



Effects of Trunk Inclination on Respiratory Mechanics in Patients with COVID-19–associated Acute Respiratory Distress Syndrome: Let’s Always Report the Angle!

To the Editor:

The role of trunk inclination on respiratory function has been explored in patients with “typical” acute respiratory distress syndrome (ARDS) (1–3). Data regarding patients with coronavirus disease (COVID-19)–associated ARDS (C-ARDS) are currently lacking.

The aim of our study was to assess the effects of changes in trunk inclination on lung mechanics and gas exchange in mechanically ventilated patients with C-ARDS.

Methods

This single-center physiological crossover study (ethical committee approval #70-11022021) was conducted on adult patients admitted to our COVID-ICU between March 3 and May 4, 2021. Diagnosis of C-ARDS, deep sedation, paralysis, and volume-controlled mechanical ventilation were the inclusion criteria. Contraindications to mobilization (e.g., intracranial hypertension, spinal cord injury, tracheal lesions) and pregnancy constituted exclusion criteria. Patients were enrolled according to study personnel availability. A 5-F esophageal balloon (CooperSurgical) was inserted. The balloon was inflated with 1 ml of air, and the correct position/function was verified before each measurement (4). Mechanical ventilation parameters, kept constant throughout the study, were set by the attending physician. Usually, positive end-expiratory pressure (PEEP) is set according to the best respiratory system compliance (C_{RS}) assessed with a recruitment maneuver followed by a decremental PEEP trial. Of note, trunk inclination during PEEP selection is not standardized.

Patients underwent three 15-minute steps in which trunk inclination was changed from 40° (semirecumbent, baseline) to 0° (supine-flat), and back to 40° during the last step. At the end of each step, partitioned respiratory mechanics, arterial/central venous blood gas analysis, and basic hemodynamics were recorded. Ventilatory ratio was calculated.

Statistical analysis. Continuous variables are expressed as median (interquartile range). One-way ANOVA for repeated

measures or the Friedman test was applied, as appropriate. Bonferroni and Dunn’s *post hoc* comparisons were used, respectively. A $P < 0.05$ was considered statistically significant (GraphPad Software).

Results

Twenty patients were enrolled (11 male; 67 [59–70] years; body mass index, 30 [28–35] kg/m²; Simplified Acute Physiology Score-II, 36 [32–45]). ARDS was mild in 1, moderate in 9, and severe in 10 patients. Patients were studied 2.5 (2.0–4.5) days after intubation. V_T was 5.9 (5.7–6.3) ml/kg of predicted body weight, and PEEP was 14 (12–14) cm H₂O.

After changing trunk inclination from 40° to 0°, driving pressure decreased from 13 (12–15) to 10 (9–11) cm H₂O ($P < 0.0001$) and C_{RS} increased from 29 (24–35) to 38 (33–48) ml/cm H₂O ($P < 0.0001$). Compared with the values obtained at baseline (semirecumbent), the supine-flat position was associated with increased chest wall compliance (C_{CW}) (131 [101–170] vs. 215 [175–300] ml/cm H₂O; $P < 0.01$) and increased lung compliance (C_{Lung}) (38 [30–46] vs. 46 [40–62] ml/cm H₂O; $P < 0.01$).

A significant reduction in both PaCO₂ (52 [47–57] vs. 50 [46–54] mm Hg; $P < 0.001$) and ventilatory ratio (1.81 [1.47–2.02] vs. 1.68 [1.43–1.96]; $P < 0.001$) was recorded when patients were placed supine-flat. Moreover, a positive correlation ($r = 0.66$; $P = 0.002$) between the drop of driving pressure and the reduction of PaCO₂ was observed. Oxygenation was not significantly affected by changes in trunk inclination. Changes in respiratory mechanics and PaCO₂ were rapidly reversed once patients were repositioned in the semirecumbent position (Table 1 and Figure 1).

Discussion

The change in trunk inclination from semirecumbent to supine-flat in patients with C-ARDS: 1) increased C_{RS} owing to both an increase in C_{CW} and C_{Lung} ; 2) improved CO₂ clearance; and 3) had no considerable effect on oxygenation.

These findings have several implications. First, it is of interest to understand the mechanisms leading to such a remarkable, quick, and reversible improvement in the mechanical characteristics of the respiratory system. Compliance improvements in patients with ARDS are frequently attributed to the recruitment of previously collapsed alveoli, and therefore to an increase in end-expiratory lung volume (EELV). Another possible mechanism is a certain degree of lung derecruitment accompanied by intratidal recruitment (5). Finally, the reduction in overdistension of previously overstretched lung regions could play a role (i.e., a reduction in the aeration of ventilated alveoli) (6).

Our results are not sufficient to clearly identify the underlying mechanisms, as we did not assess EELV and regional ventilation distribution. However, a major role of alveolar recruitment is unlikely in the present context, given the rapidity of the observed improvement and its reversibility once placed back in the semirecumbent position. Moreover, although intratidal recruitment might play a role, we think that the major pathophysiological mechanism likely explaining our findings is a reduced overdistension of some lung regions.

Ⓔ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern (dgern@thoracic.org).

Author Contributions: F.M., S.S., R.F., and T.L. conceived the study. F.M., S.S., and T.L. performed data analysis and prepared the first draft of the manuscript. All authors were responsible for data acquisition and interpretation, reviewed the manuscript, and approved the final submitted version.

Originally Published in Press as DOI: 10.1164/rccm.202110-2360LE on January 4, 2022

Table 1. Effect of Trunk Inclination on Ventilatory Parameters, Gas Exchange, and Hemodynamics

	First Step (40°)	Second Step (0°)	Third Step (40°)	P Value
Ventilatory parameters				
Peak inspiratory pressure, cm H ₂ O	32 (29–36)	28 (26–34)*	32 (29–36) [†]	<0.0001
Mean airway pressure, cm H ₂ O	18 (16–19)	17 (16–19)*	18 (16–19) [†]	<0.01
Plateau pressure, cm H ₂ O	27 (25–28)	24 (21–25)*	27 (26–28) [†]	<0.0001
End-expiratory airway pressure, cm H ₂ O	14 (12–14)	14 (12–14)	14 (12–14)	0.47
Driving pressure, cm H ₂ O	13 (12–15)	10 (9–11)*	13 (12–15) [†]	<0.0001
End-inspiratory esophageal pressure, cm H ₂ O	11 (9–16)	14 (13–17)*	11 (10–16) [†]	<0.001
End-expiratory esophageal pressure, cm H ₂ O	8 (6–14)	12 (11–16)*	9 (6–13) [†]	<0.0001
End-inspiratory transpulmonary pressure, P _{Les} , cm H ₂ O	15 (13–18)	9 (7–10)*	14 (12–17) [†]	<0.0001
End-inspiratory transpulmonary pressure, P _{Ler} , cm H ₂ O	20 (19–23)	19 (17–22)*	20 (18–22)	0.027
Driving transpulmonary pressure, cm H ₂ O	10 (8–12)	8 (6–10)*	10 (8–12) [†]	<0.01
C _{RS} , ml/cm H ₂ O	29 (24–35)	38 (33–48)*	29 (24–35) [†]	<0.0001
C _{CW} , ml/cm H ₂ O	131 (101–170)	215 (175–300)*	143 (99–181) [†]	<0.001
C _{Lung} , ml/cm H ₂ O	38 (30–46)	46 (40–62)*	39 (31–48) [†]	<0.01
Gas exchange and ABG parameters				
PaO ₂ /F _{IO} ₂	145 (115–189)	140 (102–175)	144 (109–181)	0.74
SaO ₂ , %	96 (95–97)	96 (94–98)	96 (95–97)	0.94
PaCO ₂ , mm Hg	52 (47–57)	50 (46–54)*	52 (48–57) [†]	<0.001
pH	7.39 (7.35–7.42)	7.38 (7.36–7.43)*	7.39 (7.34–7.42) [†]	<0.01
Lactate, mmol/L	1.14 (0.9–1.4)	1.11 (0.9–1.4)	1.14 (0.9–1.4)	0.82
Shunt, % (n = 19)	33 (23–42)	33 (26–42)	34 (26–40)	0.70
Ventilatory ratio	1.81 (1.47–2.02)	1.68 (1.43–1.96)*	1.77 (1.39–2.01) [†]	<0.001
Hemodynamics				
HR, n/min	75 (58–85)	74 (54–89)	77 (56–88)	0.25
MAP, mm Hg	78 (71–88)	84 (73–92)	81 (73–89)	0.23
CVP, mm Hg	8 (6–10)	10 (8–12)	8 (6–10)	0.036

Definition of abbreviations: ABG = arterial blood gas; C_{CW} = chest wall compliance; C_{Lung} = lung compliance; C_{RS} = compliance of the respiratory system; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; P_{Ler} = end-inspiratory transpulmonary pressure calculated from elastance ratio (10); P_{Les} = end-inspiratory transpulmonary pressure calculated from esophageal pressure.

Data are expressed as median (interquartile range).

*P < 0.05 second step (0°) versus first step (40°).

[†]P < 0.05 third step (40°) versus second step (0°).

In other words, it is conceivable that placing patients in the supine position caused a cephalad displacement of the diaphragm, resulting in a reduction in EELV and alveolar overdistension. This hypothesis is upheld by both the available literature, demonstrating that the supine-flat position is associated with a reduction in EELV (1–3, 7) and by the significant reduction in PaCO₂ in this position.

Our results regarding changes in respiratory mechanics are in line with previous studies performed on patients with typical ARDS (1–3). Put together, these studies convey a clear clinical and methodological message: trunk inclination should be measured and reported when assessing respiratory mechanics. From a clinical perspective, to monitor patients' respiratory mechanics, it appears to be of the utmost importance to standardize trunk inclination when respiratory mechanics are assessed. In addition, although there is likely no correct angle, we think that trunk inclination should always be stated in the methods to improve the reliability and reproducibility of clinical studies dealing with respiratory mechanics. Another important clinical implication of our study is that a simple intervention, such as placing the patient supine-flat, markedly reduces driving pressure and lung stress (transpulmonary pressure) (8). Moreover, the improved CO₂ clearance could potentially allow reduction of the respiratory rate, further lowering the mechanical power delivered to the lungs and thus the risk of ventilator-induced lung injury (9).

As the study steps were relatively short, we can draw no conclusions on the long-term effects on gas exchange and ventilator-induced lung injury. Other limitations of our study are the lack of gastric pressure measurement and the high and relatively homogenous PEEP levels.

Conclusions. The change in body position from semirecumbent to supine-flat improved respiratory mechanics and CO₂ clearance and did not worsen oxygenation in C-ARDS. Given the remarkable effect of trunk inclination on respiratory mechanics, we think that reporting the angle of trunk inclination is of extreme importance to obtain a reliable assessment and monitoring of the respiratory mechanics in mechanically ventilated patients. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgments: The authors thank Gianpaola Monti, M.D.; Paola Previtali, M.D.; Jacopo Colombo, M.D.; Fernando Arnaiz Guerrero, M.D.; Manuela Paradiso, M.D.; Nicola Suardi, M.D.; Chiara Borromeo, M.D.; and all the physicians and nurses of the Rossini and other COVID-19 intensive care units of Niguarda Hospital.

Francesco Marrazzo, M.D.*
Stefano Spina, M.D.*
Clarissa Forlini, M.D.

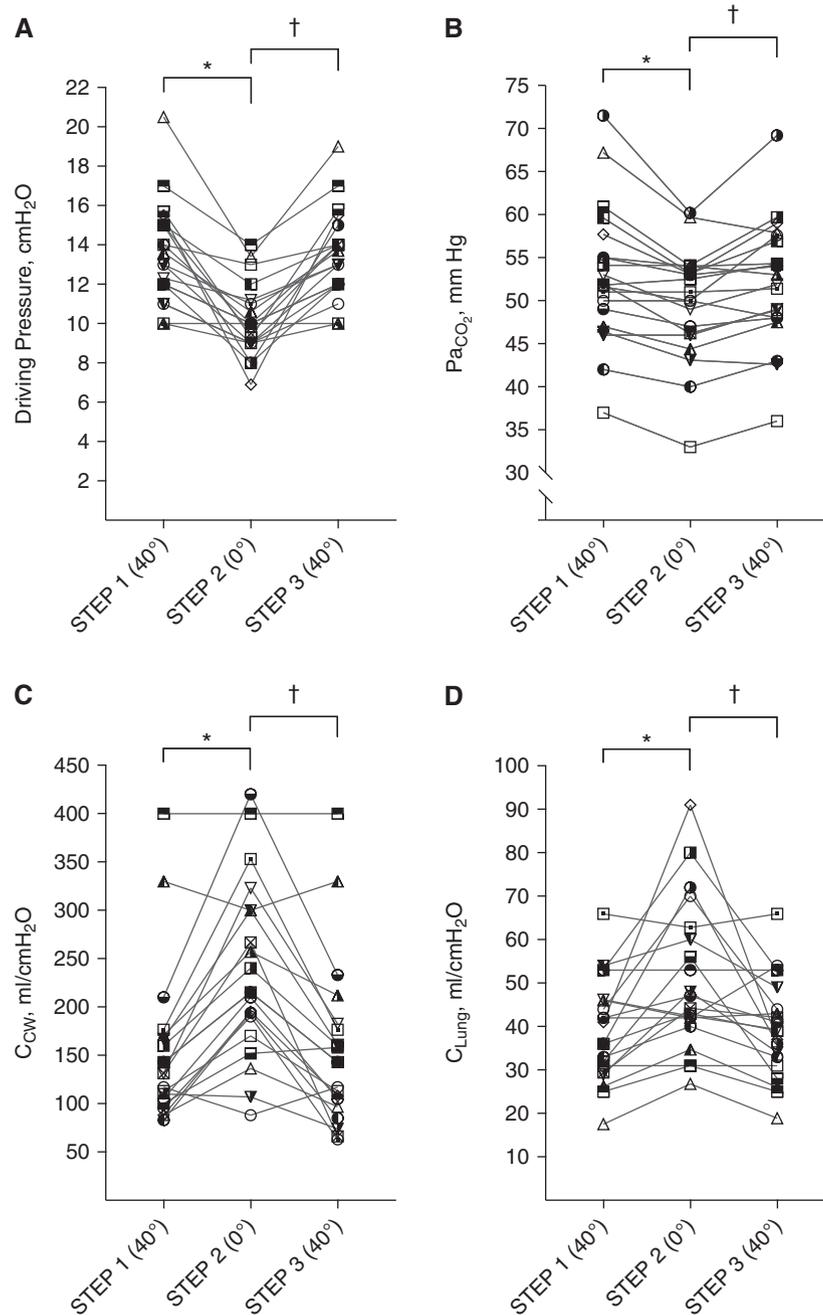


Figure 1. Driving pressure, PaCO₂, chest wall compliance, and lung compliance. (A) Driving pressure, (B) PaCO₂, (C) chest wall compliance, and (D) lung compliance have been reported as individual values. A combination of symbol and color was assigned to each patient and was kept constant in the four graphs to allow their identification. * $P < 0.05$ second step (0°) versus first step (40°); † $P < 0.05$ third step (40°) versus second step (0°). C_{CW} = chest wall compliance; C_{Lung} = lung compliance.

Marcello Guarnieri, M.D.
 Riccardo Giudici, M.D.
 Gabriele Bassi, M.D.
 Luca Bastia, M.D.
 Maurizio Bottiroli, M.D.
 ASST Grande Ospedale Metropolitano Niguarda
 Milano, Italy

Roberto Fumagalli, M.D.
 Thomas Langer, M.D.†

ASST Grande Ospedale Metropolitano Niguarda
 Milano, Italy

and

University of Milan-Bicocca
 Milan, Italy

ORCID IDs: 0000-0001-5407-6615 (F.M.); 0000-0003-3210-1714 (S.S.);
 0000-0002-1858-1080 (C.F.); 0000-0002-1922-6996 (M.G.);
 0000-0002-1579-7767 (M.B.); 0000-0003-0398-1329 (R.F.);
 0000-0002-9725-8520 (T.L.).

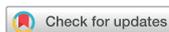
*Co-first authors.

†Corresponding author (e-mail: thomas.langer@unimib.it).

References

1. Mezidi M, Guérin C. Effect of body position and inclination in supine and prone position on respiratory mechanics in acute respiratory distress syndrome. *Intensive Care Med* 2019;45:292–294.
2. Dellamonica J, Lerolle N, Sargentini C, Hubert S, Beduneau G, Di Marco F, *et al.* Effect of different seated positions on lung volume and oxygenation in acute respiratory distress syndrome. *Intensive Care Med* 2013;39:1121–1127.
3. Richard J-CM, Maggiore SM, Mancebo J, Lemaire F, Jonson B, Brochard L. Effects of vertical positioning on gas exchange and lung volumes in acute respiratory distress syndrome. *Intensive Care Med* 2006;32:1623–1626.
4. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, *et al.*; PLUG Working Group (Acute Respiratory Failure Section of the European Society of Intensive Care Medicine). The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med* 2014;189:520–531.
5. Chen L, Del Sorbo L, Grieco DL, Junhasavasdikul D, Rittayamai N, Soliman I, *et al.* Potential for lung recruitment estimated by the recruitment-to-inflation ratio in acute respiratory distress syndrome: a clinical trial. *Am J Respir Crit Care Med* 2020;201:178–187.
6. Rezoagli E, Bastia A, Grassi A, Chiericato A, Langer T, Grasselli G, *et al.* Paradoxical effect of chest wall compression on respiratory system compliance: a multicenter case series of patients with ARDS, with multimodal assessment. *Chest* 2021;160:1335–1339.
7. Spooner AJ, Corley A, Sharpe NA, Barnett AG, Caruana LR, Hammond NE, *et al.* Head-of-bed elevation improves end-expiratory lung volumes in mechanically ventilated subjects: a prospective observational study. *Respir Care* 2014;59:1583–1589.
8. Chiumello D, Carlesso E, Cadringer P, Caironi P, Valenza F, Polli F, *et al.* Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008;178:346–355.
9. Gattinoni L, Tonetti T, Cressoni M, Cadringer P, Herrmann P, Moerer O, *et al.* Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016;42:1567–1575.
10. Yoshida T, Amato MBP, Grieco DL, Chen L, Lima CAS, Roldan R, *et al.* Esophageal manometry and regional transpulmonary pressure in lung injury. *Am J Respir Crit Care Med* 2018;197:1018–1026.

Copyright © 2022 by the American Thoracic Society



Major Decrease in Lung Transplantation for Patients with Cystic Fibrosis in France

To the Editor:

Cystic fibrosis (CF), a genetic disease related to mutations in the gene encoding for the CF transmembrane conductance regulator (CFTR)

†This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Author Contributions: C.M., C.L., and P.-R.B. designed the study and contributed to data management and analysis. C.M. and P.-R.B. wrote the first draft of the manuscript. All authors revised and approved the first draft of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202109-2121LE on December 15, 2021

protein, often results in progressive development of respiratory failure. Lung transplantation appears as a therapeutic option that prolongs survival and improves quality of life in patients with advanced CF pulmonary disease in whom medical therapy is not sufficient to control disease progression (1), and CF remains one of the major indications for lung transplantation worldwide.

Over the past 10 years, small molecules directly targeting the CFTR defect, called CFTR modulators, have been developed and have provided clinical benefits to patients with CF (2). The first CFTR modulator, ivacaftor, is considered a highly effective CFTR modulator, including in patients with advanced CF pulmonary disease, with the potential of preventing evolution to end-stage disease and lung transplantation (3). However, only a limited number of patients with CF have CFTR mutations eligible for ivacaftor (~5% in France). Double combination therapy (lumacaftor–ivacaftor and tezacaftor–ivacaftor) target approximately 40–50% of patients with CF but have only a moderate effect on lung function (4, 5), especially in patients with advanced pulmonary disease. Furthermore, lumacaftor–ivacaftor had to be discontinued in up to 28% of patients with advanced pulmonary disease, in most cases owing to the occurrence of respiratory adverse effects (4). In marked contrast with these double combinations, triple combination of elexacaftor–tezacaftor–ivacaftor has been developed for patients with at least one Phe508del CFTR allele (corresponding to 80–85% of patients with CF) and induces large improvement in lung function, respiratory symptoms, exacerbation frequency, and nutritional status.

In a recent study, our group described the effects of elexacaftor–tezacaftor–ivacaftor in 245 French patients with CF with advanced pulmonary disease (6). Our data showed rapid improvement in lung function and body mass index with an acceptable safety profile. Initiation of elexacaftor–tezacaftor–ivacaftor was further associated with improvement in gas exchange leading to discontinuation of long-term oxygen and noninvasive ventilation in 30–50% of patients (6). Importantly, most patients who were listed for lung transplantation were removed from the transplant list, and those who were under active evaluation for transplantation listing showed such an improvement that they were no longer considered for lung transplantation at the end of our study (6). Data obtained from the French Agence de la Biomédecine Registry, which collects all transplant-related data in France, further indicated that lung transplantation for CF was reduced by 55% in 2020 as compared with 2018–2019 (6). Altogether, these data suggested an effect of elexacaftor–tezacaftor–ivacaftor in reducing the need for lung transplantation in patients with advanced CF pulmonary disease. However, the study was performed at the time when the coronavirus disease (COVID-19) pandemic was surging in France and was having a profound effect on the ability to perform lung transplantation (7–9). Thus, it was suggested that at least some of the reduction in lung transplantation observed in our study could have been related to the COVID-19 pandemic (10). Indeed, data from the United Network for Organ Sharing registry also reported a decrease in lung transplant volume at the onset of the COVID-19 pandemic (11).

Here, we present more recent data on first lung transplantation (excluding lung retransplantation as patients with CF living with a lung transplant are not currently eligible to receive elexacaftor–tezacaftor–ivacaftor) in France (Figure 1). Figure 1A shows that a marked decrease in lung transplant volume occurred in the first 6 months of 2020, but that lung transplant activity largely resumed, although to a lower level, during the second half of 2020