ANESTHESIOLOGY

Early Physiologic Effects of Prone Positioning in COVID-19 Acute Respiratory Distress Syndrome

Francesco Zarantonello, M.D., Nicolò Sella, M.D., Tommaso Pettenuzzo, M.D., Giulio Andreatta, M.D., Alvise Calore, M.D., Denise Dotto, M.D., Alessandro De Cassai, M.D., Fiorella Calabrese, M.D., Annalisa Boscolo, M.D., Paolo Navalesi, M.D.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The use of prone positioning to treat COVID-19 critically ill mechanically ventilated intubated patients with acute respiratory distress syndrome is now universally accepted. In non–COVID-19 acute respiratory distress syndrome, available evidence suggests it enhances homogeneous distribution of ventilation between dorsal and ventral regions of the lung without significant changes in perfusion.
- Its physiologic effects in COVID-19 have not been systematically investigated.

What This Article Tells Us That Is New

- Using electrical impedance tomography, the authors assessed the percent variation of ventilation-perfusion matching before and after 90 min of the first cycle of prone positioning in 30 intubated, sedated, and paralyzed adult COVID-19 acute respiratory distress syndrome patients along with additional secondary pulmonary physiologic endpoints.
- Overall, prone positioning improved ventilation-perfusion matching significantly with a median difference of 8% with no change in dorsal perfusion. Lung overdistention was also significantly reduced.
- Pao_2/fraction of inspired oxygen improved overall, although 30% of the cohort were classified as nonresponders (less than 20% increase from baseline).

ABSTRACT

Background: The mechanisms underlying oxygenation improvement after prone positioning in COVID-19 acute respiratory distress syndrome have not been fully elucidated yet. The authors hypothesized that the oxygenation increase with prone positioning is secondary to the improvement of ventilation-perfusion matching.

Methods: In a series of consecutive intubated COVID-19 acute respiratory distress syndrome patients receiving volume-controlled ventilation, the authors prospectively assessed the percent variation of ventilation-perfusion matching by electrical impedance tomography before and 90 min after the first cycle of prone positioning (primary endpoint). The authors also assessed changes in the distribution and homogeneity of lung ventilation and perfusion, lung overdistention and collapse, respiratory system compliance, driving pressure, optimal positive end-expiratory pressure, as assessed by electrical impedance tomography, and the ratio of partial pressure to fraction of inspired oxygen (Pao_2/Fio_2; secondary endpoints). Data are reported as medians [25th to 75th] or percentages.

Results: The authors enrolled 30 consecutive patients, all analyzed without missing data. Compared to the supine position, prone positioning overall improved ventilation-perfusion matching from 58% [43 to 69%] to 68% [56 to 75%] ($P = 0.042$), with a median difference of 8.0% (95% CI, 0.1 to 16.0%). Dorsal ventilation increased from 39% [31 to 43%] to 52% [44 to 62%] ($P < 0.001$), while dorsal perfusion did not significantly vary. Prone positioning also reduced lung overdistension from 9% [4 to 11%] to 4% [2 to 6%] ($P = 0.025$), while it did not significantly affect ventilation and perfusion homogeneity, lung collapse, static respiratory system compliance, driving pressure, and optimal positive end-expiratory pressure. Pao_2/Fio_2 overall improved from 141 [104 to 182] mmHg to 235 [164 to 267] mmHg ($P = 0.019$). However, 9 (30%) patients were nonresponders, experiencing an increase in Pao_2/Fio_2 less than 20% with respect to baseline.

Conclusions: In COVID-19 acute respiratory distress syndrome patients, prone positioning overall produced an early increase in ventilation-perfusion matching and dorsal ventilation. These effects were, however, heterogeneous among patients.

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Patients with novel COVID-19 associated acute respiratory distress syndrome (ARDS), despite sharing some features with non–COVID-19 ARDS,[1–4] may present clinical characteristics not completely explained by the typical ARDS pathophysiologic mechanisms.[5,6] In COVID-19 ARDS, alveolar injury is associated with severe pulmonary vascular disruption and small- and mid-sized pulmonary

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Francesco Zarantonello, M.D.: Institute of Anesthesia and Intensive Care, Padua University Hospital, Padua, Italy.

Nicolò Sella, M.D.: Institute of Anesthesia and Intensive Care, Padua University Hospital, Padua, Italy; Department of Medicine, University of Padua, Padua, Italy.

Tommaso Pettenuzzo, M.D.: Institute of Anesthesia and Intensive Care, Padua University Hospital, Padua, Italy.

Giulio Andreatta, M.D.: Department of Medicine, University of Padua, Padua, Italy.

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vessels thrombosis,[7,8] mainly ascribable to the COVID-19 related hypercoagulable state.[9]

Radiologic studies assessing lung ventilation and perfusion by subtraction computed tomography angiography showed a high prevalence of perfusion abnormalities, with hypoperfusion predominantly sited in areas of noninjured lungs, and hyperperfusion in the areas of ground-glass opacities, attributed to local inflammation.[10,11] Using electrical impedance tomography, in a small series of COVID-19 patients with ARDS, Mauri *et al.* reported a high rate of mismatched lung units, the extent of dead space exceeding that of shunt.[12] The same group had also found, in non–COVID-19 ARDS patients, the greater mismatch to be correlated with higher mortality.[13]

Prone positioning has been extensively used in COVID-19 ARDS. In a series of 1,057 COVID-19 intubated and mechanically ventilated patients, Langer *et al.* report that 648 patients (61%) received at least one cycle of prone positioning, which was effective in improving oxygenation in the majority of patients for whom data were available, but the underlying mechanisms remain unclear.[14] While in non–COVID-19 ARDS the prone position causes, in general, a more homogenous distribution of ventilation between the dorsal and ventral regions of the lung without significant changes in lung perfusion,[15,16] no definitive data are currently available for COVID-19 ARDS patients.

We previously described the case of one COVID-19 ARDS patient who showed, after only 60 min of prone positioning, improvement of the arterial partial pressure of oxygen to fraction of inspired oxygen ratio (Pao_2/Fio_2) associated with enhanced ventilation-perfusion matching.[17] Therefore, we hypothesized that in COVID-19 ARDS, arterial oxygenation increases with prone positioning consequent to an improvement of ventilation-perfusion matching, as suggested by a preliminary anecdotal observation.[17] To confirm this hypothesis, we designed this prospective observational study to evaluate the early response to the first cycle of prone positioning in intubated and mechanically ventilated COVID-19 ARDS patients.

Materials and Methods

Patients

The study, conducted in the intensive care unit (ICU) of the University Hospital of Padua (Padua, Italy), followed the "Strengthening the Reporting of Observational Studies in Epidemiology" statement guidelines for observational cohort studies[18] (Supplemental Digital Content, http://links.lww.com/ALN/C872). The study, approved by the local Institutional Ethical Committee (reference No. 4853AO20), was conducted in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained according to the national regulation.

We included all consecutive intubated, sedated, and paralyzed adult patients undergoing controlled mechanical ventilation because of ARDS[19] secondary to confirmed ARDS COVID-2 infection,[20] who were admitted between December 1, 2020, and April 1, 2021, and received at least one cycle of prone positioning[15] according to regional guidelines.[21] All patients received low-dose steroids[22] and intermediate doses of low-molecular-weight heparin.[23] All patients were studied in the course of the first cycle of prone positioning. Exclusion criteria were age less than 18 yr, and contraindications to prone positioning[15] and/or to electrical impedance tomography assessment.[24] Patients were considered prone-responders if they showed an increase in Pao_2/Fio_2 greater than 20% after 1 h of prone position.[25]

Endpoints

We assessed the effects determined by 90 min of prone position. Our primary endpoint was assessing the percent variation of ventilation-perfusion matching consequent to prone positioning, as evaluated by electrical impedance tomography. Secondary endpoints were the changes in the distribution and homogeneity of lung ventilation and perfusion, lung overdistention and collapse, respiratory system compliance, driving pressure, optimal positive end-expiratory pressure (PEEP), as assessed by electrical impedance tomography, and Pao_2/Fio_2.

Protocol and Measurements

The study protocol and variables are depicted in figure 1. No other interventions, such as pharmacologic interventions, bronchoscopic toilette, or physiotherapy, were allowed during the study period. Mechanical ventilation settings,[21] criteria for starting prone positioning,[21] electrical impedance tomography ventilation[12] and perfusion[17] measurements, and electrical impedance tomography PEEP titration technique[24] were all standardized. All patients were mechanically ventilated in volume-controlled mode, with tidal volume 6 ml/kg or less of ideal body weight, at constant inspiratory flow rate set to 60 l/min, and driving pressure maintained at 14 cm H_2O or lower.[21,26] All patients were sedated and under neuromuscular blockade to ensure no spontaneous breathing effort. PEEP was titrated by electrical impedance tomography during a 2-cm H_2O-step decremental PEEP trial from 28 cm H_2O to 8 cm H_2O after a 30 cm H_2O continuous positive airway pressure lung recruitment maneuver lasting 30 s, as previously described.[24,27] Briefly, PEEP was set identifying the intersection between the curves representing the cumulative percentage

Alvise Calore, M.D.: Department of Medicine, University of Padua, Padua, Italy.

Denise Dotto, M.D.: Department of Medicine, University of Padua, Padua, Italy.

Alessandro De Cassai, M.D.: Institute of Anesthesia and Intensive Care, Padua University Hospital, Padua, Italy.

Fiorella Calabrese, M.D.: Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy.

Annalisa Boscolo, M.D.: Institute of Anesthesia and Intensive Care, Padua University Hospital, Padua, Italy.

Paolo Navalesi, M.D.: Institute of Anesthesia and Intensive Care, Padua University Hospital, Padua, Italy; Department of Medicine, University of Padua, Padua, Italy.

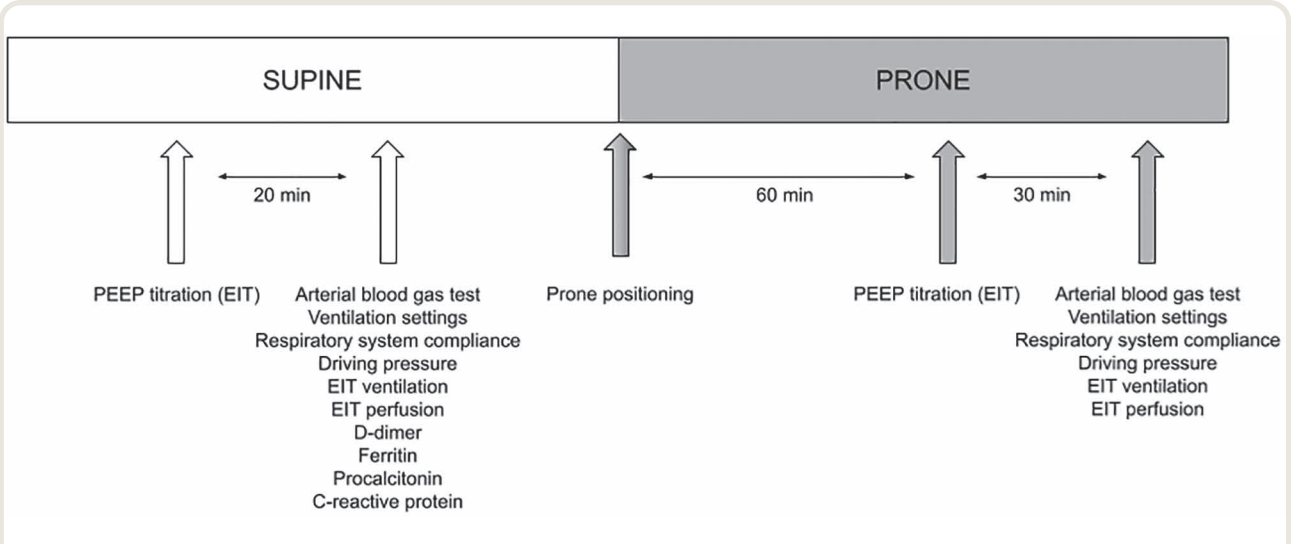

Fig. 1. Study protocol. ABG, arterial blood gas; PEEP, positive end-expiratory pressure.

of lung compliance loss due to either collapse or overdistension.[24,27] FIO_2 was set to maintain an arterial oxyhemoglobin saturation measured by pulse oximetry between 88% and 95%.[28] Plateau pressure and total PEEP were measured at points of zero flow during end-inspiratory and end-expiratory pauses, respectively.[26] Driving pressure was calculated as the difference between plateau pressure and total PEEP, while respiratory system quasi-static compliance was calculated as the ratio between tidal volume and driving pressure.[29]

Electrical impedance tomography measurements were obtained through Pulmovista 500 (Draeger, Germany), applying a 16-electrode belt around the patient's thorax in the transversal plane corresponding to the fifth intercostal space. The position of the electrical impedance tomography belt was marked with a dermographic pen to avoid belt displacement after turning patients prone.[24] For lung perfusion assessment, the indicator technique was used, as previously described in two case reports.[17,30] This technique has already been validated against positron emission tomography in an animal study.[31] Electrical impedance tomography images were continuously recorded at a sampling frequency of 50 Hz. After prone positioning, all measurements were repeated, as depicted in figure 1.

Electric Impedance Tomography Data Analysis

Both lung ventilation and perfusion-related impedance changes were analyzed through electrical impedance tomography pixel by pixel. In particular, the pixel tidal ventilation was calculated as the difference between end-inspiratory and end-expiratory impedance, and then lung pixels were classified as nonventilated if their tidal variation was 10% or less of the maximal pixel impedance variation.[12]

For PEEP titration, we estimated the variations of regional lung compliance during a decremental PEEP trial performed after maximal lung recruitment,[24] identifying the loss of compliance at the higher and lower PEEP as the consequence of alveolar overdistension and collapse, respectively. The PEEP value identified by the intersection between the electrical impedance tomography curves representing the cumulative percentage of compliance loss due to overdistension and collapse is defined as optimal PEEP, which assures the best compromise between the two conditions.[24,27]

The per-pixel perfusion was calculated after excluding pixels belonging to the cardiac area using a spatio-temporal approach that removed from the analysis the impedance signals due to the transit of the bolus inside the heart chambers. Pixels with an impedance drop signal 10% or less of the maximal pixel impedance variation were classified as nonperfused.[12]

The lung area was divided into the following zones, as previously described[13]:

(1) perfused area, defined by all perfused pixels;
(2) ventilated area, defined by all ventilated pixels;
(3) percent matched area, defined by all pixels that were both ventilated and perfused divided by the sum of ventilated and perfused pixels;
(4) percent dead space area, defined by all pixels that were ventilated, but not perfused, divided by the sum of ventilated and perfused pixels;
(5) percent shunt area, defined by all pixels that were perfused, but not ventilated, divided by the sum of ventilated and perfused pixels;
(6) percent total unmatched area (total mismatch), *i.e.*, the sum of shunt and dead space area;
(7) dead space to shunt ratio, *i.e.*, the ratio between dead space area and shunt area.[13]

The thorax was divided into two symmetrical zones, separated by a horizontal line that equally divides it into

ventral and dorsal areas. The following parameters were also calculated:

(a) dorsal ventilation, representing the percentage of total ventilated lung area that is located in the dorsal half of the thorax;
(b) dorsal perfusion, representing the percentage of total perfused lung area that is located in the dorsal half of the thorax;
(c) ventilation and perfusion homogeneity indices. The inhomogeneity index is a value that has been previously described and summarizes the inhomogeneity of lung ventilation and perfusion[32] and ranges from 1 to 0. The homogeneity index, calculated as 1 minus the inhomogeneity index, is easier to understand, with higher values representing more homogeneous lung ventilation and perfusion.

Statistical Analysis

A data analysis and statistical plan were written and filed with the study protocol approved by the local Institutional Ethical Committee before data were accessed. No sample size calculation was possible due to the lack of previous studies on the same main outcome. No imputation for missing data was applied, as all the analyzed cases were complete. Quantitative variables are expressed as median (interquartile range) and compared with the Wilcoxon–Mann–Whitney test. Categorical data are reported as absolute numbers and percentages and compared with the Fisher exact test. Changes between supine and prone positions are calculated and reported as medians and 95% CI. All statistical analyses were conducted with R version 4.0.5 (R Core Team, Austria).

Results

We enrolled 30 consecutive patients after a median of 10 [interquartile range, 7 to 13] days since symptom onset and 4 [interquartile range, 2 to 7] days since hospital admission. The study enrollment flowchart is presented in figure 2, while patients' baseline characteristics are reported in table 1. Twenty-four patients (80%) were discharged alive from the ICU, after a median stay of 16 [interquartile range, 10 to 24] days. No electrical impedance tomography belt repositioning was necessary between measurements, after turning patients prone.

The variations after prone positioning, as compared to baseline values in the supine position, are shown in table 2.

The physiologic effects of 90 min of prone position varied among individuals, as indicated by different behavior in two sample patients, as depicted in figure 3. However, as shown in figure 4, there was an overall significant increase of ventilation-perfusion matching from 58% [interquartile range, 43 to 69%] to 68% [interquartile range, 56 to 75%] ($P = 0.042$). Dead space area (40% [interquartile range, 27 to 55%] *vs.* 29% [interquartile range, 24 to 41%], for supine and prone position, respectively, $P = 0.103$) and shunt area (2% [interquartile range, 1 to 4%] *vs.* 1% [interquartile range, 0 to 3%], for supine and prone position, respectively, $P = 0.178$) did not vary between the two positions, while total mismatch area overall decreased from supine to prone (42% [interquartile range, 31 to 57%] *vs.* 32% [interquartile range, 25 to 43%], respectively, $P = 0.045$). Prone positioning increased the proportion of dorsal lung ventilation from 39% [interquartile range, 31 to 43%] to 52% [interquartile range, 44 to 62%] ($P < 0.001$; fig. 5A), while it did not affect dorsal perfusion (52% [interquartile range, 42 to 64%] *vs.* 57% [interquartile range, 50 to 61%], $P = 0.224$; fig. 5B). Also shown in table 2, the median electrical impedance tomography-based optimal PEEP was no different between supine and prone position (14 [interquartile range, 12 to 15] cm H_2O *vs.* 14 [interquartile range, 12 to 16] cm H_2O, respectively, $P = 0.086$). Individual data points are available as Supplemental Digital Content (http://links.lww.com/ALN/C872). Plateau pressure, driving pressure, and respiratory system quasi-static compliance did not show significant differences between supine and prone positions (fig. 6, A and B). The loss of lung compliance due to overdistension decreased with prone positioning from 9% [interquartile range, 4 to 11%] to 4% [interquartile range, 2 to 6%] ($P = 0.025$; fig. 6C), while no variation was observed with respect to the loss of compliance secondary to lung collapse (4% [interquartile range, 2 to 7%] *vs.* 7% [interquartile range, 4 to 9%], $P = 0.336$; fig. 6D).

Twenty-one patients (70%) were prone-responders.[25] The median Pao_2/Fio_2 increased from 141 [interquartile range, 104 to 182] mmHg to 235 [interquartile range, 164 to 267] mmHg ($P < 0.001$), while $Paco_2$ and pH were no different between supine (45 [interquartile range, 40 to 52] mmHg and 7.38 [interquartile range, 7.31 to 7.43], respectively) and prone (45 [interquartile range, 42 to 52] mmHg and 7.37 [interquartile range, 7.33 to 7.42], respectively) position ($P = 0.350$ and 0.611 for $Paco_2$ and pH, respectively). The oxygenation improvement allowed Fio_2 reduction from 0.6 [interquartile range, 0.4 to 0.9] to 0.5 [interquartile range, 0.4 to 0.6] ($P = 0.008$) after study protocol completion.

Discussion

In this prospective observational study, conducted in intubated and mechanically ventilated COVID-19 ARDS patients, we found that (1) prone position was associated with increased ventilation-perfusion matching; (2) turning patients prone increased dorsal ventilation and reduced lung overdistension, while it did not affect dorsal perfusion, lung collapse, driving pressure, and respiratory system quasi-static compliance; and (3) after 90 min of prone position, Pao_2/Fio_2 overall increased, with 70% of patients classified as prone-responders.[25]

In a recent multicenter observational study evaluating the effects of prone positioning in 78 patients with COVID-19 ARDS, Langer *et al.* reported 78% of patients experiencing

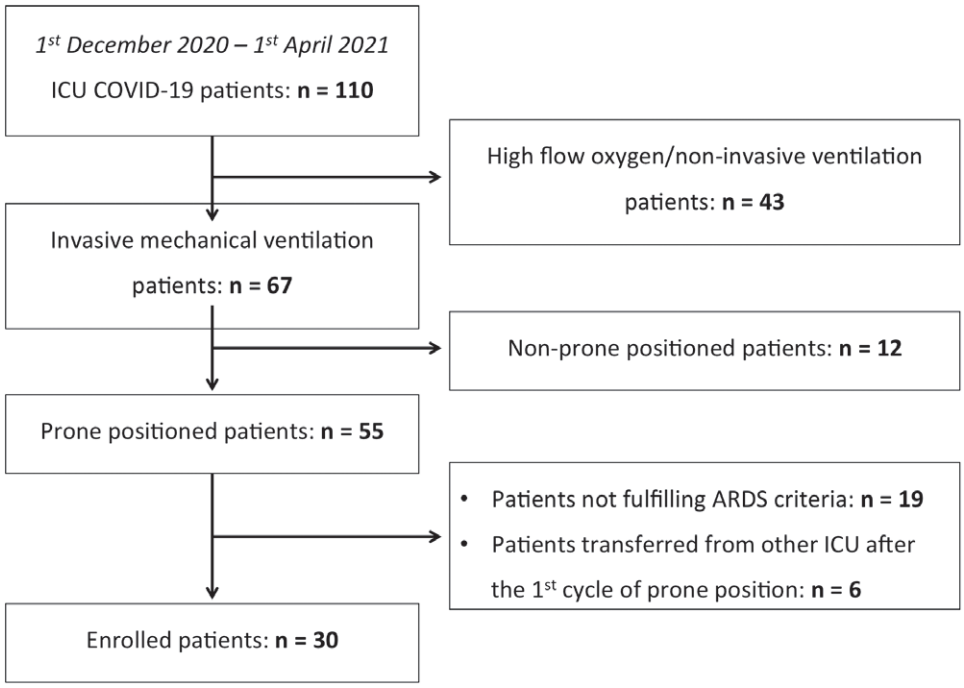

Fig. 2. Study enrollment flowchart. ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Table 1. Patients' Baseline Characteristics

Patients' Characteristics (n = 30)		Median [Interquartile Range] or n (%)
Demographic variables	Age (yr)	62 [53, 72]
	Weight (kg)	85 [77, 118]
	Body mass index (kg/m^2)	29 [25, 38]
	Sex (male, n, %)	22 (73%)
	Arterial hypertension (n, %)	13 (43%)
	COPD (n, %)	2 (7%)
	SOFA score	4 [3, 4]
	Days since symptoms onset*	10 [7, 13]
	Days since hospital admission	4 [2, 7]
	Days since intubation	0 [0, 1]
Laboratory and clinical data	C-reactive protein (mg/l)	100 [55, 180]
	Procalcitonin (µg/l)	0.16 [0.07, 0.52]
	D-dimer (µg/l)	434 [210, 1090]
	Ferritin (µg/l)	670 [616, 1530]
	Prone positioning cycle length (hours)	17.5 [14.2, 27.0]
Ventilator setting	Tidal volume (ml/kg ideal body weight)	5.6 [5.6, 6.0]
	Respiratory rate (breaths/min)	22 [20, 22]

*Symptoms compatible with severe acute respiratory syndrome COVID-2 infection were considered (cough, dyspnea, fever).
COPD, chronic obstructive pulmonary disease; SOFA, Sequential Organ Failure Assessment.

an increase in Pao_2/Fio_2 greater than or equal to 20 mmHg, without improving either driving pressure or respiratory system quasi-static compliance.[14] This finding led the authors to speculate that the main mechanism determining the improvement of arterial oxygenation during pronation of COVID-19 ARDS patients is not lung recruitment, but rather the improvement of the ventilation-perfusion matching.[14] In keeping with the results of that study[14] and of another previous investigation,[33] we also found that prone positioning was not associated with improvement of respiratory system quasi-static compliance or driving pressure, which were recently correlated with ICU mortality in COVID-19 ARDS

Table 2. Variations between Supine and Prone Positions

		Supine	Prone	*P* Value	Difference (Median and 95% CI)
Ventilator setting	FIO_2	0.6 [0.4, 0.9]	0.5 [0.4, 0.6]	0.008‡	–0.20 (–0.07 to –0.37)
	PEEP (cm H_2O)	14 [12, 15]	14 [12, 16]	0.086	1.0 (0.0 to 2.5)
Arterial blood gases	PaO_2 (mmHg)	80 [68, 92]	105 [85, 142]	< 0.001‡	30 (14 to 49)
	PaO_2/FIO_2 (mmHg)	141 [104, 182]	235 [164, 267]	0.019‡	86.9 (118.8 to 57.7)
	$PaCO_2$ (mmHg)	45 [40, 52]	45 [42, 52]	0.350	1.2 (–1.0 to 3.4)
	pH	7.38 [7.31, 7.43]	7.37 [7.33, 7.42]	0.611	0.00 (–0.02 to 0.01)
Respiratory mechanics	Plateau pressure (cm H_2O)	23 [20, 26]	23 [22, 26]	0.335	0.50 (–0.99 to 1.99)
	Driving pressure (cm H_2O)	11 [8, 11]	10 [9, 11]	0.656	0.0 (–1.0 to 0.5)
	Respiratory system quasi-static compliance (ml/cm H_2O)	40 [34.5, 47.8]	39.1 [34.5, 50.0]	0.948	0.1 (–4.3 to 3.6)
Electrical impedance tomography-based variables	Dorsal ventilation (%)	39 [31, 43]	52 [44, 62]	< 0.001‡	16 (10 to 20)
	Dorsal perfusion (%)	52 [42, 64]	57 [50, 61]	0.224	3 (–3 to 10)
	Global homogeneity index ventilation	0.48 [0.47, 0.52]	0.50 [0.48, 0.54]	0.103	0.02 (0.00 to 0.04)
	Global homogeneity index perfusion	0.14 [0.05, 0.27]	0.25 [0.10, 0.33]	0.077	0.07 (0.00 to 0.15)
	Matched area (%)	58 [43, 69]	68 [56, 75]	0.042‡	8.0 (0.1 to 16.0)
	Dead space area (%)	40 [27, 55]	29 [24, 42]	0.103	–6.6 (–15.8 to 1.3)
	Shunt area (%)	2 [1, 4]	1 [0, 3]	0.178	–0.8 (–2.2 to 0.3)
	Total unmatched area (%)	42 [31, 57]	32 [25, 43]	0.045‡	–7.8 (–16.0 to –0.1)
	Dead space to shunt ratio	24 [7, 85]	18 [10, 78]	0.350	–6.6 (–55.3 to 28.5)
	Lung compliance loss as assessed by electrical impedance tomography lung overdistension (%)	9 [4, 11]	4 [2, 6]	0.025‡	–3.5 (–7.4 to –0.5)
	Lung compliance loss as assessed by electrical impedance tomography lung collapse (%)	4 [2, 7]	7 [4, 9]	0.336	1.2 (–1.5 to 4.0)
Hemodynamic variables*	Heart rate (beats per minute)	78 [67, 84]	75 [70, 87]	0.803	–1 (–4 to 3)
	MAP (mmHg)	62 [61, 64]	62 [61, 65]	0.802	–1 (–2 to 1)
	Hypotension requiring norepinephrine † (n, %)	23 (76.7)	22 (73.3)	1.000	

Data are expressed as median [interquartile range].

*Hemodynamic variables were registered at the time of electrical impedance tomography perfusion assessment. †Norepinephrine was administered to assure a mean arterial pressure greater than 60 mmHg, with doses ranging from 0.05 to 0.2mcg/kg·min. ‡*P* values less than 0.05

FIO_2, fractional inspired oxygen tension; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure.

patients.[34] Nonetheless, since we did not separately measure lung and chest wall compliance, the latter known to decrease in prone position,[15] we cannot exclude that lung compliance actually improved, as also suggested by the increased dorsal ventilation and the reduced lung overdistension. Worth remarking, in agreement with Perier *et al.*,[35] electrical impedance tomography-based optimal PEEP value, as defined by the best compromise between lung overdistension and collapse, was no different between the supine and prone positions, further confirming the hypothesis by Langer *et al.*[14]

In keeping with Perier *et al.*, who assessed electrical impedance tomography perfusion in nine patients with COVID-19 ARDS,[36] we found that prone positioning did not alter the distribution of lung perfusion, which remained predominantly in the dorsal areas. However, different from Perier *et al.*,[36] who did not evaluate the total mismatch, we observed an increased ventilation-perfusion matching. Unlike Perier *et al.*,[36] who measured cardiac output to assess ventilation to perfusion ratio and reported a reduction in dead space, primarily consequent to changes in ventilation distribution in the ventral area, without a decrease in shunt, we did not find significant variations in both shunt and dead space between the supine and prone positions. Differences in the technique adopted and in the timing of assessment, and, worth remarking, a definitely larger sample size, may all contribute to explaining these discrepancies. Indeed, the baseline dead space values found in the current study are in keeping with those reported in a previous case series assessing shunt and dead space through electrical impedance tomography in the supine position.[12] Different from that study,[12] however, we found very low values of baseline shunt, likely ascribable to the fact that we included patients at an early stage of disease, when low ventilation-perfusion ratio due to the loss of regulation of perfusion and hypoxic vasoconstriction may be the main factor in determining hypoxemia, as already proposed by Gattinoni *et al.*[37]

In keeping with our previous observation describing the increased ventilation-perfusion matching after prone positioning in a single COVID-19 ARDS patient,[17] and supporting the hypothesis deriving from previous investigations,[14] the current study shows that an improvement in ventilation-perfusion matching rather than lung recruitment is the main mechanism for oxygenation amelioration in the prone position. It is important to remark, however, that the extent of ventilation-perfusion matching amelioration was just 10%, which might explain why we did not observe a concomitant reduction of $PaCO_2$, whose median baseline value, worth remarking, was not altered.

Despite the overall increase in ventilation-perfusion matching, our population shows a heterogeneous response

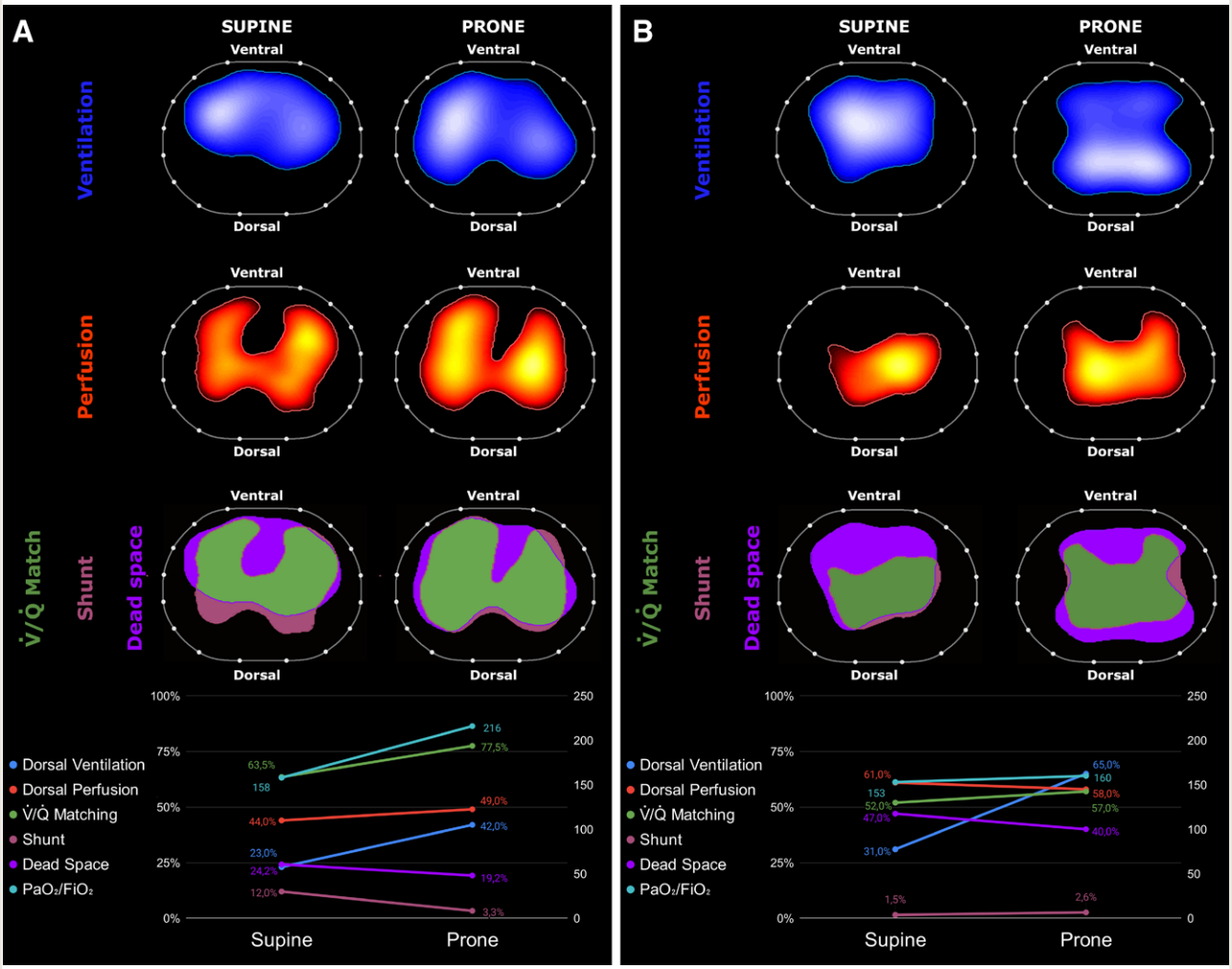

Fig. 3. Effects of prone positioning on ventilation and perfusion, as evaluated by electrical impedance tomography, in two representative patients. From top to bottom, lung ventilation (*blue-white gradient area*), perfusion *(red-yellow area*), and ventilation-perfusion (V̇/Q̇) matching are depicted. The *graph* at the bottom provides variations of dorsal ventilation and perfusion, V̇/Q̇ matching, shunt, dead space, and Pao_2/FIo_2 values in the supine and prone positions. The first patient (*A*) exhibits improved Pao_2/FIo_2 and increased distribution of ventilation to the dorsal regions, resulting in improvement of V̇/Q̇ matching. The second patient (*B*) does not improve Pao_2/FIo_2 and shows no increase in V̇/Q̇ matching despite increased dorsal ventilation. FIo_2, fractional inspired oxygen tension.

to pronation among patients, as shown in figures 3, 4, and 5, thus suggesting other potential mechanisms underlining the improvement in oxygenation secondary to prone positioning. Although the COVID-19 pandemic led some authors to question the definition of ARDS itself,[38,39] similar to *"typical"* ARDS [4], COVID-19 ARDS is *per se* a heterogeneous disorder combining various pathologic features (tracheobronchitis, diffuse alveolar damage, and vascular injury).[7] If on the one hand the pulmonary vessels are characterized by inflammation, vasculitis, microthrombi, and, in some cases, macrothrombi, on the other hand, viral infection in areas of ongoing active injury contributes to persistent and temporally heterogeneous lung damage.[7]Virus-related pathophysiologic injuries affect to varying extents both alveoli and pulmonary vasculature, resulting in different pathologic phenotypes.[8] Such heterogeneity cautions ICU physicians on basing COVID-19 treatments on simplistic phenotypic models and highlights the role of a more comprehensive and individualized ventilatory management.

A point of strength of our study is that our patient population is quite homogenous, as it includes patients (1) with moderate ARDS due to the same etiology, (2) at the first cycle of prone positioning, (3) in the first day after endotracheal intubation (thus justifying the moderate severity of the disease), and (4) enrolled after a maximum of 11 days since hospital admission, thereby limiting (a) the risk of confounding factors, such as ventilator-associated pneumonia, and (b) the potential loss of prone responsiveness observed in the advanced phases of the disease.[40]

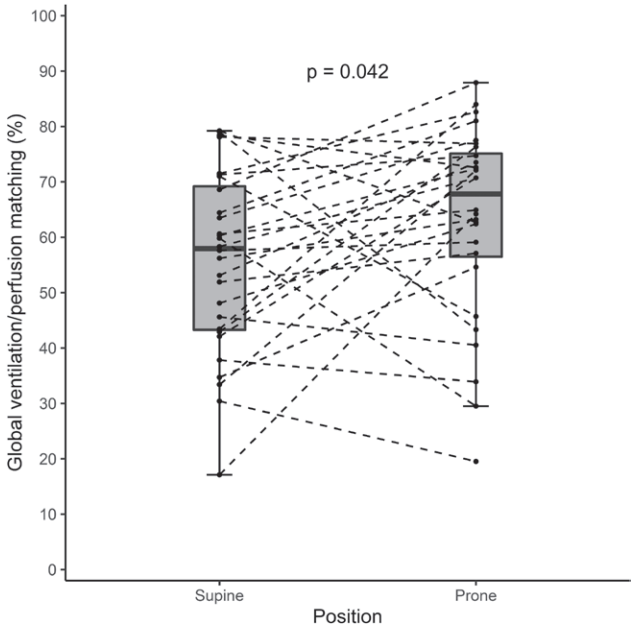

Fig. 4. Percentage of ventilation-perfusion matching, as assessed by electrical impedance tomography, in the supine and prone position. The *boxplot*'s hinges represent the first and third quartile of the data, the *upper and lower whiskers* indicate the highest and lowest values within 1.5 times the interquartile range, and the *bold line* indicates the median. Individual data points are also plotted, with *dashed lines* connecting the two measurements in the supine and prone position.

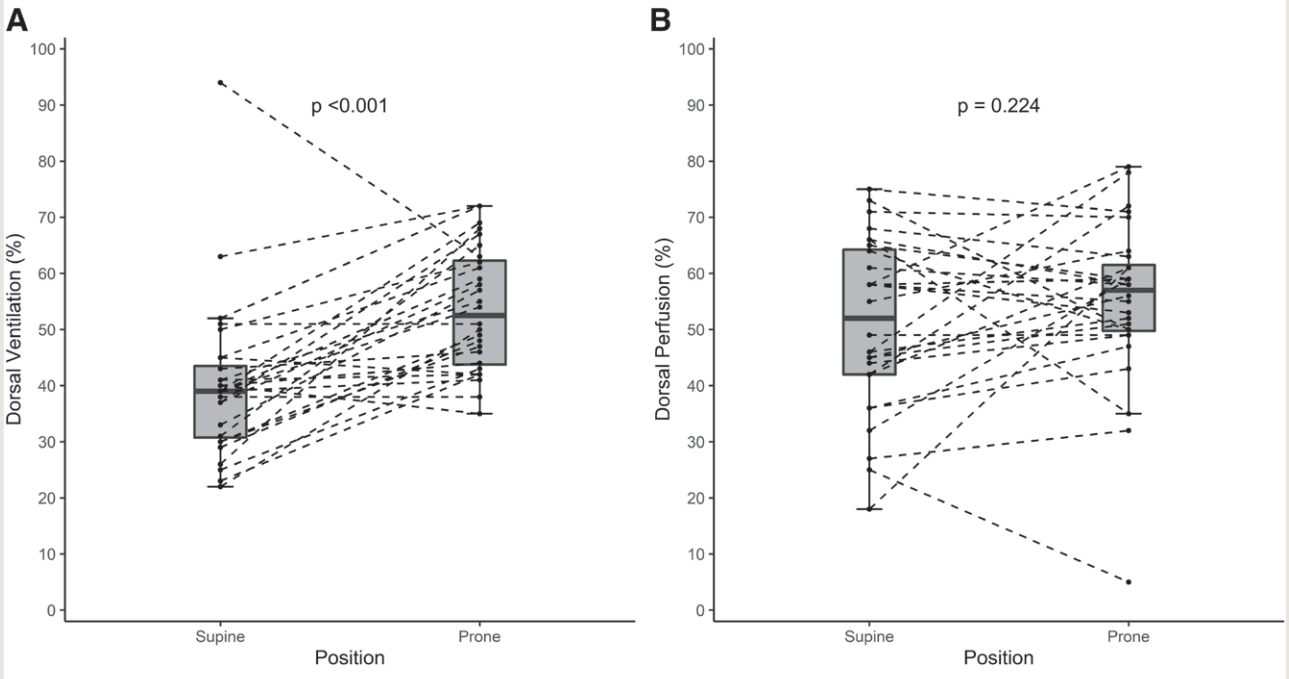

Fig. 5. Percentage of ventilation (*A*) and perfusion (*B*) of the dorsal part of the lung, as assessed by electrical impedance tomography, in the supine and prone positions. The *boxplot*'s hinges represent the first and third quartile of the data, the *upper and lower whiskers* indicate the highest and lowest values within 1.5 times the interquartile range, and the *bold line* indicates the median. Individual data points are also plotted, with *dashed lines* connecting the two measurements in the supine and prone position.

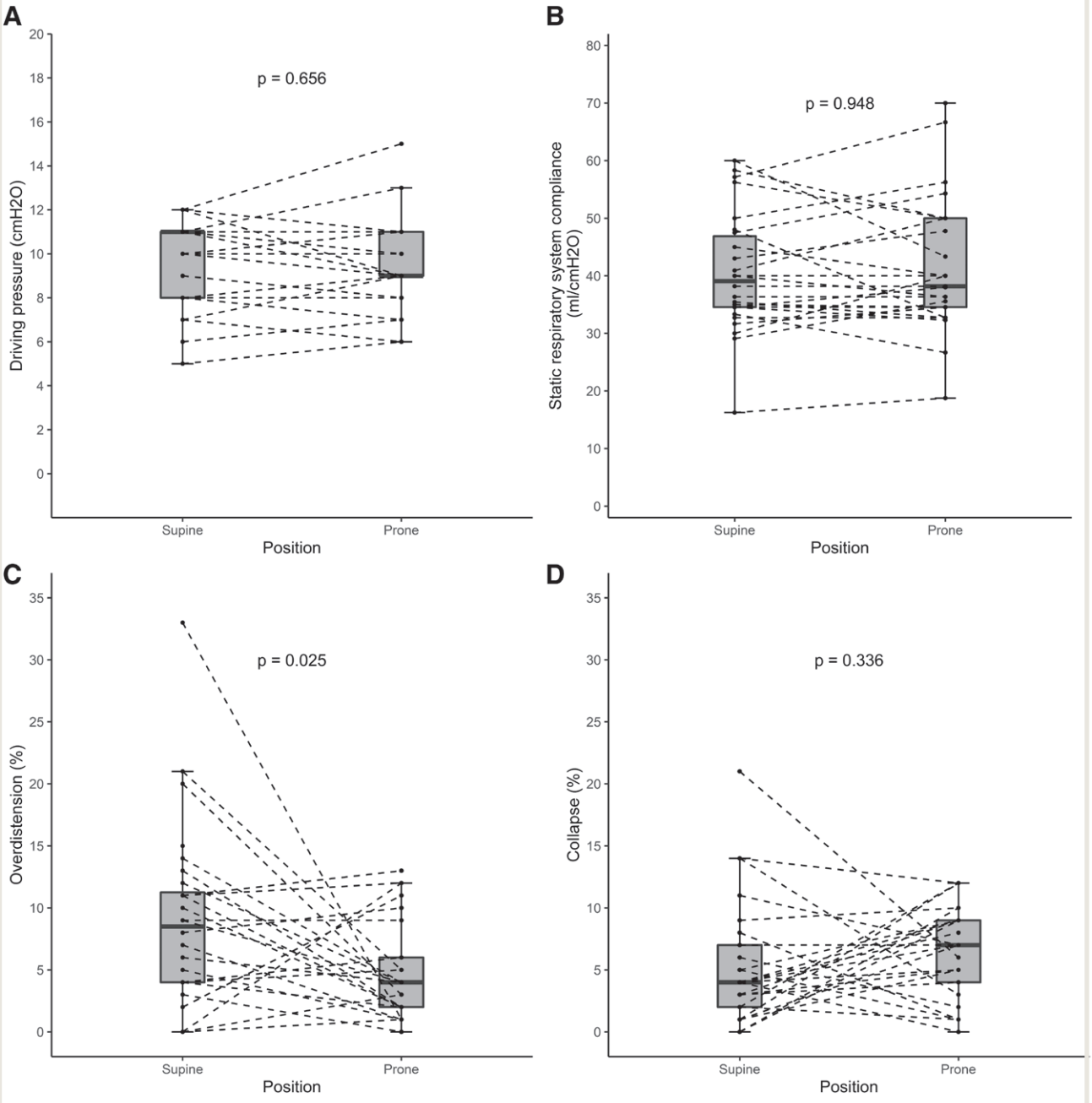

Fig. 6. Driving pressure (*A*) and static compliance of the respiratory system (*B*) before and after prone positioning. Percentage of lung compliance loss due to overdistension (*C*) and collapse (*D*) as assessed by electrical impedance tomography before and after prone positioning. Positive end-expiratory pressure was selected as the best compromise between overdistension and collapse at both time points. The *boxplot*'s hinges represent the first and third quartile of the data, the *upper and lower whiskers* indicate the highest and lowest values within 1.5 times the interquartile range, and the *bold line* indicates the median. Individual data points are also plotted, with *dashed lines* connecting the two measurements in the supine and prone positions.

Our study has several limitations. No causal inferences can reliably be drawn due to the pre-post design in a single group without controls, since several measured and unmeasured factors may interfere during the study period. Moreover, although we explored a much larger patient population than in previous similar physiologic investigations,[12,36] we cannot exclude that our study was not adequately powered.

It is important that electrical impedance tomography perfusion assessment by slope analysis of saline dilution is still experimental and has been validated only in two animal studies.[31,41]

In particular, Bluth *et al.*[31] conducted a head-to-head comparison between a reference standard technique (positron emission tomography) and electrical impedance tomography in pigs. The authors found that electrical impedance tomography underestimated the relative perfusion in the dependent thoracic regions, and overestimated it in the nondependent ones, partly ascribable to software limitations, related to anatomical characteristics of the animals, and incomplete masking of the heart region. This possibly incorrect estimation of perfusion in dependent/nondependent regions might lead to a decreased ventral-dorsal gradient of lung perfusion and then to a reduced estimation of ventilation-perfusion matching. Worth mentioning, however, compared to the work of Bluth *et al.*,[31] we used a more advanced version of the electrical impedance tomography perfusion software. Also, electrical impedance tomography has a limited spatial resolution and explores only the area of the lung surrounded by the belt, which might not be representative of the whole pulmonary parenchyma.[24]

In keeping with a previous study,[36] we assessed the early effects of prone position to guarantee a stable position of the electrical impedance tomography belt between measurements, which is of paramount importance considering our study design.[24] Nevertheless, since prone positioning is commonly applied for much longer periods of time, we cannot exclude that the number of responders was underestimated, as some patients might have shown a later response. Moreover, as in previous studies exploring the response to prone positioning,[14,25] we did not assess the oxygenation response when the patient was turned back to the supine position.

Finally, we neither measured esophageal pressure to partition the chest wall and lung compliances nor systematically ruled out pulmonary thromboembolism in all our patients. It is worth mentioning that all patients were treated with intermediate doses of low-molecular-weight heparin,[24] and in nine patients (30%) who underwent computed tomography pulmonary angiography for clinical indications, we found no thromboembolic involvement of major lung vessels.

Conclusions

In this observational study in COVID-19 ARDS patients undergoing invasive mechanical ventilation, early prone positioning was overall associated with improved ventilation-perfusion matching, increased dorsal ventilation, reduced overdistension, and increased Pao_2/Fio_2, while not affecting dorsal perfusion, lung collapse, driving pressure, and respiratory system quasi-static compliance. These physiologic effects were, nonetheless, heterogeneous among patients.

Further larger clinical studies are necessary to assess whether the electrical impedance tomography analysis could reliably predict prone responsiveness based on early variations in the distribution of lung ventilation and perfusion.

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Competing Interests

Dr. Navalesi receives royalties from Intersurgical SPA (Mirandola, Italy) for the Helmet Next invention. He also received speaking fees from Draeger (Lubeck, Germany), Intersurgical SPA, Getinge (Goteborg, Sweden), MSD (Rahway, New Jersey), Gilead (Foster City, California), Philips (Milan, Italy), Respmed (El Paso, Texas), and Novartis (Basel, Switzerland). His research laboratory received research grants and/or research equipment from Intersurgical SPA, Draeger, and Gilead. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Navalesi: via V. Gallucci 13, 35125 Padova, Italy. paolo.navalesi@unipd.it. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Supplemental Digital Content

Strengthening the Reporting of Observational Studies in Epidemiology Checklist and Supplemental Figure, http://links.lww.com/ALN/C872

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Sertürner Isolates Morphine! And Eventually…Himself

Orphaned at age 15, Friedrich Wilhelm Sertürner (1783 to 1841, *right*) soon became a pharmacy apprentice at the court in Paderborn, Prussia. During his free time, he researched opium (*lower left*), the wondrous latex that oozed from scored poppy bulbs (*upper left*). While experimenting with a myriad of solvents in 1804, Sertürner discovered that ammonia applied to opium led to the formation of "completely colorless and regular" crystals. He named this pure alkali "morphium," after Morpheus, the Greek god of dreams. When morphium relieved a toothache that opium could barely touch, Sertürner convinced three teenagers to help him explore its physical effects. After consuming a total of 90 mg each, the four young men fell ill with "stomachache, weakness, and marked stupefaction bordering on unconsciousness." Subsequent ingestion of vinegar provoked retching; constipation, stupor, and headache lingered for days. Sertürner reported his findings in an 1817 paper that captivated French chemist Joseph Louis Gay-Lussac, who renamed the substance "morphine" with the suffix "-ine" to herald the birth of the alkaloid class. With opium's active ingredient now isolated, analgesia could be dosed incrementally. But while morphine decreased the risk of overdose from variably potent opium, it could still engender addiction. Sertürner himself became hooked on the drug and grew increasingly isolated with time. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

Jane S. Moon, M.D., Assistant Clinical Professor, Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, California.