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ORIGINAL

Feasibility and safety of ultra-low tidal volume ventilation without extracorporeal circulation in moderately severe and severe ARDS patients

J. C. Richard[1,2,3*], S. Marque[4], A. Gros[5], M. Muller[6], G. Prat[7], G. Beduneau[8,9], J. P. Quenot[10], J. Dellamonica[11], R. Tapponnier[12], E. Soum[13], L. Bitker[1,2,3], J. Richecoeur[14] and the REVA research network

Abstract

Purpose: Mechanical ventilation with ultra-low tidal volume (VT) during ARDS may reduce alveolar strain, driving pressure and hence ventilator-induced lung injury, with the main drawback of worsening respiratory acidosis. We hypothesized that VT could be reduced down to 4 ml/kg, with clinically significant decrease in driving pressure, without the need for extracorporeal CO_2 removal, while maintaining pH > 7.20.

Methods: We conducted a non-experimental before-and-after multicenter study on 35 ARDS patients with $PaO_2/FiO_2 \leq 150$ mmHg, within 24 h of ARDS diagnosis. After inclusion, VT was reduced to 4 ml/kg and further adjusted to maintain pH ≥ 7.20, respiratory rate was increased up to 40 min^{-1} and PEEP was set using a PEEP–FiO_2 table. The primary judgment criterion was driving pressure on day 2 of the study, as compared to inclusion.

Results: From inclusion to day 2, driving pressure decreased significantly from 12 [9–15] to 8 [6–11] cmH_2O, while VT decreased from 6.0 [5.9–6.1] to 4.1 [4.0–4.7] ml/kg. On day 2, VT was below 4.2 ml/kg in 65% [$CI_{95\%}$ 48%–79%], and below 5.25 ml/kg in 88% [$CI_{95\%}$ 74%–95%] of the patients. 2 patients (6%) developed acute cor pulmonale after inclusion. Eleven patients (32%) developed transient severe acidosis with pH < 7.15. Fourteen patients (41%) died before day 90.

Conclusion: Ultra-low tidal volume ventilation may be applied in approximately 2/3 of moderately severe-to-severe ARDS patients, with a 4 cmH_2O median reduction in driving pressure, at the price of transient episodes of severe acidosis in approximately 1/3 of the patients.

Keywords: Acute respiratory distress syndrome, Permissive hypercapnia, ECMO, ECCO2R, ultraprotective ventilation, Driving pressure

*Correspondence: j-christophe.richard@chu-lyon.fr
[1] Service de Médecine Intensive Réanimation, Hôpital De La Croix Rousse, Hospices Civils de Lyon, 103 Grande Rue de la Croix Rousse, 69004 Lyon, France
Full author information is available at the end of the article

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Introduction

Despite improvement in acute respiratory distress syndrome (ARDS) management by using protective ventilation (i.e., tidal volume (VT) 6 ml.kg^{-1} of predicted body weight (PBW) and plateau pressure (P_{Plat}) below 30 cmH_2O) and use of prone positioning, ARDS mortality remains high in observational studies [1], and recent randomized controlled trials (RCTs) [2–4]. Clinical data strongly suggests that harmful mechanical ventilation (MV) settings might partly explain the current mortality of ARDS. Indeed, 30% of ARDS patients under protective ventilation exhibit tidal hyperinflation on computed tomography, associated with an increase in pro-inflammatory mediators in broncho-alveolar lavage (BAL) [5], suggesting excessive VT. Increased driving pressure (ΔP, i.e., the ratio of VT over respiratory system compliance) is independently associated with higher mortality [6–8], and may reflect that a given VT is too high relative to the end-expiratory lung volume. In a recent observational study [9], an increase of 1 ml.kg^{-1} in initial VT was associated with a 23% increase in mortality, suggesting that small VT variations at the initial phase of ARDS may impact prognosis. Reducing VT from 6 to 3–4 ml.kg^{-1} [ultra-low tidal volume ventilation (ULTV)] combined with extracorporeal CO_2 removal (ECCO2R) is associated with a decrease in pro-inflammatory mediators in BAL [10], and lower ventilator-free days (VFD) in the most hypoxemic ARDS patients [11]. However, ECCO2R has, to date, not shown any beneficial effect on ARDS survival, is associated with a high rate of treatment-related adverse events [12], and may increase the burden of healthcare-related costs. As tolerating mild level of hypercapnia is the standard of care in ARDS [13], and since the lowest tolerable pH without adjustment of MV tend to decrease in recent RCTs [2, 14], we hypothesized that the VT could be reduced down to 4 ml.kg^{-1}, with clinically significant decrease in ΔP and without the need for ECCO2R, while maintaining the pH in the range targeted in recent RCTs.

Materials and methods

Study design

This trial is a non-experimental before-and-after multicenter study, performed at 11 intensive care units (ICU). The trial was registered at ClinicalTrials.gov (NCT02816372) and the protocol was approved by an ethics committee (RCB 2016-A00503-48). Patients were enrolled between October 2016 and March 2018.

Take-home message

Ultra-low tidal volume ventilation without extracorporeal circulation is feasible in approximately 2/3 of moderately severe-to-severe ARDS patients. It is associated with a 4 cmH_2O median reduction in driving pressure, at the price of transient episodes of severe acidosis in approximately 1/3 of the patients.

Patients

Eligible participants were aged 18 years or older, under invasive MV, with ARDS according to the Berlin definition [15], and a $PaO_2/FiO_2 \leq 150$ mmHg.

Exclusion criteria were ARDS onset > 24 h, planned duration of invasive MV < 48 h, intracranial hypertension, chronic obstructive pulmonary disease, chronic respiratory failure under home oxygen or non-invasive ventilation, pneumothorax or air leak, morbid obesity (body weight > 1 kg.cm^{-1} body height), sickle cell disease, recent bone marrow transplantation, chemotherapy-induced neutropenia, burn injury on more than 30% of the body surface, hepatic cirrhosis with Child–Pugh score C, treatment by extracorporeal membrane oxygenation or ECCO2R, pregnancy, advance directives to withhold or withdraw life-sustaining treatment, previous inclusion in present study, inclusion in another MV trial during the same ICU stay, patient under a legal protective measure, lack of affiliation to social security, lack of informed consent by patient's relative.

Protocol description

After inclusion (H_0, day 1), MV was performed in volume-assist control mode with VT lowered by 1 ml.kg^{-1} PBW steps down to 4 ml.kg^{-1} PBW and further refined using a dedicated algorithm (Table 1), aiming to achieve the following goals: $P_{Plat} \leq 30$ cmH_2O, $55 \leq PaO_2 \leq 80$ mmHg (or $88\% \leq SpO_2 \leq 95\%$), and $7.20 \leq pH \leq 7.45$. ARDS adjunctive therapies were protocolized as follows: administration of neuromuscular blocking agent (NMBA) during 48 h [14], and daily prone positioning during at least 16 h if $PaO_2/FiO_2 < 150$ mmHg, until achievement of a $PaO_2/FiO_2 \geq 150$ mmHg with a PEEP ≤ 10 cmH_2O and a $FiO_2 \leq 60\%$ in the supine position [2].

From day 3, a PEEP weaning trial (Online Resource 1) was performed daily if PaO_2/FiO_2 was > 150 mmHg in the supine position. After successful completion of this trial, ventilation was performed in volume-assist control mode with VT 6 ml.kg^{-1} PBW or pressure support targeting VT between 6 and 8 ml.kg^{-1} PBW, and weaning criteria were screened daily to perform a spontaneous breathing trial (Online Resource 2).

Sedation was adjusted using Richmond Agitation-Sedation Scale (RASS) score [16], as follows: −5 during NMBA administration, −5 to −4 during prone

Table 1 Summary of the ventilation procedure

Ventilatory mode: volume-assist control
Instrumental dead space: minimize by using a heated humidifier and a low-volume endotracheal tube connector
Initial VT: stepwise reduction by 1 ml.kg^{-1} PBW steps at intervals ≤ 2 h down to 4 ml.kg^{-1} PBW
RR: increase up to 40 min^{-1} to maintain VE constant (35 min^{-1} if intrinsic PEEP > 2 cm H_2O)
Ratio of the duration of inspiration to the duration of expiration: adjust between 1:2 and 1:4 to maintain intrinsic PEEP ≤ 2 cm H_2O
Ventilatory goals: plateau pressure ≤ 30 cm H_2O; 55 ≤ PaO_2 ≤ 80 mm Hg or 88% ≤ SpO_2 ≤ 95%; 7.20 ≤ pH ≤ 7.45
Allowable combinations of PEEP (cm of H_2O) and FiO_2: 5 and 30%, 8 and 30%, 10 and 30%, 12 and 30%, 14 and 30%, 14 and 40%, 16 and 40%, 16 and 50%, 18 and 50%, 20 and 50%, 20 and 60%, 20 and 70%, 20 and 80%, 22 and 80%, 22 and 90%, 22 and 100%, 24 and 100%
Procedure when PaO_2 < 55 mm Hg despite adjustments of FiO_2 and PEEP (in the following order as needed): (1) use PP if PaO_2/FiO_2 < 150 mm Hg with PEEP > 10 cm H_2O and FiO_2 > 60%; (2) add NMBA; (3) add iNO; (4) consider ECMO
Procedure when PaO_2 > 80 mm Hg (in the following order as needed): (1) stop iNO; (2) stop NMBA if administration > 48 h; (3) adjust FiO_2 and PEEP
Procedure when plateau pressure is > 30 cm H_2O (in the following order as needed): (1) inject a bolus of NMBA; (2) reduce VT to 4 ml.kg^{-1} PBW (if pH ≥ 7.2); (3) decrease PEEP down to a minimum of 5 cm H_2O
Procedure when pH < 7.20 (in the following order as needed): (1) increase sedation/NMBA dose to achieve good patient–ventilator synchrony; (2) increase RR up to 40 min^{-1} (35 min^{-1} if total PEEP > 2 cm H_2O); (3) may administer IV bicarbonate; (4) increase VT by 1 ml.kg^{-1} PBW step up to 8 ml.kg^{-1} PBW if pH < 7.15; (5) consider ECCO2R or ECMO
Procedure when pH > 7.45 (in the following order as needed): (1) decrease VT down to 4 ml.kg^{-1} PBW; (2) decrease RR
Procedure when VT > 4 ml.kg^{-1} PBW and pH > 7.20: attempt to decrease VT down to 4 ml.kg^{-1} PBW at least twice daily

ECCO2R extracorporeal CO_2 removal, *ECMO* extracorporeal membrane oxygenation, *FiO_2* fraction of inspired oxygen, *iNO* inhaled nitric oxide, *NMBA* neuromuscular blocking agent, *PaO_2* partial pressure of arterial oxygen, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *PP* prone positioning, *RR* respiratory rate, *SpO_2* oxyhemoglobin saturation measured by pulse oximetry, *VE* minute-ventilation, *VT* tidal volume

positioning, −3 to −2 until successful PEEP weaning trial, and −2 to 0 until successful spontaneous breathing trial.

Data collection

The following variables were recorded at inclusion: demographic and anthropometric data, time of ARDS identification, admission category, immunodeficiency, Mac Cabe and SAPS 2 scores, and ARDS risk factors. Ventilatory settings, RASS score, arterial blood gas and body position were recorded at H_0, H_2–H_6, H_8–H_{12}, H_{16}–H_{18}, and daily until day 8 of the study in mechanically ventilated patients. Body weight, hemodynamic variables, vasopressor and sedation doses, SOFA score, and ARDS adjunctive therapies were recorded at inclusion, and daily until day 8 in mechanically ventilated patients. Septal kinetic, end-diastolic right and left ventricle areas were assessed by echocardiography at inclusion, and on day 2 and 3. Missing data are reported in Online Resource 3.

Measurements

Total PEEP ($PEEP_{tot}$), intrinsic PEEP (PEEPi), and P_{Plat} were measured after 3-s end-expiratory, and end-inspiratory occlusions. ΔP was computed as P_{Plat} minus $PEEP_{tot}$. Mechanical power (MP) was computed as previously described [17], and partitioned into 3 components:

$$\text{VT} - \text{related MP} = 0.0098 \times \text{RR} \times \text{VT}^2 \times \frac{1}{2} El_{\text{rs}},$$

$$\text{PEEP} - \text{related MP} = 0.0098 \times \text{RR} \times \text{VT} \times \text{PEEP}_{\text{tot}},$$

$$\text{Resistive MP} = 0.0098 \times \text{RR}^2 \times \text{VT}^2 \times \frac{(1 + I:E)}{60 \times I:E} R_{\text{aw}},$$

with RR = respiratory rate, El_{rs} = elastance of the respiratory system, $I{:}E$ = inspiratory-to-expiratory ratio, and R_{aw} = airway resistance.

Acute cor pulmonale (ACP) was defined by the association of septal dyskinesia and end-diastolic right ventricle area/end-diastolic left ventricle area > 0.6.

Follow-up and endpoints

Follow-up was performed for 90 days following inclusion. The primary endpoint was change in ΔP between day 2 of the study and inclusion. Secondary endpoints were: (1) rate of patients who achieved VT ≤ 4.2 ml.kg^{-1} (i.e., 4 + 5% to account for measurement error) during the first 2 days; (2) change in respiratory parameters, vasopressor and sedation dose during the first 2 days; (3) safety endpoints: change in end-diastolic right ventricle/left ventricle area during the first 2 days, rate of ACP, pneumothorax and any adverse event by category during the study; (4) 90-day mortality.

Successful PEEP weaning was defined as survival with PEEP ≤ 5 cmH_2O for > 48 h before day 28. Successful sedation weaning was defined as survival with sedation withdrawal for > 48 h before day 28. Successful extubation was defined as survival without the need for invasive

MV for > 2 days before day 28. VFD were computed as the number of days between weaning from invasive MV and day 28. Patients who died before weaning were considered to have 0 VFD. Severe acidosis was defined by a pH < 7.15.

Statistical analysis

We computed that with a sample of at least 33 patients, the study would have an 80% power to detect an absolute ΔP reduction of 3.5 cmH_2O between H_0 and day 2, using a two-sided test with a 0.05 type I error, assuming a standard deviation of ΔP at inclusion of 7 cmH_2O [6]. This value of ΔP was chosen as clinically relevant since it was associated with a relative risk reduction in mortality of 1.20 [6]. We decided conservatively to include 35 patients.

Numerical variables are expressed as median [1st quartile–3rd quartile], and categorical variables as counts (percentages). 95% confidence intervals ($CI_{95\%}$) for proportions were calculated using Wilson score test. The bias-corrected and accelerated bootstrap method was used to compute $CI_{95\%}$ for median [18]. Quantitative variables repeatedly measured over time were fitted with a linear mixed model using time as a categorial variable with fixed effect, and patient as variable with random effect. The impact of body position was tested by adding an interaction term in the models. Multiple comparisons between time points and H_0 were performed using Dunnett's test. Binary variables were fitted with a logistic regression model, and independent variables with a p value below 0.2 in the univariate analyses were considered for inclusion in a multivariable logistic regression model, using backward stepwise descending selection. $CI_{95\%}$ for area under curve (AUC) were computed using the DeLong method. The optimal cut-off points were computed by maximizing the Youden index.

Statistical analysis was performed using *R* (version 3.5.1) with packages PropCIs [19], lme4 [20], lmerTest [21], multcomp [22], pROC [23], OptimalCutpoints [24], and boot [25, 26]. A *p* value below 0.05 was chosen for statistical significance.

Results

Characteristics at inclusion

35 patients were included and the centers enrolled a median of 3 [1–4] patients. One patient's next of kin withdrew consent leaving 34 analyzable patients. Patients' characteristics at inclusion are reported in Table 2. 6 patients (18%) presented with a pH ≤ 7.20 at inclusion.

Physiological variables

Changes in ventilatory parameters, arterial blood gas and SOFA sub-scores over the first 4 days are presented in

Table 2 Characteristics at inclusion

Variables	Median [IQR] or count (%)
Age (year)	67 [53–73]
Male gender	25 (74%)
Admission category	
Medical	32 (94%)
Urgent surgery	2 (6%)
SAPS 2 at ICU admission	50 [35–58]
Mac Cabe score	
No disease or non-fatal disease	31 (91%)
Ultimately fatal disease	2 (6%)
Rapidly fatal disease	1 (3%)
Immunosuppression	6 (18%)
ARDS risk factor	
Pneumonia	29 (85%)
Aspiration	5 (15%)
Non-pulmonary sepsis	3 (9%)
Other	2 (6%)
ARDS severity at inclusion	
Moderate	17 (50%)
Severe	17 (50%)
Time from ARDS identification (h)	9 [4–15]
Tidal volume ($ml.kg^{-1}$ PBW)	6.0 [5.9–6.1]
Respiratory rate (min^{-1})	28 [23–30]
PEEP ($cm\ H_2O$)	10 [8–12]
PEEPi ($cm\ H_2O$)	1 [0–1]
Plateau pressure ($cm\ H_2O$)	23 [19–27]
Driving pressure ($cm\ H_2O$)	12 [9–15]
PaO_2/FiO_2 (mm Hg)	101 [78–132]
$PaCO_2$ (mm Hg)	46 [40–52]
pH	7.34 [7.26–7.39]
Bicarbonate ($mmol.L^{-1}$)	23 [21–27]
Base excess ($mmol.L^{-1}$)	− 1.8 [− 5.7 to 1.8]
Vasopressor dose ($\mu g.kg^{-1}.min^{-1}$)	0.23 [0.04–0.56]
Vasopressor administration (%)	27 (79%)
Arterial lactate ($mmol.L^{-1}$)	1.9 [1.3–2.8]
Cumulative fluid balance since admission (kg)	0 [0–1]
SOFA score	13 [11–14]
Acute cor pulmonale	2 (6%)
Neuromuscular blocking agent administration	31 (91%)
Inhaled nitric oxide	1 (3%)
Prone position	7 (21%)
Renal replacement therapy	4 (12%)

FiO_2 fraction of inspired oxygen, *ICU* intensive care unit, *IQR* interquartile range, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *PEEP* positive end-expiratory pressure, *PEEPi* intrinsic PEEP, *SAPS 2* simplified acute physiology score, *SOFA* Sequential Organ Failure Assessment score

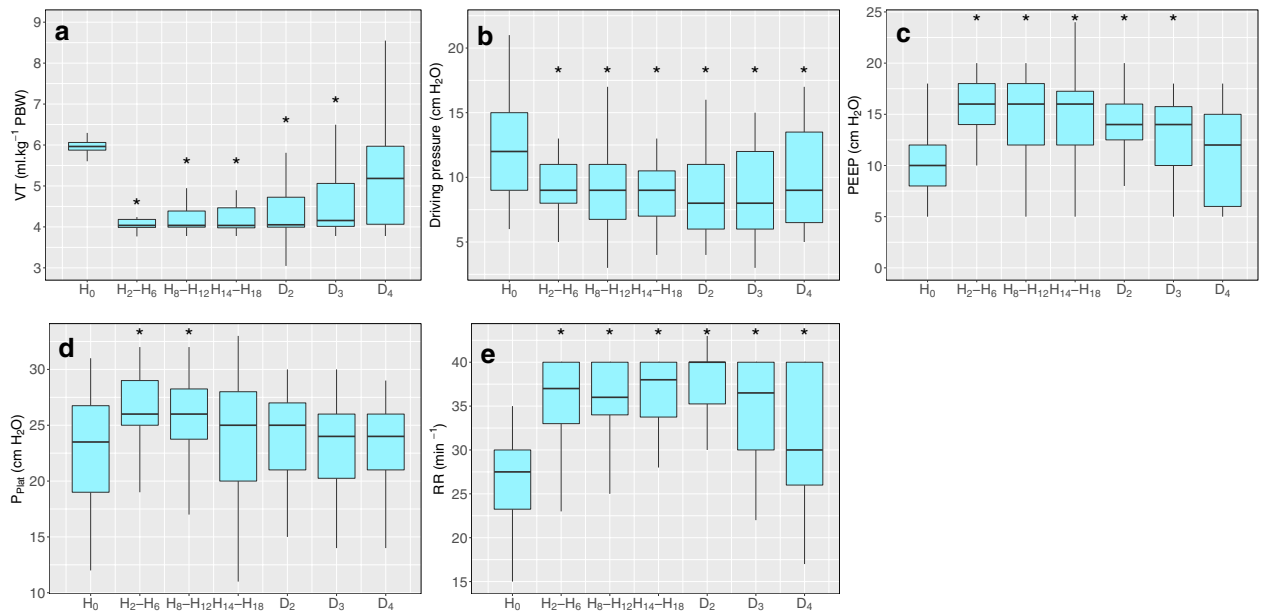

Fig. 1 Ventilatory parameters over the first 4 days following inclusion. *$p < 0.05$ vs. H_0. H_0, H_2–H_6, H_8–H_{12}, H_{14}–H_{18} = time intervals in hours following inclusion (day 1); D_2, D_3, D_4 = study day 2–4; *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, P_{Plat} plateau pressure, *RR* respiratory rate, *VT* tidal volume

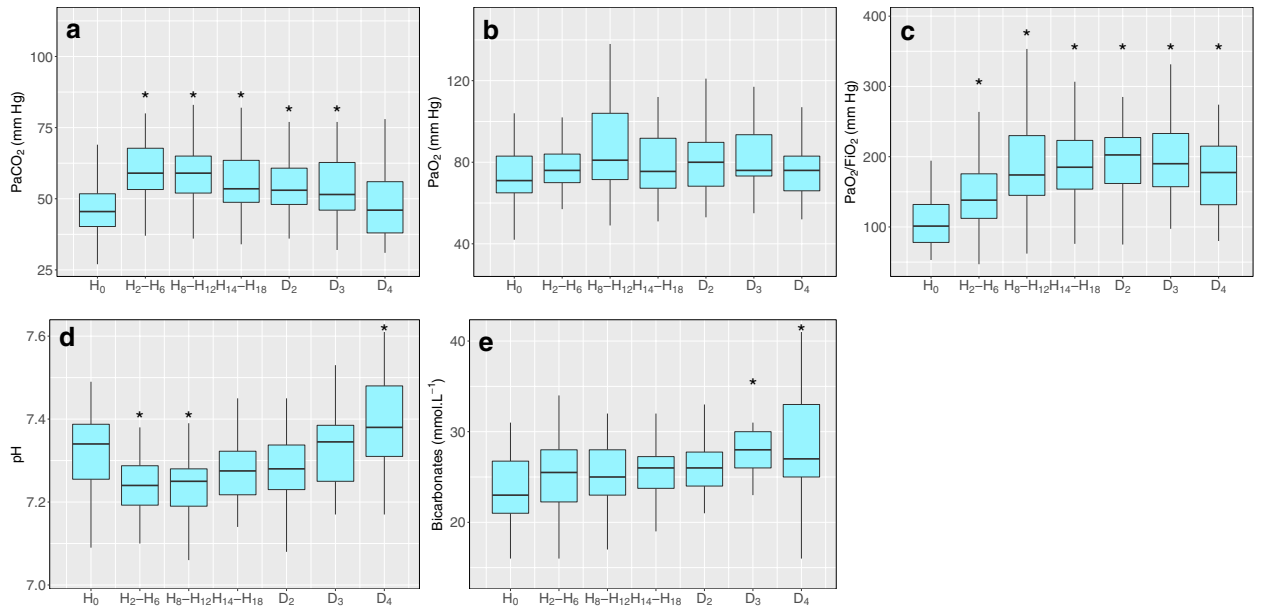

Fig. 2 Arterial blood gas over the first 4 days following inclusion. *$p < 0.05$ vs. H_0. H_0, H_2–H_6, H_8–H_{12}, H_{14}–H_{18} = time intervals in hours following inclusion (day 1); D_2, D_3, D_4 study day 2–4, FiO_2 fraction of inspired oxygen, $PaCO_2$ arterial partial pressure of carbon dioxide, PaO_2 arterial partial pressure of oxygen

Figs. 1 and 2, and in Online Resource 4 and 5. Between baseline and D_2, VT decreased significantly from 6.0 [5.9–6.1] to 4.1 [4.0–4.7] ml.kg^{-1} PBW, and RR increased significantly from 28 [23–30] to 40 [35–40] min^{-1}. PEEP was significantly increased from H_2 to H_6 to D_3 as compared to baseline, while PEEPi was not significantly

modified during the first 4 days. PaO_2/FiO_2 and $PaCO_2$ increased significantly from baseline values as early as H_2–H_6 up to D_3, while pH was significantly lower than baseline only at H_2–H_6 and H_8–H_{12} (Fig. 2).

ARDS adjunctive therapies

Rate of use of ARDS adjunctive therapies over the first 4 days is reported in Online Resource 6. Sedation drugs were not significantly modified over the first 4 days following inclusion.

Efficacy

The median difference in ΔP between day 2 and H_0 amounted to -4 cmH_2O ($CI_{95\%}$: -7 to -3). The interaction between body position (supine or prone) and time of measurement was not significantly associated with ΔP, suggesting that body position had no detectable impact on ΔP measurements. On day 2, VT was ≤ 4.2 ml.kg^{-1} in 22 patients (65% [$CI_{95\%}$ 48%–79%]) and on day 3 VT was ≤ 4.2 ml.kg^{-1} in 16 patients (52% [$CI_{95\%}$ 36%–69%]). VT was ≤ 5.25 ml.kg^{-1} (i.e., 5 ml.kg^{-1}+5%) in 30 patients (88% [$CI_{95\%}$ 73%–95%]) on day 2, and VT was ≤ 5.25 ml.kg^{-1} in 24 patients (77% [$CI_{95\%}$ 63%–90%]) on day 3. Patients were ventilated with a VT ≤ 4.2 ml.kg^{-1} or ≤ 5.25 ml.kg^{-1} during median times amounting to 2 [0–2] and 2 [1–4] days, respectively. Four patients (18%) with VT ≤ 4.2 ml.kg^{-1} on day 2 presented at least one episode of severe acidosis during the study, as compared to 7 (58%) with VT > 4.2 ml.kg^{-1} on day 2. Multivariate analysis identified coagulation SOFA sub-score and pH at inclusion as variables independently associated with VT ≤ 4.2 ml.kg^{-1} PBW on day 2 (Online Resource 7). pH at inclusion predicted VT ≤ 4.2 ml.kg^{-1} PBW on day 2 with an AUC of 0.72 [$CI_{95\%}$ 0.52–0.92, $p < 0.05$], with a sensitivity of 95% and a specificity of 42% at a threshold of 7.21.

Mechanical power

Total MP was computed in 11 patients and was not significantly modified over the first 4 days of the study (Online Resource 8). VT-related MP significantly decreased after inclusion, while PEEP-related MP increased. Resistive MP significantly decreased as a consequence of R_{aw} decrease at higher PEEP.

Outcome (online resource 9)

Duration of MV was 11 [8–20] days. Fourteen patients (41%) died before day 90 with median delay between inclusion and death amounting to 16 [9–22] days, among which 6 (43%) died from refractory shock (Online Resource 10).

Safety markers

Adverse events are reported in Table 3. Sixteen episodes of severe acidosis were reported in 11 patients (32%) and were the only adverse event directly connected to the study by attending physicians. Renal SOFA sub-score, pH, base excess and bicarbonate at inclusion were associated with the occurrence of at least one episode of severe acidosis (Online Resource 11). Multivariate analysis identified renal SOFA sub-score and pH at inclusion as variables independently associated to the occurrence of at least one episode of severe acidosis. In addition to the two patients with ACP at study inclusion, two additional patients (6%) developed ACP after inclusion. Right ventricle/left ventricle ratio increased non-significantly from 0.50 [0.50–0.72] at H_0 ($n = 29$) to 0.66 [0.60–0.76] on day 2 ($n = 27$) and 0.73 [0.56–0.79] on day 3 ($n = 14$).

Discussion

The main findings of the study are the following: (1) VT may be reduced down to 4 ml.kg^{-1} in approximately 2/3 of moderately severe-to-severe ARDS patients, and to 5 ml.kg^{-1} in approximately 90%, without ECCO2R, while targeting arterial pH above 7.20; (2) this strategy is associated with a 4 cmH_2O median decrease in ΔP 24 h after inclusion, at the price of substantial increase in RR and transient episodes of severe acidosis in approximately 1/3 of the patients; 3-selecting patients with pH > 7.20 may increase the rate of patients in which ULTV is achievable.

Efficacy

While several studies including one RCT combining ULTV and ECCO2R have been performed [10–12, 27, 28], the present study is the first prospective study testing the safety and feasibility of this strategy applied from the early phase of ARDS until oxygenation improvement without extracorporeal devices. Compared to the largest observational study on ECCO2R during ARDS [12], patients were more severely hypoxemic in the present study ($PaO_2/FiO_2 = 101$ mmHg vs. 173 mmHg), had higher SOFA score (13 vs. 7), and similar ΔP (12 vs. 13 cmH_2O). Interestingly, the rate of patients achieving ULTV on day 2 was only slightly lower in the present study (65%) than in Combes et al. study (82%), with similar magnitude in ΔP reduction between inclusion and day 2. As expected, $PaCO_2$ was substantially higher on day 2 in the present study (53 vs 46 mmHg).

However, whether the low VT strategy tested in the present study is truly ultraprotective is questionable, since 1-RR (a minor component of MP relative to ΔP [29]) had to be increased up to 40 min^{-1} in order to maintain pH in an acceptable range, and 2-total MP was unchanged after inclusion. However, recent experimental

Table 3 Adverse events after inclusion

Adverse events	Number of episodes	Number of patients (%)	Delay of occurrence (day)
Metabolic events			
Severe mixed acidosis with pH < 7.15	16	11 (32%)	0 [0–1]
Other metabolic events	1	1 (3%)	0 [0–0]
Respiratory events			
Pneumothorax	2	2 (6%)	6 [4–7]
Refractory hypoxemia requiring ECMO	1	1 (3%)	1 [1–1]
Other	6	6 (18%)	6 [3–14]
Infectious events			
Nosocomial pneumonia	14	13 (38%)	8 [6–14]
Non-respiratory infection site	4	3 (9%)	9 [8–11]
Bacteremia	8	7 (21%)	4 [2–6]
Cardiovascular events			
Shock	5	5 (15%)	13 [6–15]
Cardiac arrest	3	3 (9%)	13 [7–17]
Acute cor pulmonale	2	2 (6%)	1 [1–1]
Supraventricular tachycardia	3	2 (6%)	1 [1–6]
Neurological events			
ICU-acquired weakness	5	5 (15%)	11 [9–16]
Central nervous system disease	5	5 (15%)	7 [6–11]
Acute kidney injury	8	8 (24%)	3 [2–8]
Digestive events	5	4 (12%)	10 [7–13]
Acute liver failure	3	3 (9%)	5 [3–7]
Multi-organ failure	2	2 (6%)	14 [12–15]
Hemorrhage	3	3 (9%)	15 [14–15]

Values are number of episodes, number of patients with corresponding percentage, or median [1st quartile, 3rd quartile]

ECMO extracorporeal membrane oxygenation, *ICU* intensive care unit

studies have shown a beneficial effect of lowering VT while keeping total MP constant [30, 31]. Furthermore, both resistive and VT-related MP significantly decreased after inclusion, but this was counterbalanced by a significant increase in PEEP-related MP, whose contribution to ventilator-induced lung injury (VILI) has been questioned [32], as there is no mechanical movement at a given PEEP level. Finally, RR is indeed associated with ARDS mortality [33], but may only reflect the clinician's attempt to normalize $PaCO_2$ in the most severe patients.

Assuming ΔP is a surrogate of dynamic strain [6], the 33% decrease of this parameter combined with a 32% decrease in inspiratory time between H_0 and day 2 in the present study, suggests that the current strategy would significantly decrease dynamic strain without significantly modifying strain rate (i.e., the ratio of strain over inspiratory time), another important determinant of VILI [34]. However, it is still unknown whether reducing VT below 6 $ml.kg^{-1}$ is beneficial in unselected ARDS patients. A post hoc analysis of a RCT on ULTV combined with ECCO2R [11] identified a beneficial effect of this strategy on VFD in the subgroup of patients with $PaO_2/FiO_2 \leq 150$ mmHg (i.e., the population selected in the present study). Selecting patients with high ΔP seems appealing, but the lack of indisputable safety value regarding this parameter [6–8], and the confounding influence of chest wall elastance questions the reliability of such strategy. Finally, the high PEEP strategy used in the present study [35] may have increased static strain, whose contribution to VILI is minimal relative to dynamic strain [36].

Safety

The main safety concern regarding the tested strategy is uncontrolled hypercapnia leading to severe acidosis in patients with acute kidney injury and low pH. The concept of permissive hypercapnia was coined after 2 seminal studies [37, 38] performed in the early 1990s. In these non-controlled studies, ARDS patients were managed targeting a peak inspiratory pressure < 30 cmH_2O, using low RR, and allowing the $PaCO_2$ to increase to values similar to our study, and hospital mortality rates

were below 30% (a value strikingly low for the era). While hypercapnia may have beneficial effects (such as inhibition of proinflammatory cytokines synthesis or attenuation of inflammation related to VILI), it was also shown to be deleterious on other physiological processes (such as inhibition of lung epithelial cell repair, inhibition of myogenic tone or increase of renal vascular resistance, among others) [39]. Hence, the net impact of severe hypercapnia remains to date unclear. Moreover, although hypercapnia ≥ 48 mmHg is an independent risk factor for ACP, the rate of ACP was lower in the present study (12%) than in the largest observational study in ARDS (22%) [40], in line with the protective effect of ΔP reduction on ACP occurrence. However, we acknowledge that the high rate of missing echocardiographic values in the present study may have led to an underestimation of the ACP rate.

Finally, in the present study, 90-day mortality was similar to hospital mortality observed in the latest observational study on ECCO2R (38%), despite greater severity of illness, suggesting that both strategies are credible candidates to be tested in future RCTs on ARDS.

Strengths and limits

Some limitations of the present study should be acknowledged. First, the non-controlled design precludes accounting for the effect of time on ΔP and other variables. Second, the ratio of screened to enrolled patients is unknown, as no screening log was recorded. Third, 5 patients who did not experienced severe acidosis did not achieve ultra-low VT settings on day 2, an indirect evidence of protocol violation suggesting that some investigators may not have been at ease with severe levels of hypercapnia. Fourth, the study does not provide any evidence regarding efficacy of ULTV on ARDS outcome.

Nevertheless, the present study demonstrates the feasibility of ULTV without ECCO2R, with a multicenter design including both academic and non-academic ICUs. Furthermore, it provides estimates of the effect of lowering VT on ΔP and of the adverse events rate, while identifying ARDS patients with pH > 7.20 as credible candidates for future RCTs.

Finally, it should be stressed that this study is a hypothesis-generating pilot study, and that ΔP reduction was achieved at the price of severe acidosis in one-third of patients, uncontrolled hypercapnia, and increased RR, whose effects on ARDS morbidity and mortality may outweigh the benefits of a potential reduction in VT-related VILI.

Conclusion

ULTV may be applied in approximately 2/3 of moderately severe-to-severe ARDS patients without ECCO2R, with a 4 cmH_2O median reduction in ΔP, at the price of transient episodes of severe acidosis in approximately 1/3 of the patients.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05776-x) contains supplementary material, which is available to authorized users.

Author details
[1] Service de Médecine Intensive Réanimation, Hôpital De La Croix Rousse, Hospices Civils de Lyon, 103 Grande Rue de la Croix Rousse, 69004 Lyon, France. [2] Université de Lyon, Université LYON I, Lyon, France. [3] CREATIS INSERM 1044 CNRS 5220, Villeurbanne, France. [4] Service de Réanimation Polyvalente, Centre Hospitalier Sud-Francilien, Corbeil-Essonnes, France. [5] Service de Réanimation Médico-Chirurgicale, Hôpital André Mignaud, Le Chesnay, France. [6] Service de Réanimation, Centre Hospitalier Annecy Genevois, Pringy, France. [7] Service de Réanimation Médicale, CHU de la Cavale Blanche, Brest, France. [8] Medical Intensive Care Department, University Hospital Centre Rouen, Rouen, France. [9] Inserm U 1096, Institute for Research and Innovation in Biomedicine (IRIB), Rouen University, Rouen, France. [10] Service de Réanimation Médicale, Hôpital François Mitterrand, Dijon, France. [11] Service de Réanimation Médicale, Hôpital Archet 1, Nice, France. [12] Service de Réanimation, Centre Hospitalier Lyon Sud, Pierre-Bénite, France. [13] Service de Réanimation Médicale Polyvalente, CHU Gabriel-Montpied, Clermont-Ferrand, France. [14] Service de Réanimation Polyvalente, Centre Hospitalier de Beauvais, Beauvais, France.

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Statement of human rights
The authors state that the study has been approved by a national research ethics committee (Comité de Protection des Personnes Sud-Est IV—RCB 2016-A00503-48) and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statement on the welfare of animal
This article does not contain any studies with animals performed by any of the authors.

Informed consent
Informed consent was obtained from all individual participants included in the study.

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