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LETTER TO THE EDITOR

Flow-controlled ventilation may reduce mechanical power and increase ventilatory efficiency in severe coronavirus disease-19 acute respiratory distress syndrome

To the Editor,

The prevention of ventilator-induced lung injury (VILI) is the mainstay of the management of mechanical ventilation in patients with acute respiratory distress syndrome (ARDS).[1] Official guidelines have focused on tidal volume, plateau pressure (Pplat), positive end-expiratory pressure (PEEP), and driving pressure (DP), i.e., the difference between Pplat and PEEP, to identify lung-protective ventilation strategies.[2] However, even values of tidal volumes and Pplat that are normally considered safe may result in injurious ventilation.[3]

Mechanical power (MP) represents the total energy transferred from the mechanical ventilator to the lungs during inflation and includes dynamic variables such as inspiratory flow rate and breathing frequency.[3] Some studies suggest that MP may predict mortality in ARDS patients[3] and that higher inspiratory flow rates increase the risk of VILI in patients with mild to moderate ARDS.[4]

The lungs of patients with coronavirus disease (COVID)-19 related ARDS are characterized by parenchymal heterogeneity, leading to regional differences in pulmonary mechanical properties.[5] Consequently, higher velocities of lung inflation may drive a greater fraction of tidal volume to alveolar units with shorter time constant and unevenly amplify lung stress in some regions.[3] Therefore, reducing flow rates might be beneficial.

Flow-controlled ventilation (FCV) (Evone®, Ventinova Medical, Eindhoven, The Netherlands) is a ventilatory mode where both inspiratory and expiratory flow rates are maintained constant and < 20 L/min throughout the respiratory cycle by regulating tracheal pressure, as measured through a dedicated lumen opening at the distal end of the endotracheal tube.[6] During FCV, the inspiratory flow rate, inspiratory to expiratory ratio, peak inspiratory pressure (Ppeak), end-expiratory pressure (EEP), and the inspiratory concentration of oxygen are pre-set, whereas tidal volume and respiratory rate vary depending on ventilator settings and the patient's respiratory mechanics.[7] Some studies observed improved lung recruitment, more homogeneous lung aeration,[6,8,9] better gas exchange,[8-12] and attenuated experimental lung injury with FCV,[12,] compared to volume-targeted mechanical ventilation (conventional mechanical ventilation, CMV). We hypothesize that FCV would reduce MP and ventilatory ratio (VR) in COVID-19 patients developing refractory hypoxemia despite optimization of CMV and prone positioning.

This pilot study was performed in 10 sedated and paralyzed COVID-19 ARDS patients admitted to the intensive care unit with arterial partial pressure of oxygen to inspired oxygen fraction ratio (PaO2/FiO2) < 150 mmHg during CMV while in prone position for at least 12 consecutive hours.[2] Inspiratory and expiratory flow rates were initially set at 15 L/min with inspiratory to expiratory ratio 1:1, while EEP was equal to PEEP and Ppeak to Pplat during CMV, thereby maintaining approximately the same DP and consequently similar tidal volumes. All measurements were obtained in CMV prior to switching to FCV (CMV1), after 4 hours of FCV, and then again after 4 hours of CMV (CMV2). All variables are reported as median (interquartile range) and compared using the Friedman test, followed by pairwise comparison with Wilcoxon signed-rank test and *post-hoc* Bonferroni correction. All statistical tests were two-tailed and statistical significance was defined as $p<0.05$.

Patient age was 59 (55-57) years and the predicted body weight 65 (59-68) kg. Nine (90%) patients survived the hospital stay. As reported in Table 1, during FCV inspiratory flow rate, respiratory rate, and minute ventilation were all decreased, compared to both CMV1 and CMV2. During FCV the MP was 10.8 (9.9-13.4) J/min, as opposed to CMV1 [22.7 (20.3-25.6) J/min (p=0.006)] and CMV2 [20.1 (19.0-24.0) J/min (p=0.006)], and VR was 1.40 (1.28-1.44), as compared with CMV1 [2.22 (1.90-2.56) (p=0.006)] and CMV2 [2.20 (1.79-2.57) (p=0.006)]. Arterial partial pressure of carbon dioxide, pH, and PaO2/FiO2 were not significantly different among the three conditions.

Our study evaluating a series of 10 consecutive patients affected by COVID-19 with refractory hypoxemia, despite prone positioning while receiving CMV, suggests that FCV may be associated with some advantages. First, the application of FCV resulted in decreased MP, as a consequence of lower inspiratory flow rates and breathing frequencies, potentially reducing the dissipated energy.[7,12,13] Indeed, FCV was shown to reduce MP[11] and attenuate VILI through

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Table 1 Ventilatory settings, mechanical properties of the respiratory system, and outcome variables

Variable	CMV1	FCV	CMV2	p-value[a]	Kendall's W
Ventilatory settings					
Respiratory rate (breaths/min)	26 (24-28)	17 (16-18)[b,c]	25 (22-26)	<0.001	0.930
Tidal volume (mL/kg PBW)	6.9 (6.8-7.3)	6.8 (6.5-7.3)	6.8 (6.5-7.2)	0.968	0.003
Minute ventilation (L/min)	11.8 (10.2-12.8)	7.7 (7.1-8.2)[d,e]	10.8 (9.6-12.1)	<0.001	0.830
Peak pressure (cmH_2O)	27 (25-28)	23 (20-25)[b,c]	26 (25-28)	<0.001	0.810
Plateau pressure (cmH_2O)	21 (20-23)	21 (19-23)	22 (21-23)	0.015	0.420
PEEP (cmH_2O)	9 (8-10)	9 (7-10)	9 (8-10)	0.772	0.030
Inspiratory flow (L/min)	26 (23-26)	15 (14-15)[d,e]	22 (22-26)	<0.001	0.800
Gas exchanges					
pH	7.37 (7.30-7.42)	7.39 (7.36-7.42)	7.34 (7.27-7.42)	0.280	0.130
$PaCO_2$ (mmHg)	49 (43-51)	45 (42-48)	51 (45-56)	0.275	0.130
PaO_2/FiO_2 (mmHg)	128 (116-134)	136 (115-147)	134 (106-152)	0.275	0.150
Ventilatory ratio	2.22 (1.90-2.56)	1.40 (1.28-1.44)[d,e]	2.20 (1.79-2.57)	<0.001	0.770
Mechanical properties of the respiratory system					
Crs (mL/cmH_2O)	36 (34-38)	35 (34-40)	36 (33-39)	0.704	0.040
Driving pressure (cmH_2O)	13 (12-13)	12 (11-13)	13 (12-14)	0.331	0.110
Mechanical power (J/min)	22.7 (20.3-25.6)	10.8 (9.9-13.4)[d,e]	20.1 (19.0-24.0)	<0.001	0.760

Abbreviations: CMV, conventional mechanical ventilation; FCV, flow-controlled ventilation; PBW, predicted body weight; PEEP, positive end-expiratory pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2/FiO_2, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; Crs, compliance of the respiratory system.

All measurement were obtained in CMV prior to switching to FCV (CMV1), after 4 hours of FCV, and then again after 4 hours of CMV (CMV2). During CMV, plateau pressure (Pplat) and total PEEP were measured at the points of zero flow during an end-inspiratory and end-expiratory pause, respectively, while during FCV Pplat is displayed every 10 cycles after an automatic pressure drop in the pressure curve. Driving pressure was computed as the difference between Pplat and total PEEP, during CMV, and the difference between peak pressure (Ppeak) and end-expiratory pressure, during FCV. Crs was calculated as the ratio between tidal volume and driving pressure. Inspiratory flow during CMV was calculated as the ratio between tidal volumes and inspiratory time, while inspiratory flow during FCV is set on the ventilator.

Ventilatory ratio was calculated as the ratio between the product of measured minute ventilation (mL/min) and measured PaCO2 and the product between predicted minute ventilation (PBW*100 mL/min) and expected PaCO2 (37.5 mmHg) (10.1164/rccm.201804-0692OC). Mechanical power was calculated as follows: 0.098*respiratory rate*tidal volume*[Ppeak-1/2*(Pplat-PEEP)] (10.1186/s13054-020-03116-w).

Variables are reported as median (interquartile range) and were compared using the Friedman two-way analysis of variance, followed by pairwise comparison with Wilcoxon signed-rank test and *post-hoc* Bonferroni correction, when indicated. The Kendall's W value is the effect size estimate for Friedman test and ranges from 0.1-0.3 (small effect) to >0.5 (large effect).

[a] p-value from the Friedman two-way analysis of variance.
[b] $p<0.05$ between FCV and CMV1 after *post-hoc* Bonferroni correction.
[c] $p<0.05$ between FCV and CMV2 after *post-hoc* Bonferroni correction.
[d] $p<0.01$ between FCV and CMV1 after *post-hoc* Bonferroni correction.
[e] $p<0.01$ between FCV and CMV2 after *post-hoc* Bonferroni correction.

this mechanism in porcine models.[12] Second, our results are in keeping with preclinical[8,9,12] and clinical studies,[6,] demonstrating higher ventilatory efficiency, probably related to improved intrapulmonary distribution of ventilation with FCV. Third, although we did not observe any significant improvement in gas exchange with FCV, previous studies reported better oxygenation and carbon dioxide elimination with this mode.[8-12,] Therefore, our study extends to the critical illness setting the current evidence, mainly limited to preclinical studies and small clinical studies performed in the operating room, suggesting that FCV might reduce VILI, while maintaining adequate gas exchanges.

Our study has important limitations. First, the small sample size makes our findings exploratory and hypothesis-generating. Larger prospective studies are necessary to confirm these results and support clinical studies ascertaining the impact of FCV on clinical outcomes. Second, the external validity and the generalizability of our findings to patients with acute respiratory failure of different etiology need to be assessed. Furthermore, we cannot rule out that different dead space of the ventilator apparatus may have contributed to the improvement of VR with FCV. However, this is unlikely because we always used an active humidifier before the Y-piece of the respiratory circuit during CMV.

In conclusion, FCV reduced MP and VR in a small cohort of severely hypoxemic COVID-19 patients receiving CMV and prone positioning.

Authors' contributions

Conception and design of the study: AG, TP. Acquisition of the data: AG, FB, RC. Analysis of the data: AG, TP, NS. Interpretation of the data: all authors. Drafting of the manuscript: AG, TP, NS, PN. Critical revision of the manuscript for important intellectual content: All authors. Final approval of the version to be submitted: all authors.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

PN research lab received grants/research equipment by Draeger, Intersurgical SPA, and Gilead. PN receives royalties from Intersurgical SPA for Helmet Next invention. He also received speaking fees from Getinge, Intersurgical SPA, Gilead, MSD, Draeger, and Medicair. PN has no conflict of interest to declare in relation to this manuscript. The other authors have no competing interests to declare.

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Ethics approval and consent to participate

The study was approved by the Local Ethical Committee (Comitato Etico di Sperimentazione Clinica ULSS 2 Marca Trevigiana, protocol n. 0235105/21) and was conducted in accordance with the principles of the Helsinki Declaration. Informed consent was obtained according to the national regulation.

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