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Review / Derleme

Building on the Shoulders of Giants: Is the use of Early Spontaneous Ventilation in the Setting of Severe Diffuse Acute Respiratory Distress Syndrome Actually Heretical?

Devlerin Omuzlarındaki Bina: Şiddetli Yaygın Akut Solunum Sıkıntısı Sendromunda Erken Spontan Ventilasyon Kullanımı Gerçekten Sıra Dışı mı?

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Abstract / Öz

Acute respiratory distress syndrome (ARDS) is not a failure of the neurological command of the ventilatory muscles or of the ventilatory muscles; it is an oxygenation defect. As positive pressure ventilation impedes the cardiac function, paralysis under general anaesthesia and controlled mandatory ventilation should be restricted to the interval needed to control the acute cardio-ventilatory distress observed upon admission into the critical care unit (CCU; "salvage therapy" during "shock state"). Current management of early severe diffuse ARDS rests on a prolonged interval of controlled mechanical ventilation with low driving pressure, paralysis (48 h, too often overextended), early proning and positive end-expiratory pressure (PEEP). Therefore, the time interval between arrival to the CCU and switching to spontaneous ventilation (SV) is not focused on normalizing the different factors involved in the pathophysiology of ARDS: fever, low cardiac output, systemic acidosis, peripheral shutdown (local acidosis), supine position, hypocapnia (generated by hyperpnea and tachypnea), sympathetic activation, inflammation and agitation. Then, the extended period of controlled mechanical ventilation with paralysis under general anaesthesia leads to CCU-acquired pathology, including low cardiac output, myoneuropathy, emergence delirium and nosocomial infection. The stabilization of the acute cardio-ventilatory distress should primarily itemize the pathophysiological conditions: fever control, improved micro-circulation and normalized local acidosis, 'upright' position, minimized hypercapnia, sympathetic de-activation (normalized sympathetic activity toward baseline levels resulting in improved micro-circulation with alpha-2 agonists administered immediately following optimized circulation and endotracheal intubation), lowered inflammation and 'cooperative' sedation without respiratory depression evoked by alpha-2 agonists. Normalised metabolic, circulatory and ventilatory demands will allow one to single out the oxygenation defect managed with high PEEP (diffuse recruitable ARDS) under early spontaneous ventilation (airway pressure release ventilation+SV or low-pressure support). Assuming an improved overall status, $PaO_2/FiO_2 \geq 150$-200 allows for extubation and continuous non-invasive ventilation. Such fast-tracking may avoid most of the CCU-acquired pathologies. Evidence-based demonstration is required.

Keywords: ARDS, low tidal volume, high PEEP, transpulmonary pressure, controlled mechanical ventilation, spontaneous breathing, pressure support, APRV, cooperative sedation, sympathetic de-activation, alpha-2 agonist, clonidine, dexmedetomidine

Akut solunum sıkıntısı sendromu (ARDS), solunum kaslarının nörolojik komutada bir başarısızlığı değildir. Bu bir oksijenasyon bozukluğudur. Pozitif basınçlı ventilasyon kalp fonksiyonunu engellediği için, genel anestezi altındaki paralizi ve kontrollü zorunlu ventilasyon, hasta kritik bakım ünitesine (CCU) kabul edildiğinde gözlenen akut kardiyo-respiratuar sıkıntısını kontrol etmek için gerekli aralıklarla sınırlandırılmalıdır. Erken şiddetli ARDS'nin güncel yönetimi, düşük basınçlı kontrollü mekanik ventilasyon, paralize (48 saat, çok sık aşırı uzatılmış), erken pron pozisyon ve ekspirasyon sonu pozitif basınca (PEEP) dayanmaktadır. Bu nedenle, CCU'ya varış ile spontan ventilasyona geçiş arasındaki zaman aralığı, ARDS'nin patofizyolojisinde yer alan farklı faktörlerin normalize edilmesine odaklanmamaktadır: ateş, düşük kalp debisi, sistemik asidoz, periferik kapanma (lokal asidoz), sırtüstü pozisyon, hipokapni (hiperpne ve taşipne kaynaklı), sempatik aktivasyon, inflamasyon ve ajitasyon. Daha sonra, genel anestezi altında paraliz ile kontrollü mekanik ventilasyonun uzatılmış süresi, düşük kalp debisi, miyonöropati, deliryum gelişmesi ve nozokomiyal enfeksiyonu içeren CCU kökenli patolojiye yol açar. Akut kardiyo-respiratuar distresinin stabilizasyonu öncelikle patofizyolojik durumları ortaya çıkarmalıdır: ateş kontrolü, iyileşmiş dolaşım, asidozun düzeltilmesi, mikro dolaşımın iyileştirilmesi, "dik" pozisyon, minimize edilmiş hiperkapni, sempatik deaktivasyon (optimize edilmiş dolaşım ve endotrakeal entübasyondan hemen sonra uygulanan alfa-2 agonistleri ile daha iyi mikro-dolaşım ile sonuçlanır), inflamasyonun azalması ve alfa-2 agonistleri ile respiratuar depresyon olmaksızın "kooperatif" sedasyon. Normalize edilmiş metabolik, dolaşım ve ventilasyon talepleri, erken spontan ventilasyon (hava yolu basıncı bırakma ventilasyonu + SV veya düşük basınç desteği) altında yüksek PEEP (diffüz rekrüit edilebilir ARDS) ile yönetilen oksijenasyon defektini seçmeye olanak sağlar. Genel durumun iyileştiğini varsayarsak, $PaO_2/FiO_2 \geq 150$-200 ekstübasyona ve sürekli non-invazif ventilasyona izin verir. Bu hızlı tedavi ile, CCU kökenli patolojilerin çoğu engellenebilir. Kanıta dayalı veriler gerekmektedir.

Anahtar Kelimeler: ARDS, low tidal volüm, yüksek PEEP, transpulmoner basınç, kontrollü mekanik ventilasyon, spontan solunum, basınç desteği, APRV, kooperatif sedasyon, sempatik deaktivasyons, alfa-2 agonist, klonidin, deksmedetomidin

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Indroduction

Nanos gigantum humeris insidentes: discovering truth by building on previous discoveries. Bernard of Chartres[1]

The present management (1) of severe acute diffuse respiratory distress syndrome [ARDS; PAO_2/FiO_2 (P/F)<100 on positive end-expiratory pressure (PEEP) ≥5 cm H_2O, bilateral infiltrates without cardiac involvement (2)] lowered mortality remarkably from 52%-45% (2) to 32%-24% (3, 4)). Nevertheless, this approach generates a high incidence of critical care unit (CCU)-acquired diseases. Following others (5-9), we extend the use of use spontaneous breathing in the setting of early severe ARDS, given *strict* physiological guidelines.

Irrespective of the causal disease, *diffuse* ARDS is a failure of terminal airways to stay open during end-expiration because of inflammation or lung water (on top of atelectasis i.e. focal ARDS). This generates an oxygenation defect: ARDS is not a failure of the respiratory generator, the nerves innervating the ventilatory muscles or the ventilatory muscles. Hence, ARDS should be opposed to failure of the respiratory generator or of its output (e.g. Guillain-Barre, poliomyelitis, etc.), or to acute failure of ventilatory muscles observed during decompensation of chronic obstructive pulmonary disease (COPD). Thus, in ARDS, resting the exhausted ventilatory muscles for a period of time is not required, as in decompensated COPD. In the healthy supine volunteer, spontaneous breathing perfectly matches the ventilation to the perfusion [lowered inspiratory intrathoracic pressure, increasing venous return; diaphragmatic contraction compressing the hepato-splanchnic circulation, furthering venous return (10); and increased heart rate during inspiration, lowering intrapulmonary shunt (11)]. In the setting of diffuse ARDS, pathophysiology requires only the terminal airways to remain open at end-expiration and reduced work of breathing with inspiratory assistance (i.e. pressure support).

Controlled mechanical ventilation (CMV) with paralysis is required only during the restoration of circulation and pH (12), i.e. only during treatment of the acute cardio-ventilatory distress ('shock state' or 'shock'), to suppress further metabolic acidosis. Therefore, swiftness is of much importance. Indeed, ARDS presents with different phases: a) the acute cardio-ventilatory distress when the patient is admitted to the CCU (13) b) early severe diffuse ARDS proper, i.e. stabilized circulatory- and metabolically-wise and c) late ARDS, not considered here. The three phases require three different therapeutics. Also, ARDS includes a spectrum of ventilatory distress ranging from mild ARDS [hopefully treated with non-invasive ventilation (NIV) (e.g. helmet NIV)] up to severe ARDS and refractory hypoxemia. Further, the stabilization of the acute cardio-ventilatory distress observed in severe ARDS is obviously longer than the stabilization observed in the setting of mild ARDS. Handling single organ failure of a young patient (e.g. flu generating severe ARDS) requires less time to achieve stabilization of the acute cardio-ventilatory distress than that required in the setting of multiple organ failures in an elderly patient presenting with comorbidities [e.g. flu and peritonitis leading to severe ARDS and septic shock requiring renal replacement therapy coupled to veno-venous CO_2 removal to achieve ultra-low tidal volume (Vt)]. Hopefully, within 3-24 h, the shock is circulatory- and metabolically-wise stabilized, allowing one to address early severe ARDS *proper*, i.e. the oxygenation defect, hypoxemia and hypoxic drive. Thus, the hypothesis developed here applies in a differentiated manner according to the severity of the syndrome (9).

Given the achievements of conventional management (3, 4), if early spontaneous ventilation (SV) in the setting of early severe stabilized diffuse ARDS is to further improve the outcome, an exacting approach is required. SV is defined here as invasive mechanical ventilation with unimpeded spontaneous breathing effort+pressure support (PS) or airway pressure release ventilation (APRV)+SV (5); SV is opposed to volume-assist control mode (14). Progress beyond the state-of-the-art (3, 4, 15) requires revisiting its rationale: during the acute cardioventilatory distress observed upon arrival into the CCU, paralysis is used for 24 h (16) or 48 h (3) to synchronize perfectly the patient to the ventilator and reduce breath-stacking, lung inflammation and VO_2. Thus, the time interval necessary to control shock should be used not only for control of shock itself but also to address separately ('analytical' management), as early as possible, the multiple factors involved in the pathophysiology of ARDS (ARDS complex: ARDS 'conundrum'), including circulation[2] (17-19), position, metabolic demands (fever), ventilatory demands (acidosis and CO_2)[3] (20-22), sympathetic activation, inflammation (21), agitation. Hypoxemia is considered below separately.

Pitfalls of current management: The step-by-step pathophysiological approach to the acute cardioventilatory distress (13) relies on sound cardio-ventilatory physiology (13). The current management (3, 4, 13) relies on general anaesthesia, paralysis and positive pressure controlled ventilation.

a) General anaesthesia [light 'total intravenous anaesthesia' (TIVA); 'analgosedation' with opioids, Ramsay<3, –5<RASS<–3): General anaesthesia does not allow one to ad-

1 https://en.wikipedia.org/wiki/Standing_on_the_shoulders_of_giants

2 'Low PvO_2 effect' (17), patent foramen ovale (18), right ventricular dysfunction (19).

3 Systemic acidosis; local acidosis that implies a thorough improvement of the micro-circulation and a suppression of the metabo-reflex; high PaCO2; all these factors generate high respiratory drive leading to increased Vt and respiratory rate [RR] (20, 21). The metabo-reflex is the metabolic reflex originating in skeletal muscle, activated when blood flow to contracting muscles is insufficient to warrant both O2 delivery and metabolite washout (22), typically in the setting of local low flow and local acidosis.

dress, *separately*, the factors delineated above. Rather general anaesthesia masks all the symptoms of heightened respiratory drive simultaneously, which, therefore, cannot be assessed separately anymore. The intensivist is waiting for a miraculous healing of the ARDS complex, rather than acting speedily and tediously to disentangle the factors delineated above, one after the other.

b) Paralysis: Paralysis did not come out of the blue (6). Rather, the use of paralysis is a biased conclusion of experiments showing that i) controlled mandatory ventilation offsets cardiac output redistribution and mortality in the setting of acute experimental tamponade (23) and ii) intracerebroventricular infusion of sodium salicylate leads to hyperventilation, suppressed by paralysis under barbiturates (24). Both experiments demonstrate the need to suppress hyperventilation, acidosis, and ventilatory fatigue. However, none of these experiments can claim that general anaesthesia with controlled mandatory ventilation and paralysis is the only way to achieve minimized work of breathing. Fever control, improved cardiac output and micro-circulation, minimized hypo/hypercapnia, lowered inflammation and cooperative sedation with reduced hyperventilation, all lead to normalised respiratory drive and minimized work of breathing. General anaesthesia and paralysis should stay in the armamentarium of the intensivist just as one useful 'rescue therapy' for the shortest time-interval. Moreover, paralysis is too often extended well beyond the recommended 24 (16) or 48 (3) h limit, generating CCU-acquired pathology.

c) Circulatory impediment: Switching early from controlled mandatory ventilation to spontaneous breathing will reduce the circulatory burden imposed on an unstable patient. Firstly, active squeezing of the hepato-splanchnic sphere by contracting the diaphragm increases the venous return (10) and lowers vasopressor requirement. Secondly, minimized impediment to the right ventricular ejection and left ventricular diastolic filling improves cardiac function.

Given these pitfalls, what would be an alternative to general anaesthesia and paralysis?

A. Metabolic demands. Lowering the temperature by 1°C lowers VO_2 by 8%-10% (25), allowing one to reduce VO_2 by 30%-40% when temperature drops from 39.5°C to 35.5°C. In isolated early severe ARDS, metabolic demands should be addressed as soon as possible by lowering VO_2 ('fever control', i.e. evoked normothermia) (26, 27) with a muscle relaxant (for a time interval as short as possible), paracetamol, surface cooling and/or alpha-2 agonists. Alpha-2 agonists lower the hypothalamic activation threshold of cold defense effectors (28), suppress shivering (29), lower VO_2 (30) and lower the temperature to approximately 35.5°C[4] (29-35).

B. Circulation. As far as ARDS is concerned, the goal of circulatory improvement is to help addressing separately lung dysfunction, i.e. oxygenation, hypoxemia and hypoxic drive, as opposed to the other factors delineated above. Therefore, immediate circulatory optimization, such as volume, vasopressor, a pulmonary vasodilator and inotrope (17, 36), based on accepted criteria (lactate, 'CO_2 gap' and arteriovenous difference) will normalise a low PvO_2 effect (17), improving P/F. Checking for a patent foramen ovale (18) will allow one to inform the use of high vs. low PEEP. Evidently, iterative echocardiography will address venous return, right ventricular systolic function and left ventricular diastolic and systolic function (37). The right ventricle should be assessed at least after switching from CMV to SV and after any increase in PEEP.

C. Chemoreflex and respiratory drive. The physiological normalization of the chemoreflex response should progressively normalise Vt and RR. This needs itemization.

1) CO_2 vs. inflammation: A tight control of $PaCO_2$ will minimize its influence on the respiratory generator in the setting of late ARDS with rapid shallow breathing (38) and lowered CO_2 drive, reducing transpulmonary pressure swings (39). In the setting of early severe ARDS, after control of shock, increased respiratory drive exists despite suppression of the CO_2 drive by hypocapnia observed under spontaneous ventilation (21); possibly, inflammation acting on the respiratory generator evokes the persisting hyperpnea and tachypnea (21). This view (21) supports using the anti-inflammatory effect of alpha-2 agonists (35, 40, 41) to minimize this inflammatory drive impinging on the respiratory generator.

2) Hyperpnea and hypocapnia in early severe ARDS: A larger Vt is observed in patients requiring, on a clinical basis, endotracheal intubation (20) ('intubation'). No major differences are observed with respect to pH and $PaCO_2$ between patients failing the NIV test as opposed to patients who can be managed under NIV (pH, 7.45 and 7.41; $PaCO_2$, 32 and 36, respectively) (20). A high respiratory drive is postulated. If unrelated to systemic or local acidosis and CO_2 (20, 42), this heightened drive may be linked to inflammation (21) or fever, with hypoxemia considered separately below. This heightened drive possibly contributes to intra-lung dyscoordination ('pendelluft'), observed when SV is superimposed on assisted pressure control ventilation (43). In addition, SV generates more negative pressure from capillary to pleura (transvascular pressure) and a larger fluid shift to the interstitium, i.e. more oedema (44).

i) Pendelluft was reported in one acidotic (pH=7.28, BE=−8) patient (43) presenting with a large Vt (538 mL). No other group report or clinical trial has documented pendelluft. This large Vt suggests a tight control of acidosis (45); a pH>7.30 is necessary before switching to spontaneous ventilation (46). The take-home message is simple: no strong inspiratory effort

4 The lowest temperature in an healthy human at night. Alpha-2 agonists lower VO_2 (31, 32), especially in the setting of increased demands (29, 30). Furthermore, noradrenaline administration increases VO_2 (33), whereas alpha-2 agonists lower noradrenaline requirements in the setting of septic shock (34), (35). The overall effect of evoked-normothermia under alpha-2 agonists and lowered NA requirements needs assessment.

under spontaneous ventilation, despite high PEEP [legend of figure 1 of (9)]. In a restrictive lung ('baby lung'), 'protective' ventilation (i.e. driving pressure<15 cm H_20 (15), Vt<6 mL kg^{-1} (14)) applies, irrespective of controlled mandatory ventilation or spontaneous breathing.

ii) Lymph formation is favoured throughout the ventilatory cycle during SV, at variance with CMV (47, 48); high transvascular pressure (44) and oedema may be offset by higher lymph formation reabsorbed in the bloodstream.

3) The respiratory alkalosis observed in early severe ARDS (20) is converted, after intubation, to respiratory acidosis as a consequence of low driving pressure/Vt combined with general anaesthesia and paralysis. Thus, VCO_2 should be reduced, to avoid the effect of major respiratory acidosis and hypercapnia on the right ventricle (49) and the respiratory generator (increased Vt and RR), well before the withdrawal of paralysis and general anaesthesia. This implies lowering VO_2 (see above) and/or using veno-venous CO_2 removal.

4) Systemic vs. local acidosis: Improving the circulation will normalise the micro-circulation, metabolic/lactic acidosis and a high acidotic respiratory drive. Such a high acidotic drive is associated with a failed trial of spontaneous breathing in the setting of early severe ARDS, under extracorporeal membrane oxygenation (ECMO) (21). Accordingly, patients presenting with ARDS present low PCO_2 on blood entering the oxygenator (21). Is this surprising fact a consequence of impaired micro-circulation evoking low CO_2 return? In addition, in the setting of multiple organ failures and early severe ARDS, renal replacement therapy may help to suppress the acidotic drive on the respiratory generator, when improved cardiac output and micro-circulation and lowered ventilatory and metabolic demands are insufficient to rapidly normalise acidosis.

D. Position. 'Upright' position (reverse Trendelenburg, 60° head-up, 45° leg-down) (50-52) improves the mechanics of the diaphragm (greater excursion of the diaphragm and unfolding of the juxta-diaphragmatic alveoli). Indeed, the upright position increases P/F in responding severe ARDS (52).

E. Implementation. The hours following admission to the CCU are busy implementing a shock bundle: a) Therapeutic: normalization of volemia, intubation, ventilation with high FiO_2, high PEEP, vasopressor and inotrope if appropriate. b) Diagnostic: computed tomography (CT) scan, fibre optic bronchoscopy if indicated, iterative arterial and venous blood gases, echocardiography and passive leg raising. c) Physiological interventions: positioning, VO_2, systemic and local acidosis, VCO_2, mild permissive hypercapnia. Although the factors delineated above are addressed in a systematic manner, the hypoxic drive is addressed separately:

1) PEEP: CT findings ('focal' vs. 'diffuse' ARDS) will allow one to select low vs. high PEEP, respectively (53). The objective is not to fully reopen the lung ('open lung strategy') (54, 55), but only to recruit a penumbra area, i.e. poorly ventilated alveoli with a low VA/Q ratio. PaO_2 and shunt co-relate with the poorly aerated lung, not with atelectatic lung (56, 57). A meta-analysis (58) suggests using high PEEP in severe diffuse ARDS. After stabilization of the acute cardioventilatory distress under CMV with paralysis, PEEP can be set according to either the NIH table (59) [high PEEP (15-24 cm H_20) rather than high FiO_2] or oxygenation (trial-PEEP to SaO_2>88%-92% in the setting of CMV) or lung mechanics (Plat≤25-32 cm H_20 (60) vs. end-inspiratory (61) vs. end-expiratory (62) transpulmonary pressure. Spontaneous breathing requires no large transpulmonary pressure swings (high transpulmonary pressure) documented with an oesophageal catheter to achieve acceptable end-inspiratory transpulmonary pressure (<28 cm H_20 in spontanously breathing healthy volunteers (63); <25 cm H_20 in ARDS patients under CMV (61, 62)) with end-expiratory pressure added as necessary (62). In the setting of spontaneous breathing, this is delineated in legend of figure 1 of reference (9) and has been termed "inverted settings" (64) i.e. high PEEP-low PS. In addition, before switching to SV, a high intrinsic PEEP (65), observed in the setting of early ARDS, will be taken into account to decrease the expiratory work of breathing.

2) Spontaneous breathing: As soon as some improvement is observed (17) with ventilatory and metabolic demands being met (see above), CMV should be switched immediately to SV. This requires setting up PS exactingly: 100% automatic compressed circuit volume compensation ['automatic tube compensation' (66)], low expiratory (67) and inspiratory triggers and steep pressure ramp slope (68). In our hands, the Smart Care software (69) (Evita4XL/Infinity V500, Drager) performs very well in the setting of early severe stabilized ARDS (70) generating low PS without fatigue (low PS-high PEEP). With PS set as delineated above, PS level will compensate primarily for the circuit, the valves (71) and the tracheal tube (72).

Switching from CMV to SV has circulatory (see above) and ventilatory benefits. First, the lowered intrathoracic pressure will allow one to increase PEEP while keeping Pplat as low as possible[5]. In turn, high PEEP allows for faster alveolar recruitment (73), addressing the causal process leading to diffuse alveolar damage (recruitable ARDS: inflammation, lung water and atelectrauma in addition to atelectasis). Second, under high PEEP, the sick lung operates on the steepest (74) part of its expiratory pressure-volume curve [legend of figure 1 in (9) for details]. Under spontaneous ventilation and high PEEP, the benefits of a relatively higher compliance are i) a reduction of the work of breathing and ii) low level of PS generating adequate Vt and minimizing 'ventilatory fatigue' (anxiety, nasal flaring, sternal notch re-

5 Simplistically, under CMV: driving pressure, 20 cm H20+PEEP, 10 cm H20=Pplat≤30 cm H20; under SV: driving pressure, 10 cm H20+PEEP, 20 cm H20=Pplat≤30 cm H20. Although the formula is wrong, the rationale stands out.

traction, use of accessory muscles and thoracoabdominal dys-coordination). The implication is that, after withdrawal of a course of neuromuscular blockers as short as possible, iterative clinical observation should document the absence of ventilatory fatigue. In addition to the clinical observation, a physiological study using an oesophageal catheter is needed (see above). Third, under SV, high PEEP improves lung function; lung dys-coordination restricted to the triggering phase of inspiration, recruitment of peri-atelectatic regions (poorly ventilated areas with low VA/Q), VA/Q and shunt, improved maximal oxygenation, inspiratory effort and transpulmonary pressure and lowered sedative requirements (75). Fourth, APRV+SV better preserves the VA/Q ratio when compared to PS (5), by allowing diaphragmatic contraction throughout inspiration. The spontaneous expiratory brake evoked by the diaphragm delays the expiratory closure of alveoli (76). APRV+SV lowers ventilation days and CCU stay, approaching significance with respect to mortality in a small sample (77). Accordingly, APRV+SV is undergoing a large epidemiological trial (BIRDS). Clearly, a systematic approach (57) is needed with respect to modes of spontaneous breathing. Thus, recent data (20, 21, 39) reinforce the necessity to a) use CMV with paralysis for a very short interval to avoid patient-self inflicted lung injury (78) only if this time interval is put to proper use, i.e. addressing the factors delineated above b) to switch to SV as soon as the situation has improved (17).

3) Respiratory rate: To achieve spontaneous ventilation without fatigue, lowering RR is the next critical factor (79). As the acidotic and CO_2 drives are minimized during control of shock under CMV with paralysis, hypoxemia should be the only variable left stimulating the respiratory generator under spontaneous ventilation. The conventional target (SaO_2>88%-95%) (59, 80), applicable to early stabilised severe ARDS under CMV, is not applicable to early stabilised ARDS under spontaneous ventilation. The data show that, under SV, the hypoxic drive will increase RR (81). Thus, under spontaneous ventilation, simultaneously lowering (59) PEEP and FiO_2 appears unwise. By contrast, under SV, the alternative is, first, to lower O_2 to, e.g. FiO_2 from 1 to 0.3-0.4 as rapidly as possible (O_2 toxicity). Although FiO_2 is lowered, high PEEP is unchanged; this will maintain SaO_2>95%-100% and RR as low as possible. Second, under SV with 95%<SaO_2<100%, high PEEP is reduced progressively to 10 cm H_2O. Should the etiological treatment improve the disease causing ARDS and the analytical management improve ARDS, P/F will increase from well below 100 to above 150-200, over 12-96 h, with a kinetics similar as observed earlier (62, 82). Then, invasive ventilation will be converted to continuous NIV.

4) Normalised sympathetic activity and agitation: During stabilization of shock, sympathetic activation, inflammation and agitation are to be considered separately as they also generate high metabolic demands. In this respect, alpha-2 agonists (dexmedetomidine and clonidine) help pharmacologically the physiological management described above. Indeed, alpha-2 agonists a) normalize the sympathetic hyperactivity back toward baseline levels and b) simultaneously, evoke 'cooperative' (83) sedation[6] (84, 85). Accordingly, alpha-2 agonists suppress hyperventilation evoked by pain and anxiety (70, 86-88)[7]. Therefore, immediately (85, 89) following volume loading (90) and intubation, continuous administration of an alpha-2 agonist[8] (without bolus[9]) (91-93) generates sympathetic de-activation, improves micro-circulation (94, 95), lowers VO_2 (29, 30) during stabilization of shock, reduces intrapulmonary shunt (96, 97) and pulmonary hypertension (98), allows for spontaneous ventilation (99) without respiratory depression (100) or hyperventilation (86), lowers the $PaCO_2$ threshold (32), minimizes emergence delirium (101), lowers inflammation (35, 40, 41) and increases diuresis (102). In addition, at variance with general anaesthesia with paralysis, alpha-2 agonists do not interfere with the elastic recoil of the rib cage ("spring out" force). This will leave the chest wall functional residual capacity and diaphragmatic inspiratory and expiratory (76) functions intact.

To conclude, by capitalizing on previous results (3, 4, 13), the present analytical bundle aims at standing on the shoulders of previous investigators (3, 4, 13). Our goal is just to shorten the duration of controlled mandatory ventilation, paralysis and prone position by dissecting the different factors involved in the pathophysiology of early severe diffuse ARDS, including fever control, cardiac output and microcirculation, upright position, normalized chemoresponse to acidosis and CO_2, normalized work of breathing with low PS-high PEEP, lowered inflammation and early spontaneous

6 If needed, neuroleptics may be added to alpha-2 agonists (84), (85) (e.g. –3<RASS<–2 under CMV or –2<RASS<0 under SV).

7 Following alpha-2 agonist administered to healthy volunteers (reference 32), lowered Vt and lowered sensitivity to CO2 may explain the absence of hyperventilation and patient-ventilator dyssynchrony in the setting of early severe ARDS or related settings (70, 87, 88) under low PS-high PEEP-alpha-2 agonists and mild permissive hypercapnia.

8 With paralysis for the shortest interval to address the acute cardioventilatory distress.

9 The dose [dexmedetomidine, 1.5 μg kg^{-1} h^{-1} (91) or clonidine, 2 μg $kg^{-1}.h^{-1}$ (92)] is tentative. It is unknown whether the alpha-2 agonist should achieve a) adequate sedation to allow for nursing (–3<RASS<0) b) vs. the lowest vasopressor requirement or improved micro-circulation (capillary refill, diuresis, lactate<2mM and CO2 gap<5–6 mm Hg)?) The speed of the administration of the alpha-2 agonist is important. Obviously when volume is adequate, administration of dexmedetomidine or clonidine, respectively at 1.5 and 2 $\mu g.kg^{-1}.h^{-1}$, from intubation onwards is the simplest alternative with conventional sedation withdrawn or preferably not administered at all. When volemia (septic shock and severe ARDS) or auriculo-ventricular (A-V) conduction is inadequate, volemia and/or A-V conduction should be restored first. Then, the alpha-2 agonist is administered and the speed of administration increased step-wise (0.25 μg kg^{-1} h^{-1} for 3 h, followed by iterative echocardiography and passive leg raising and volume loading if appropriate, followed by 0.5 μg kg^{-1} h^{-1} for 3 h with echocardiography, passive leg raising and volume loading, up to maximal dose). No conventional sedation should be administered (ref 84, 89). Rescue sedation (93) using iterative bolus of midazolam allows for stabilization of the sedation evoked by the alpha-2 agonist during the 2-6 h interval needed to achieve sedation with alpha-2 agonists.

ventilation with alpha-2 agonists. An integrative, analytical management leaves, after handling the factors delineated above, hypoxemia as the only factor left to generate a high respiratory drive and to be treated as such with high PEEP and high FiO_2 (with inspiratory assistance). Will this fast-track management lead to early extubation and continuous NIV? Does this fast-track management skip late ARDS (fibrosis, myoneuropathy, emergence delirium and CCU-acquired pathology)? This proposal (70, 87, 103-105) requires evidence-based demonstration with respect to physiology and outcome. If the fast-track fails, the intensivist will revert early to 'rescue' therapy that includes CMV, paralysis (3), proning (4), nitric oxide (NO) and ECMO.

Note added in proof : The CO_2 drive within the genesis of increased ventilatory demand (Carteaux, 2016; ref 20) in early (Crotti, 2017; ref 21)) and late ARDS (Mauri, 2016; ref 39) was emphasized (21, 39). However, suppressing the CO_2 input on the respiratory generator makes little difference with respect to ventilatory demand. Crotti, 2017 (ref 21) emphasizes systemic inflammation to explain the increased ventilatory demand observed during the acute cardio-ventilatory distress or the early ARDS. Local inflammation or local acidosis at the level of the respiratory generator or pulmonary receptors also require study.

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