CORRESPONDENCE

Inspiratory Effort and Lung Mechanics in Spontaneously Breathing Patients with Acute Respiratory Failure due to COVID-19: A Matched Control Study

To the Editor:

A great debate has started as to whether acute respiratory failure (ARF) induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease [COVID-19]) should be classified as a classic form of acute respiratory distress syndrome (ARDS) or a subtype of lung injury with different pathophysiological characteristics (1) and mechanisms of progression (2). The magnitude of inspiratory effort correlated with the need to switch to invasive ventilation in patients without COVID-19 suggest that self-inflicted lung injury could play a role (3).

We aimed to describe and compare the inspiratory effort (primary outcome) and the breathing pattern of spontaneously breathing patients with ARF due to COVID-19 and historically matched patients without COVID-19, either type a candidate for noninvasive mechanical ventilation (NIV).

Patients with COVID-19 were treated at the Respiratory Intensive Care Unit and the Intensive Care Unit of the University Hospital of Modena (from August 1, 2020, to March 15, 2021) and 1:1 propensity matched (by Pa_{O_2}/FI_{O_2} ratio, age, body mass index, and Sequential Organ Failure Assessment score) with non–COVID-19 patients extracted from our dataset (period 2016 to 2021). The logit of the score was taken with a caliper of 0.2 to maximize the number of patients without compromising the match. All patients were in a similar phase from onset of ARF, unable to maintain $Sa_{O_2} > 92\%$ despite optimized high-flow oxygen, and thus were candidates to receive NIV according to local protocol. The study was conducted in accordance with the local "AVEN Ethics Committee" approval (protocol 4485/CE) and represents a report of ancillary data of a registered protocol (www. clinicaltrials.gov [NCT03826797]).

On admission, demographics, clinical characteristics and severity, respiratory function, and peripheral blood lactate and D-dimer concentrations were recorded.

A nasogastric tube with pressure transducer and monitoring system (NutriVent and OptiVentTM, SIDAM, Mirandola-I) to record swings in esophageal pressure (Pes) and dynamic transpulmonary pressure (PL) was placed as previously described (3). For recording, we always referred to ΔPes and ΔPL from the end-expiratory level, calculated as recommended (4). Expiratory tidal volume (VTE) was obtained by numerical integration of the flow signal and adjusted to the predicted body weight (in kilograms).

The VTE/ΔPL ratio was measured as a surrogate for lung compliance ("dynamic compliance"). A simplified surrogate of mechanical power ("dynamic mechanical power") was calculated as $0.098 \times RR \times VTE \times (\Delta PL + \text{positive end-expiratory pressure})$, where RR represents respiratory rate (5).

Measures were recorded for patients of both groups under standardized conditions with unassisted breathing (5 min long) and then 2 hours after starting NIV (Engström Carestation [GE Healthcare]). Pressure support was started at 10 cm H_2O and then adjusted according to Carteaux and colleagues (6) to target a peripheral oxygen saturation as measured by pulse oximetry >92% with a delivered $FI_{O_2} < 0.7$. Endotracheal intubation rate and 28-day death rate were recorded.

The Student's *t* test assessed the between-group difference when data were distributed normally; otherwise, the Mann-Whitney *U* test was used. A comparison between dichotomous variables was performed with the χ^2 test or Fisher exact test. ANOVA was used to test as an interaction for whether the change in physiological variables 2 hours after NIV was different between groups.

Table 1 shows the characteristics of patients at admission and the clinical outcomes. Compared with the non–COVID-19 group, patients with COVID-19 before NIV showed lower values of inspiratory effort as assessed by ΔPes (Figure 1). Shown are baseline values of lung mechanics, RR, $\dot{V}E$, VTE, and dynamic mechanical power at baseline and 2 hours after NIV are resumed (Table 1). The COVID-19 group showed lower values of RR ($P < 0.001$), VTE ($P = 0.003$), $\dot{V}E$ ($P < 0.001$), and dynamic mechanical power ($P < 0.001$) and higher dynamic compliance ($P < 0.001$) compared with the non–COVID-19 group. After NIV, a reduction in ΔPes and RR and an increase in dynamic mechanical power was reported for both groups, whereas no change was noted in either dynamic compliance or VTE. Despite there being no group interactions or changes in the physiological variables after NIV, ΔPL showed a significant increase in the COVID-19 group. In this group, the baseline value of dynamic mechanical power was considerably lower than in the non–COVID-19 group (27 vs. 95 J/min, $P < 0.0001$) and was significantly increased following NIV. This may suggest an unfavorable interaction between kinetic energy transferred from the respiratory muscles and the NIV to the lungs of these patients, at least early. Nevertheless, the absolute value of dynamic mechanical power was lower in patients with COVID-19 than in non–COVID-19 patients.

To our knowledge, this is the first report assessing inspiratory effort and respiratory mechanics in spontaneously breathing patients with COVID-19 developing ARF. At their early onset of ARF, these patients showed different mechanical characteristics and breathing patterns when compared with non–COVID-19 patients.

It has been speculated that the progression across COVID-19 may be triggered by excessive inspiratory drive activation (7). We have previously found that patients with moderate to severe ARDS exhibited very high inspiratory effort—even early during NIV—which was associated with unfavorable outcomes (3). Because the mean arterial pH was 7.48 in both groups, patients with COVID-19 also appeared to have a (relatively) high respiratory drive. However, the inspiratory effort of patients with COVID-19 was lower than in non–COVID-19 patients, thus suggesting a mismatch between lung mechanics and hypoxia, at variance with the typical form of ARDS. Indeed, a different lung morphology, as compared with ARDS, might explain this: the

Table 1. Characteristics of the Study Groups at Inclusion, Ventilatory Settings, and Clinical Outcome and Mechanical Variables before and after NIV

Clinical Variables	COVID-19 (n = 30)	Non–COVID-19 (n = 30)	P Value
Age, yr	68 (57–77)	68 (57–78)	0.9
Sex, M	23 (77)	22 (73)	0.9
BMI, kg/m^2	24 (21–27)	24 (20–26)	0.9
Charlson index score	3 (2–4)	4 (2–5)	0.1
Kelly scale score	1 (1–1)	1 (1–1)	0.9
SOFA score	3 (3–4)	3 (3–4)	0.9
Pa_{O_2}/Fi_{O_2}, mm Hg*	127 (100–138)	124 (100–133)	0.9
Pa_{O_2}/Fi_{O_2} 2 h after NIV, mm Hg	133 (118–155)	139 (119–158)	0.4
pH	7.48 (7.46–7.5)	7.48 (7.44–7.5)	0.7
pH after NIV	7.45 (7.44–7.46)	7.46 (7.43–7.48)	0.5
Pa_{CO_2}, mm Hg	33 (30–38)	34 (30–40)	0.7
Pa_{CO_2} after NIV	35 (32–37)	35 (32–36)	0.7
Blood lactate, mmol/L	1 (0.7–1.2)	1.7 (1–2.2)	0.001
Serum creatinine, mg/dl	0.7 (0.6–0.9)	0.7 (0.5–0.9)	0.8
D-dimer, mg/dl†	1,310 (862–9,400)	815 (540–1,233)	0.01
PEEP, cm H$_2$O†	10 (8–10)	10 (8–11)	0.7
PSV, cm H$_2$O†	12 (10–12)	12 (10–16)	0.2
ETI	9 (30)	11 (37)	0.8
28-d mortality	6 (20)	5 (17)	0.9

Mechanical Variables	Baseline	2 Hours after NIV	P Value	Baseline	2 Hours after NIV	P Value	Interaction Test (ANOVA)
ΔPes, cm H$_2$O	12.5 (11.8–17.3)	7.6 (6–10)	<0.0001	32 (25–38)	18 (12–34)	<0.0001	0.1
ΔPL, cm H$_2$O	12.5 (11.8–17.3)	18.4 (16.9–21.3)	<0.0001	32 (25–38)	32 (26–43)	0.1	0.1
RR, breaths/min	28 (25–30)	24 (21–26)	<0.0001	35 (30–41)	31 (24–38)	0.02	0.1
V̇E, L/min	20 (17–23)	18 (15–22)	0.1	27 (23–32)	24 (20–28)	0.004	0.6
VTE, ml/kg of PBW	9.2 (8.1–10.3)	10.1 (8.7–11.2)	0.3	10.9 (9.3–12)	10.2 (9.9–12)	0.8	0.6
Dynamic compliance, ml/cm H$_2$O	55 (40–69)	41 (31–52)	0.1	25 (19–31)	21 (16–34)	0.7	0.2
Dynamic mechanical power, J/min	27 (19–40)	56 (41–60)	<0.0001	95 (68–107)	102 (66–130)	0.1	0.2

Definition of abbreviations: BMI = body mass index; COVD-19 = coronavirus disease; ETI = endotracheal intubation; IQR = interquartile range; NIV = noninvasive mechanical ventilation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; Pes = esophageal pressure; PL = dynamic transpulmonary pressure; PSV = pressure support value; RR = respiratory rate; SOFA = Sequential Organ Failure Assessment; VTE = expiratory tidal volume.
Data are presented as number (percentage) for dichotomous values or median (IQR) for continuous values.
*The values of the Pa_{O_2}/Fi_{O_2} ratio used for matching these groups as well as pH and P_{CO_2} values were those measured during high-flow nasal oxygen (see inclusion criteria earlier) immediately before starting NIV.
†PEEP and PSV values reported were those measured during the first 2 hours of NIV.

higher presence of areas with a low V̇/Q̇ ratio (i.e., ground glass = poorly aerated tissue with higher compliance) as compared with true shunted areas (atelectasis = consolidations with lower compliance) may be the basis of these findings. This study showed that, when spontaneous breathing is preserved, the dynamic compliance of the respiratory system is twice as high in patients with COVID-19 compared with the matched non–COVID-19 patients; furthermore, the abnormally elevated mean D-dimer value found in patients with COVID-19 (Table 1) suggests microvasculature involvement in the mechanism of ARF.

Nevertheless, previous reports (8, 9) led to the recommendation of similar ventilatory strategies in patients with hypoxemic ARF, without any regard as to whether they follow COVID-19 or non–COVID-19 underlying conditions (10). At least in the early phase of ARF, the magnitude of inspiratory effort in patients with COVID-19 is lower than in non–COVID-19, probably limiting the likely significance of self-inflicted lung injury. Indeed, a simple surrogate marker of mechanical power was considerably lower in patients with COVID-19. Although the application of NIV resulted in

a significant reduction of inspiratory effort and RR (Table 1), ΔPL increased, thus calling into question the optimal time to start ventilation.

Our study suffers from several limitations. First, it represents an exploratory analysis with no sample size assessment, a limited number of patients, and a monocentric design. Second, the higher baseline blood lactate value in the non–COVID-19 group may reflect a difference in terms of balance from oxygen delivery to tissue metabolic needs, with a potential influence on the breathing pattern. An elevated value of lactic anions as a nonmechanical factor, even in the absence of blood acidosis, might have boosted the ventilatory response, influencing the different behavior between groups. Third, the observational nature of the study design does not allow us to draw firm conclusions about respiratory response to NIV application. Nevertheless, we believe that this preliminary observation supports the implementation of continuous monitoring of the patient's inspiratory effort during episodes of hypoxemic ARF. In contrast with non–COVID-19 patients, the findings indicate a limited inspiratory effort in the early phase of ARF in patients with
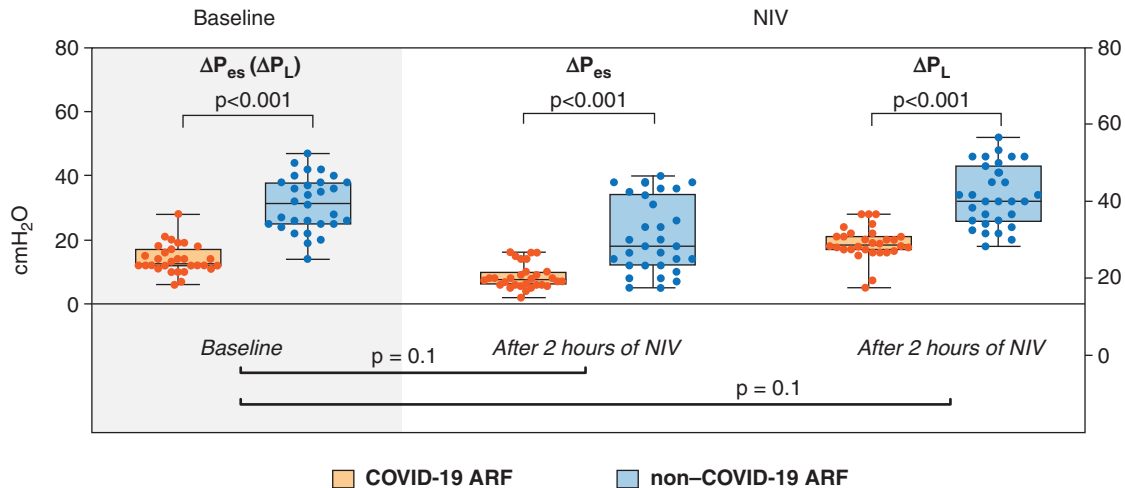
Figure 1. Measured individual values of change in esophageal pressure (ΔPes) and change in dynamic transpulmonary pressure (ΔPL) in the matched study groups at baseline and 2 hours after initiating noninvasive mechanical ventilation (NIV). No statistical difference was found when testing as an interaction for whether the change of ΔPes and ΔPL 2 hours after starting NIV was different between coronavirus disease (COVID-19) and non–COVID-19 ARF ($P = 0.1$ and $P = 0.1$, respectively). ARF = acute respiratory failure.

COVID-19, thus suggesting that caution should be taken when considering early endotracheal intubation to anticipate protective mechanical ventilation in these individuals. ∎

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Rodin's Thinker: An Alternative Position in Awake Patients with COVID-19

To the Editor:

Prone positioning is indicated in invasively ventilated patients with acute respiratory distress syndrome and coronavirus disease (COVID-19) (1, 2). It improves $\dot{V}/\dot{Q}$ matching and oxygenation while allowing for greater lung protection (3)

Because of the high influx of patients, heavily burdening ICU capacities during the COVID-19 pandemic, clinicians worldwide have sought strategies to avoid invasive ventilation. The use of prone positioning in awake, nonintubated, spontaneously breathing patients (possibly combined with noninvasive respiratory support) has been investigated by several groups. Awake prone positioning is a feasible strategy and is well tolerated by most patients, with a clear benefit to oxygenation, although the effect on outcome is still unclear (4–6).

However, a significant number of patients, ranging between 8.9% and 63.3%, are unable to tolerate this position (4–6). Moreover, a recent study investigating the use of a patient-directed prone positioning protocol was stopped early owing to poor protocol adherence (7).

In a context characterized by a lack of resources, we therefore sought an alternative strategy that would retain the pathophysiological benefits of prone positioning in awake patients while being more tolerable. We began to invite patients to lie chest forward on a flat surface while sitting (Figure 1). This position is reminiscent of the famous sculpture "The Thinker" by Auguste Rodin (1840–1917) (Figure 1A), and we therefore named it "Rodin's position," although it is better known as "tripod position" (8).

Methods

Patient population. We retrospectively reviewed the records of patients admitted to respiratory high-dependency units at San Gerardo Hospital (Monza, MB, Italy) between November 1, 2020, and January 15, 2021, during the second COVID-19 wave. The local protocol was to place all patients with COVID-19 acute respiratory distress syndrome in Rodin's position for at least 3 hours daily. Data were collected in a local online registry as part of the STORM study (Spallanzani Institute approval number 84/2020; NCT04424992), which did not include the present evaluation as a prespecified endpoint. Patients' consent was waived. Patients were enrolled if they were receiving noninvasive respiratory support and had undergone at least 3 hours in Rodin's position. Lack of a complete set of arterial blood gases within a specified time range (*see* what follows) was the only exclusion criterion.

Study protocol. Patients were invited to sit on a chair and rest their chest on a flat, elevated surface (i.e., their bed or a desk, at intermammillary line), thus placing the chest in a "semiprone" position (Figures 1B and 1C). The head was laid on the arms, elevated and crossed. Respiratory support variables (interface, $F_{I_{O_2}}$, and positive end-expiratory pressure [PEEP]) were left unchanged between the different time points.

We collected data on patient age; medical history C-reactive protein; platelet count; D-dimer; ventilation interface and parameters ($F_{I_{O_2}}$ and PEEP); arterial blood gas and respiratory rate in semisupine position before Rodin's position (supine$_{PRE}$), while in Rodin's position, and in semisupine position after Rodin's position (supine$_{POST}$); incidence of intubation; and death. Data were considered only in a window of 3 hours before supine$_{PRE}$ and after supine$_{POST}$.

Statistical analysis. Data are described as number (percentage) for categorical variables and as mean $\pm$ SD or median (interquartile range) for continuous variables, depending on their distribution. Normality was assessed using the Shapiro-Wilk test. A one-way ANOVA for repeated measures was performed to compare arterial blood gas values and respiratory rates at the three different time points.

Results

During the study period, 147 patients were admitted to the respiratory high-dependency units at San Gerardo Hospital. Of these, 37 patients did not undergo Rodin's position—it was not indicated by clinicians for 34 patients (26 patients too mild, 4 bleeding risk, and 4 admitted for palliation), and it was not tolerated by 3 patients (2 had psychiatric disorders, and 1 had dementia). A total of 110 patients underwent at least one cycle of Rodin's position; 85 were excluded from the study (no arterial blood gas at all specified time points), and a total of 25 patients were included in the present analysis.

Most patients were male, aged 65.0 ± 8.6 years; about half (44%) had hypertension, 12% had diabetes, and 12.0% had a malignancy. All patients were receiving continuous positive airway pressure by helmet, with an $F_{I_{O_2}}$ of 60 (50–77.5), a PEEP of 10 cm H_2O (8–10), and a baseline $Pa_{O_2}/F_{I_{O_2}}$ of 146.2 ± 62.7 mm Hg. Rodin's position was initiated 4.2 ± 3.4 days after hospitalization, and patients underwent 5.4 ± 3.4 cycles. No clinically relevant side effects were reported. Of these 25 patients, 18 also underwent cycle(s) of prone position (in 9 cases before the first Rodin cycle), but not during the supine$_{PRE}$-to-