary condition was observed; c) deaths associated to respiratory failure were few; d) a high incidence of pneumothorax (14%) and subcutaneous emphysema was observed

- b) Amato: Using CT scan, combined to driving pressure < 15–20 cm H_2O , similar use of high PEEP reopened most of the whole collapsed lung [40]. Schematically, in patients presenting with a median P/F = 94, volume loaded to minimize delta pulse pressure, PEEP was increased up to 45 cm H_2O (increments in PEEP lasting 2 min, total interval for study: 20 min; driving pressure = 15 cm H_2O ; Pplat up to = 60 cm H_2O). This led to near-complete recovery of oxygenation ($PaO_2 + PaCO_2 > 400$) and near-complete reversal of alveolar collapse (Fig. 1 in [82]). After these "recruitment maneuvers", PEEP settled to high levels: 20 ± 5 cm H_2O . As earlier [39], a bi-modal distribution of opening pressures was observed, implying that a subgroup of patients definitely needs very high opening pressures (≈ 60 cm H_2O upon recruitment maneuvers at the end-inspiration: is this a consequence of re-absorption atelectasis? (Fig. 1 in [82])). A decrease of hyper-inflation was observed in non-dependent regions. The incidence of barotrauma was only 8%. Circulatory side effects were minimal. Transient acidosis (pH = 6.95 ± 0.11) and hypercapnia ($PaCO_2 = 95 \pm 34$) during the challenge itself appeared well tolerated

Amato insists on a low driving pressure ≤ 15 –20 cm H_2O rather than a fixed Pplat ≤ 28 –30 ($V_t < 6$ mL kg^{-1} , RR < 30, $PaCO_2 < 80$ mm Hg, pH > 7.2; low driving pressure = Pplat-PEEP < 20 cm H_2O , peak inspiratory pressure < 40 cm H_2O , pressure-limited mode of ventilation including pressure support ventilation, n = 29 vs. $V_t = 12$ mL kg^{-1} , RR = 10–24 to achieve normocapnia, n = 24) [17, 40, 131]. Accordingly, Amato [17] addressed retrospectively low driving pressure as a criterion for survival:

- i) a high driving pressure is associated with a low survival
- ii) the protective effects of high PEEP are observed only when associated with decreases in driving pressure: "studies of higher PEEPs did not show consistent survival benefits; PEEP increments might be protective only when the increased PEEP values result in a change in lung mechanics so that the same V_t can be delivered with a lower driving pressure. This hypothesis is consistent with recent physiological studies suggesting that the benefits of PEEP are found mainly in patients with greater lung recruitability, with some harm reported when PEEP caused overdistention"
- iii) survival in the V_t trials is linked to reduction in driving pressure, not to reduction in V_t . Similarly, survival in the high PEEP trials is linked to a reduction of driving pressure, not to increased PEEP: high PEEP translates into lowered stiffness
- iv) V_t is a strong predictor of survival when normalized to compliance, but *not* to ideal body weight, at variance with accepted practice [105]

2) P-V curve combined to cardiac output:

The "best" PEEP (mean ≈ 8 cm; range: 0–15 cm H_2O) combines maximum O_2 transport, lowest dead-space (V_d), and highest slope on P-V curve ("best compliance"); recruitment superseded overdistension [126]. Translating this into practice is difficult

- a) circulatory optimization (§ I A) is mandatory
- b) dead space is not a concern in the setting of early ARDS [64]. The level of PEEP does not have an important effect on the dead-space fraction [64]. Decreased $PaCO_2$ in the setting of prone positioning indicates reventilation of recruited alveoli and suggests good outcome [77]. Conversely, an increase in $PaCO_2$ suggests an increased alveolar dead-space induced by PEEP, an indirect sign of alveolar overinflation or possible structural changes in the lung (fibrosis) [77]. Thus, the greater the increase in $PaCO_2$ in the setting of prone positioning, the higher the mortality
- c) setting up PEEP is the issue at stake. The more FRC is lowered, the more efficacious the PEEP is. Patients with emphysema and a high FRC do not benefit from PEEP in ARDS [126]

3) P-V curve: inspiratory vs. expiratory inflexion points:

When a clear-cut lower inflexion point exists on the *incremental* (inspiratory) limb of the P-V curve (critical opening pressure, low inflexion point: LIP, Pflex), PaO_2 and shunt strikingly improve (Fig. 6 in [128]). Indeed, a clear-cut inflexion was observed with early ARDS (chest X-ray: purely interstitial pattern). Accordingly in the setting of early ARDS (2–4 days), a large hysteresis is observed on the P-V curve but not in the setting of late ARDS [3, 128] (Figs 1 and 4 in [3]). By contrast, an absence of inflexion is often associated with PEEP inefficacy [3, 127]. Accordingly, no inflexion was observed with late ARDS (chest X-ray: alveolar pattern as opposed to fewer alveolar opacities and increased interstitial markings) [128]

However, the critical opening pressure measured on the incremental (inspiratory) limb of the P-V curve is different from critical closing pressure measured on the *decremental* (expiratory) limb [3]. Investigators now agree: an inspiratory curve cannot be used to determine an expiratory variable [151, 172]. Thus, to prevent end-expiratory collapse, PEEP should be above critical closing pressure [173]. In case of early ARDS, setting PEEP above the inflexion of the expiratory limb of the P-V curve reduced shunt considerably (concavity: 15 ± 2 cm H_2O ; Fig. 1 in [3]; loop B in rabbits: Fig. 5 in [174]) [3]. By contrast, in the setting of late ARDS, as the fibrosis led to loss of inflexion on the inspiratory and expiratory limbs, no clear relationship between PEEP and shunt was observed (Fig. 4 in [3]). Therefore, little improvement was observed following PEEP. Taken together, as PEEP aims at expiratory recruitment, a better correlation between PEEP and shunt is observed when PEEP level is based on the expiratory ("decremental PEEP") rather than on the inspiratory limb of the P-V curve ("incremental PEEP") [3]

→

Table 6. (cont'd.). PEEP and tidal volume strategies**4) Trial PEEP:**

When recruitment maneuvers (continuous airway pressure: CPAP = 40 cm H₂O*40s) are performed, followed by PEEP = 20 cm H₂O, then PEEP decreased to a drop in SaO₂ < 90%, "optimal" PEEP is defined as the PEEP level immediately preceding the drop in SaO₂ < 90%. The "optimal" PEEP set in such a way had to be lowered from 12 ± 5 cm H₂O to 9 ± 5 mm Hg: presumably some patients had their initial PEEP set too high [129]

Following recruitment (40 cm H₂O*40s), in the setting of stepwise decremental PEEP from 24 cm H₂O (Pplat < 32 cm H₂O), another "optimal" PEEP (12 ± 4 cm H₂O; range: 8–20) is defined as the PEEP which prevents derecruitment i.e., immediately above which a P/F decrease by ≥ 20% is observed (FiO₂ = 0.8) [130].

The maximum slope of the P-V curve (best compliance) during a decremental PEEP trial will determine the minimum PEEP to prevent end-expiratory collapse of alveoli inflated at end-inspiration [175] by end-inspiratory recruitment (i.e., high Ppeak or high Pplat or sighs): the PEEP needed to prevent end-expiratory collapse ("decremental PEEP") is lower than the PEEP determined in the setting of incremental PEEP trial ("incremental PEEP"). As stated (§ recruitment maneuvers), the issue is to prevent derecruitment of alveoli, i.e. prevention of cyclical collapse at end-expiration by positive end-expiratory pressure (loop B in rabbits: Fig. 5 in [174]) rather than to recruit alveoli by recruiting maneuvers, at end-inspiration

Finally, a comparison showed differences between trial-PEEP (PEEP at which the greatest PaO₂ improvement is observed [80]) as opposed to Pflex-PEEP: trial PEEP: 14 ± 2 cm H₂O; Pflex-PEEP: 8 ± 3 [80]. Similarly, "among different bedside PEEP selection methods [134], the one based on oxygenation criteria [similar but not identical to table 4A, part I] was most closely related to lung recruitability" [5]: the sicker and the more recruitable the patient is, the higher the PEEP should be. Apparently, trial-PEEP gives better, or at least more easily implemented, results than physiologically-based PEEP (P-V curve) results "PEEP levels necessary to reach acceptable oxygenation and to fully keep open the lung are not necessarily the same" [1]. In this respect, the latest conventional ventilation trial uses PEEP as high as 24 cm H₂O (initial PEEP = 20 cm H₂O) [103], as the earliest high PEEP low Vt trial [131]. To sum up, PEEP should be individualized using an esophageal catheter or, alternatively, using "trial" PEEP (SaO₂ > 88–92% in intubated patients under CMV [141, 160]; SaO₂ > 98–100% under SV-PS [161]). High PEEP (≥ 10–20 cm H₂O or higher) increases P/F from < 100 to > 150–200 over 12–72 h (Tables 4, part I and 2, part II)

A 12 h trial of high PEEP allows one to separate recruiters from non-recruiters (Figs 1 and 3 in [171]). Grasso [92] clarifies the discussion of responders vs. non-responders:

- typical responders are patients with early, severe ARDS and diffuse loss of aeration (see also Rouby [87, 88])
- "patients with higher potential for recruitment experience dramatic improvement in oxygenation and lung mechanics without significant [circulatory] derangement, provided that the volemic status is optimized before the lung recruitment phase" (emphasis added by us). By contrast, overdistension and [circulatory] impairment make the "open lung approach" unsafe in non-responders
- Gattinoni [34] and Grasso [92] suggest that assessment of ARDS, given a PEEP = 5 cm H₂O is critical: the Berlin criteria should be strictly adhered to in order to classify ARDS. Indeed mild ARDS in the setting of pre vs. post "open lung approach" (clinical PEEP = 8 ± 2 to 16 ± 2 cm H₂O leading to an increase in P/F = 216 to 311) would have been classified as moderate or even severe ARDS at PEEP = 5 cm H₂O [92]

↳ These data suggest (Table 1, part II) to:

- ascertain severe ARDS: P/F < 100 after 30 min (Vt ~7 mL kg⁻¹, PEEP = 10 cm H₂O, and FiO₂ = 1) [20] or preferably PEEP = 5 cm H₂O according to the Berlin definition [19] and Grasso [92]
- perform investigations (CT scan, fiberoptic bronchoscopy, etc.) and iterative echocardiography/circulatory optimization upfront
- move early to alveoli recruitment (minimize alveolar "penumbra") using an esophageal catheter or a trial-PEEP (keeping in mind that an SaO₂ = 88–92% is to be considered in the setting of CMV [141, 160], while an SaO₂ = 95–100% is to be considered in the setting of SV [161]↔)

5) Transpulmonary end-inspiratory vs. end-expiratory pressure: see text**6) Tidal Volume:**

A design similar to [32] was used by Ranieri [85]: lowered mortality (28 days) was observed in the protective ventilation group: 38 vs. 58%, ns (protective ventilation: RR = 10–15, Vt to Pplat < Upper inflexion point on P-V curve (UIP) or as a second best: Plat ≤ 35 cm H₂O, PEEP > Pflex+2–3 cm, or as a third option: PEEP = 15 cm H₂O vs. control group: RR = 10–15, 35 < PaCO₂ < 40 mm Hg, Pplat ≤ 35 cm H₂O, PEEP increment up to 15 cm H₂O to achieve the largest improvement in SaO₂ without drop in mean arterial pressure) [85]

The ARIES study [31] randomized ARDS patients to conventional vs. protective ventilation (ARIES: *Acute Respiratory España Study*; P/F < 200 after standardized FiO₂ ≥ 0.5, PEEP ≥ 5 for 24 h; conventional: Vt = 10 mL kg⁻¹ PBW, PEEP ≥ 5, FiO₂ appropriate to obtain an SaO₂ > 90%, n = 45; protective: Vt = 5–8 mL kg⁻¹ PBW, PEEP = Pflex + 2 cm H₂O, n = 50). When Pflex and UIP could not be determined, Vt and PEEP were set to 5–8 mL kg⁻¹ and 15 cm H₂O, respectively. The low Vt/Pflex approach led to reduced CCU mortality (32 vs. 53%; –21%, P = 0.04), decreased hospital mortality (34 vs. 55%) and death from respiratory failure (12 vs. 25%), reduced of duration of mechanical ventilation (–45%) and lowered MOF [31]

- Compression atelectasis develops as a consequence of increased lung weight during the end-expiratory collapse of small airways. The airways may re-open after applying low transmural pressure (~12–20 cm H₂O). Gravity-dependent densities shift from dorsal to ventral within a few minutes in the prone position [78] (Fig. 6 in [81]). A "baby lung" is a functional and not a fixed anatomical viewpoint [78] (Fig. 6 in [81] and Fig. 1 in [82]). These gravity-dependent dorsal densities are linked to a massive loss of aeration [78, 82] resulting from the heart and lung weight and increased IAP but are not primarily linked to increased lung water/edema. Blood flow continues primarily to the (unventilated) lower lobes (large denominator in the VA/Q ratio), thereby increasing the intra-pulmonary shunt (Fig. 1 in [38]).
- Reabsorption atelectasis requires a high opening pressure (~30–35 cm H₂O; Pplat ~70 cm H₂O) and may be linked to the reabsorption of gases (Fig. 81 in ([83]) when

the uptake exceeds the delivery (“sticky” atelectasis; see anatomical heterogeneity; Fig. 1 in [82] and Table 4, part I).

Finally, a forgotten issue is the *non-linear* relationship between the collapsed lung and the shunt (Fig. 6 in [84]). *A minor loss of aeration or a true atelectasis generates a large shunt.* For instance, a lung collapsed to 15% leads to a 30–40% shunt, whereas a lung collapsed to 55% leads to an 83% shunt [84] with major therapeutic consequences (see intraabdominal pressure).

Diffuse vs. focal ARDS: The clinical literature does not clearly differentiate between alveolar collapse [36, 78], inflammation [85] and early vs. late increased water content [13, 86] (details in [5]). More work has been devoted to alveolar collapse and the loss of respiratory muscle/diaphragmatic tone and position as opposed to increased lung water. Atelectasis leading to intrapulmonary shunting represent the core mechanism underlying ARDS [36, 40, 78]. However, increased lung water generates also intrapulmonary shunting [13] without necessitating a true collapse. Schematically, focal vs. diffuse ARDS may be opposed with different prognostics (“focal vs. “patchy” vs. “diffuse” ARDS [87, 88]; Fig. 1 in [89] and Fig. 2 in [87]; mortality in diffuse ARDS: 75%; focal ARDS: 42%). Nevertheless, this very convenient description [87] from a pathophysiologic and a therapeutic (Fig. 2 in [88]) perspective was not incorporated within the Berlin definition [19] (footnote in Table 1).

Lung volume: In the healthy volunteer, the functional residual capacity (FRC) is reduced by 0.8–1.0 L when the subject is changed from an upright to supine position. An additional decrease (0.4–0.5 L) is observed upon anesthesia induction [36]. As atelectasis progresses, the volume at which the small airways close at end-expiration, the closing volume, increases above the FRC [90] (Fig. 2 in [36]) and reduces the area available for O₂ diffusion at end-expiration (small airway closure). A supine position, obesity, aging, pregnancy, abdominal surgery and heart failure worsen the possibility of the closing volume increasing above the FRC [90]. A functional ventilation-perfusion mismatch (Fig. 1 in [38]) contributes to an anatomical intrapulmonary shunt. However, the actual value of the FRC (available on ventilators such as the GE-Engstrom) compared to its expected value is not as important as knowing the response of the FRC to the interventions, within the course of the disease [91]. What matters is not the absolute FRC itself but the changes that occur over time or following intervention (Figs 1 and 3 in [171]).

“Baby” lung [5, 78]: In ARDS, the amount of aerated tissue at end-expiration is 200–500 g [78] (i.e., the size of the aerated tissue of a 5–6 year old boy; “baby lung”: (Fig. 6 in [81] and Fig. 1 in [82]). Thus, a high Vt/driving pressure de-

stroys the remaining healthy aerated tissue and stiffens the remaining lung (Fig. 2 in [17]). To keep the dependent zones (dorsal regions in the supine position and ventral regions in the prone position; Fig. 6 in [81]) open, the PEEP may overdistend the already open lung (upper lobes). The Vt should not be set on the predicted body weight but to the *actual* size of the “baby lung” assessed on a CT scan (Fig. 6 in [81] and Fig. 1 in [82]), electrical impedance tomography [92], compliance or transpulmonary end-inspiratory pressure [17]. The compliance is related to the amount of aerated tissue but not the amount of non-aerated tissue. As a rule of thumb, “a compliance = 20 mL cm H₂O⁻¹ corresponds roughly to 20% open ventilable lung, 50 mL cm H₂O⁻¹ to 50% and so on” [5]. Thus, compliance is an index of the amount of healthy lung [78] (Fig. 2 in [93]): “the aerated lung... is not stiff but small, with nearly normal... compliance in preserved areas” [17]. However, despite near-normal mechanical properties in severe ARDS, the baby lung presents with one hallmark of inflammation: increased permeability of endothelial-epithelial barrier [5]. Given this severe restrictive disease, a very small window exists between alveolar derecruitment and overdistension (Fig. 1 in [94]). For instance, given a Pplat ≤ 30 cm H₂O, a Vt of ~5–6 mL kg⁻¹ overdistends 30% of ARDS patients [95]. A safer limit is < 28 cm H₂O (Fig. 2 in [96] and Fig. 2 in [95]) or < 26 cm H₂O [41] when the RV is considered (§ I A 2).

Respiratory muscles [36] and *diaphragm* (Fig. 1 in [97]): The decrease in FRC observed upon anesthesia induction seems to be related to the loss of respiratory muscle tone. Several effects occur following thiopentone-meperidine anesthesia: the FRC is reduced from 3.0 to 2.38 L with no further decrease following muscle paralysis. The fraction of the airway pressure actually transmitted to the lung (i.e., transpulmonary pressure) is increased from 2.8 cm H₂O to 12.2 cm H₂O, without a further increase following muscle paralysis. In this respect, anesthesia alters the chest wall (CW) properties, leading to the reduction of FRC and an increase in the static lung retractive force. Additionally, low volume breathing generates atelectasis [98]. These aspects are not observed following ketamine administration, which preserves muscle tone. This loss of respiratory muscle tone shifts the balance between the elastic recoil force of the lung and chest wall towards lower lung volume, airway closure, atelectasis, and lower compliance. Atelectasis occurs as often in young individuals as in elderly patients. [→ Therefore, the common treatments used in the setting of ARDS (muscle relaxants, anesthetics, sedatives, and high FiO₂) “certainly” adds to the collapse and consolidation caused by ARDS itself [36] ←].

The normal functioning of the diaphragm is impeded in *supine* patients under CMV. Muscle relaxation shifts the diaphragm rostrally without moving the dependent re-

gions [97, 99]. Thus, atelectasis and/or consolidation occur preferentially in supine dependent caudal regions. The shunt increases as gravity directs the flow to poorly aerated/atelectatic regions. When supine, the PEEP accentuates the gravity dependence of the blood flow [100] and worsens the VA/Q ratio. Under CMV in the supine position, the Vt preferentially distributes itself anteriorly (i.e., ventrally) [97, 101] towards non-dependent and less perfused areas. After paralysis, a PEEP = 10 cm H₂O primarily displaces the anterior diaphragm without any unfolding of the alveoli of the dependent posterior lower lobes. Increases in the PEEP or Vt cannot restore ventilation in dependent regions in the supine paralyzed subject [97]; only the prone position may restore ventilation [97]. To recruit alveoli, the recommendation is to use either the prone position [27], a high PEEP [8] or both.

Prone position: The prone position complements protective ventilation because it: a) achieves redistribution of atelectasis within minutes (Fig. 6 in [81]) [78, 81]; b) promotes the recruitment of juxta-diaphragmatic lung regions by decreasing chest wall compliance through a limitation of the expansion of the cephalad thorax and reduced overdistension in "focal" ARDS; in contrast, proning in diffuse ARDS does not result in the reversal of ventral hyperinflation [100]; c) reduces the shunt as the ventilation increases in well-perfused areas [102]; d) may improve lymphatic drainage as the heart moves ventrally, lowering hydrostatic edema [5]; e) reduces the interfaces between closed and open units ("stress focusing junctions"), thus inflammation. Thus, early prolonged proning reduces mortality to low levels (prone, 16%; supine, 33%) in patients with severe ARDS (P/F < 150; 4 sessions of 17 h) [27]. The mortality (33%) in this supine group [27] was similar to the mortality in the latest trials (conventional group: 35% [103] or 41% [104]; low Vt: 31% [105]). Moreover, proning (2–8 h) in non-intubated patients increases the P/F in moderate ARDS (pre: 124 ± 50; prone: 187 ± 72; post: 141 ± 64) [106].

Upright position: Moving from a supine to an upright position (reverse Trendelenburg, trunk at + 60°, and legs down at 45°) [107, 108] increases the P/F in 32% of ARDS patients, "especially for... severe ARDS" [109], and in 5 out of 7 patients presenting with severe ARDS [110].

[→ After adopting an upright position, SV decreases the pleural pressure and actively unfolds the "zone 3" alveoli (the recruitment of the former is dependent on the caudal lung set in the supine position), which are preferentially perfused by gravity (Fig. 11 in [111]). The reader should keep in mind that West's zones were described in the isolated upright lung (Fig. 11 in [111]), at odds with what occurs in the supine ARDS patient. SV in awake/anesthetized supine humans leads to a caudal diaphragmatic movement that is predominant in the dependent regions (Fig. 1 in [97]).

SV improves VA/Q matching by preferentially ventilating the peri-diaphragmatic regions [76]. In pigs with ARDS, SV combined with airway pressure release ventilation (APRV) leads to increased ventilation and pulmonary blood flow to the dorsal juxta-diaphragmatic regions. Diaphragmatic contractions reduce the curvature of the diaphragm, unfold the alveoli, recruit flooded or collapsed areas (better ventilation) and counteract hypoxic vasoconstriction to these newly recruited areas (better perfusion) [112]. In humans, APRV + SV improved the VA/Q distribution [113]. In contrast, although PS improved both the PaO₂ and shunt, the results were not as good as those observed under APRV + SV [113]. Because the active contraction of the diaphragm is better preserved under APRV+SV than under PS in patients with severe ARDS, active contraction of the diaphragm throughout inspiration is presumably very important: APRV+SV increases the aeration of atelectatic areas more powerfully than PS [114]. The lung tissue recruited by the active contraction of the diaphragm stays open with spontaneous breathing, whereas slow derecruitment occurs with mechanical breathing [36]. Finally, in the VA/Q ratio, the circulation needs to be considered because a) the lowered intrathoracic pressure favors venous return; and b) the diaphragm actively compresses the hepato-splanchnic venous pool, furthering also the venous return [71].

Upright positioning [107–110] is a logical step in handling early severe ARDS, especially when increased IAP or morbid obesity are present ←].

Pulmonary vs. extra-pulmonary ARDS: ARDS of pulmonary origin ("pulmonary ARDS") is associated with consolidation and a stiff lung that does not improve by increasing the PEEP. Thus, more inflation of the already open alveoli may occur (overdistension) in pulmonary ARDS. In contrast, extrapulmonary ARDS is associated with a stiffer thoracoabdominal wall, interstitial edema and alveolar collapse and a more compliant lung that improves with PEEP. Thus, alveolar recruitment occurs in extrapulmonary ARDS [115]. This view was later questioned [116, 117] because the alveolar recruitment appeared to be similar in pulmonary and extrapulmonary ARDS [117].

Intrathoracic and intraabdominal pressures (IAP): In upright humans, gravity and active diaphragmatic contraction stretch out the caudal lobes. In healthy volunteers with a closed glottis, tilting from a standing position to a supine position raises the lung pressure by 6–8 mm Hg due to the viscerae acting against the diaphragm [118]. In contrast, in supine humans, gravity (i.e. heart and IAP) squeezes the caudal dependent lobes, especially in the setting of obesity, increased IAP or paralysis. [→ Thus, the supine position is the worst position for handling ARDS.

Reverse thinking will conclude that a) repositioning the patient from the supine to the upright position reduces

the intrathoracic pressure by ~ 9 cm H₂O and b) switching from CMV to PS will lower the intra-thoracic pressure due to the subtraction of several cm of H₂O [119] (i.e., the P_{plat} decreases by ≥ 5 –10 cm H₂O from supine + CMV to upright + SV). Thus, arithmetically, much higher PEEP levels are possible. For instance, if the P_{plat} is ≤ 25 –32 cm H₂O and the driving pressure is ≤ 15 cm H₂O under CMV, then the PEEP may only be increased up to 10–17 cm H₂O. Conversely, under spontaneous ventilation with a P_{plat} ≤ 25 –32 cm H₂O and PS ≤ 5 –10 cm H₂O, the PEEP may increase up to 15–27 cm H₂O \leftarrow].

Minor or moderate atelectasis generates a high shunt (Fig. 6 in [84]). Under a high IAP, the viscerae push the lower lobes rostrally to generate atelectasis and shunt. When combined with the transmission of a high IAP on the dependent lung, this effect can explain the severity of the ARDS observed in supine morbidly obese patients presenting with mild to moderate pulmonary infection located on the peri-diaphragmatic areas (basis of the lung: “focal” [87] ARDS, acute hypoxemic non-hypercapnic failure). [\rightarrow Thus, focal ARDS in a morbidly obese patient requires: a) from a physiological point of view, a low PEEP (5–10 cm H₂O) to reopen the dependent atelectasis itself [87] (Fig. 2 in [87]); and b) from a practical point of view, a high PEEP to withstand the high IAP [120, 121]. In this specific setting, a high PEEP takes precedence over a low PEEP \leftarrow]. Performing a fiberoptic bronchoaspiration, or not, is dictated by the clinical condition.

The IAP (\approx bladder pressure [122]) is ~ 0 and 5–8 mm Hg under SV and CMV, respectively [123]. An IAP > 15 –20 mm Hg increases the P_{plat} (~ 25 –80% transmission through the diaphragm) [122]. Increased IAP is present in approximately 25% of CCU patients [123]. Thus, bowel obstruction deteriorates respiratory mechanics. Conversely, abdominal decompression shifts the pressure-volume (P-V) curve of the whole respiratory system [124] (i.e., chest wall and lung) upward and leftward. Presumably, this holds true when the ascites, intra-abdominal edema, third spacing, permeability changes and Ogilvie syndrome are considered [124]. [\rightarrow Incidentally, these findings regarding abdominal decompression suggest the facilitation of bowel movements early following arrival to the CCU, when indicated \leftarrow]. Taken together, if a high PEEP is required in patients with a high IAP, a low V_t should be considered despite hypercapnia [124].

2. MECHANICAL VENTILATION

Exposing improvements in mechanical ventilation refers primarily to driving pressure/V_t and PEEP. Because the key defects are a restriction of the surface available for O₂ diffusion, lowered compliance and increased WOB, PEEP will be examined first as a means to increase the O₂ diffusion and lower the WOB. Then, driving pressure (= P_{plat}-PEEP) or V_t will be

examined to avoid overdistension and lung stiffening [17]. P_{plat} is used as a surrogate for peak alveolar pressure.

a. PEEP

PEEP [4] (Table 6, part I) is used for 2 reasons: oxygenation (Table 4A, part I) and preventing the opening-closing of the alveoli [1]. PEEP increases the FRC above the closing volume, resets the lung to the highest slope of the P-V curve (Fig. 2 in [93]), minimizes opening-closing, thus atelectrauma-inflammation. In addition to the controversy surrounding the “low stretch” vs. the “open lung” strategy, other controversies (Table 6, part I) exist. For instance, should the lung be thoroughly re-opened? Should PEEP be set above the critical closing pressure? Should PEEP be set to the highest level compatible with the acceptable end-inspiratory pressure (lung mechanics)? If so, how should the acceptable end-inspiratory pressure be defined (arbitrary P_{plat} [125] or end-inspiratory transpulmonary pressure [lung mechanics]) [11]? Conversely, should end-expiratory transpulmonary pressure be combined with oxygenation (lung mechanics + oxygenation) [10]?

Overview: to overview the controversy (physiology vs. oxygenation vs. anatomy) on PEEP, the reader is referred to Tables 6 and 7, part I, and Fig. 1 in [82]. From a *chronological* point of view,

- i) PEEP was increased to very high levels to lower the functional intrapulmonary shunt [39] or to almost completely reduce atelectasis on a CT scan [40, 82].
- ii) an adequate CO was combined to the highest slope on the P-V curve representing a *compromise between optimized circulation* (“avoid low P_vO₂ effect” [24, 42]) and *ventilation* (“best compliance” [126]); alveolar recruitment of a “penumbra” area).
- iii) PEEP was set above the inflexion point of the incremental (P_{flex}, P_{inf}) [127] (Fig. 6 in [128]) or preferably the decremental (Figs 1 and 4 in [3]) P-V curve.
- iv) “trial PEEP” was lowered from a high PEEP to the level sufficient to stay above a certain cut-off point delineated by the PO₂ (e.g., > 60 mm Hg) or SaO₂ (> 90 –95%) [129, 130] in *stabilized* early ARDS patients *under* CMV.
- v) Given a fixed V_t < 6 mL kg⁻¹ [105] or driving pressure < 15 –20 cm H₂O [17, 40, 131] together with a fixed P_{plat} ≤ 30 cm H₂O [125], the PEEP was increased up to the fixed P_{plat} ≤ 30 cm H₂O.
- vi) Using the same logic, given a high chest wall (i.e., thorax + abdomen) elastance, the present technique titrated the end-inspiratory transpulmonary pressure immediately below [11] the accepted cut-off [132].
- vii) Conversely, the end-expiratory transpulmonary pressure was raised up to 10 cm H₂O [10] according to the NIH table (Table 4, part I).

Table 7. Pathophysiology vs. epidemiology (Fig. 4 in [8])

How does one explain the discrepancy between neatly designed physiologically- vs. epidemiologically-oriented trials? The analytical answer is delineated below: the ARDS is a very heterogeneous syndrome ("focal" vs. "diffuse", recruitable vs. non-recruitable, mild vs. severe). An epidemiology trial should be rigorously designed, which is at variance with looking for a common denominator in the initial design. The key example is the progressive refinement of the prone positioning studies which went from case reports through negative trials over 30 years but culminated into the last design (P/F < 150 only, early proning, prolonged prone session, etc.) [27] and was concluded by a low mortality. Pathophysiology should lead epidemiology, not the opposite

Alveoli trial: PEEP was applied according to a fixed PEEP/FiO₂ table (Table 4) and *not titrated to physiological end-points* (e.g., Pflex; n = 549) [141]. Hospital mortality was nearly identical (~9%) when a Vt = 6 mL kg⁻¹ and a Pplat ≤ 30 cm H₂O was applied with high vs. low PEEP (13 ± 2 cm H₂O; minimum = 12–14 cm H₂O for the first 48 h; [range: 5–24] vs. 8 ± 3 cm H₂O. When 983 patients [167] (LOV trial) with a P/F < 250 were randomized to Vt = 6 mL kg⁻¹, Pplat < 30 cm H₂O, and PEEP = 10 ± 3 cm H₂O vs. Vt = 6 mL kg⁻¹, Pplat < 40 cm H₂O, recruitment maneuvers and PEEP = 15 ± 3 cm H₂O, the results were also disappointing: low vs. high PEEP, respectively: hospital mortality: 40 vs. 36%, barotrauma: 9 vs. 12%, death from refractory hypoxemia: 9 vs. 4% [167]

Express: This trial [125] was set to simple *lung mechanics* (Pplat as opposed to *oxygenation* in NIH table; n = 767; P/F < 300, Vt = 6 mL kg⁻¹ PBW): PEEP was individually set to a Pplat < 28–30 cm H₂O (PEEP = 8 ± 2 vs. 16 ± 3 cm H₂O). The rationale (avoid overdistension while optimizing recruitment) used by Mercat [125] and Grasso [11] is identical: in one trial the Pplat relative to atmospheric pressure is set to 28–30 cm H₂O. In the other trial, the transmural pressure relative to esophageal pressure (end *inspiratory* transpulmonary pressure PL = 25 cm H₂O) is used, accounting for chest wall elastance, given an upper limit ≈ 27 cm H₂O at partial inspiration in volunteers [132]. In the Express trial, the mortality was unchanged. The duration of mechanical ventilation and incidence of MOF were reduced in the high PEEP group. Pplat is a better end-point than oxygenation but may not capture differences in CW elastance [139]. No increased barotrauma were observed. The high PEEP patients required less rescue therapy (prone position, NO, almitrine) for refractory respiratory failure (19 vs. 35%) [125]

Meta-analyses showed no reduced hospital mortality but a reduced CCU mortality in the high PEEP group, a reduced rescue therapy for refractory hypoxemia, and a benefit from high PEEP restricted to the severe/moderate ARDS group (hospital mortality: 34% vs. 39%; difference: -10%; P = 0.049). By contrast, *harm to patients with mild ARDS was observed with high PEEP*: a threshold effect was observed for a P/F = 200, rather than a linear increase in mortality [168]. Recruitability is the issue

Clinical heterogeneity with respect to inclusion (Fig. 2 in [21]): Patients included in [31] presented a persistent ARDS (P/F < 200) after a trial (Vt = 10 mL kg⁻¹, PEEP ≥ 5, FiO₂ ≥ 0.5): severe/moderate ARDS patients exhibited higher mortality (68%) as opposed to mild ARDS patients (300 < P/F < 200) (23%) [31]. Thus, in the large trials [125, 141, 167], a disproportionate number of mild ARDS patients were randomized to the control arm. Therefore, the low mortality associated with mild ARDS presumably diluted the beneficial effect of the high PEEP treatment [21]

Physiological heterogeneity in the setting of PEEP trial:

The outcome of the ARMA trial [105] was a function of baseline pulmonary compliance. *Patients with a more compliant lung did poorly when Vt was lowered*. In contrast, patients with less compliant lungs did well when Vt was lowered [176]. Vt is relevant to ventilator-induced lung injury (VILI). However, *considered apart from lung mechanics and PEEP, Vt bears an unpredictable relationship to injury risk* [177]. Thus, the attention shifted from actual Vt to the actual pressure that distends the alveoli, i.e., transalveolar/transpulmonary pressure (see below: transpulmonary end-inspiratory vs. transpulmonary end-expiratory pressure) [76] and driving pressure [17]. No "magic" number exists for Vt [95] nor PEEP: *individual titration maximizes recruitment and minimizes overdistension* [78], implying *individualized "right" PEEP* [88] and *individualized low Vt*

Changes in PEEP (9 ± 2 cm to 16 ± 1 cm H₂O *12 h) segregate recruiters (alveolar recruitment = 587 ± 158 mL; P/F = 150 ± 36 to 396 ± 138) vs. non-recruiters (70 ± 38 mL; P/F = 149 ± 38 to 142 ± 36) [171] (Figs 1 and 3 in [171]). In the setting of high PEEP period, more fluids had to be administered in non-recruiters as opposed to recruiters (1344 ± 1280 mL vs. -194 ± 1279 mL, respectively). Moreover, in non-recruiters, PEEP had to be increased significantly more than in recruiters in order to match the oxygenation target. Finally, in non-recruiters, an increase in PaCO₂ was observed and suggests a PEEP-induced increase in alveolar dead space, a sign of overinflation. Therefore, in addition to or beside the assessment of a P-V curve, *a 12 h trial of high PEEP allows one to segregate recruiters from non-recruiters* (Fig. 3 in [171]; Table 6). Hence the standardization of PEEP-FiO₂ combinations according to the NIH table (Table 4A, part I) may lead to unpredictable results. A second reason may be linked to the progression of the disease: patients ventilated for 7 ± 1 days present much less recruitable lung than patients ventilated for 1 ± 0.3 day [149]. A last factor in explaining the absence of reduced mortality in large trials may be the inclusion of patients with high intra-abdominal, pleural or esophageal pressures [10]

Anatomical heterogeneity: Before applying PEEP to highly recruitable lungs, assessing recruitability with a CT scan is needed. Now, electrical impedance tomography allows one to avoid transportation of unstable patients to the CT scan [92]. In the setting of early ARDS (< 10 days) a) 27% of the patients present lower lobes with mechanical/compression/atelectasis (pure loss of aeration) while 73% of the patients present inflammatory atelectasis (loss of aeration + excess of lung tissue) b) ARDS may be characterized by evenly distributed diffuse alterations (23% of the patients; mortality rate: 75%; lower inflection point: 8 ± 2 cm H₂O) vs. lobar attenuations predominating in the lower lobes (36%; mortality: 42%; LIP: 5 ± 2 cm H₂O) vs. patchy attenuations unevenly distributed in the 2 lungs (40%; mortality: 41%; LIP: 6 ± 3 cm H₂O) [87, 89]. This classification was simplified to «diffuse» vs. «focal» acute non-hypercapnic hypoxic failure [86, 88]. Deep sedation, muscle paralysis and increased intra-abdominal pressure contribute to diaphragmatic displacement [89]. Different patterns, according to CT scans, lead to different therapies: diffuse alterations are amenable to recruitment without overdistension in the upper lobes with high PEEP. By contrast, in patients with lobar attenuations, PEEP induces mild recruitment with overdistension of previously aerated areas (upper lobes and non-dependent regions): lower levels of PEEP combined to upright/prone position are advisable [178]. Regionalization of the disease is to be considered (high PEEP trial: diffuse, bilateral densities, X-ray: "white" lungs vs. low PEEP trial: focal loss of aeration, i.e., bilateral hyperdensities predominating in lower lobes; Fig. 2 in [87]). A majority of ARDS patients present normally aerated lung regions coexisting with edematous and atelectatic areas on zero PEEP (ZEEP). Accordingly, a minority of ARDS present without normally aerated lung regions on ZEEP. Thus, high vs. low PEEP (10–25 cm vs. 5–12 cm H₂O) is to be titrated, according to chest X-ray, CT scan and P-V curve (Fig. 2 in [88]). In the lobar as opposed to diffuse ARDS, prone position reduces more non-aerated lung and overinflated areas. Patients with diffuse ARDS showed no reversal of ventral overinflation [100]

The effect of PEEP is a function of the recruitable lung. Patients with P/F < 300 (19 patients with 200 < P/F < 300: mild ARDS; 49 patients with P/F < 200: moderate ARDS), after 5–6 days of mechanical ventilation, present highly variable recruitable lung. The percentage of recruitable lung is related to the severity of lung injury: to open the most dependent parts of the lungs, opening pressure should be set up to 45 cm H₂O [78]. However, approximately 24% of the lung cannot be recruited even at Pplat = 45 cm H₂O ("core disease") [34]. By contrast, Pplat = 60 cm H₂O opens up nearly all the collapsed lung (Fig. 1 in [82]). The patients presenting with the highest percentage of recruitable lung had a lower P/F, a higher PaCO₂, a higher dead space, a lower respiratory-system compliance, and the highest risk of death: *high recruitability is a marker of the severity of the disease* [34]. Patients presenting with high vs. low recruitment were not different with respect to duration of intubation (≈ 5–6 days) [34]. This fact is at variance with other observations in which late ARDS (5–10 d of mechanical ventilation) present no response to recruitment maneuvers as opposed to early ARDS (1–2 d of mechanical ventilation) [149]. Patients with the highest lung recruitability treated with higher PEEP had a better outcome than patients with high recruitability treated with lower PEEP (14 ± 4 vs. 10 ± 2 cm H₂O) [179]: the implication is that *setting the PEEP too low reduces survival in this subset of patients*. The very same Pplat that causes devastating injury, when insufficient PEEP is used, inflicts minimal damage when applied with adequate PEEP (high PEEP-low driving pressure as opposed to low PEEP-high driving pressure): a 5 cm H₂O difference in PEEP allowed one to observe a very large benefit in a small number of patients. The mortality was lowered from 53% to 32% in 95 patients [31]. In the setting of severe diffuse ARDS, early in the disease, when recruitability is expected to make important difference in mortality, *early ventilator management is key* [177]: *high PEEP-low Vt are beneficial in severe early diffuse ARDS* [8]. Accordingly, *in early mild diffuse ARDS, Grasso observes that increasing PEEP lowers driving pressure* [92]. A meta-analysis [169] confirms that the higher the predicted mortality, the greater the mortality reduction associated with high PEEP: the sicker the patients, the higher the PEEP should be

viii) Recently, transpulmonary pressure was estimated *without* the use of an esophageal catheter [133]. This last method awaits independent validation.

When methods of setting up PEEP are compared (lung mechanics: Express and stress index; absolute esophageal pressure; acceptable oxygenation based on a Table similar to Table 4A, part I, to $88 < \text{SaO}_2 < 93\%$), the trial-PEEP set to oxygenation appears superior: a) it is weakly related to recruitability assessed from a CT Scan (i.e., amount of lung edema and ARDS severity); and b) it is easier to set up than the physiologically-based PEEP [134]; thus trial-PEEP is of interest during night call.

Physiology-based trials (Table 6, part I): Protective ventilation open lung-permissive hypercapnia was opposed to conventional ventilation [131] (protective group: $\text{Vt} < 6 \text{ mL kg}^{-1}$, $\text{RR} < 30$, $\text{PaCO}_2 < 80 \text{ mm Hg}$, $\text{pH} > 7.2$, low driving pressure = $\text{Pplat-PEEP} < 20 \text{ cm H}_2\text{O}$, pressure limited mode of ventilation including PS, PEEP set 2 cm above Pflex at 16.3 ± 0.7 , $n = 29$; conventional group: $\text{Vt} = 12 \text{ mL kg}^{-1}$, $\text{RR} = 10\text{--}24$ to normocapnia, $\text{PEEP} = 6.9 \pm 0.8 \text{ cm H}_2\text{O}$, $n = 24$). Mortality and barotrauma were reduced despite a *higher* PEEP (up to $24 \text{ cm H}_2\text{O}$; 28 day mortality: 38 vs. 71%, $P < 0.001$; hospital mortality: ns; barotraumas: 7% vs. 42% [131]). This trial was criticized based on the high mortality in the control group that was presumably linked to the use of a high Vt (12 mL kg^{-1}). Nevertheless, the conclusion holds: a high Vt is detrimental. A low Vt is associated with higher survival when the APACHE-II, P/F, arterial pH and compliance are considered [135]. Accordingly, a re-analysis of the ARDS Network database [105] suggested that a Vt reduction from 12 to 6 mL kg^{-1} predicted body weight (PBW) had a beneficial effect regardless of the Pplat before the Vt reduction [136]. Similar designs led to similar results [31, 85] (Table 6, part I).

Transpulmonary end-inspiratory pressure: The Pplat cannot be considered by itself without considering the effect of the chest wall in determining lung expansion and stress. The Pplat at end-inspiration is likely to overestimate the transpulmonary pressure of the lung itself when abdominal distension or CW stiffness are prominent [137]. Therefore, in these patients a $\text{Pplat} > 30 \text{ mm Hg}$ may be acceptable *only* during “Friday night ventilation” [1]. Conversely, the Vt should be reduced as early as possible. Because the respirator should ventilate only the “baby lung” as opposed to the CW expansion (no overdistension with adequate recruitment), the esophageal pressure should be measured as soon as possible [1]. Transpulmonary pressure is the actual distending pressure applied to the lung [138]. Thus, high transpulmonary end-inspiratory pressure leads to overdistension injury [139]. The CW elastance contributes to the elastance of the whole respiratory system by up to 50% [123]. In severe ARDS, a $\text{Vt} = 6 \text{ mL kg}^{-1}$ may generate

a $\text{Pplat} > 30 \text{ cm H}_2\text{O}$, especially in obese, pregnant and high IAP patients, due to the high CW elastance [1] (i.e. low chest wall compliance). This is not always the case because CW stiffness is not necessarily related to the body mass index [140]).

Transalveolar pressure is a tool to partition the elastance of the lung as opposed to the elastance of the chest wall [12]. This measurement is key to avoiding both alveolar end-inspiratory overdistension (i.e. set up a low Vt) [11] and cyclical end-expiratory alveolar collapse (i.e. set up a high PEEP) [10]. The transalveolar pressure can be calculated as Palv [alveolar]-Pinterstitium (Palv-Ppl [pleural]) or $\text{PL} = \text{Pairway-Pes}$ (esophageal). In young healthy volunteers, the limit before overdistension (end-inspiratory transpulmonary pressure) is approximately 27 and $44 \text{ cm H}_2\text{O}$ when measured at partial and maximal inspiration, respectively (Table 3 in [132]). Accordingly, the distending pressure of the normal relaxed human respiratory system (equivalent to the Pplat) at total lung capacity is $\sim 37 \text{ cm H}_2\text{O}$ ([136] quoting [118]). To partition the respiratory mechanics between the lung and chest wall [12], the Pplat is broken down to the PlatL , which refers to the plateau pressure imposed on the lung. Conversely, PplatRS refers to the Pplat imposed on the respiratory system as a whole (lung + chest wall). Normally, the chest wall elastance and the lung elastance are similar (ratio = 0.5). In the setting of ARDS, the ratio may vary from 0.2 (“soft” chest wall) to 0.8 (“stiff” chest wall). Thus, given an end-inspiratory plateau pressure of the respiratory system of $\text{PplatRS} = 30 \text{ cm H}_2\text{O}$ (pressure applied to the airway), the end-inspiratory transpulmonary pressure will be 15 and $6 \text{ cm H}_2\text{O}$ when the chest wall is normal and stiff, respectively (calculus in [123]). This makes a major difference when customization of the transpulmonary end-inspiratory pressure is necessary [11]. Therefore, the balloon allows customizing Pplat at end-inspiration to the lung itself [11] as opposed to a standardized Pplat of $\leq 28\text{--}30 \text{ cm H}_2\text{O}$ [125].

Patients referred to the Torino center for extracorporeal membrane oxygenation (ECMO) were partitioned according to the end-inspiratory plateau pressure (PplatL) before undergoing ECMO (identical $\text{PplatRS} = 31 \text{ cm H}_2\text{O}$ and $\text{Vt} = 5 \text{ mL kg}^{-1}$ in both groups, obesity in 8/14 patients; $\text{PplatL} = \text{PplatRS-PplatCW}$) [11]. The 2 groups exhibited different transpulmonary plateau pressure, obviating in one group the need for ECMO (no-ECMO group: $\text{PplatL} \sim 17 \text{ cm H}_2\text{O}$, $\text{P/F} = 67 \pm 5$ on $\text{PEEP} \geq 10$ vs. ECMO group: $\text{PplatL} \sim 27 \text{ cm H}_2\text{O}$; $\text{PF} = 75 \pm 10$ [11]). In the no-ECMO group, the end-inspiratory transpulmonary pressure $\text{PplatL} \approx 17 \text{ cm H}_2\text{O}$ was still below the limit of $27 \text{ cm H}_2\text{O}$ [132] despite a $\text{PplatRS} = 31 \text{ cm H}_2\text{O}$ [11]. Therefore, the baby lung was ventilated with minimal end-inspiratory distension. The end-inspiratory plateau pressure that referred to the chest wall PplatCW was much lower in the ECMO group ($4 \text{ cm H}_2\text{O}$) than in the no-ECMO

group (15 cm H₂O): *the lungs in the ECMO group were sicker with no possibility for further recruitment*. In contrast, in the no-ECMO group with an identical PplatRS, the difference in the PlatCW allowed the lung *itself* to be recruited as opposed to the chest wall [11], resulting in an increase in the end-inspiratory transpulmonary pressure PplatL, PEEP and P/F. Simultaneously, the PaCO₂ was lowered from 55 to 43 mm Hg (presumably due to the lowered dead space) without changes in systolic pressure and cardiac output over 30 min (no-ECMO: PplatRS from 31 to 38 cm H₂O; PplatL: 17 to 25 cm H₂O; PEEP: 18 ± 1 to 22 ± 1 cm H₂O; P/F: 67 to 180). As observed elsewhere without a balloon but with higher increments in PEEP [39, 40], the P/F was “cured” (i.e., P/F > 150) over 30 min by increasing the PEEP only minimally (4 cm H₂O) and thus the patients avoided the need for ECMO [11]. Because a standardized Pplat does not fit all patients, the PEEP should be set using a customized [11] approach using an esophageal catheter rather than a standardized [125] Pplat approach.

Transpulmonary end-expiratory pressure [10]: Oxygenation coupled to lung mechanics prevented cyclic alveolar end-expiratory collapse without overdistension (Pplat ≤ 30 cm H₂O) despite a higher PEEP in the esophageal catheter group (i.e., the balloon group) (Vt = 6 mL kg⁻¹ PBW, Pplat ≤ 30 cm H₂O in both groups throughout study; transpulmonary pressure < 25 cm H₂O at end-inspiration and 0–10 cm H₂O at end-expiration). During the interval t = + 72 h, the PEEP in the balloon group was 18 ± 5 cm H₂O and the end-expiratory transpulmonary pressure varied from 10 to 0 cm H₂O according to the FiO₂, whereas in the conventional group the PEEP was 12 ± 5 cm H₂O and was set according to the NIH table ([141]; Table 4, part I). Patients in the balloon group often exhibited substantial (up to 16–20 cm H₂O) increases in the PEEP, and the balloon-identified patients who would benefit from a high PEEP [10]. The P/F increased more and earlier (balloon: 147 ± 56 to 280 ± 126; conventional: 145 ± 57 to 191 ± 71 at + 72 h) [10]. Mortality was reduced in the balloon group [10] (P = 0.049 at 28 days given a small-sized trial; balloon, n = 30 and conventional, n = 31). In the control group, the transpulmonary pressure was measured but not used “per protocol”. Thus, the transpulmonary end-expiratory pressure remained negative (Fig. 2E in [10]) and was compatible with cyclic end-expiratory alveolar collapse; indeed, few patients in the control group experienced changes in the PEEP. Unfortunately, CT scans were not used to document a reduction in lung collapse at end-expiration [142].

Epidemiology-based trials: Large trials addressing PEEP have been disappointing (Fig. 4 in [8]). There is a clear-cut methodological difference between trials set to oxygenation (NIH table, Table 4A, part I) and trials set to respiratory mechanics (Pplat or end-inspiratory transpulmonary pressure, Pflex).

Why was a reduction in mortality only observed in the physiology-based trials [10, 31, 85, 131]? Why did the ARDS network trial show no difference in mortality when comparing high vs. low PEEP [141]? The answers are that a high clinical, anatomical, or physiological *heterogeneity* exists at inclusion or in the PEEP (Table 7, part I) [143]. Conversely, Papazian [50] and Guerin [27] led well-designed epidemiological trials that included only *severe early ARDS*; *homogeneity in inclusion* led to clear-cut results (Table 7, part I). Physiologically-minded design generated epidemiological advances.

Intrinsic PEEP (PEEPi; Figs 1 and 3 in [144]): An ARDS lung may present not only a restrictive disease but *also* an obstructive disease as a consequence of inflammation or preexisting COPD or asthma. Therefore, the *expiratory* flow limitation in ARDS patients generates increased *expiratory* resistance and PEEPi [144]. When respiratory failure of pulmonary origin is considered, the expiratory flow limitation comprises 44 ± 25% of the Vt (range 11–85%; PEEPi = 7.1 cm H₂O; range 3–13); additionally, the PEEPi is co-related to the peak airway pressure (i.e., the severity of the lung disease) [145]. The PEEPi is higher in the setting of early ARDS compared to late ARDS (6.5 vs. 3.5 cm H₂O, respectively) [146]. This phenomenon is lessened when the patient is moved from the supine to the semi-recumbent position [144]. Salbutamol lowered the expiratory flow limitation in 2 out of 8 ARDS patients [144]. *PEEPi should be measured using the software present on modern ventilators and then taken into account to tailor the extrinsic PEEP to the considered patient.*

To sum up, “higher PEEP associated with low Vt are beneficial in severely hypoxemic ARDS patients when administered early in the course of ARDS and when ARDS is diffuse” [8].

b. Tidal volume/driving pressure

Over the years, attention has switched from a high Vt to permissive hypercapnia and then to a low Vt (Table 6, part I) or better a low driving pressure [17]. The use of Pplat as the key variable to avoid overdistension has been replaced by driving pressure. Very recently, data [17] “scale[d] the delivered breath to the size of the lung available to participate in gas exchange [i.e. compliance as an indicator of the healthy lung [5]], rather than scaling to body size” [138] using driving pressure instead of normalized Vt. Therefore, the Vt story appears to be more straightforward than the PEEP story.

High Vt: Under anesthesia, progressive atelectasis generates hypoxemia and impairs oxygenation within ~1 h as a quasi-linear function of PaCO₂; the higher the PaCO₂, the larger the decrease in PaO₂. Hyperventilation improves oxygenation presumably by end-inspiratory recruitment. Therefore, recruitment maneuvers (RM) allow re-oxygenation to

baseline levels [38]. A large V_t (15–20 mL kg^{-1}) was used to handle ARDS, leading to volutrauma. Indeed, it took forty years to rediscover that the V_t of all mammals was ~ 6 mL kg^{-1} [147]. Nevertheless, the interpretation of this paper [38] should be careful [80]: “*the atelectasis occurring with time... was not likely due to compression (...an immediate phenomenon), but rather to progressive gas reabsorption caused by a regional gas uptake greater than supply*” (Table 4, part I). Thus the lung collapse, directed related to hypoventilation, may be equally prevented either by large V_t , delivered e.g. intermittently [80] (“sigh”), or PEEP.

Recruitment maneuvers: Alveolar recruitment occurs throughout inspiration. What remains open at end-expiration with PEEP is the tissue that was opened by the preceding inspiration. Derecruitment resulting from decreasing V_t can be reversed by increasing PEEP [5]. However, the effects of RM are transient if the PEEP is identical *before and after* the RM. Conversely, improved oxygenation seems to be based on the selection of the PEEP *post*-RM [30]. Indeed, RM improve or deteriorate oxygenation only *transiently* (66 recruitment maneuvers resulted in 10 increases and 14 decreases in O_2) [148]. The improvement lasted from 20–60 min [80, 148, 149]. This is observed also in the setting of sighs combined to PS [150]. [→Therefore, contrary to the view that the lung should be thoroughly reopened [39, 40] or kept fully open [33], these data [149] do *not* imply full recruitment. This is *at variance* with a thorough re-inflation of the lung, following lung surgery, before thorax closure. “[W]hat seems very important...is to convince clinicians to limit airway pressure in ARDS” [151]. Given the possibility of RV dysfunction [9] and increased IAP [152], just enough alveoli should be recruited for the *shortest* possible period to minimize overdistension (Tables 1 and 2, part II): “*PEEP levels necessary to reach acceptable oxygenation and to fully keep open the lung are not necessarily the same*” [1] ←].

Plateau pressure (Figs 2 in [96], 2 in [95] and 2 in [153]): Based on the numbers measured from healthy volunteers at total lung capacity (partial inspiration, 27 cm H_2O ; maximal inspiration, 37–44 cm H_2O [118, 132, 136]), lowering the Pplat appears to be quite relevant for a restrictive disease such as ARDS. Given a constant APACHE score and V_t , the Pplat on day 1 after randomization *independently* predicted mortality (Fig. 2 in [153]). Reducing the Plat to ≤ 30 cm H_2O reduced mortality due to ARDS of pulmonary origin [32] (“historical” group: $V_t = 13 \pm 2$ mL kg^{-1} ; Pplat = 39 ± 4 cm H_2O , PEEP = 10 ± 4 , $\text{PaCO}_2 = 39 \pm 4$ mm Hg, mortality = 64%; “recent” group: Plat = 25 ± 4 , PEEP = 6 ± 4 , $\text{PaCO}_2 = 51 \pm 10$ mm Hg, mortality = 32%). Accordingly, lowering the V_t from 12 to 6 mL kg^{-1} reduced the mortality (31 vs. 40%: –22%; $n = 861$) [105] (Plat < 45–50 cm H_2O to 30 cm H_2O).

Permissive hypercapnia: In *status asthmaticus*, the Ppeak was set to < 50 cm H_2O to allow for “permissive” hypercapnia

[154]. Survival was observed in all patients as opposed to the 10–35% mortality reported for historical controls [154]. This remarkable result [154] *reset the goal from normocapnia to accepting permissive hypercapnia* [78]. Accordingly, Ppeak in ARDS was set to < 30–40 cm H_2O using synchronized intermittent mandatory ventilation (SIMV) (V_t as low as 5 mL kg^{-1} , $\text{PaCO}_2 = 69 \pm 26$ mm Hg, PEEP = 9 ± 6 cm H_2O [range 0–25], with a degree of tachypnea, hypercapnia and acidosis in some patients) [28]. The mortality was reduced (expected 39%; observed 16%; difference –60%) [28].

Driving pressure: Early trials using protective ventilation proposed a low driving pressure (< 15–20 cm H_2O) [40, 131]. Accordingly, the driving pressure was most strongly associated with survival even when protective Plat and Vt ventilation were used [17]. A rough analogy may oppose the amount of stress continuously applied to a rubber band (PEEP) as opposed to the amplitude of stress imposed intermittently to the same rubber band (V_t /driving pressure). V_t and PEEP observed on day 1 were not associated with survival. Conversely, *reductions in V_t or increases in PEEP driven by random treatment-group assignment were beneficial only if they were associated with decreases in the driving pressure* (data in [92]; Fig. 2 in [17]). The rationale of a low V_t combined with a high PEEP holds: this is the rationale behind conventional “protective” mechanical ventilation, high frequency oscillation (“safe window” in Fig. 1 in [94]) or end-inspiratory transpulmonary pressure [11]. Only sound physiological principles translate into epidemiological advances.

The trade-off between overdistension and hypercapnia calls for manipulation of VCO_2 as well as CO_2 removal or normothermia as opposed to hyperthermia. To achieve a low driving pressure and high PEEP, an ultra-low V_t can be achieved using CO_2 removal [37] or high frequency ventilation. As CO_2 is much more diffusible than O_2 , venovenous CO_2 removal using a low flow through extra-renal replacement (ERR) will allow [37] the use of an ultra-low V_t and increases in the PEEP with an acceptable Pplat (≤ 25 –30 cm H_2O) and PaCO_2 . Accordingly, arterio-venous CO_2 removal allowed earlier weaning in patients with mild + severe ARDS (P/F < 150), lowered the midazolam + sufentanil requirements and increased spontaneous ventilation [155]. Two HFV trials showed increased mortality in the HFV group (control: 35 vs. HFV: 47% [103] and control: 41 vs. HFV: 42% [104]). As sound physiopathology was considered in design (no overdistension, low V_t ; high recruitment, high PEEP/mean airway pressure; Fig. 1 in [94]), this result is disappointing and may be related either to increased airway pressure, vasopressors or sedation/muscle relaxation requirements, all associated with multiple end-organ. The accompanying editorial balances the comfort of the patient with avoiding paralysis or heavy sedation [156] (Table 1, part II).

Tidal volume ($V_t \leq 5 \text{ mL kg}^{-1}$, Fig. 2 in [157]), or, better, driving pressure $\leq 15 \text{ cm H}_2\text{O}$ [17], are the next logical variables to be optimized, leading to no overdistension.

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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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