OBSERVATIONAL STUDY

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Timing of Intubation in Coronavirus Disease 2019: A Study of Ventilator Mechanics, Imaging, Findings, and Outcomes

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For the NU COVID Investigators

OBJECTIVES: Determine the variation in outcomes and respiratory mechanics between the subjects who are intubated earlier versus later in their coronavirus disease 2019 course.

DESIGN: Retrospective cohort study.

SETTING: Northwestern Memorial Hospital ICUs.

PATIENTS: All patients intubated for coronavirus disease 2019 between March 2020 and June 2020.

INTERVENTIONS: Patients were stratified by time to intubation: 30 subjects were intubated 4–24 hours after presentation and 24 subjects were intubated 5–10 days after presentation. Baseline characteristics, hospitalization, ventilator mechanics, and outcomes were extracted and analyzed. Ten clinically available CT scans were manually reviewed to identify evidence of pulmonary vascular thrombosis and intussusceptive angiogenesis.

MEASUREMENTS AND MAIN RESULTS: Median time from symptom onset to intubation was significantly different between the early and late intubation cohorts, with the latter being intubated later in the course of their illness (7.9 vs 11.8 d; $p = 0.04$). The early intubation cohort had a lower mortality rate than the late intubation cohort (6% vs 30%, $p < 0.001$) without significantly different respiratory mechanics at the time of intubation. The late intubation cohort was noted to have higher dead space ratio (0.40 vs 0.52; $p = 0.03$). On review of CT scans, the late intubation cohort also had more dilated peripheral segments on imaging (two segments vs five segments).

CONCLUSIONS: The question as to whether delaying intubation is beneficial or harmful for patients with coronavirus disease 2019-induced hypoxemic respiratory failure has yet to be answered. As our approaches to coronavirus disease 2019 continue to evolve, the decision of timing of intubation remains paramount. Although noninvasive ventilation may allow for delaying intubation, it is possible that there are downstream effects of delayed intubation that should be considered, including the potential for pulmonary vascular thrombosis and intussusceptive angiogenesis with delayed intubation.

KEY WORDS: coronavirus disease 2019; intubation; noninvasive ventilation; pulmonary vascular injury; respiratory distress syndrome; respiratory mechanics

The management and pathophysiology of coronavirus disease 2019-induced acute respiratory distress syndrome (C-ARDS) continue to evolve, but the optimal timing of intubation remains a subject of uncertainty

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and controversy. The definitions of early versus late intubation vary across publications, which has resulted in various descriptions of lung mechanics and outcomes among these cohorts (1, 2). The question as to whether delaying intubation is beneficial or harmful for patients with coronavirus disease 2019 (COVID-19)-induced hypoxemic respiratory failure and to what extent timing of intubation has on the unique pathophysiology of C-ARDS remains unanswered.

Early reports suggested that patients may benefit from early intubation during a period defined by severe hypoxemia but apparently relatively normal lung compliance. Following reports of very high mortality in intubated patients (3) practice seemed to move toward delayed intubation in favor of oxygenation support with high-flow oxygen systems (4). This practice raised, for some, concerns related to induction of patient self-induced lung injury (P-SILI) (5, 6). P-SILI is a controversial concept that describes exacerbation of lung injury due to intense respiratory effort in a spontaneously breathing patient (7). It is thought to occur because of abnormal swings in transpulmonary and intravascular pressures driving worsening barotrauma and potentially vascular trauma in the already injured lung (8).

More recently, the focus on pathophysiology in COVID-19-induced lung injury has shifted to an exploration of pulmonary vascular thrombosis and intussusceptive angiogenesis (9). Ackerman et al (9) demonstrated that the frequency of intussusceptive angiogenesis is increased in COVID-19 compared with influenza, and the degree of angiogenesis is increased the longer the length of hospitalization for COVID-19. It is important to highlight that, in this study, none of the patients who died from COVID-19 with the aforementioned angiogenesis had been treated with standard mechanical ventilation. Furthermore, Patel et al (10) demonstrated a radiographic correlate of microthromboses with the use of CT scans and the description of a "vascular tree-in-bud" pattern. In this study, they demonstrated an association with vascular dilatation and dead space.

Here, we describe the clinical characteristics and outcomes of early and late intubation cohorts at a single urban academic center with a particular focus on lung mechanics and pulmonary vascular thrombosis with radiographic correlates.

MATERIALS AND METHODS

This is a retrospective cohort study conducted using data from ICUs within Northwestern Memorial Hospital in Chicago, IL. This study included all subjects with a positive polymerase chain reaction test for COVID-19 who had a first intubation between March 4, 2020, and June 30, 2020. During this time period, our institution was not limited by ventilator, provider, or ICU bed availability, and thus, clinical decisions were not based on scarcity of resources. Only subjects who had reached an end point between this time (death or discharge) were included in the analysis. Data were obtained from the electronic medical record with a combination of automatic extraction using the electronic data warehouse and manual chart review. Dead space ratios (DSRs) and ventilatory ratios were calculated: DSR was calculated using the alveolar ventilation equation and carbon dioxide production, which was calculated from the resting energy expenditure that was estimated from the unadjusted Harris-Benedict estimate (11). Ventilatory ratio was calculated as a ratio of actual versus predicted minute ventilation, also as previously described (12).

Data were stratified based on time from hospital admission to time of intubation. The "early intubation cohort" was defined as those subjects intubated between 4 and 24 hours after admission to the hospital; the "late intubation cohort" consisted of subjects intubated between 5 and 10 days after admission. Patients intubated within 4 hours of arrival were excluded for two reasons. First, those who were severely hypoxic immediately upon arrival were often unable to provide a date of symptom onset prior to intubation. Additionally, the initial mortality rate among those intubated rapidly was exceedingly high (47% for those intubated within 1 hr of arrival), which points toward a more sick and less well-defined cohort that, if included, could potentially bias our cohort comparisons.

The primary outcome of this study was mortality. Secondary outcomes included length of ventilation, length of hospitalization, and respiratory mechanics. A supplementary analysis of radiographic data is also included.

CT scans with pulmonary embolism protocol were obtained clinically in 11 of the subjects: seven from the early cohort and four from the late cohort. These CT scans were reviewed for peripheral vascular

tortuosity and dilation, as described previously (10). The CT scans were considered evaluable if there were at least two well-aerated lobes available for analysis. A lobe was not considered well-aerated if it contained at least 50% consolidation obscuring the underlying vessels. One patient from the early cohort was excluded due to insufficient clear lobes. A segment refers to bronchial segments, of which there are 19 total segments.

Categorical variables were analyzed using chi-square testing, and continuous variables were analyzed using a two-tailed Mann-Whitney *U* test with a *p* value of less than 0.05 considered significant. All values reported below are medians with interquartile ranges unless otherwise noted.

This study was approved by the Northwestern University Institutional Review Board (STU00212283) with a waiver of informed consent.

RESULTS

Baseline characteristics are described in **Table 1**. There were 30 subjects in the early intubation cohort and 24 in the late intubation cohort. The median date of intubation in both cohorts was April 13, 2020. Demographics are notable for higher body mass index and more subjects of Hispanic ethnicity in the early intubation cohort. The late intubation cohort had more Black subjects and more tobacco exposure, hypertension, and underlying chronic kidney disease.

TABLE 1.
Demographics and Comorbid Characteristics of the Early and Late Intubation Cohorts

Demographics	Early Intubation Cohort (*n* = 30)	Late Intubation Cohort (*n* = 24)	*p*
Age (yr)	58 (42–69)	62 (50–69)	0.32
Body mass index	33 (30–42)	28 (25–31)	<0.01[a]
Male	21 (70%)	16 (66%)	0.72
Race			
Black	8 (26%)	12 (57%)	<0.001[a]
White	12 (41%)	8 (35%)	
Other	9 (31%)	2 (8%)	
Hispanic	14 (48%)	4 (17%)	
Comorbidities			
Hypertension	13 (43%)	18 (75%)	<0.01[a]
Diabetes	13 (43%)	13 (54%)	0.28
Chronic kidney disease	3 (10%)	9 (37.5%)	<0.001[a]
End-stage renal disease	1 (3%)	6 (25%)	<0.001[a]
Coronary artery disease	4 (13%)	3 (12.5%)	0.9
Congestive heart failure	4 (13%)	2 (8%)	0.47
Chronic obstructive pulmonary disease	4 (13%)	2(8%)	0.47
Asthma	1 (3%)	1 (4%)	0.82
Smoking history	8 (28%)	12 (50%)	0.01[a]

[a]$p < 0.05$.
All values are reported as *n* (%) or median (interquartile range).

Data regarding baseline COVID parameters are reported in **Table 2**. Median time from symptom onset to intubation was significantly different between the early and late intubation cohorts, with the latter being intubated later in the course of their illness (7.9 vs 11.8 d; $p = 0.04$). At presentation, the early intubation cohort had higher WBC count, C-reactive protein, and D-dimer. At the time of intubation, however, the difference in laboratory data between the groups was not statistically significant with the exception of the early intubation cohort having a lower ferritin level than the late intubation cohort. There was no difference in Sequential Organ Failure Assessment (SOFA) scores between the cohorts at time of ICU admission, but the late intubation cohort had a higher median SOFA score at time of intubation (8 vs 12; $p = 0.01$). There was no difference between the cohorts in the oxygen support devices used prior to intubation; however, significantly more patients in the late intubation cohort used self-prone positioning prior to intubation (20% vs 58%, $p = 0.004$). The late intubation cohort had higher exposure to hydroxychloroquine, but otherwise, there were no COVID-19-specific therapeutic intervention differences between the groups.

At the time of intubation, we noted no difference in respiratory mechanics between the early versus late intubation cohorts, as described in **Table 3**. Median Pao_2-to-Fio_2 (P/F) ratios (184 vs 186; $p = 0.93$), lung compliance (31 vs 33 mL/cm H_2O; $p = 0.53$), driving pressure (12 vs 13 mm Hg; $p = 0.25$), and positive end-expiratory pressure (PEEP) (10 vs 10 mm Hg; $p = 0.53$) were the same between the early intubation and late intubation cohorts. However, the late intubation cohort was noted to have a higher calculated DSR (0.40 vs 0.52; $p = 0.03$).

A total of 11 CT scans were obtained in the cohort with 10 of the scans being evaluable for peripheral "vascular tree-in-bud": six scans in the early intubation cohort and four scans in the late intubation cohort. A representative image is shown in **Figure 1**. The early intubation cohort demonstrated a lower absolute number of segments with dilatation (median two segments vs five segments). Furthermore, when the number of segments was standardized to the duration of time from symptom onset to CT scan acquisition, the early intubation cohort had a lower frequency of dilation (0.05 vs 0.26 segments/d) compared with the late intubation cohort. (**Table 4**) Finally, there were more acute pulmonary emboli documented in the early cohort than the late cohort (6 vs 1, respectively).

Subjects in the early intubation cohort had a lower mortality rate than the late intubation cohort (6% vs 30%; $p < 0.001$) and less vasopressor use (60% vs 80%; $p = 0.02$) during their ICU course. The early intubation cohort also had a significantly shorter median hospital length of stay (19 vs 29 d; $p = 0.04$) despite similar ICU length of stay and duration of mechanical ventilation (10 vs 10 d; $p = 0.36$). There was no difference in the need for tracheostomy between early versus late intubation cohorts. Subjects in the early intubation cohort also were more likely to be discharged home and less likely to require posthospital facility placement; however, this was not statistically significant (Table 3).

DISCUSSION

In a retrospective cohort study of critically ill subjects with hypoxemic respiratory failure related to COVID-19 pneumonia, we demonstrate that later intubation was associated with a higher mortality rate than early intubation. However, at the time of intubation, the early compared with the late intubation cohort did not seem to have significant differences in parameters of worsening ARDS such as lung compliance, P/F ratios, PEEP usage, or driving pressure. The main difference in lung mechanics that we demonstrated between the early and late intubation cohorts was a higher DSR in the late intubation cohort. Coupled with the finding of higher DSR, we also demonstrated that the late cohort had more radiographically dilated and tortuous peripheral vessels than the early cohort despite lower frequencies of demonstrated acute pulmonary emboli.

The timing of intubation was unique in this study and stands in contrast to prior studies that describe the impact of intubation timing on lung mechanics and mortality. Although the original query to the electronic data warehouse was based on the timing of intubation compared with date of hospitalization, further manual chart review elucidated the date of symptom onset. During this wave of the pandemic, in the setting of ICU bed shortages, it was common practice at our institution to document the date of symptom onset to help inform the likelihood of impending clinical deterioration. Using this information, we were able to demonstrate that those in the late cohort were on average 4 days longer into the disease course (as defined from

TABLE 2.
Patient Characteristics and Predictors of Disease Severity

Hospitalization Characteristics	Early Intubation Cohort ($n = 30$)	Late Intubation Cohort ($n = 24$)	p
Sx onset to hospitalization (d)	7 (6–14)	4 (2–8)	0.02[a]
Sx onset to ICU (d)	7.2 (5.7–14.1)	9.3 (7.6–14.0)	<0.001[a]
Sx onset to intubation (d)	7.9 (6.5–14.3)	11.8 (8.5–15.9)	0.04[a]
Sx onset to CT scan	$n = 6$; 21.7 (16.4–37.0)	$n = 4$; 15.8 (10.4–22.1)	[b]
Severity marker analysis			
SOFA score at ICU admission	6 (3–8)	4 (1–7)	0.33
SOFA score at time of intubation	8 (7–9)	11.5 (8–13)	0.004[a]

Serologic Characteristics	At Admission/ Intubation	At Admission	At Intubation	At Admission	At Intubation
Laboratory markers					
WBCs	8.0 (6–11)	6.1 (4.5–7.2)	7.4 (6.0–10.1)	0.003[a]	0.61
Absolute lymphocytes	0.9 (0.8–1.3)	0.8 (0.6–1.2)	0.8 (0.8–1.2)	0.14	0.29
C-reactive protein	18.4 (13.8–24.6)	6.9 (4.0–10.1)	16 (13.2–22.8)	<0.001[a]	0.99
d-dimer	1,463 (326–838)	315 (285–570)	512 (367–943)	0.03[a]	0.29
Ferritin	949 (414–1,533)	447 (223–927)	1,556 (728–4,612)	0.14	0.04[a]
Procalcitonin	0.39 (0.17–1.68)	0.13 (0.06–0.49)	0.61 (0.29–10.1)	0.14	0.1

Therapeutic Characteristics	At Admission/ Intubation	At Admission	At Intubation	At Admission	At Intubation
Therapeutic analysis					
O_2 delivery prior to intubation					
NC	12 (40%)	6 (25%)		0.25	
High-flow NC	15 (50%)	17 (71%)		0.12	
Bilevel positive airway pressure	3 (10%)	1 (3%)		0.42	
Self-proning	6 (20%)	14 (58%)		0.004[a]	
Adjunctive therapies					
Remdesivir	7 (23.3%)	5 (21%)		0.77	
Anti-interlukin-6	8 (26.7%)	7 (29%)		0.78	
Steroids	7 (23.3%)	8 (33%)		0.25	
Hydroxychloroquine	1 (3.3%)	4 (17%)		<0.001[a]	

NC = nasal cannula, SOFA = Sequential Organ Failure Assessment, Sx = symptom.

[a]$p < 0.05$.

[b]Sample size too small to calculate Mann-Whitney U score and p.

All values are reported as n (%) or median (interquartile range).

TABLE 3.
Patient Outcomes

Outcomes	Early Intubation Cohort (*n* = 30)	Late Intubation Cohort (*n* = 24)	*p*
ICU course			
Vasopressor >4 hr	18 (60%)	20 (83%)	0.02[a]
Prone positioning	13 (43%)	11 (46%)	0.8
Neuromuscular blockade	12 (40%)	6 (25%)	0.13
Inhaled nitric oxide	1 (3%)	2 (8%)	0.17
New renal replacement therapy	3 (10%)	7 (29%)	0.07
Extracorporeal membrane oxygenation	5 (17%)	1 (4%)	0.1
Tracheostomy	6 (20%)	5 (21%)	0.92
Respiratory and ventilator mechanics			
Pao_2/Fio_2 ratio at intubation	184 (114–245)	186 (116–235)	0.93
Compliance at intubation	31 (27–53)	33 (27–35)	0.53
Driving pressure at intubation	12 (8.5–15)	13 (10–17)	0.25
Dead space fraction	0.40 (0.35–0.52)	0.52 (0.40–0.59)	0.03[a]
Ventilatory ratio	1.42 (1.15–1.65)	1.64 (1.55–2.03)	0.4
Positive end-expiratory pressure at time of intubation	10 (10–14)	10 (10–12)	0.53
Hospital course			
Hospital length of stay	19 (10–28)	29 (19–33)	0.04[a]
ICU length of stay	12 (5–17)	15 (10–19)	0.13
Duration of mechanical ventilation	10 (5–15)	10 (7–19)	0.36
Disposition			
Home	18 (60%)	7 (29%)	0.14
Acute inpatient rehabilitation	5 (16%)	3 (13%)	
Skilled nursing	2 (6%)	4 (17%)	
Long-term acute care	3 (10%)	3 (13%)	
Mortality	2 (6%)	7 (29%)	<0.001[a]

[a]$p < 0.05$.
All values are reported as *n* (%) or median (interquartile range).

symptom onset) than the early cohort. Additionally, patients in the late cohort used more self-prone positioning prior to intubation, indicating likely an active effort to delay intubation on the part of patients or providers.

A recent article by Zhang et al (13) did note that mortality was the highest among those who were intubated more than 2 days after their presentation to the hospital. A similar study on respiratory mechanics found no difference in lung mechanics or mortality

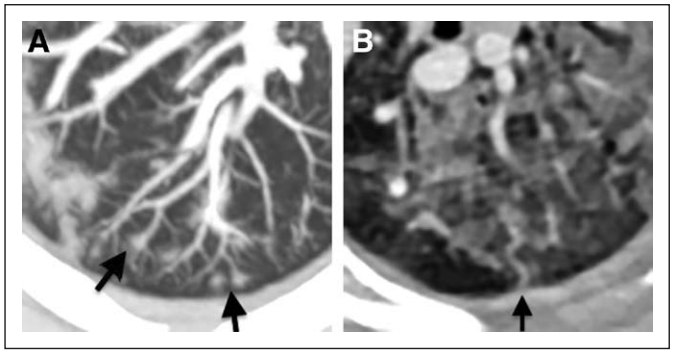

Figure 1. Representative computed tomographic radiographic images of pulmonary vascular dilatations demonstrating abnormal pulmonary vascular morphology. A, Axial maximal intensity projection (MIP) image of the right lower lobe shows small nodules (*arrows*) at the terminal end of multiple vascular structures. B, Axial MIP image of the left lower lobe shows a dilated and tortuous vascular structure (*arrow*) extending to the pleural surface.

among early and late intubation cohorts, but notably referenced timing of intubation as the time from ICU admission to intubation. This group defined the late cohort as any patient intubated greater than 24 hours after ICU admission (1). A separate study that defined intubation as time from hospital admission found that their late cohort (median of 4 d from admission) had worse lung mechanics than their early cohort (2). This stands in contrast to our findings that demonstrated no difference in ventilatory mechanics, but a significantly higher DSR in the late intubation cohort.

Our finding of significantly elevated DSR, in the context of preserved respiratory mechanics, with the late intubation cohort is of particular interest. There has been extensive discussion of COVID-19-associated coagulopathy, intussusceptive angiogenesis, and the implications of pulmonary microthrombi on unique C-ARDS pathophysiology (9, 10, 14, 15). Upon analysis of the radiographic evidence, we found that the late intubation cohort had more dilated and tortuous peripheral vessels than the early intubation cohort. As described by Patel et al (10), these findings may be suggestive of pulmonary thrombotic angiopathy. Interestingly, among the studied patients, there were more acute pulmonary emboli diagnosed in the early intubation cohort than the late intubation cohort. These findings, when considered together, may suggest that pulmonary microangiopathy, as appreciated by peripheral vascular dilatations on CT scans, is driving the increased dead space fractions in the late cohort. One possibility is that the increased time to intubation may allow for more time for development of microthrombi, thereby increasing the DSR. Another hypothesis is that increased vascular shear stress from the intense unchecked respiratory effort in the late cohort may contribute to pulmonary microthrombosis and an increase in dead space, a form of vascular patient-induced lung injury (8).

Earlier literature has supported the use of low-tidal volume ventilation in the management of patients with ARDS to prevent volume-induced lung injury and improve mortality (16). Although P-SILI remains a theoretical compilation of intense unchecked intrathoracic respiratory swings, the mechanism of this purported injury is unclear and may be proportional to alveolar injury or pulmonary vascular shear stress. With the increased reported frequency and complication of pulmonary microangiopathy, cadaveric intussusceptive angiogenesis, and vascular thrombotic complications with COVID-19, delayed intubation and subsequent increased vascular shear stress may promote this unique pathophysiologic injury in C-ARDS. This may

TABLE 4.
Computed Tomography Findings Among Subjects With Available Imaging

CT Angiography–Pulmonary Embolism Radiographic Findings		
Finding	**Early Intubation Cohort, *n* = 6**	**Late Intubation Cohort, *n* = 4**
Pulmonary embolism	6 (85%)	1 (25%)
Segments with dilated tortuous peripheral vessels	2 (0.8–4.5)	5 (2.5–6.8)
Number of segments/d from symptom onset to CT (segments/d)	0.07 (0.2–0.5)	0.26 (0.2–0.6)

All values are reported as *n* (%) or median (interquartile range). Findings were characterized based on presence of radiographically confirmed macrovascular embolic material or radiographically confirmed tortuous dilated peripheral vessels. The number of dilated segments recorded were standardized to the number of days between symptom onset and date of image acquisition.

be supported by our findings of preserved lung mechanics in the setting of increased DSR and radiographic pulmonary vascular dilatation/tortuosity in the late intubation cohort. As such, early intubation and low-tidal volume ventilation may prevent this process and impact mortality. This hypothesis remains a challenge to be studied prospectively, as randomization to an early versus late intubation strategy may prove technically and ethically challenging. As it stands, in light of no randomized trials, there likely remains clinical equipoise as to whether to intubate early to prevent P-SILI and sudden decompensation or to delay by the use of HFNC or NIV.

The significant limitations of this study are the size and retrospective nature. Furthermore, confounding by indication is another limitation as the decision to intubate was likely based on clinical factors and individual practitioner assessment not typically gleaned from retrospective review or SOFA scores. As such, there may be intrinsic differences between the patients who were intubated early compared with later in their hospital course. For instance, the higher frequency of tobacco users, patients with chronic kidney disease, and patients with hypertension in the late intubation cohort likely introduces confounding in the mortality outcome assessment. There is also reporter bias with regard to patient reported date of symptom onset that may impact internal validity. Additionally, there is selection bias in our radiographic evaluation as these images were obtained as part of clinical practice and likely selects for a population with suspicion for pulmonary vascular dysfunction.

CONCLUSIONS

As our approaches to treatment of COVID-19 continue to evolve, the decision of timing of intubation remains paramount. Although noninvasive ventilation may allow for delaying intubation, it is possible that there are downstream effects of delayed intubation that should be considered.

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REFERENCES

1. Hernandez-Romieu AC, Adelman MW, Hockstein MA, et al; Emory COVID-19 Quality and Clinical Research Collaborative: Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: A single-center cohort study. *Crit Care Med* 2020; 48:e1045–e1053
2. Pandya A, Kaur NA, Sacher D, et al: Ventilatory mechanics in early vs late intubation in a cohort of COVID-19 patients with acute respiratory distress syndrome: A single center's experience. *Chest* 2020; 159:653–656
3. Richardson S, Hirsch JS, Narasimhan M, et al; the Northwell COVID-19 Research Consortium: Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA* 2020; 323:2052–2059
4. Agarwal A, Basmaji J, Muttalib F, et al: High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: Systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. *Can J Anaesth* 2020; 67:1217–1248
5. Gattinoni L, Chiumello D, Caironi P, et al: COVID-19 pneumonia: Different respiratory treatments for different phenotypes? *Intensive Care Med* 2020; 46:1099–1102
6. Marini JJ, Gattinoni L: Management of COVID-19 respiratory distress. *JAMA* 2020; 323:2329–2330
7. Arnal JM, Chatburn R: Paying attention to patient self-inflicted lung injury. *Minerva Anestesiol* 2019; 85:940–942
8. Grieco DL, Menga LS, Eleuteri D, et al: Patient self-inflicted lung injury: Implications for acute hypoxemic respiratory failure and ARDS patients on non-invasive support. *Minerva Anestesiol* 2019; 85:1014–1023
9. Ackermann M, Verleden SE, Kuehnel M, et al: Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med* 2020; 383:120–128
10. Patel BV, Arachchillage DJ, Ridge CA, et al: Pulmonary angiopathy in severe COVID-19: Physiologic, imaging, and hematologic observations. *Am J Respir Crit Care Med* 2020; 202:690–699
11. Beitler JR, Sands SA, Loring SH, et al: Estimating dead-space fraction for secondary analyses of acute respiratory distress syndrome clinical trials. *Crit Care Med* 2015; 43:1026–1035
12. Sinha P, Fauvel NJ, Singh S, et al: Ventilatory ratio: A simple bedside measure of ventilation. *Br J Anaesth* 2009; 102:692–697
13. Zhang Q, Shen J, Chen L, et al: Timing of invasive mechanic ventilation in critically ill patients with coronavirus disease 2019. *J Trauma Acute Care Surg* 2020; 89:1092–1098
14. Mihaila RG, Dragos Mihaila M. Coagulation disorders in SARS-CoV-2 infection. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2020; 164:226–235
15. Iba T, Connors JM, Levy JH: The coagulopathy, endotheliopathy, and vasculitis of COVID-19. *Inflamm Res* 2020; 69:1181–1189
16. Ney L, Kuebler WM: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury. *N Engl J Med* 2000; 343:812–814