Early View

Original research article

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Awake prone position in COVID-19 acute respiratory failure: a randomized crossover study using electrical impedance tomography

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Abstract

Background

The goal of this study was to determine whether an awake prone position (aPP) reduces the global inhomogeneity (GI) index of ventilation measured by electrical impedance tomography (EIT) in COVID-19 patients with acute respiratory failure (ARF).

Methods

This prospective crossover study included COVID-19 patients with COVID-19 and ARF defined by PaO_2:FiO_2 of 100-300 mmHg. After baseline evaluation and 30-min EIT recording in the supine position (SP), patients were randomized into one of two sequences: SP-aPP or aPP-SP. At the end of each 2-h step, oxygenation, respiratory rate, Borg scale, and 30-min EIT were recorded.

Results

Ten patients were randomized in each group. The GI index did not change in the SP-aPP group (baseline 74±20%, end of SP 78±23% and end of aPP 72±20%, p=0.85) or in the aPP-SP group (baseline 59±14%, end of aPP 59±15% and end of SP 54±13%, p=0.67). In the whole cohort, PaO_2:FiO_2 increased from 133±44 mmHg at baseline to 183±66 mmHg in aPP (p=0.003) and decreased to 129±49 mmHg in SP (p=0.03).

Conclusion

In spontaneously breathing non-intubated COVID-19 patients with acute respiratory failure, aPP was not associated with a decrease of lung ventilation inhomogeneity assessed by EIT, despite an improvement in oxygenation.

This study was registered as NCT04632602 in the clinicaltrials.gov database (https://clinicaltrials.gov/)

Keywords:

Acute respiratory failure; Coronavirus disease 2019; Awake prone position; Electrical impedance tomography; Lung ventilation inhomogeneity.

List of abbreviations

ABG: Arterial blood gas

aPP: Awake prone position

ARDS: Acute respiratory distress syndrome

ARF: Acute respiratory failure

CoV: Center of ventilation

COVID-19: Coronavirus disease related to SARS Cov-2

CT: Computed tomography

EIT: Electrical impedance tomography

GI index: Gobal inhomogeneity index

ICU: Intensive care unit

PEEP: Positive end expiratory pressure

RT-PCR: Reverse-transcriptase polymerase chain reaction

SoV: Surface of ventilation

SP: Supine position

VA/Q: Ventilation to perfusion ratio

Introduction

Acute respiratory failure (ARF) related to COVID-19 pneumonia is associated with severe impairment in oxygenation, and initially, there is only moderate evidence of respiratory distress [1]. The pathophysiology of underlying hypoxemia includes intrapulmonary shunt, ventilation to perfusion (VA/Q) mismatch, pulmonary artery embolism, and microvascular coagulation despite relatively preserved lung-gas volumes at the onset of the disease [2, 3]. VA/Q mismatch is the result of ventilation and/or perfusion inhomogeneity [4]. In intubated and mechanically ventilated patients, a prone position (PP) improves oxygenation notably through redistribution of the tidal volume towards the dorsal region and by increasing VA/Q matching. Therefore, a prolonged repeated PP is recommended for moderate-to-severe acute respiratory distress syndrome (ARDS) [5] and decreases mortality.

Preliminary studies have evaluated the feasibility of an awake prone position (aPP) for COVID-19 patients admitted to the ICU [6,7], and a randomized meta-trial combing aPP and high flow O_2 nasal cannula has shown a decrease in the need for intubation [8]. Electrical impedance tomography (EIT) is a bedside, non-invasive, functional method for monitoring lung ventilation and measuring variations in chest impedance with a thoracic belt [9]. For a mechanically ventilated patient, EIT can be used to evaluate lung recruitment, which is assessed by positive end expiratory pressure (PEEP) [10,11], and to personalize ventilation [12].

EIT has been investigated in ventilated patients with COVID-19 [13], but investigations on non-intubated and spontaneously breathing patients are scarce [14,15]. Therefore, the main objective of the study was to evaluate lung inhomogeneity assessed by EIT in COVID-19 patients with ARF in a supine position

(SP) and PP. The secondary objectives were to compare respiratory function and derived EIT indices in both positions.

Materials and Methods

Study design and population

We conducted this prospective cross-over cohort study in a tertiary university hospital in Marseille, France. We screened all patients > 18 years old who were admitted to the ICU with COVID-19 confirmed by RT-PCR. We included patients who were awake and spontaneously breathing with ARF and hypoxemia (PaO_2:FiO_2 100-300 mmHg) requiring O_2 supply. Patients were not included if they had evidence of respiratory distress with a high probability of intubation within the next hours (respiratory frequency > 35 cycles/min, respiratory muscles fatigue, agitation or confusion) or a pacemaker (a contraindication for EIT monitoring). Pregnant or breastfeeding women and patients deprived of liberty or lacking health insurance were also not included.

Study approval was obtained according French legislation (ethics committee, *comité de protection des personnes, Ile de France 1*). Each subject gave written informed consent. The study was registered as NCT04632602 in the clinical trials database (https://clinicaltrials.gov/)

Baseline assessment and data collection

The following parameters were recorded in the electronic case report form of each subject: age, gender, body mass index, comorbidities, dates of first COVID-19

symptoms, RT-PCR positivity, and hospital and ICU admission. Baseline respiratory parameters included SpO_2, respiratory frequency, O_2 supply, arterial blood gas (ABG), $PaO_2:FiO_2$, and Borg scale ranking. $PaO_2:FiO_2$ was calculated with FiO_2 for patients who received O_2 with a high-flow nasal cannula or estimated for those who received O_2 through non-rebreathing-masks with the following formula.

FiO_2 = 21% + oxygen flow rate in L/min × 3 [16]

Thoracic CT-scan was performed as routine exam at ICU admission and findings were collected. The following clinical events and outcomes were also recorded: intubation, duration of mechanical ventilation, and ICU and hospital mortality.

Design of the study

Patients were randomized to undergo one of two mutually exclusive sequences, SP and then aPP (SP-aPP group) or aPP and then SP (aPP-SP group). Each step lasted 2 hours with a washout period of 30 min between them. A 30-min EIT recording was performed at baseline and at the end of each step. SpO_2, respiratory frequency, O_2 supply, ABG, $PaO_2:FiO_2$, and Borg scale ranking were also assessed at the end of each step. The study design is provided in Figure 1.

EIT analysis

EIT monitoring was performed using a Pulmo Vista 500 ® monitor (Dräger, Lübeck, Germany), which was connected to a belt with 16 electrodes placed around the patient's chest at the fifth or sixth intercostal space. EIT measurements were

generated by passing a weak alternating electrical current through the belt. Regional variations in impedance (ΔZ) during ventilation were used to map the tidal volume distribution in the lungs. The EIT terms used have been described previously [9].

Our main EIT parameter of interest was the global inhomogeneity (GI) index [17]. Briefly, the GI index is the difference in impedances between end-inspiration and end-expiration and the variations in its pixel values within a predefined lung area. The calculation of GI is based on the difference between each pixel value and the median value of all pixels. These values are normalized by the sum of impedance values within the lung area:

GI = Σ (pixel differences from median) / Σ(pixels), where Σ(pixels) = Σ (ΔZ_j), Σ (pixel differences from median) = Σ (ΔZ_j – ΔZ median), ΔZ_j is the fEIT image value in pixel j, ΔZ median is the median image value, and all sums are calculated for all pixels in the image.

Additional EIT indices studied were the surface of ventilation (SoV) and the centre of ventilation (CoV). SoV represents the number of pixels with variation of impedance. CoV is a measure of anteroposterior distribution of tidal volume and computed by the following formula:

CoV [%] = (Height weighted pixel sum) / (Pixel sum).

CoV yields a value between 0 and 100%, where 0% indicates all image amplitude at the top, and 100% indicates all amplitude at the bottom of the image. As the centre of the distribution of ventilation moves dorsally, CoV increases [9]. All EIT recordings were analysed offline by two operators (TB and CG) who were blinded to the sequence allocation.

Statistical analysis

The methodology of analysis complies with the Consolidated Standards of Reporting Trials Statement (CONSORT, http: // www.consort-statement.org/consort-statement/). The statistical analysis and figures were generated using SPSS Version 20 (IBM SPSS Inc., Chicago, IL, USA). We postulated that PP would be associated with a decrease in the GI index of 20% (with a standard deviation of 20%). With a power of 80% and α risk of 5%, we needed to include 10 patients in each group. A cross-over design was chosen to avoid the risk of important inter-individual heterogeneity and was sufficient with a global cohort of 10 patients.

A washout period of 30 min was used to decrease the risk of sequence effect (carryover effect). However, in case of a sequence effect, a higher number of anticipated patients (10 patients for each sequence) counteracted this risk of loss of power. In case of no association between the sequence and the position (aPP and SP), the effect of the position was tested with an analysis of covariance (ANCOVA). Then, a paired T-test for repeated measurements was performed between each time point (baseline and end of step 1, end of step 1 and end of step 2, baseline and end of step 2). We also tested the correlation between $PaO_2:FiO_2$ and GI at each time point with Pearson's test. A *p* value < 0.05 was considered as significant.

Results

A flow chart of the study is shown in Figure 2. Initially, 22 patients gave their consent and were included in the study. One patient was rapidly intubated after consent, and another withdrew his consent; therefore, data were available for 20 patients. The

Table 1 shows the demographics, medical history, gravity scores, thoracic CT-scan findings, respiratory function, and support at ICU admission and clinical outcomes of the studied population.

Three patients were intubated during their ICU stay, and one of them died. The overall ICU and hospital mortality rate was 5%. Ten patients were randomized into each group (SP-aPP and aPP-SP). One patient in the SP-aPP group could not tolerate aPP, so all time points were available for only 9 patients in this group. An example of EIT measurements for one patient in each group is provided in Figure 3. Respiratory function at baseline was not different between the two groups. Mean respiratory frequency was 28±7 /min in the aPP-SP group and 29±9 /min in the SP-aPP group (p=0.74). Mean $PaO_2:FiO_2$ was 135±25 mmHg in the aPP-SP group and 152±60 /min in the SP-aPP group (p=0.55). Borg scale ranking was 4±2 in the aPP-SP group and 6±3 in the SP-aPP group (p=0.14).

EIT analysis

Concerning the GI index, we did not find an association between sequence and position (p=0.053). We also found no significant change in GI index from the comparison of each time point in the SP-aPP group (baseline 74±20%, end of SP 78±23%, and end of aPP 72±20%, p=0.85) and in the aPP-SP group (baseline 59±14%, end of aPP 59±15%, and end of SP 54±13%, p=0.67) (Figure 4). In the whole cohort, the centre of ventilation did not significantly change during the study (49±7 at baseline, 49±7 during aPP, and 47±7 during SP, p=0.62). Furthermore, the surface of ventilation did not significantly change during the study (330±78 at baseline, 328±71 during aPP, and 332±68 during SP, p=0.98).

Oxygenation and clinical respiratory parameters

In the whole cohort, $PaO_2{:}FiO_2$ increased from 133±44 mmHg at baseline to 183±66

mmHg in aPP (p=0.003) and decreased to 129±49 mmHg in SP (p=0.03). $PaO_2{:}FiO_2$

in aPP increased in 18 of 19 patients, and the mean increase was 41±49%. The

respiratory rate significantly decreased in aPP compared with baseline (22±5 and

27±6, p=0.002, respectively) but was not significantly different from that in SP (22±5

and 23±6, p=0.68, respectively). The Borg scale ranking did not significantly change

during the study and remained relatively low (2.4±2.2 at baseline, 1.7±1.6 in aPP

(p=0.13), and 2.1±2.1 in SP; p=0.46). $PaO_2{:}FiO_2$ and the GI index were not

correlated at any time point of the study (Figure 5).

Discussion

This prospective cross-over study was performed with awake, non-intubated,

spontaneously breathing COVID-19 patients with ARF. PP did not decrease

ventilation inhomogeneity assessed by EIT, it did not modify the centre or surface of

ventilation assessed by EIT, it increased oxygenation and decreased respiratory rate,

and it did not modify the dyspnea Borg score. aPP has widely been adopted by

clinicians since the early beginning of the pandemic in both ICU settings and ~~in~~

general wards. Numerous studies have evaluated its feasibility and clinical effects [6-

7]. However, its potential benefit in critically ill COVID-19 patients is still being

questioned in regard to preventing intubation [18,19] or decreasing mortality [8].

The physiological effects of aPP in spontaneously breathing, non-intubated COVID-

19 patients have not yet been fully described. In intubated and mechanically

ventilated patients with non-COVID ARDS, improvement in oxygenation in PP is mainly due to redistribution of tidal volume towards dorsal regions and therefore where perfusion is still prominent and therefore decreasing VA/Q mismatch [20]. Dalla Corte et al. [21] showed that PP was associated with recruitment of dorsal regions and increased lung ventilation homogeneity in mechanically ventilated and paralyzed intubated ARDS patients.

Despite improvement in oxygenation in both groups, Dos Santos Rocha et al. found no redistribution of regional ventilation induced by aPP in COVID-19-related ARDS patients who were non-invasively ventilated (NIV), whereas PP of invasively ventilated patients led to redistribution of regional ventilation from the ventral to the dorsal lung areas. Therefore, since regional aeration was not significantly modified by aPP in NIV patients, they hypothesized that the benefit in oxygenation was predominantly explained by the redistribution of pulmonary blood flow and optimization of ventilation-perfusion matching rather than alveolar recruitment or aeration change.

Additionally, we hypothesize that patients included at a relatively early state of the disease had a normal elastance ("phenotype L") according to Gattinoni et al. [22]. We may reasonably consider that patients at a later stage of the disease with high elastance ("phenotype H") could have a redistribution of ventilation and a decrease of GI during aPP. Previous studies have investigated lung perfusion with dual energy or SPECT/PET CT scan in COVID-19 patients. They found that perfusion preferentially occurred in areas of non-ventilated inflamed lungs, suggesting complete loss of hypoxic vasoconstriction [23] aside from large perfusion defects that may or may not be related to pulmonary embolisms [24]. Also, in 10 intubated and mechanically ventilated COVID-19 ARDS patients, Mauri et al. [25] found a decrease of the GI

index from 70±11 to 59±10% when increasing PEEP from 5 to 15 cm H_2O. Seven of the patients were investigated using a modified EIT device allowing pulmonary perfusion distribution. The authors found a median VA/Q mismatch of 34% (interquartile range 32–45%).

The improvement in oxygenation that we observed during aPP without any variation of EIT indices suggests redistribution of lung perfusion toward ventral regions. To support this hypothesis, we performed dual-energy CT iodine mapping on one of the included patients, who was awake and breathing spontaneously. This was done first in SP and then after 4 hours in aPP. We observed a redistribution of lung perfusion towards the ventral part of the lung (dependent lung in the PP) with no change in lung condensations/atelectasis topography (still prominent in dorsal regions). In the meantime, we observed significant an improvement in respiratory function (Appendix A, supplementary data).

Other studies have investigated the aeration response to aPP in patients with acute respiratory failure related to COVID-19 using ultrasound scores [26-29]. Consistent results were observed with an improvement in aeration of the dorsal regions of the lungs during and after aPP, particularly in patients who benefited from the combination of aPP and high-flow O_2 nasal cannula [26, 28] or non-invasive ventilation [27]. Interestingly, in those studies, the duration of aPP was longer (range 3 to 8 hours) compared with those investigated in our study (2 hours) and could at least partly explain the difference from our results, besides the different monitoring used. The relatively low Borg score ranking and respiratory rates contrast with the moderate hypoxemia that we observed and support the concept of "silent" or "happy" hypoxemia reported in COVID-19 disease, for which mechanisms have not been totally elucidated [30].

Our study suffers from some limitations. Besides the small sample size, we were not able to measure all EIT indices, particularly those related to pulmonary recruitment and atelectasis. These indices are only available when patients are ventilated on positive pressure with a decremental PEEP trial. We also cannot rule out redistribution of ventilation with longer periods of PP.

We could not investigate pulmonary perfusion with our EIT device. Indeed, this requires a specific device and a currently experimental technique is not wide spread. It also requires a saline injection via a central line during breath holds of several seconds, which was not applicable in our clinical setting. Finally, our results cannot be generalized to patients with more severe disease (PaO_2:FiO_2 <100 mmHg).

Conclusion

In spontaneously breathing non-intubated COVID-19 patients with ARF, aPP is not associated with a decrease of lung ventilation inhomogeneity assessed by EIT, despite an improvement in oxygenation. Further studies investigating lung perfusion or intra-pulmonary shunting are warranted to explain the mechanism or potential clinical benefits.

Authors' contributions

CG designed the study. KB and CG developed the protocol and the statistical analysis plan. TB, EP, JA, CS, SS, NP, JMF, SH, AR, and CG included the patients and performed all procedures of the study and data acquisition. KB performed the statistical analysis of the data. TB and CG wrote the first draft of the manuscript. LP, SH, and AR revised the first draft of the manuscript. All authors contributed to the

revision, read, and approved the final version of the manuscript. CG takes responsibility for the integrity of the work, from inception to publication.

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Figure legends

Figure 1: Study design

PP, prone position; SP, supine position; RR, respiratory rate; ABG, arterial blood gas; EIT, electrical impedance tomography.

Figure 2: Flow diagram of the study.

Figure 3: Representative images of EIT indices in a) one patient in the supine-prone group and b) one patient in the prone-supine group.

Figure 4: Global inhomogeneity index measured by electrical impedance tomography at baseline, end of prone position, and end of supine position in a) the whole cohort, b) the supine-prone group, and c) the prone-supine group. The thick black lines represent the mean.

Figure 5: Correlations between global inhomogeneity index and $PaO_2:FiO_2$ in the whole cohort of patients: a) at baseline, b) at the end of prone position, and c) at the end of supine position.

PP-SP group

Baseline
= 2 hours in **supine position**

RR, ABG, Borg ranking scale, 30 minutes EIT recording

Step 1 = 2 hours in **prone position**

RR, ABG, Borg ranking scale 30 minutes EIT recording

Washout period of 30 minutes in **supine position**

Step 2 = 2 hours in **supine position**

RR, ABG, Borg ranking scale 30 minutes EIT recording

Step 1 = 2 hours in **supine position**

Washout period of 30 minutes in **prone position**

Step 2 = 2 hours in **prone position**

SP-PP group

63 patients admitted for COVID-19 pneumonia
between 1st September and 31th October 2020

Excluded:
Mechanically ventilated within 24 hours (n=23)
PaO2:FiO2 ≤100 mmHg (n=12)
Refused to participate (n=3)
Protected by law (n=2)
Pace maker (n=1)

22 patients with informed consent

Withdraw consent (n=1)
Emergency intubation (n=1)

20 patients included in the analyze

a)

	Baseline	Supine	Prone
GI index			
	56	65	56
Surface of Ventilation			
	281	249	277
Center of Ventilation			
	38	39	39

b)

	Baseline	Prone	Supine
GI index			
	61	52	56
Surface of Ventilation			
	276	312	282
Center of Ventilation			
	60	57	58

a)

R²=0.35, p=0.125
Y=0.15x + 46

Global Inhomogeneity Index (%)

PaO2 / FiO2 (mmHg)

Baseline

b)

R²=0.37, p=0.119
Y=0.10x + 47

Global Inhomogeneity Index (%)

PaO2 / FiO2 (mmHg)

Prone Position

c)

R²=0.03, p=0.877
Y=0.01x + 64

Global Inhomogeneity Index (%)

PaO2 / FiO2 (mmHg)

Supine position

Table 1. Demographics, gravity scores, respiratory function and support at ICU admission and outcomes

Number of patients, n	20
Age, years, mean±sd	60±15
Female sex, n (%)	4 (20)
Body mass index, mean±sd	27±3
Medical history, n (%)	
Hypertension	7 (35)
Diabetes	8 (40)
Ischemic cardiomyopathy	3 (15)
Stroke	1 (5)
Chronic lung disease	1 (5)
Solid organ cancer, hematologic malignancy	3 (15)
Chronic renal failure	0 (0)
Simplified acute physiology score 2, mean±sd	31±12
Sepsis organ failure assessment score, mean±sd	3±2
Delay between onset of symptoms to ICU admission, days, mean±sd	7±4
Respiratory function at ICU admission	
Transcutaneous peripheral saturation, %, mean±sd	93±4
Respiratory rate, cycles per minute, mean±sd	29±8
Borg scale ranking, mean±sd	3±2
Arterial pH, mean±sd	7.49±0.03
$PaCO_2$, mmHg, mean±sd	33±4
PaO_2:FiO_2, mmHg, mean±sd	146±39
Arterial oxygen saturation, %, mean±sd	96±2
Arterial lactate, mmol.l^{-1}, mean±sd	1.5±0.6
CT-scan characteristics at ICU admission, n (%)	
Diffuse and bilateral pattern	20 (100)
Ground-glass opacities	
< 25%	4 (20)
25-50%	9 (45)
>75%	7 (35)
Consolidation	5 (25)
Crazy paving	7 (35)
Respiratory support at ICU admission	
O_2 non-rebreathing mask, n (%)	4 (20)
O_2, liters.min^{-1}, mean±sd	12±2
High flow nasal cannula, n (%)	16 (80)
O_2, flow liters.min^{-1}, mean±sd	47±7
O_2 inspired fraction, %, mean±sd	59±17
Outcomes	
Intubation during ICU stay, n (%)	3 (15)
Duration of mechanical ventilation, days, mean±sd	15±6
ICU mortality, n (%)	1 (5)
Hospital mortality, n (%)	1 (5)

sd, standard deviation; ICU, intensive care unit.