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Ventilatory load reduction by combined mild hypothermia and ultraprotective mechanical ventilation strategy in severe COVID-19-related acute respiratory distress syndrome: A physiological study

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Abstract:

We report the feasibility of a combined approach of very low low tidal volume (VT) and mild therapeutic hypothermia (MTH) to decrease the ventilatory load in a severe COVID-19-related acute respiratory distress syndrome (ARDS) cohort. Inclusion criteria was patients ≥18-years-old, severe COVID-19-related ARDS, driving pressure ΔP >15 cmH_2O despite low-VT strategy, and extracorporeal therapies not available. MTH was induced with a surface cooling device aiming at 34°C. MTH was maintained for 72 h, followed by rewarming of 1°C per day. Data were shown in median (interquartile range, 25%–75%). Mixed effects analysis and Dunnett's test were used for comparisons. Seven patients were reported. Ventilatory load decreased during the first 24 h, minute ventilation (VE) decreased from 173 (170–192) to 152 (137–170) mL/kg/min ($P = 0.007$), and mechanical power (MP) decreased from 37 (31–40) to 29 (26–34) J/min ($P = 0.03$). At the end of the MTH period, the VT, *P*, and plateau pressure remained consistently close to 3.9 mL/kg predicted body weight, 12 and 26 cmH_2O, respectively. A combined strategy of MTH and ultraprotective mechanical ventilation (MV) decreased VE and MP in severe COVID-19-related ARDS. The decreasing of ventilatory load may allow maintaining MV within safety thresholds.

Keywords:

Acute respiratory distress syndrome, COVID-19, hypoxemia, lung protective ventilation, mild hypothermia

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Introduction

Protective mechanical ventilation (MV) is a lifesaving therapy. This approach reduces mortality in acute respiratory distress syndrome (ARDS).[1] In patients with very low respiratory system compliance (C_{RS}), the low-VT strategy can generate driving pressure ΔP and plateau pressures (Pplat) higher than the harmful limits, and very low-VT (VT <4 mL/kg of predicted body weight [PBW]) is recommended.[2,3] Still, it may lead to unfavorable consequences such as severe respiratory acidosis. Thus, extracorporeal CO_2 removal ($ECCO_2$-R) is

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usually an adjuvant therapy.[4,5] However, the availability of extracorporeal respiratory support is scarce, especially in limited resource settings.[6]

Therapeutic hypothermia is the controlled decrease of body temperature for clinical use. Hypothermia induces a hypometabolic state, which is helpful in many situations such as cardiopulmonary bypass, after cardiac arrest, among others. Therapeutic hypothermia decreases global oxygen consumption and CO_2 production, which might benefit severe ARDS, reducing the ventilatory load in patients with very low C_{RS}. In these conditions, a very low-VT could be used.

Our primary endpoint was to investigate the effects of ultraprotective ventilation combined with mild therapeutic hypothermia (MTH) on ventilatory load in severe COVID-19-related ARDS patients, refractory to MV, prone position, and neuromuscular blockade. Therefore, the secondary endpoints were to evaluate effects on gas exchange and safety of combined strategies.

Case Report

Ethical approval for this study was obtained from Servicio de Salud Metropolitano Central Ethics Committee in Santiago, Chile on the date of July 14, 2021 with approval number of 423/2021 on the date of July 14, 2021, with approval number of 423/2021," and informed consent was obtained from the next of kin. We included patients equal to or older than 18 admitted due to SARS-CoV-2 respiratory failure to a dedicated COVID-19 ICU between July 1st, 2020, and July 31st, 2021. We included patients with severe COVID-19-related ARDS and one of the following criteria for more than 6 hours: failure to maintain ΔP <15 cmH_2O despite VT <6 mL/kg; or a PaO_2/FIO_2 ratio <80 mmHg; or an arterial blood pH <7.2 with an arterial partial pressure of carbon dioxide of at least 65 mmHg. In all cases, extracorporeal therapies were not available. We excluded patients with uncontrolled superinfection, active bleeding, signs of severe brain injury, or end-of-life care.

In our institution, MTH is proposed as a compassionate treatment. Hypothermia was induced by Blanketrol® III (Cincinnati Sub-Zero) automated surface cooling device, aiming for 34°C servo-controlled core body temperature. Core body temperature was measured by an esophageal probe. MTH is maintained for 72 h, followed by a rewarming phase of 1°C per day until normothermia (36°C), based on previous reports of MTH in ARDS.[7,8]

We routinely use low VT targeting ΔP <15 cmH_2O and active heather humidifiers in severe ARDS. VT was progressively lowered to obtain a ΔP <15 cmH_2O, aiming at 4 mL/kg PBW in volume-controlled ventilation. Positive end-expiratory pressure (PEEP) set so as not to exceed a Pplat of 30 cmH_2O. FIO_2 was adapted to obtain an SaO2 between 88% and 95% and a PaO_2 55–80 mmHg. Once VT ≈ 4 mL/kg was achieved, respiratory rate (RR) was lowered, although maintaining pH ≥7.2 and $PaCO_2$ <60 mmHg.

Demographic and clinical data were recorded, including daily arterial blood gases, ventilatory parameters, temperature, and tissue perfusion markers (arterial lactate, central venous oxygen saturation, and venous-to-arterial CO_2 gradient). Gas exchange measurements were corrected to the patient's core body temperature at the time of blood sampling. The ventilatory load was measured with minute ventilation (VE) and the previously reported comprehensive formula for mechanical power (MP).[9] Lymphocyte count, C-reactive protein, ferritin, and D-dimer were registered before and after MTH. We actively monitored the development of new bacterial and fungal superinfections and bleeding.

All analyses were performed with GraphPad Prism® 9.5.0. Normality distribution was assessed by Anderson–Darling test, and data were shown in median (interquartile range, 25%–75%). Mixed effects analysis and Dunnett's test were used for comparisons. Significance was set at $P < 0.05$.

One hundred and seventy severe COVID-19 patients were screened, and 7 (5 males and 2 females) were enrolled. Their median age was 54-years-old (44–58), PBW was 68 kg (60–72 kg), 85.7% had comorbidities: Four patients had morbid obesity, and two had arterial hypertension. All subjects were in prone position, with deep sedation and neuromuscular blockade, and 6 received recruitment maneuvers. Median PaO_2/FIO_2 ratio was 98 mmHg (72–113), $PaCO_2$ was 69 (68–73), VT was 5.4 ml/kg PBW (5–5.9), ΔP was 16 cmH_2O (15–18), Pplat 31 cmH_2O (30–33), PEEP was 14 cmH_2O (13–15), C_{RS} was 19.4 ml/cmH_2O (17.9–25.4), and RR was 34/min (32–34) at baseline. In addition, five patients had septic shock, 5 acute kidney injury (3 required renal replacement therapy), and one received therapeutic plasma exchange.

The baseline temperature was 37.4°C (37–37.6), reaching the target temperature within 69 min (52–84). After 48 h of MTH, VT decreased a 29.6% (95% confidence interval [CI]: 13.1%–38.7%, $P < 0.01$), ΔP decreased 31% (95% CI: 9.8%–52.7%, $P < 0.01$), and $PaCO_2$ decreased 13.6% (95% CI: 1.2%–26.1%, $P = 0.034$), without changes in C_{RS}. Ventilatory load had a significant decrease during the first 24 h, as shown by reduction of VE in 12% (95% CI: 1%–32%, $P = 0.007$) and MP in 14% (95% CI: 6.8%–21%, $P = 0.002$). At the end of the MTH period, the VT, ΔP, and Pplat remained consistently close to 3.9 mL/kg PBW, 12 and 26 cmH_2O, respectively. Survivors had a slow improvement in oxygenation, and slight (no significant)

increase in VT (close to 4.4 mL/kg PBW, $P = 0.6$) after rewarming [Figure 1].

At the end of MTH period, there was a significant decrease in C-reactive protein (232 [171–243] to 11 [10–30] mg/L, $P = 0.04$), and a trend to decrease procalcitonin (0.56 [0.24–0.93] to 0.24 [0.18–0.26] ng/mL, $P = 0.08$), ferritin (1540 [848–1782] to 829 [658–889] ng/mL, $P = 0.14$), and D-dimer (445 [388–1025] to 330 [220–735] mg/mL, $P = 0.23$).

None of the global dysoxia markers worsened over time [Figure 2]. Three patients presented bacterial superinfections (*Pseudomona aeruginosa* and *Klebsiella pneumoniae* identified in tracheal cultures) and one hemoptysis.

Five patients survived till hospital discharge, and two patients died due to multiple organic failure. MV was discontinued on day 60 (46–64), tracheostomy was removed on day 71 (57–75), supplementary oxygen was discontinued on day 95 (88–107), and discharged home on day 100 (92–108) after admission.

Discussion

We report a compassionate use of MTH for severe COVID-19-related ARDS that allowed a very low-VT strategy to reduce ΔP, Pplat, and ventilatory load over the lungs (VE and MP). In some severe ARDS patients, it is challenging to preserve appropriate gas exchange while maintaining protective MV. In these cases, very low-VT combined with MTH allows minimizing the mechanical load on lungs with profoundly reduced C_{RS}, allowing a slow recovery of lung function, and reasonable survival. C_{RS} lower than 30 mL/cmH_2O is a known independent predictor of mortality in COVID-19 ARDS.[10] The protective pathophysiological effects of MTH on the lungs have been reported in preclinical and small clinical studies.[7,8,11,12] Interestingly, MTH granted a marked reduction in ventilatory load due to the use of very low-VT and ΔP within safe limits, allowing a slow and sustained improvement in gas exchange, such as those described in other ultraprotective MV cohorts.[3,4]

The main risks related to MTH are nosocomial infections, which occurred in almost half of the patients. Bleeding was infrequent. Both risks are present in other rescue therapies that permit very low VT combined with $ECCO_2$-R®.[13,14] Both complications must be closely monitored during MTH.[15]

Limitations

The small number of patients might lead to type II error. Second, we did not measure cardiac output, which would have provided data on hemodynamical repercussions of

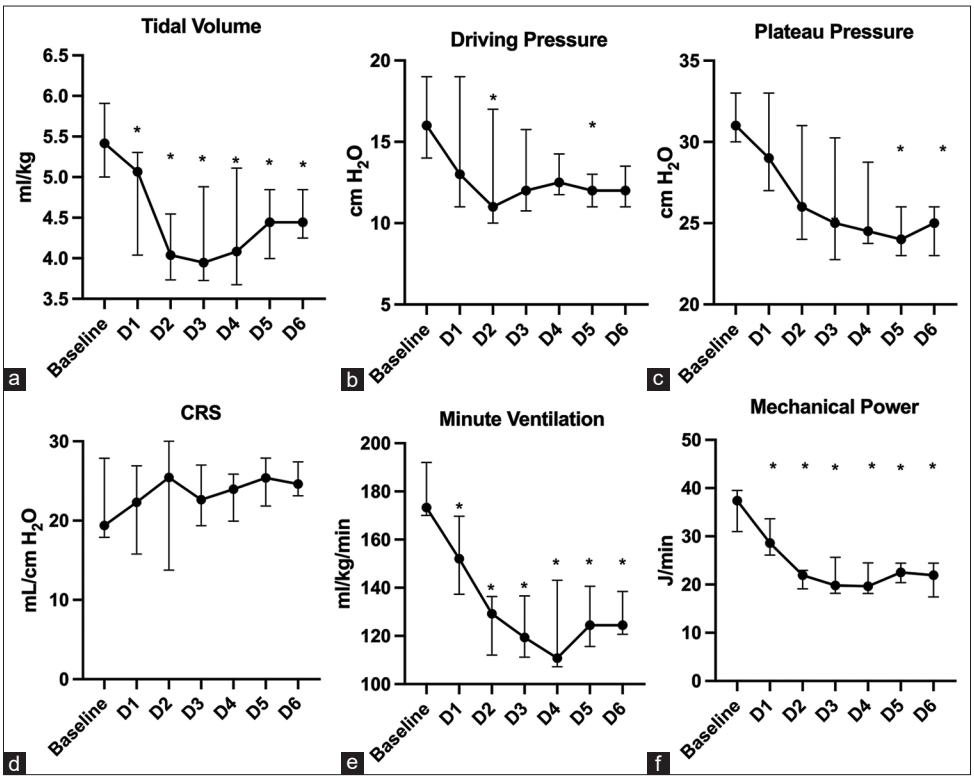

Figure 1: Respiratory mechanics and ventilatory load parameters over time of patients with very severe COVID-19-related ARDS. (a) Tidal volume, ml/kg; (b) Driving pressure, cmH2O; (c) Plateau pressure, cmH2O; (d) Compliance of the respiratory system, ml/cmH2O; (e) Minute Ventilation, mL/kg/min; (f) Mechanical Power, J/min. *$P < 0.05$, random effect model multiple comparisons with baseline. ARDS: Acute respiratory distress syndrome

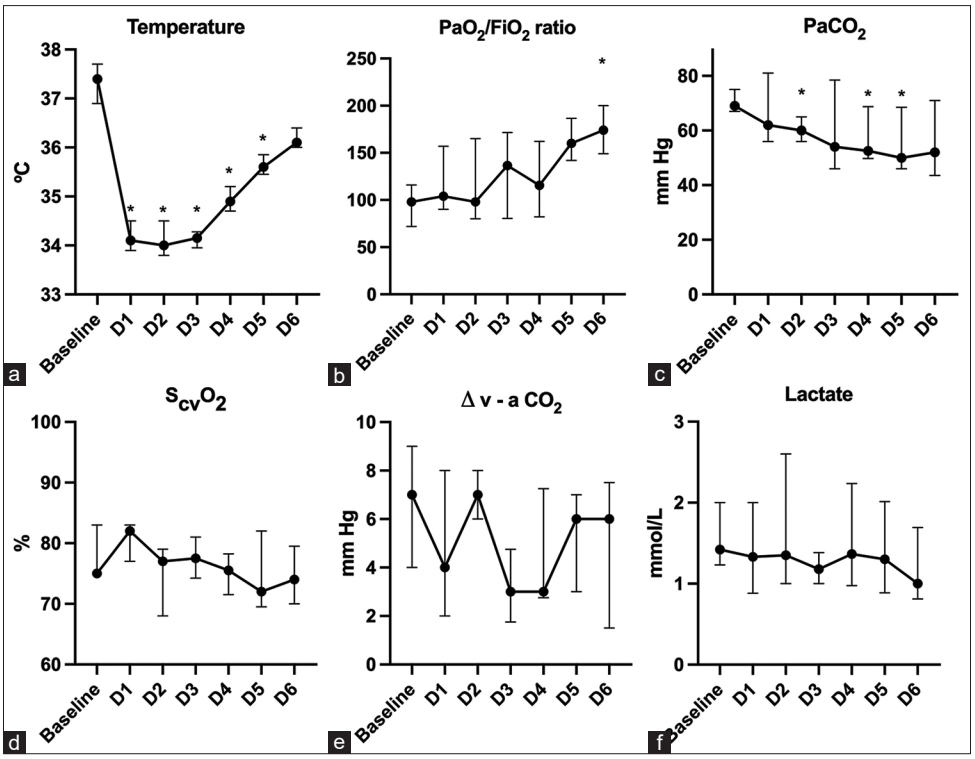

Figure 2: Temperature, gas exchange, and tissue perfusion parameters over time of patients with very severe COVID-19-related ARDS. (a) Temperature, Celsius degrees; (b) Ratio of arterial oxygen partial pressure, PaO_2, to fraction of inspired oxygen, FiO_2; (c) Arterial carbon dioxide partial pressure, $PaCO_2$, mmHg; (d) Superior cava vein oxygen saturation, $S_{CV}O_2$, %; (e) venous to arterial carbon dioxide partial pressure difference, v-a CO_2, mm Hg; (f) Lactate, mmol/L. *$P < 0.05$, random effect model multiple comparisons with baseline. ARDS: Acute respiratory distress syndrome

hypothermia. Third, the results cannot be extrapolated to other hypothermia devices.

Conclusion

We report the use of very low-VT ventilation (≈4 mL/kg PBW) combined with MTH allows decreasing ventilatory load and maintaining ventilatory parameters within safety limits. This approach might be helpful in the rescue of patients with severe ARDS due to COVID-19 and severely decreased C_{RS}.

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Author's contribution
PC and FD conceived the study, designed the study, analyzed data, wrote the preliminary draft, had full access to all the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis. DM, SR, and YR collected and curated data, analyzed data, and edited and reviewed the final manuscript. All authors read and approved the final manuscript.

Conflicts of interest
None Declared.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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