Abstract: Introduction: As alpha-2 agonists preserve ventilator drive, patients presenting with acute respiratory distress syndrome (ARDS, PaO2/FiO2 < 200) were managed using sedation with an alpha-2 agonist, clonidine, combined to spontaneous ventilation (SV) + pressure support ventilation (PS).

Methods: Sedation was provided by an alpha-2 agonist, clonidine 1-2 µg.kg⁻¹.h⁻¹, without bolus administration, and supplemented with a neuroleptic, loxapine, if needed. Four patients presenting with ARDS were managed with pressure support ventilation (PS = 8 cm H₂O, rarely 10-12 cm H₂0) and high PEEP (10-20 cm H₂0). Energy requirements were minimized, if appropriate, with hypothermia caused by extra-renal replacement therapy or intentional hypothermia (35-36°C). Repeated echocardiographic examinations revealed no right ventricular failure.

Results: Recovery of ARDS, i.e. sustained increase of P/F > 200 for > 24 h, was observed, over 2-5 days. Conclusion: Use of an alpha-2 agonist as first-line sedative agent led to absence of respiratory depression and spontaneous ventilation. Upon ARDS, the lowered intrathoracic pressure observed with SV+PSV allowed one to recruit alveoli with high levels of PEEP, without impairing right ventricle function.

Key words: Acute respiratory distress syndrome; spontaneous ventilation; pressure support ventilation; PEEP; high PEEP; alpha-2 adrenergic agonist; alpha-2 agonist; clonidine; respiratory drive; neuroleptic; loxapine.

INTRODUCTION

Acute respiratory distress syndrome (ARDS: PaO2/FiO2 = P/F < 200) (1, 2) imposes controlled mechanical ventilation (CMV) and conventional sedation. Upon severe ARDS (P/F < 120), prone positioning, NO administration or extracorporeal membrane oxygenation (ECMO) may be required. Given that a) spontaneous ventilation + airway pressure release ventilation (APRV) has been used in the setting of acute lung injury (ALI: 200 < P/F < 300) or ARDS (3), b) diaphragmatic weakness occurs rapidly following CMV (4, 5) c) reduction of length of mechanical ventilation has been observed following use of alpha-2 agonists (6), d) alpha-2 agonists increase phrenic nerve activity (“respiratory drive”), in vitro (7), and lower pulmonary artery impedance (8), we reasoned that, in the setting of early severe diffuse ARDS, alpha-2 agonists will preserve spontaneous ventilation (SV) while high PEEP combined to SV-Pressure support (PS) would improve oxygenation.

METHODS

Patients were selected based on the criteria of the American European Consensus Conference (AEC) (1): a) acute onset of respiratory distress b) P/F < 200 regardless of PEEP level c) bilateral infiltrates on frontal chest radiograph (X ray) d) left atrial pressure < 18 mm Hg (ascertained here from echocardiographies obtained at least daily by experienced cardiologists; adequacy of cardiac output

was assessed at least four times per day based on SscCO\(_2\) > 70-75% and lactates concentrations). The observations are sketched out in figure 1 (patient A) and table 1. Fiberoptic broncho-alveolar lavages were performed in all patients to ascertain complete absence of mucus plugs. The ventilatory mode was PS = 8 (rarely10-12) cm H\(_2\)O, 100% automatic tube compensation and the lowest level of trigger possible on the considered ventilator. Permissive hypercapnia up to PaCO\(_2\) \(\approx\) 60 mm Hg was used. PS was set to no or minimal activity of the sternocleidomastoid muscle (9), nor sternal notch retraction, nor thoraco-abdominal dyscoordination. Respiratory rate (RR) was kept < 20-25 breaths per min at all intervals, to avoid respiratory fatigue, using mild hypothermia (35-36°C), if necessary. Firstly, PEEP was set to high level (usually 15-20 cm H2O). Secondly, FiO\(_2\) was lowered to 0.4 stepwise each 6-12 h, to achieve a 50 < PaO\(_2\) < 100 mm Hg. Thirdly, PEEP was lowered stepwise by 5 cm H\(_2\)O each 24 h to achieve a stable P/F > 200 for > 24 h. Ppeak was set \(\leq\) 32 mm Hg (10). As Pplat could not be ascertained in the PS mode (Evita 4, Drager), our assumption was Pplat = Ppeak. Midazolam-sufentanil infusion was stopped abruptly in all patients and clonidine infusion begun (1 µg.kg\(^{-1}\).h\(^{-1}\)), without bolus administration, to 3 < Ramsay < 4. Then, if necessary, clonidine infusion was increased up to 2 µg.kg\(^{-1}\).h\(^{-1}\) (11), and supplemented, if necessary with a neuroleptic (loxapine 100 mg\(*4\) through a nasogastric tube), especially in bellicose patients to achieve 3 < Ramsay < 4. Then, loxapine was lowered to 25 mg\(*4\) as appropriate. Midazolam (3-5 mg bolus) was administered if appropriate for nursing or in one instance (patient C) to bridge to extubation upon early morning hours. Clonidine was lowered to 1 µg.kg\(^{-1}\).h\(^{-1}\) in most patients before extubation, to 2 < Ramsay < 3, and early transition to a rigorous regime of non-invasive ventilation (NIV) for 23 out of 24 h (23/24 h) with identical parameters as used before extubation (e.g.: FiO\(_2\) = 0/4, PEEP =

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**Fig. 1.** — Chest Xray on day 3 (P/F = 56, right) and 7 (P/F = 262, left). Throughout this time interval, Mrs A was sedated with clonidine (1 [D3 to D5] then 2 µg.kg\(^{-1}\).h\(^{-1}\)), supplemented with loxapine (D5 to D7), and ventilated using high PEEP (10 on D2 to D3, 15 on D3 to D4, then 20 cm H\(_2\)O on D4 to D6)-spontaneous ventilation with pressure support (PS = 8-12 mm Hg to a PaCO\(_2\) \(\leq\) 60 mmHg ; see text for details). Note the improvement in “white lung”, especially on right side, between D3 and D8. Abbreviations : D = right side ; Au lit = Chest Xray taken in bed.

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<table>
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<th>time</th>
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<th>FiO(_2)</th>
<th>PaO(_2)/FiO(_2)</th>
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<td>55*</td>
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ER : emergency room ; CCU : critical care unit ; PSV : pressure support ventilation ; CMV : controlled mandatory ventilation under midazolam-sufentanil-cisatracurium for broncho-alveolar lavage ; *lowest PaO\(_2\) on D2 = 51 on FiO\(_2\) = 1 ; **extubation to non invasive ventilation in the morning of D9 (duration of intubation : 8 days). Changes in PEEP levels were performed on the morning round following blood gas analysis.
10, PS = 6-8 cm H₂O) combined to physiotherapy. NIV was continued for 18/24 h, then 12/24 h, and then 6/24 h, under continued clonidine infusion.

RESULTS

In all instances, the combination of high PEEP, low PS, and clonidine 1-2 µg.kg⁻¹.h⁻¹ allowed one to observe a recovery of P/F > 200 over 2-5 days (figure 1 and table 1) : accordingly, FIO₂ and PEEP were lowered to 0.4 and 10 cm H₂O respectively. When this improvement of P/F > 200 was sustained for at least 24 h, extubation followed by NIV led to full recovery, and discharge from the CCU, unless a complication unrelated to ventilation (e.g. stroke in patient B) occurred.

DISCUSSION

Limitations : This heterogeneous group report is descriptive, at variance with a double-blind randomized prospective trial : a) Patient A presented a mixture of fluid overload, leading to acute respiratory decompensation when supine in the CT scan, and aspiration upon tracheal intubation leading to severe ARDS proper (P/F = 51) b) P/F improved from 51 to 56 following a 12 h course of myorelaxant (patient A) : thus, ARDS was not cured by 12 h of myorelaxation c) most patients were transitioned from midazolam-sufentanil to clonidine abruptly. However, given the long elimination half-life of midazolam-sufentanil, some interaction cannot be ruled out. Such interaction is highly unlikely, as all patients needed either increasing clonidine dose, or supplementation with a neuroleptic, 6-24 h after midazolam-sufentanil discontinuation. d) as there is no control group (e.g. low dose midazolam-sufentanil combined to high PEEP-low PS) opposed to the PS-clonidine group, there is no evidence that the patients did any better than expected : this report assesses feasibility of a combined approach (alpha-2 agonists with spontaneous ventilation), and nothing more ; it does not convey any clinical message. e) no attempt was made to look for a delayed outcome (e.g. 30 days mortality) beyond an improvement of P/F or extubation.

The issues pertaining to complex interactions between the brain, the lung and the heart are to be disentangled in an itemized manner.

Brain : central respiratory control vs. sedation vs. doses vs. choice of the alpha-2 agonist are to be considered.
Firstly, alpha-2 agonists increase the respiratory drive in the brain stem of neonate mice (7), and do not depress ventilation in volunteers (12). This report rests on this first key property of alpha-2 agonists, as opposed to conventional sedative agents.

Secondly, as opposed to conventional sedative agents, the specificity of alpha-2 agonists, is indifference to the environment (ataxia) : the patient presents slow-wave sleep (SWS) (13) and reduced delirium (14). He is able to communicate (6) and to obey orders (15), then resumes SWS when left undisturbed. This appears ideal to lighten sedation (16).

Taken together, the differences between alpha-2 agonists vs. conventional sedation are presumably the a) preservation of the reactivity of the locus coeruleus (17, 18) b) avoidance of a lengthy elimination of conventional sedation in elderly or debilitated patients c) preservation of the central control of the diaphragm (7) : the diaphragm operates thoroughly upon SV, at variance with CMV (4, 5).

Thirdly, doses of clonidine (1-2 µg.kg-1.h-1) were selected as suggested by the French Society of Critical Care Medicine (11). However, this consensus (11) does not refer to ARDS. Presumably, identical effects may be observed with dexmedetomidine (1-1.5 µg.kg-1.h-1) (19), combined to haloperidol (20).

Fourth, our use of loxapine reflects its use when combative patients (21) or delirium tremens (22) are considered. Its administration through the gastric tube avoids brisk changes in afterload, when sympatholysis is already prominent. Another neuroleptic, haloperidol, appears suitable to supplement another alpha-2 agonist, dexmedetomidine (20).

Lung : To our knowledge, these observations are the first ones to document the use of an alpha-2 agonist from severe ARDS (P/F range : 40-123 at the nadir ; P/F range : 56-123 upon beginning of clonidine administration) to extubation : usually alpha-2 agonists are selected to wean the patient from the respirator (11), after improvement of oxygenation. By contrast alpha-2 agonists were used here to accelerate improvement of oxygenation. Several issues are to be considered : definition of ARDS, SV vs. CMV, level of PEEP, level of PS, morbid obesity.

The classical definition of ARDS (1) has been criticized (23). As the Berlin definition of ARDS was published (2) after submission of this report, the AECC definition was used.

Secondly, SV was used here. By contrast, most groups stick to CMV, or assist-control mode, upon severe ARDS. The rationale for SV has been detailed elsewhere (3, 24, 25) : ARDS is a disease of oxygenation, i.e. not linked to failure of respiratory muscles and CO2 elimination. Once the acute phase of the distress is taken care of (minimized work of breathing, lowered RR : see below), weaning may take place early on, only if sedation does not suppress respiratory drive. Investigators advocating a 48 h course of myorelaxation upon ARDS switch their patient over to PS immediately after 48 h of myorelaxation (26) : this has been overlooked by most commentators. The combination of alpha-2 agonists and SV allows one to skip this 48 h course of myorelaxation : SV using the PS mode avoids a) ventilator-patient asynchrony b) the rapid diaphragmatic dysfunction which occurs under CMV (4, 5).

Thirdly, SV lowered intrathoracic pressure. This allowed one to set the highest PEEP compatible with a Pplat < 26-32 cm H2O (10, 27, 28), as proposed earlier with controlled ventilation (29). This led to a high PEEP (usually 15-20 cm H2O), as proposed upon early diffuse severe ARDS (30). Previous investigators set the PEEP to 15-16 cm H2O, when they were unable to assess the inflexion of a pressure-volume curve (31, 32). In our patients, this led to an improvement of P/F > 200 over 2-5 days : this time course is identical to previous observations (33-36). Thus, a relatively rapid extubation followed the combination of alpha-2 agonists and SV. This fits with a reduced length of mechanical ventilation under alpha-2 agonists (6).

Fourthly, to minimize baro-trauma, setting Pplat ≤ 26-32 cm H2O led to a lowered Vt (37), i.e. 4-6 ml.kg-1, here. By contrast, upon weaning from CMV, the conventional setting of PS is usually 15-25 cm H2O. Such a setting of PS would have led to a very high Vt, a large transalveolar pressure (38) and possibly volu-trauma. Here, PS had to be set to a low level : 8-12 cm H2O (most often 8 cm H2O). How PS may be set so low so early upon weaning in ARDS ? When a high PEEP opens up the alveoli above the opening volume, the ascending limb of the pressure-volume curve is almost linear above the opening volume : thus, a low gradient of pressure (i.e. low PS) generates a large Vt. Furthermore, permissive hypercapnia allows one to further reduce Vt : this may have further minimized the driving pressure (Plat-PEEP). Could it minimize, here, ventilator-induced lung injury (31, 38, 39) ?

In turn, such a low level of PS allows one to set PEEP to a much higher level (15-20 cm H2O) : an addition shows that Pplat = PEEP [20]+PS[10] ≤ 32 cm H2O and is arithmetically equal to high driv-
ing pressure (e.g. 20 cm H2O under CMV) with low PEEP (e.g. 10 cm H2O) = 30 cm H2O. However the clinical result may be at variance.

Our first key concern upon using high PEEP (here 15-20 cm H2O) was a possible increased incidence of pneumothoraces: none was observed in this short series. Previous data observed a faster decrease in plateau pressure when high PEEP is used (31, 33, 40). Meta-analyses observed no higher (41, 42) or lower (43) incidence of barotrauma upon high PEEP.

Fifth, patient A presented with morbid obesity. Prone positioning is more difficult in morbidly obese patients: this prompted us to use a combination of alpha-2 agonist and SV-PS-high PEEP. Later, this was extended to other patients, including patients presenting with ARDS for several days. As stated above, this report conveys no clinical message but restricts itself to feasibility.

Caveats:

Firstly, this technique may be applicable only upon early diffuse severe ARDS: a CT scan combined to an automated pressure-volume curve (44) should lead to the “right” PEEP (45) to refine the present approach. By contrast, focal/lobar ARDS may require lower PEEP (5-12 cm H2O) (45).

Secondly, the combination of alpha-2 agonists and SV is based on minimizing work of breathing. Clinical inspection should avoid sternal notch retraction and use of the accessory muscles (9); again, the work of breathing should be thoroughly minimized. The second element is to avoid a high RR for days, a leading cause for failure of weaning (46). Allowing a RR < 35-40 bpm may be acceptable for a few hours. By contrast, in our hands, a RR ≤ 20-25 bpm appears as a maximum tolerable, without evoking respiratory fatigue, through the 2-5 days of SV needed to improve P/F > 200 (see below: temperature). No attempt was made to use other modes of SV (PS with sighs, “noisy” PS, etc…….), which may prove superior to further minimize work of breathing. Finally, minimizing work of breathing includes a thorough regime of NIV for an extended interval following early extubation, as soon as P/F is > 200. Failure to adhere to such a strict regime may lead to re-intubation (patient D).

Thirdly, in our hands, this technique is applicable to some patients presenting with acute decompensation of chronic obstructive pulmonary disease but does not suit patients presenting with a large emphysema.

Temperature: Increased energy requirements appear as the last rationale behind controlled ventilation, especially in the early phase of ARDS (47). In this respect, alpha-2 agonists lower temperature (48) and oxygen consumption (VO2) in volunteers (49), upon weaning (50) or upon postoperative shivering (51). Here, a lowered VO2 may have enlarged the margin of safety upon early weaning under PS. Furthermore, mild hypothermia (35-36°C) was observed in several patients either as an un-intended consequence of extra renal replacement therapy or, upon sepsis, as a consequence of intentional mild hypothermia: this reduced VO2, RR (see above: minimizing work of breathing) and PaCO2.

Heart: The left and right ventricles (RV) were monitored at least daily, combining echocardiography, SvO2 and lactates. The first issue was adequate volemia, in the context of sympatholysis. In this respect, SV lowers intrathoracic pressure, increases venous return and lowers volume requirements: this may counteract partially, volume-wise, the sympatholysis associated with clonidine.

Our second key concern was the association of high PEEP with acute core pulmonale (52). Therefore, increasing PEEP levels were tested daily to the highest level, to look for RV dilatation and septal bulging (52). Clearly, RV dilatation is to be scrutinized if the present technique is to be validated any further. In this respect, the second key property of clonidine used here is decreased pulmonary impedance in the presence of sympathetic hyperactivity (8): this may have helped the RV to withstand high PEEP. Finally, low levels of PS led to permissive hypercapnia, with PaCO2 set as to avoid RV dilatation (53).

Conclusion

This combination of alpha-2 agonists and SV is a concatenation of Putensen (3), Mercat (29), Jardin (54) and Akada (55) techniques. This shows the feasibility to improve oxygenation over 2-5 days upon spontaneous ventilation without respiratory fatigue, muscle paralysis, or acute core pulmonale. Iatrogenic disease is a hallmark of ARDS (56, 57): shortening improvement of oxygenation and elimination of sedative drugs may be critical to improve survival. This feasibility study raises a question: would an “off-label” use of an alpha-2 agonist lead to preservation of respiratory drive (7, 58), lowered pulmonary artery impedance (8), SV+high PEEP, and earlier extubation? Given that this report shows feasibility, but nothing more, a double-blind trial in the setting of...
early severe diffuse ARDS ought to be conducted.

References