Wei Zhang, M.D.
PLA 900th Hospital of Joint Service Corps
Fuzhou, China

Jia-An Xia, M.D.
Jinyintan Hospital
Wuhan, China

Michael C. Sklar, M.D.
Keenan Research Centre
Toronto, Ontario, Canada
St. Michael's Hospital
Toronto, Ontario, Canada
and
University of Toronto
Toronto, Ontario, Canada

Bin Du, M.D.
Peking Union Medical College and Chinese Academy of Medical Sciences
Beijing, China

Laurent Brochard, M.D.*
Keenan Research Centre
Toronto, Ontario, Canada
St. Michael's Hospital
Toronto, Ontario, Canada
and
University of Toronto
Toronto, Ontario, Canada

Haibo Qiu, M.D.‡
Zhongda Hospital
Nanjing, China
Southeast University
Nanjing, China
and
Jinyintan Hospital
Wuhan, China

ORCID ID: 0000-0002-7512-1865 (L.C.).

*L.B. is Deputy Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.
‡Corresponding author (e-mail: haiboq2000@163.com).

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
2. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;pii:S2213-2600(20)30079-5.
3. Chen L, Brochard L. Lung volume assessment in acute respiratory distress syndrome. *Curr Opin Crit Care* 2015;21:259–264.
4. 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.
5. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, *et al*.; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307:2526–2533.
6. Chen L, Del Sorbo L, Grieco DL, Shklar O, Junhasavasdikul D, Telias I, *et al*. Airway closure in acute respiratory distress syndrome: an underestimated and misinterpreted phenomenon. *Am J Respir Crit Care Med* 2018;197:132–136.
7. Camporota L, Caricola EV, Bartolomeo N, Di Mussi R, Wyncoll DLA, Meadows CIS, *et al*. Lung recruitability in severe acute respiratory distress syndrome requiring extracorporeal membrane oxygenation. *Crit Care Med* 2019;47:1177–1183.

Ventilatory Ratio in Hypercapnic Mechanically Ventilated Patients with COVID-19–associated Acute Respiratory Distress Syndrome

To the Editor:

Lung-protective ventilation with low V_T has become a cornerstone of management in patients with acute respiratory distress syndrome (ARDS) (1, 2). However, a consequence of low-V_T ventilation is hypercapnia, which has significant physiological effects and may be associated with higher hospital mortality (2, 3).

Ventilatory ratio (VR), defined as [minute ventilation (ml/min) × Pa_{CO_2} (mm Hg)]/[predicted body weight × 100 (ml/min) × 37.5 (mm Hg)] (4), is a simple bedside index of impaired efficiency of ventilation and correlates well with physiological V_D fraction (V_D-to-V_T ratio, V_D/V_T) in patients with ARDS (4–6). However, the VR and appropriate lung ventilation strategy for coronavirus disease (COVID-19)-associated ARDS remain largely unknown.

Here, we report a case series highlighting ventilatory ratio in hypercapnic mechanically ventilated patients with COVID-19–associated ARDS in our ICU and their individualized ventilation strategies.

Case Series

The study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University. The requirement for informed consent was waived because the study was observational and the family members were in quarantine.

The First Affiliated Hospital of Guangzhou Medical University is the designated center for patients with COVID-19 in Guangdong, China. We included eight consecutive patients (seven male; mean

Supported by National Science and Technology Major Project (No. 2017ZX10204401), National Natural Science Foundation of China (81970071), the Special Project for Emergency of the Ministry of Science and Technology (2020YFC0841300), and the Special Project of Guangdong Science and Technology Department (2020B111105001).

Author Contributions: Xiaoqing Liu, Xuesong Liu, Y.X., and Y.L. conceived and designed the study; Xiaoqing Liu, Xuesong Liu, Y.X., Z.X., Y.H., and Y.L. analyzed the data and wrote the manuscript; Xiaoqing Liu, Xuesong Liu, Y.X., Z.X., Y.H., S.C., S.L., D.L., Z.L., and Y.L. reviewed and revised the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202002-0373LE on March 23, 2020

Table 1. Baseline Characteristics of Eight Patients with Acute Respiratory Distress Syndrome Infected with SARS-CoV-2

Characteristic	Patients (*N* = 8)
Exposure history	8/8
Age, yr	63.2 ± 11.0
Sex, M	7/8
Body mass index, kg/m^2	22.7 ± 2.3
Predicted body weight, kg	64.7 ± 6.0
Chronic medical illness	
Hypertension	4/8
Diabetes	3/8
Coronary heart disease	1/8
Chronic obstructive pulmonary disease	1/8
Obstructive sleep apnea syndrome	1/8
Hepatitis B	1/8
Smoker	3/8
Presenting symptoms onset	
Fever	8/8
Cough	7/8
Generalized weakness	4/8
Shortness of breath	3/8
Real-time RT-PCR of throat swab	8/8
Radiologic characteristics	
Bilateral pneumonia	8/8
Multiple mottling and ground-glass opacity	8/8
Noninvasive ventilation before intubation	1/8
Duration of noninvasive ventilation, d	1
HFNC before intubation	7/8
Duration of HFNC, d	2.6 ± 2.2
$Pa_{O_2}/F_{I_{O_2}}$ ratio, mm Hg	102.0 ± 29.7
APACHE II score	21.6 ± 5.3
SOFA score	9.1 ± 2.7
Weaning before day 28 at ICU	5/8
Discharge before day 28 at ICU	5/8
28-d mortality at ICU	0/8

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; HFNC = high-flow nasal cannula oxygen therapy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOFA = Sequential Organ Failure Assessment.
Data are presented as mean ± SD or *n*/*N* unless otherwise noted.

age, 63.2 ± 11.0 yr) who were intubated in another hospital before being transferred to our ICU. All patients had a history of exposure in Wuhan City or direct contact with patients with confirmed COVID-19. All patients reported fever, cough, shortness of breath, and generalized weakness before hospitalization and tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the basis of real-time PCR of throat swab specimens. All patients were diagnosed with ARDS according to the Berlin definition (7): $Pa_{O_2}/F_{I_{O_2}}$ ratio, 102.0 ± 29.7 mm Hg (mean ± SD), with Acute Physiology and Chronic Health Evaluation II score 21.6 ± 5.3 and Sequential Organ Failure Assessment score 9.1 ± 2.7 (Table 1).

A ventilation strategy using a low V_T of 6.0 ml/kg predicted body weight (PBW) was used in the first four consecutive patients. However, they had respiratory distress with low oxygen saturation as measured by pulse oximetry, so we immediately increased V_T to 7.0 ± 0.6 ml/kg PBW (Table 2). This resulted in an acceptable plateau pressure (23.3 ± 2.2 cm H_2O) and driving pressure (12.3 ± 1.7 cm H_2O). However, all four patients developed hypercapnia (Pa_{CO_2}, 57.7 ± 5.2 mm Hg). Respiratory system compliance was only moderately reduced (static respiratory system compliance, 35.7 ± 5.8 ml/cm H_2O). To examine this issue, we measured VR; the mean value was 2.1 ± 0.3 in the initial four patients, suggesting high V_D/V_T (4–6).

We then performed titration of V_T. An increased V_T (7.7 ± 0.8 ml/kg PBW) was applied to the initial four patients (Table 2). Pa_{CO_2} decreased significantly compared with V_T 7.0 ml/kg PBW (57.7 ± 5.2 vs. 44.1 ± 3.6 mm Hg; $P = 0.003$) with permitted plateau pressure (23.3 ± 3.1 cm H_2O) and driving pressure (13.5 ± 2.7 cm H_2O). Importantly, VR in the four patients was significantly decreased (1.7 ± 0.2 vs. 2.1 ± 0.3; $P = 0.018$) and $Pa_{O_2}/F_{I_{O_2}}$ was slightly improved (241 ± 38 mm Hg vs. 207 ± 61; $P = 0.402$) compared with V_T 7.0 ml/kg PBW. Therefore, an intermediate V_T of 7.5 ± 0.6 ml/kg PBW was applied to the subsequent four patients with COVID-19 ARDS. The Pa_{CO_2} was 41.8 ± 3.7 mm Hg, and VR was 1.6 ± 0.2.

Discussion

We found that hypercapnia was common in patients with COVID-19–related ARDS with low V_T ventilation. High VR was found in these patients, indicating inadequacy of ventilation in patients with

Table 2. Ventilator Settings

Variables	Low V_T (Initial 4 Patients)	Intermediate V_T (Initial 4 Patients)	*P* Value	Intermediate V_T (8 Patients)
V_T, ml/kg PBW	7.0 ± 0.6	7.7 ± 0.8	0.022	7.5 ± 0.6
Pa_{CO_2}, mm Hg	57.7 ± 5.2	44.1 ± 3.6	0.003	41.8 ± 3.7
$Pa_{O_2}/F_{I_{O_2}}$ ratio	207 ± 61	241 ± 38	0.402	230 ± 49
RR, beats/min	21.5 ± 2.0	21.0 ± 1.4	0.182	20.1 ± 1.5
V_E, L/min	9.1 ± 1.0	9.8 ± 1.0	0.020	9.3 ± 1.0
Ventilation ratio	2.1 ± 0.3	1.7 ± 0.2	0.018	1.6 ± 0.2
Pplat, cm H_2O	23.3 ± 2.2	23.3 ± 3.1	>0.999	23.6 ± 2.7
PEEP, cm H_2O	11.0 ± 1.2	10.0 ± 1.4	0.250	9.6 ± 1.2
ΔP, cm H_2O	12.3 ± 1.7	13.5 ± 2.7	0.080	14.1 ± 2.5
Cst, ml/cm H_2O	35.7 ± 5.8	36.1 ± 7.9	0.595	33.9 ± 7.6
EELV, ml	—	2,559 ± 61	—	2,285 ± 355

Definition of abbreviations: Cst = static respiratory system compliance; ΔP = driving pressure; EELV = end-expiratory lung volume; PBW = predicted body weight; PEEP = positive end-expiratory pressure; Pplat = plateau pressure; RR = respiratory rate.
Data are presented as mean ± SD. *P* value indicates difference between low V_T and intermediate V_T of the initial four patients using a paired *t* test.

ARDS with COVID-19. An intermediate V_T (7–8 ml/kg PBW) ventilation strategy was applied to the first four patients to increase pulmonary efficiency to eliminate CO_2, and this was used in the next four patients.

Gas exchange consists of oxygenation and ventilation. Oxygenation is quantified by the Pa_{O_2}/FI_{O_2} ratio, and this method has gained wide acceptance, particularly since publication of the Berlin definition of ARDS (7). However, the Berlin definition does not include additional pathophysiological information about ARDS, such as alveolar ventilation, as measured by pulmonary dead space, which is an important predictor of outcome (8). Increased pulmonary dead space reflects the inefficiency of the lungs to eliminate CO_2, which may lead to hypercapnia.

In our patients with ARDS with COVID-19, hypercapnia was common at ICU admission with low V_T ventilation. Assuming the anatomic portion of dead space is constant, increasing V_T with constant respiratory rate would effectively increase alveolar ventilation. Any such increase in V_T would decrease Pa_{CO_2}, which would be captured by VR (6). VR, a novel method to monitor ventilatory adequacy at the bedside (4–6), was very high in our patients, reflecting increased pulmonary dead space and inadequacy of ventilation.

With an acceptable plateau pressure and driving pressure, titration of V_T was performed. Pa_{CO_2} and VR were significantly decreased when an intermediate V_T (7–8 ml/kg PBW) was applied. We suggest that intermediate V_T (7–8 ml/kg PBW) is recommended for such patients. Therefore, low V_T may not be the best approach for all patients with ARDS, particularly those with a less severe decrease in respiratory system compliance and inadequacy of ventilation.

In summary, we found that hypercapnia was common in patients with COVID-19–associated ARDS while using low V_T ventilation. VR was increased in these patients, which reflected increased pulmonary dead space and inadequacy of ventilation. An intermediate V_T was used to correct hypercapnia efficiently, while not excessively increasing driving pressure. Clinicians must have a high index of suspicion for increased pulmonary dead space when patients with COVID-19–related ARDS present with hypercapnia. ■

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

Acknowledgment: The authors thank Dr. Arthur S. Slutsky for the invaluable assistance with the manuscript.

Xiaoqing Liu, M.D.*
Xuesong Liu, M.D.*
Yonghao Xu, M.D., Ph.D.
Zhiheng Xu, M.D., Ph.D.
Yongbo Huang, M.D., Ph.D.
Sibei Chen, M.D.
Shiyue Li, M.D.
Dongdong Liu, M.D.
Zhimin Lin, M.D.
Yimin Li, M.D., Ph.D.‡
State Key Laboratory of Respiratory Diseases
Guangzhou, China
Guangzhou Institute of Respiratory Health
Guangzhou, China
and
The First Affiliated Hospital of Guangzhou Medical University
Guangzhou, China

*These authors contributed equally to this work.
‡Corresponding author (e-mail: dryiminli@vip.163.com).

References

1. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
2. Barnes T, Zochios V, Parhar K. Re-examining permissive hypercapnia in ARDS: a narrative review. *Chest* 2018;154:185–195.
3. Tiruvoipati R, Pilcher D, Buscher H, Botha J, Bailey M. Effects of hypercapnia and hypercapnic acidosis on hospital mortality in mechanically ventilated patients. *Crit Care Med* 2017;45:e649–e656.
4. Sinha P, Fauvel NJ, Singh S, Soni N. Ventilatory ratio: a simple bedside measure of ventilation. *Br J Anaesth* 2009;102:692–697.
5. Sinha P, Fauvel NJ, Singh P, Soni N. Analysis of ventilatory ratio as a novel method to monitor ventilatory adequacy at the bedside. *Crit Care* 2013;17:R34.
6. Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay MA, *et al*. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2019; 199:333–341.
7. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, *et al*.; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307:2526–2533.
8. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, *et al*. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002;346:1281–1286.

COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome

To the Editor:

In northern Italy, an overwhelming number of patients with coronavirus disease (COVID-19) pneumonia and acute respiratory failure have been admitted to our ICUs. Attention is primarily focused on increasing the number of beds, ventilators, and intensivists brought to bear on the problem, while the clinical approach to these patients is the one typically applied to severe acute respiratory distress syndrome (ARDS), namely, high positive end-expiratory pressure (PEEP) and prone positioning. However, the patients with COVID-19 pneumonia, despite meeting the Berlin definition of ARDS, present an atypical form of the syndrome. Indeed, the primary characteristic we are observing (and has been confirmed by colleagues in other hospitals) is a dissociation between their relatively well-preserved lung mechanics and the severity of hypoxemia. As shown in our first 16 patients (Figure 1), a respiratory system compliance of 50.2 ± 14.3 ml/cm H_2O is associated with a shunt fraction of 0.50 ± 0.11. Such a wide discrepancy is virtually never seen in most forms of ARDS. Relatively high compliance indicates a

Originally Published in Press as DOI: 10.1164/rccm.202003-0817LE on March 30, 2020