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Original article

Effects of non-invasive respiratory supports on inspiratory effort in moderate-severe COVID-19 patients. A randomized physiological study

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ABSTRACT

Rationale and objective: Various forms of Non-invasive respiratory support (NRS) have been used during COVID-19, to treat Hypoxemic Acute Respiratory Failure (HARF), but it has been suggested that the occurrence of strenuous inspiratory efforts may cause Self Induced Lung Injury (P-SILI). The aim of this investigation was to record esophageal pressure, when starting NRS application, so as to better understand the potential risk of the patients in terms of P-SILI and ventilator induced lung injury (VILI).

Methods and measurements: 21 patients with early de-novo respiratory failure due to COVID-19, underwent three 30 min trials applied in random order: high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and non-invasive ventilation (NIV). After each trial, standard oxygen therapy was reinstated using a Venturi mask (VM). 15 patients accepted a nasogastric tube placement. Esophageal Pressure (Δ Pes) and dynamic transpulmonary driving pressure (Δ PLD_{dyn}), together with the breathing pattern using a bioelectrical impedance monitor were recorded. Arterial blood gases were collected in all patients.

Main results: No statistically significant differences in breathing pattern and PaO₂/FiO₂ were found. PaO₂/FiO₂ ratio improved significantly during NIV and CPAP vs VM. NIV was the only NRS to reduce significantly Δ Pes vs. VM ($-10,2 \pm 5$ cmH₂O vs $-3,9 \pm 3,4$). No differences were found in Δ PLD_{dyn} between NRS ($10,2 \pm 5$; $9,9 \pm 3,8$; $7,6 \pm 4,3$; $8,8 \pm 3,6$ during VM, HFNC, CPAP and NIV respectively). Minute ventilation (V_e) was directly dependent on the patient's inspiratory effort, irrespective of the NRS applied. 14% of patients were intubated, none of them showing a reduction in Δ Pes during NRS.

Conclusions: In the early phase of HARF due to COVID-19, the inspiratory effort may not be markedly elevated and the application of NIV and CPAP ameliorates oxygenation vs VM. NIV was superior in reducing Δ Pes, maintaining Δ PLD_{dyn} within a range of potential safety.

1. Introduction

Non-invasive respiratory support (NRS), such as, Continuous Positive Airway Pressure (CPAP), High Flow Nasal Cannula (HFNC) or non-invasive ventilation (NIV), have been successfully applied to manage moderate to severe Hypoxemic Acute Respiratory Failure (HARF) [1,2,3,4,5]. A potential drawback associated to the use of NRS in patients with HARF, is the occurrence of strenuous spontaneous inspiratory efforts leading to large negative swings in intra-thoracic pressure and large

swings of dynamic transpulmonary pressure (Δ PL_{dyn}) that may cause Patient Self Induced Lung Injury (P-SILI) [6]. Tonelli et al. recently highlighted the importance of inspiratory effort and transpulmonary pressure during NIV. They showed that a 24 h trial of NIV failed leading to intubation when inspiratory effort remained unchanged and transpulmonary pressure increased within the first 2 h of ventilation [7].

Since the onset of the COVID-19 pandemic, several studies showed that the use of out-of-ICU, CPAP, HFNC or NIV, allowed to manage moderate to severe episodes of HARF, avoiding admission to the

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Table 1
Baseline characteristics of the study group.

	N = 21
Age, years old; mean ±SD (median; iqr25-iqr75)	63,57±9,04 (62; 57-72)
Weight, kg; mean ±SD (median; iqr25-iqr75)	80,70±10,66 (81,5; 71,5-88)
Height, cm; mean ±SD (median; iqr25-iqr75)	172,95±9,36 (176; 165-178,5)
PBW, kg; mean ± SD (median; iqr25-iqr75)	67,84±9,78 (71,4; 60-73,5)
Smokers or ex smokers, n (% of N)	12(57%)
Charlson Score, points; mean ± SD (median; iqr25-iqr75)	2,19±1,25 (2; 1-3)
SAPSII, points; mean ± SD (median; iqr25-iqr75)	22±6,36 (22;18-28)
APACHE score, points; mean ± SD (median; iqr25-iqr75)	8,71±2,35 (9; 7-10)
Days from emergency ward to RICU, n; mean ± SD	0,57±0,87
Laboratory tests	
D-Dimer, mg/l; mean ± SD (median; iqr25-iqr75)	1,90±3,57 (0,55; 0,6-1,5)
CPR, mg/dl; mean ± SD (median; iqr25-iqr75)	7,97±8,30 (5,44; 0,42-11,6)
Ferritin, ng/ml; mean ± SD (median; iqr25-iqr75)	979,90±985,63 (674; 529-1079)
IL-6, pg/ml; mean ± SD (median; iqr25-iqr75)	97,18±72,52 (74; 52-134,87)
CT Radiographic features	
Bilateral involvement, n (% of N)	21 (100%)
Pattern	
Mainly interstitial, n (% of N)	16 (76,2%)
Mainly consolidative, n (% of N)	5 (23,8%)
Total CT score of the pulmonary involvement; mean ± SD (min-max)	9,38±3,25 (3-16)
Physiological parameters on RICU admission	
FiO ₂ mean ± SD (median; iqr25-iqr75)	0,5±0,1 (0,5; 0,5-0,6)
pH mean ± SD (median; iqr25-iqr75)	7,46±0,3 (7,47; 7,45-7,47)
PaCO ₂ , mmHg; mean ± SD (median; iqr25-iqr75)	34,46±4,02 (34;32-36,55)
PaO ₂ , mmHg; mean ± SD (median; iqr25-iqr75)	66,45±9,79 (66,4; 61,75-74,25)
PaO ₂ /FiO ₂ , mmHg; mean ± SD (median; iqr25-iqr75)	126,90±34,06 (125; 104-158)
RR, breaths per minute; mean ± SD (median; iqr25-iqr75)	24,62±5,44 (25; 20-28)
HR, beats per minute; mean ± SD (median; iqr25-iqr75)	80,05±12,71 (83; 76-88)
SpO ₂ %; mean ±SD (median; iqr25-iqr75)	93,40±2,70 (94; 92,7-95)
Comfort VAS; mean ± SD (median; iqr25-iqr75)	2,29±1,59 (2; 1-3)
Mean VT, ml; mean ± SD (median; iqr25-iqr75)	456,46±126,10 (420; 377,8-513,6)
VT/PBW, ml/KG _{PBW} ; mean ± SD (median; iqr25-iqr75)	6,80±1,75 (6,56; 5,72-7,47)
Mean Ve, L/m; mean ± SD (median; iqr25-iqr75)	10,92±3,08 (10; 8,8-12,56)

Quantitative data are presented as mean ± SD, Median and interquartile range values, minimum and maximum value, while counting data are presented as count (percentage of the total).

(PBW=Predicted body weight; SAPSII =Simplified Acute Physiology Score; CPR= c-Reactive Protein; IL- 6=Interleukin 6; CT= Computer Tomography; RR =Respiratory Rate; HR = Heart Rate; RICU= Respiratory Intensive Care Unit; VAS= Visual Analogue Score; VT = Tidal Volume; Ve= Minute Ventilation).

intensive care units for invasive mechanical ventilation [8,9,10]. All three NRS techniques have been indiscriminately applied, using different settings and timing of application. Some authors [11,12] pointed out that in patients with COVID-19, progressive deterioration of lung function might occur when respiratory drive is not reduced by oxygen administration and NRS. Persistent strong spontaneous inspiratory efforts simultaneously increase tissue stress and raise pulmonary transvascular pressures, vascular flows, and fluid leakage. Nevertheless, the COVID-19 syndrome causes unique lung injury that is not physiologically yet fully explored. Indeed, the physiological effects of the different NRS need to be better understood, to eventually minimize the risk of further lung damage.

A prompt evaluation of the patient's effort and the potential effects on transpulmonary pressure (PL) may be therefore desirable in these patients, in order to avoid harm. The only studies aimed to compare the physiological effects of NRS were performed in patients with de-novo HARF of various origins [2,13,14].

Table 2
Effects of different non-invasive respiratory supports on gas exchange, breathing pattern, inspiratory effort, and respiratory mechanics (fifteen patients).

N = 15	Venturi Mask	HFNC	CPAP	NIV
PaCO ₂ , mmHg; mean ± SD (median; iqr25-iqr75)	33,73±3,69 (34; 32-34,75)	33,24±4,2 (34,5; 33-36,5)	34,42±2,9 (34;32 -35,8)	34,2±3,1 (35; 31,3-37)
PaO ₂ , mmHg; mean ± SD (median; iqr25-iqr75)	64,41 ±9,2* (65; 59,8-72,7)	83,11±40,8 (73; 59-91)	90,78 ±26,1* (86,5; 76,5-95,2)	112,33 ±49,5* (86; 76,7-113)
PaO ₂ /FiO ₂ , mmHg; mean ± SD (median; iqr25-iqr75)	120,6 ±36,1† (112; 101-155)	152,2±75,4 (139,5; 96-168,2)	170,9 ±61,8† (166; 137,2-209)	207,4 ±94,2† (180,5; 145,5-213,2)
RR, breaths per minute; mean ± SD (median; iqr25-iqr75)	23,6±5,3 (24;20-28)	20,4±5,6 (20,5; 16,2-23,7)	23,2±4,3 (22; 21-26)	22,8±5 (22; 21-23,75)
MeanVT, ml mean ± SD (median; iqr25-iqr75)	450,5 ±100,6 (419,2; 404-513)	450,1±96,9 (452,2; 416-497)	502,7 ±101,7 (526,5; 438,7-559,5)	400,4±96,3 (391,6; 362,6-460,3)
VT/PBW, ml/KG _{PBW} ; mean ± SD (median; iqr25-iqr75)	6,5±1,4 (6,6; 5,7-7,2)	6,4±1,1 (6,4;5,7-7)	7,3±1,7 (7,3; 6,1-8,1)	5,8±1,4 (6,4; 4,8-6,6)
Mean Ve, L/m; mean ± SD (median; iqr25-iqr75)	10,6±2,6 (10; 8,9-11,9)	9,5±3,2 (8,6; 7,7-12,3)	11,5±3,6 (10,9; 9,1-13,8)	9±2,1 (8,9; 8- 9,5)
Mean ΔPL _{Dyn} , cmH ₂ O; mean ± SD (median; iqr25-iqr75)	-10,2±5 § (-8,6; -7,4 -13,5)	-9,9±3,8 § (-10,9; -7,3-12,7)	-9,6±5,2 § (-9,43; -5,7-11,9)	-3,9±3,38 § (-4,9; -2,1-5,9)
Mean ΔPL _{Dyn} , cmH ₂ O; mean ± SD (median; iqr25-iqr75)	10,2±5,1 (8,6; 7,4-13,5)	9,9±3,8 (10,9; 7,3-12,7)	7,6±4,3 (7,1; 5-10,9)	8,8±3,6 (8,9; 7,3 -11,1)

(HFNC= high flow nasal cannula; CPAP= continuous positive airway pressure; NIV= non-invasive mechanical ventilation; RR =Respiratory Rate; Ve= minute ventilation, VT = inspiratory tidal volume; PBW=Predicted body weight; ΔPes = tidal change in esophageal pressure, ΔPL_{Dyn}= Dynamic tidal change in transpulmonary pressure)

* p=0.001 NIV versus Venturi Mask; p=0.001 CPAP versus Venturi Mask

† p=0.002 NIV versus Venturi Mask; p=0.012 CPAP versus Venturi Mask

§ p=0.001 NIV versus Venturi Mask; p=0.000 NIV versus HFNC; p=0.002 NIV versus CPAP

Therefore, we reasoned that the recording of esophageal pressure, when starting NRS application, may allow us to better understand the potential risk of the patients in terms of P-SILI and ventilator induced lung injury (VILI). We conducted a randomized short-term physiological investigation within the first 24 h of hospital admission to compare the effects of standard oxygen therapy, HFNC, CPAP and NIV on breathing pattern, gas exchange, inspiratory effort, and dynamic transpulmonary pressure (PL_{Dyn}) in patients with moderate-to-severe HARF due to COVID-19 pneumonia.

2. Methods

This pilot randomized short-term physiological study was conducted between February and May 2021, in the respiratory ICU (RICU) of Sant'Orsola Hospital, Bologna, Italy. The local Ethic Committee approved the study (691/2020/Sper/AOUBo) and written informed

Table 3

Effects of different pressure support levels on breathing pattern, inspiratory effort, and respiratory mechanics (fifteen patients).

N = 15	NIV PS5	NIV PS10	P value
RR, breaths per minute; mean ± SD (median; iqr25-iqr75)	22,8±5 (22; 21- 23,75)	21,4±7 (23,5; 18- 26)	>0,05
MeanVT, ml; mean ± SD (median; iqr25-iqr75)	400,4±96,3 (391,6; 362,6-460,3)	489,9±123,9 (458,2; 382,5-555,5)	>0,05
VT/PBW, ml/KG _{PBW} ; mean ± SD (median; iqr25-iqr75)	5,8±1,4 (6,4; 4,8- 6,6)	7±1,3 (7,1; 6 -7,8)	>0,05
Mean Ve, L/m; mean ± SD (median; iqr25-iqr75)	9±2,1 (8,9; 8- 9,5)	10,1±2,7 (9,4; 8,4-11,5)	>0,05
Mean ΔPes, cmH ₂ O; mean ± SD (median; iqr25-iqr75)	-3,9±3,38 (-4,9; -2,1 - -5,9)	-0,03±3,2 (1,4; -2,28 - +1,7)	0,007
Mean ΔPL _{Dyn} , cmH ₂ O; mean ± SD (median; iqr25-iqr75)	8,8±3,6 (8,9; 7,3 - 11,1)	10,6±2,2 (10,4; 8,6-12,1)	>0,05

(NIV= non-invasive mechanical ventilation; RR =Respiratory Rate; Ve= minute ventilation, VT = tidal volume; PBW=Predicted body weight; ΔPes = tidal change in esophageal pressure, ΔPL_{Dyn}= Dynamic tidal change in transpulmonary pressure).

Patient consent: Obtained.

Ethics approval: Comitato Etico Indipendente dell'Azienda Ospedaliero-Universitaria di Bologna, Policlinico S. Orsola-Malpighi.

consent was obtained from all the patients. The study was prospectively registered at the Clinical Trial Registry (NCT04741659).

2.1. Patients

We considered eligible any adult patient (≥ 18 years old) with HArF and a PaO₂/FiO₂ ratio < 200 mmHg evaluated during spontaneous unassisted breathing trial (VM with FiO₂ of at least 0.40), due to pneumonia and a confirmed molecular diagnosis of COVID-19 (positive real-time polymerase chain reaction for viral RNA performed on respiratory tract specimen). Exclusion criteria were: previous clinical, radiological and histological diagnosis of pneumopathy, body mass index > 30 kg/m²; known diagnosis of sleep-disorders, restrictive pulmonary/chest wall disease, cardiac arrest, severe haemodynamic instability (> 1 vasoactive amine for at least 24 h), acute coronary syndrome (unstable angina/IMA), severe arrhythmias, inability to protect the airway, respiratory arrest and need for intubation, pregnancy or suspected, use of sedative drugs, long-term home oxygen therapy.

This study was designed as a pilot study. A priori, standardized effect size comparing Venturi mask (VM), HFNC, CPAP, and NIV is not known. For this reason, we were not able to calculate the optimal sample size. To reach a statistical power of almost 80%, we assumed to enroll 20 subjects with a minimum of 12 subjects having full data available, [15,16,17]. Similar criteria were employed by other physiological studies [13,14].

2.2. Study Protocol

After enrolment, each patient underwent a 30 min spontaneous unassisted breathing trial with a VM. FiO₂ was set to reach a SpO₂ $>92\%$ $<96\%$ and it remained unmodified throughout the whole study period.

Thereafter, three 30 min trials (HFNC, CPAP and NIV) were randomly applied. The randomization sequence was established by a computer software (Research Randomizer 4.0). In order to minimize the carryover effect, a washout period of 30 min with VM between treatments was performed.

NIV was delivered by a non-invasive mechanical ventilator (Astral 150; ResMed, USA) through a single vented circuit and a full-face mask

(Performax; Philips Respironics, USA). Investigators supervised the mask size and fitting in order to minimize leaks as much as possible.

All patients received HFNC through a cannula connected to a heated humidifier (AIRVO2; Fisher & Paykel Healthcare, Auckland, NZ). The cannula was selected to occlude patient's nostril of about 2/3. Flow rate and temperature were set at 60 L Min⁻¹ and 34 °C, respectively. During the trial period, patients were encouraged to breath by the nose.

CPAP was performed with a helmet with an integral Venturi flow driver, which included an adjustable PEEP valve (StarMed VentuKit, Italia).

PEEP during CPAP and NIV was adjusted to 10 cmH₂O. During NIV, two steps of pressure support (PS) were performed: 10 cmH₂O (NIV PS10) and 5 cmH₂O (NIV PS5). Initially, PS was set at 10 cmH₂O and eventually decreased to 5 cmH₂O if esophageal pressure swings (ΔPes) became positive during inspiration or less than -1 cmH₂O (see measurements below), or if patient intolerance or asynchronies were present.

2.3. Physiological measurements

Patient demographics and clinical characteristics were collected at study entry.

A semi-quantitative scoring system was used to estimate the lung abnormalities based on the area involved at chest CT scan. Each of the 5 lung lobes was visually scored 18.

A bioelectrical impedance monitor and a single-use Pad Set sensor placed on the surface of the chest wall were used to monitor minute ventilation (Ve) and tidal volume (VT) (ExSpirom, Respiratory Motion Inc. USA) [19,20].

With the patient in a semi recumbent position, a nasogastric tube provided with an esophageal balloon (Marquat Genie Biomedical, France) was placed to measure esophageal pressure and register tidal change in esophageal pressure. The nasogastric tube was first measured outside the chest wall in order to estimate the distance from the nostril to the xyphoid, inserted through the nostril and then pushed down to the stomach, inflated and connected to a dedicated monitoring system (FluxMed, MBMed, Argentina). Once inserted, the esophageal balloon was filled with the minimum non-stress volume of air recommended by the manufacturer, to avoid over or underestimation of the measurements [21]. Due to the impossibility to do Baydur's occlusion test in this clinical condition, the proper position of the catheter at the 1/3 lower esophageal level was ascertained by the visualization of cardiac artefacts on Pes traces. [22,23]. During CPAP and NIV, a Fleisch-type pneumotachograph, placed at the end of the inspiratory limb of the circuit, measured inspiratory flow and airway pressure (Paw).

All patients underwent standard monitoring with 5-lead ECG and SpO₂. Towards the end of each trial and during a stable period pattern of 5 minutes, VT, Ve, respiratory rate (RR), blood gases (ABG), heart rate (HR), arterial blood pressure (BP), and SpO₂ were collected. Discomfort was also assessed for each device by using 0–10 visual analogue scales (VAS).

During all the stages of the study, Pes was recorded. Flow and airways pressure were also recorded during CPAP and NIV. When a stable breathing pattern was achieved, ΔPes was calculated as the maximum decrease or increase in Pes from the end-expiratory level [24]. We measured dynamic end inspiratory/expiratory transpulmonary pressure (P_L= airway pressure minus Pes, at end inspiration/expiration) to calculate dynamic transpulmonary driving pressure (ΔPL_{Dyn}, the maximal positive variation of PL during inspiration). ΔPL_{Dyn} was taken as a surrogate for ΔP_L, due to the impossibility of performing an inspiratory/expiratory pause during spontaneous breathing. ΔPL_{Dyn} is mainly affected by VT, and it also involves the resistive load due to airflow. Therefore, for the purposes of our study, we assumed that resistive pressure was not remarkably different within the same patient. Since it was impossible to monitor Paw during HFNC and standard oxygen, it was assumed constant and equivalent to 2.5 cmH₂O, during

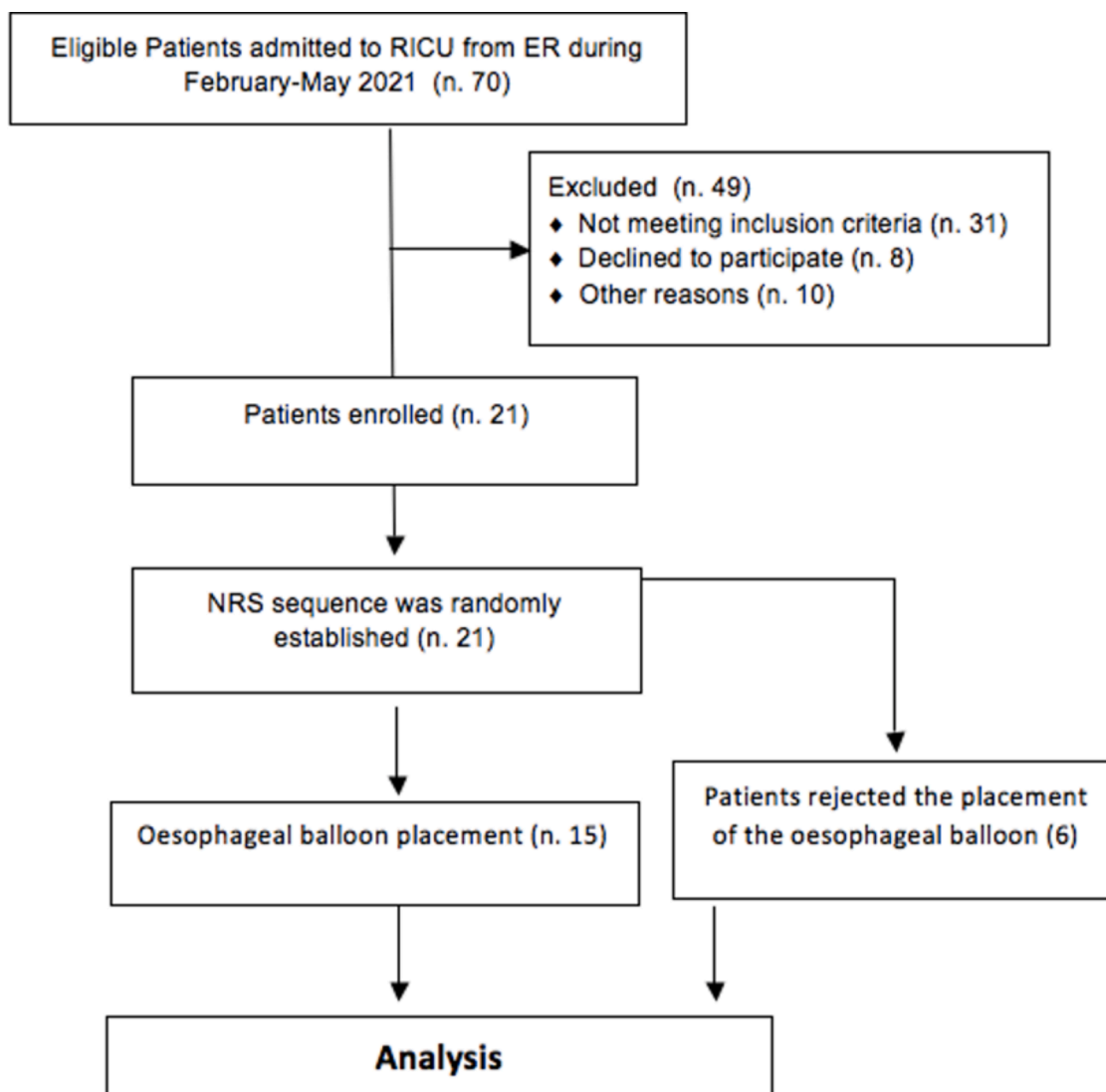


Fig. 1. Flowchart for patients. (ER=Emergency Room; n.= number; NRS= non invasive respiratory support).

HFNC and to 0 cmH₂O during VM[25].

2.4. Outcome Measures

The changes in ΔP_{es} and ΔPL_{dyn} , recorded by esophageal pressure, and the changes in respiratory pattern recorded by respiratory inductance plethysmography, were the primary outcomes. Changes in ABG, Comfort score rated using a VAS, BP and HR measurements were assessed as secondary outcomes.

2.5. Statistical analysis

Continuous variables are presented as mean value and standard deviation (+SD). Median and interquartile range values were also calculated and reported in Tables 1, 2, and 3. Differences in continuous variables between groups were analysed by one-way analysis of variance (ANOVA) and post-hoc t-tests. No adjustment was made for multiple statistical tests. Relationships between V_e , inspiratory effort expressed by ΔP_{es} and ΔPL_{dyn} were studied using the Spearman correlation. P values lower than 0.05 were considered statistically significant. The IBM SPSS Statistics software (version 21) was used for data analysis.

3. RESULTS

Table 1 shows the patients' baseline characteristics. Twenty-one patients were studied within the first 24 h after RICU admission. Six of them rejected the placement of the esophageal balloon. The flowchart

for patients in this study is shown in Fig. 1.

The mean time-lapse between emergency ward and RICU admission was $0,57 \pm 0,87$ days. Mean PaO_2/FiO_2 was $126,9 \pm 34,06$ at enrolment. Quantitative analysis of lung CT revealed a low extend of infiltrates (total CT score $9,38 \pm 3,25$).

3.1. Breathing pattern, respiratory mechanics and gas exchange Outcomes

As shown on Fig. 2, no statistically significant differences were found in RR, VT, VT normalized by predicted body weight (VT/PBW), V_e and $PaCO_2$ between treatments in all study population. Differently, VM was judged more comfortable compared to the others.

Pathophysiological features of the 15 patients undergoing respiratory mechanics measurements are reported in Table 2 and Fig. 3. RR, $PaCO_2$, VT, VT/PBW and V_e were similar in all trials. In contrast, PaO_2/FiO_2 improved using VM, HFNC, CPAP and NIV, respectively. In particular, a higher PaO_2/FiO_2 ratio was observed during NIV and CPAP trials compared to VM ($p = 0,002$ and $p = 0,012$ respectively).

Inspiratory effort progressively decreased using VM, HFNC, CPAP and NIV (mean ΔP_{es} of $-10,2 \pm 5,0$ cmH₂O vs $-9,9 \pm 3,9$ vs $-9,5 \pm 5,0$ vs $-3,98 \pm 3,4$ respectively) (Fig. 3). However, NIV was the only support able to reduce significantly ΔP_{es} compared the others [NIV vs VM ($p =$

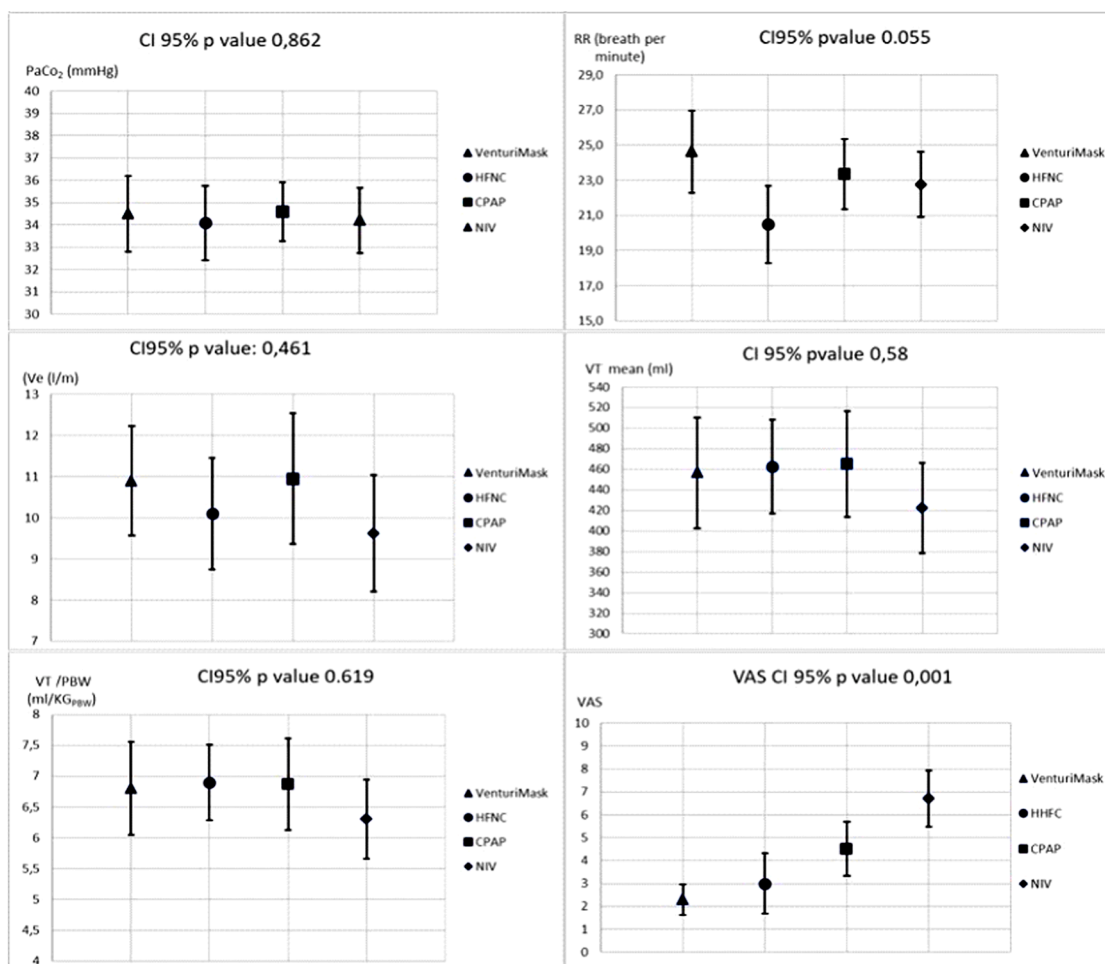


Fig. 2. Effects of different non-invasive respiratory supports on breathing pattern, ventilation, and comfort; (twenty-one patient). (HFNC= high flow nasal cannula; CPAP= continuous positive airway pressure; NIV= non-invasive mechanical ventilation; RR =Respiratory Rate; Ve= minute ventilation. VTi = inspiratory tidal volume; PBW=Predicted body weight; VAS= Visual Analogue Score).

0,001); NIV vs HFNC ($p = 0,000$) and NIV vs CPAP ($p = 0,002$], while no difference was found in ΔPL_{dyn} between treatments ($10,2 \pm 5,1$ vs $9,9 \pm 3,8$ vs $7,6 \pm 4,3$ vs $8,8 \pm 3,6$ cmH₂O; p value= 0,360)(Table 2).

ΔPes was significantly reduced from $-3,98 \pm 3,4$ cmH₂O to $0,03 \pm 3,2$ ($p = 0,007$) during NIV PS5 vs NIV PS10. No statistically significant differences were found in RR, VT, VT/PBW, Ve and ΔPL_{dyn} , between NIV PS5 and NIV PS10 (Table 3). Because during NIV PS10 ΔPes was close to zero or even positive, we decided to compare only data during NIV PS5 with other NRS.

In addition, the correlation analysis showed that Ve was directly dependent on the patient's inspiratory effort, irrespective of the type of the respiratory support applied (p value =0,001): patients with higher ΔPes experienced an increase in Ve (Fig. 4, upper part). Likewise, patients that increased Ve experienced higher ΔPL_{dyn} (p value= 0,001) (Fig. 4, lower part).

3.2. Clinical outcomes

3 of 21 (14%) patients were intubated at 24, 43 and 84 h after the end of this investigation. They were all undergoing NIV at the time of intubation. These patients did not respond to the NIV trial with PS of 10 cmH₂O in terms of ΔPes reduction ($14,5 \pm 3,1$ at baseline vs $11,2 \pm 2,3$ cmH₂O with NIV PS10).

4. Discussion

NRS are attractive treatment strategies that might avoid intubation and the risk of its complications. Although NRS have been largely used in COVID-19 population, the optimal initial respiratory support for these patients is controversial. In addition, some concerns have been raised regarding the use of NRS treatments including the risk of inappropriate delays in intubation and protective ventilation or exacerbation of lung injury by increasing VILI/P-SILI in spontaneous breathing patients.

To the best of our knowledge, this study is the first face-to-face comparison of changes in respiratory mechanics between all the 3 major forms of NRS applied in spontaneously breathing patients with COVID-19 developing HARF.

Even with the limit of the small sample size, our pilot study demonstrated that NIV might improve the inspiratory effort versus all the other devices, keeping transpulmonary pressure constant. NIV and CPAP were also associated with better gas exchange. RR remained stable among the different trials. Patients judged the VM the more comfortable device.

Three patients were intubated later in the course of the disease. Our results are in line with other studies that have applied NRS. For example, Brusasco [26] and coworkers and Oranger et al [27] showed in COVID-19 patients undergoing CPAP a failure rate of 17% and 23% respectively, while other recent studies reported NRS treatment failure of 24, 25 and 23, respectively [4,28,29]. HFNC, on the other hand, has been shown to be associated with a higher percentage of failure [8,30,

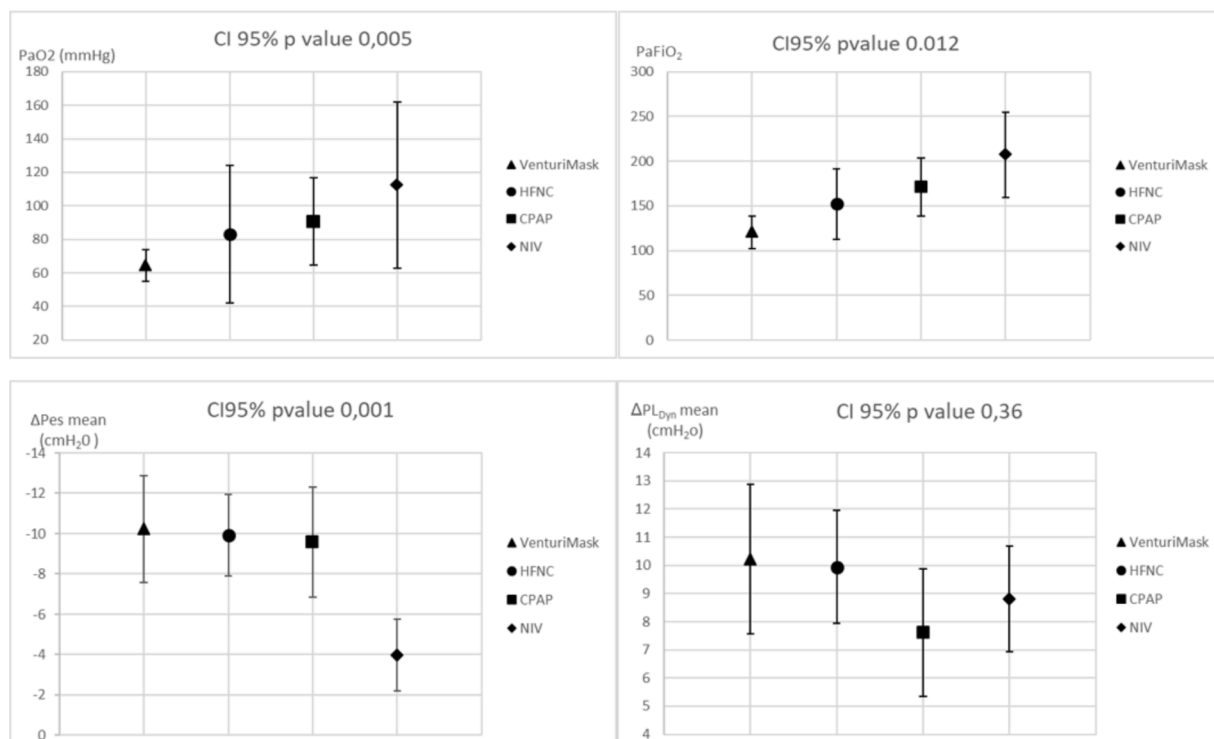


Fig. 3. Effects of different non-invasive respiratory supports on gas exchange and respiratory mechanics (fifteen patients). (HFNC= high flow nasal cannula; CPAP= continuous positive airway pressure; NIV= non-invasive mechanical ventilation; PaFiO₂ = PaO₂/FiO₂ ratio; ΔPes = tidal change in oesophageal pressure, ΔPL_{Dyn} = Dynamic tidal change in transpulmonary pressure).

31].

The pathophysiology of COVID-19 is still matter of investigation, but it has been suggested that at least in a subset of patients this form of lung injury is not similar to those with ARDS unrelated to COVID-19 [32,33,34]. Ramin et al [35] demonstrated in the early stage (median time between admission and intubation was 2 days), a static lung elastance of 19 cmH₂O/l and a low ΔPL (4 cmH₂O) on day 1 of invasive mechanical ventilation. It has been shown that the lung weight in moderate and severe spontaneous breathing COVID-19 patients treated with helmet CPAP or NIV was approximately half of what has been described in typical ARDS with similar severity, confirming the dissociation between the gas exchange and the anatomical lung characteristics, typical of Covid-19 patients at early stage of disease [18]. However, more recent studies support that within 24 h from ICU admission, in invasive mechanically ventilated patients with COVID-19, respiratory mechanics are heterogeneous but similar to those reported for "classical" ARDS [36].

According to Coppola classification [28], our patients fit well the group of "moderate-severe COVID-ARDS", characterized by a mean PaO₂/FiO₂ value of 126. Similarly, we observed low extend of infiltrates at CT scan, despite the moderate-severe impairment of gas exchange.

These results may explain the reason why the inspiratory effort was relatively low, as expected for other form of de-novo respiratory failure [37]. Coppola et al [28] also reported an average ΔPes at day 6 after hospital admission of 7.5 cmH₂O without major differences between supported and unsupported breathing. Unluckily, Coppola, studied a very small number of patients on NIV (9 vs 131 on CPAP), and no data on respiratory mechanics were reported in this subset of patients. In contrast, we observed a marked decreased in the inspiratory effort during NIV.

However, one may claim that our trial lasted "only" 30 min, but it has been shown that a progressive increase in ΔPes is already evident at one minute in condition of respiratory distress, as during an unsuccessful weaning trial, whereas breathing pattern changes may not significantly vary [38].

Recently, Grieco and coworkers [9] compared NIV vs HFNC in critically ill patients with moderate to severe HARP due to COVID-19. NIV was delivered with a helmet, using a PEEP >10 cmH₂O over a PS ranging between 10 and 15 cmH₂O. Helmet NIV was able to significantly reduce RR, ΔPes and comfort, while ΔPL was not statistically different, except for the subset of patients with low effort, where NIV increased ΔPL, compared to HFNC. Therefore, they concluded that in patients with low inspiratory effort, the use of a lower level of PS should be warranted. Similarly, we noted that the application of an inspiratory pressure of 10 cmH₂O resulted in a reduction of ΔPes close to zero or even positive, suggesting that the majority of COVID-19 patients in the early phase of their disease may act differently to other forms of de-novo respiratory failure where higher inspiratory support is usually applied.

Interestingly enough, however, during NIV, the ΔPL remained on average below the threshold of 15 cmH₂O, which it has been suggested, but not proven yet, a safety limit to avoid deterioration in lung injury [39,40].

Pes swings were mostly reduced during NIV, that is the only NRS able to provide an inspiratory support, and therefore should be considered the only "true" form of ventilatory support, compared to HFNC or CPAP.

ΔPL_{Dyn} can be split into two components, the first is the part necessary to overcome the flow resistance, and second is the pressure generated to expand the alveoli. This latter is the component of the PL that is the product of volume and elastance. PL is the result of P_{aw} (the ventilator inspiratory pressure) minus the pleural pressure, which is the ΔPes generated by inspiratory muscles. It represents the stress that alveoli are exposed to, and it has been considered, but not still firmly demonstrated, among the most important determinants of P-SILI/VILI. Like Tonelli et al (7), we saw that the VT/ΔPL ratio does not change significantly: VT did not modify significantly during any NRS trial, not even during NIV with PS10. Moreover, any NRS modify ΔPL_{Dyn}. ΔPL was kept constant: at expense of the ΔPes reduction during PS application (8.8 cmH₂O, during NIV trial) or simply at equivalent ΔPes values without PS (10,2, 9,9, 7,6 cmH₂O in VM, HFNC and CPAP trials,

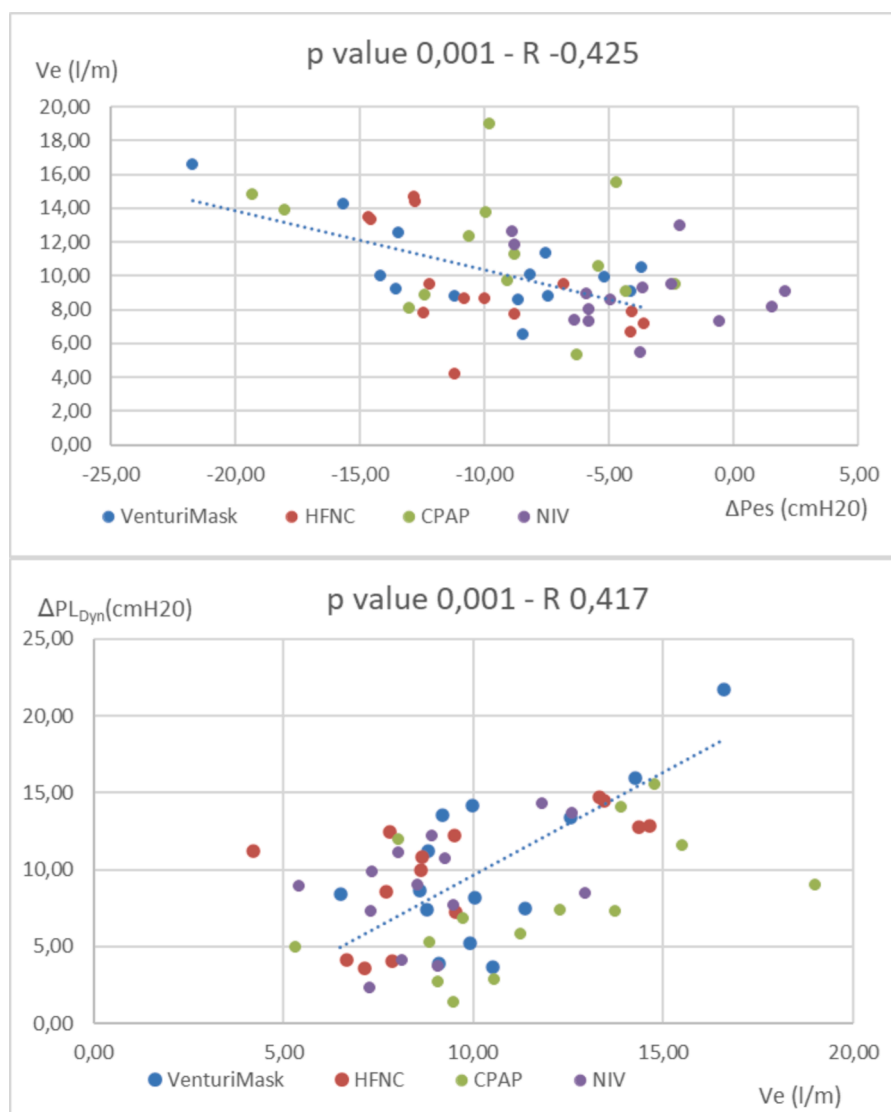


Fig. 4. Upper part: correlation analysis between minute ventilation and ΔP_{es} (inspiratory effort). Lower pan: correlation analysis between minute ventilation and $\Delta PL_{C_{ym}}$. (HFNC; High flow nasal cannula, CPAP; continuous positive airway pressure, NIV; non invasive mechanical ventilation. V_e = minute ventilation, ΔP_{es} = tidal change in oesophageal pressure. $\Delta PL_{D_{yn}}$ = Dynamic tidal change in transpulmonary pressure).

respectively). Therefore, if VT and ΔPL did not change, we assume that lung compliance ($VT/\Delta PL$ ratio) has not been modified by the application of positive pressure (not reduced by over-distension, nor increased by the fact of recruitment). Our findings are in line with the interstitial CT pattern described in our population.

On the other hand, one might think that “in clinical practice” applying NIV should increase VT. In this case, if VT increases, with a same ΔPL value, it might be related to an improvement of lung compliance due to the recruitment effect of the PEEP, as expected in classic forms of ARDS.

Finally, in our study CPAP and NIV seem to be the two NRS able to significantly improve oxygenation, while HFNC did not, despite a small increase in PaO_2/FiO_2 ratio vs. VM. These data confirm the results reported by Grieco et al [9] concerning the use of NIV and HFNC, and those of Coppola and coworkers [28] that found a statistical improvement in gas exchange when comparing CPAP with VM. Rather surprising, we did not observe changes in breathing pattern among the different trials, while other authors did. This might be related by the fact that our patients were enrolled in the early phase of their disease and despite a comparable PaO_2/FiO_2 ratio, their RR was on average lower than on other studies. As we previously described a “non-recruitable lung”

condition in this population, one hypothesis to justify the P/F improvement during NIV and CPAP, might be that CPAP or PEEP effect during NIV could redistribute the blood flow of the alveoli with low ventilation perfusion ratio (V/Q), i.e. highly perfused, generating a redistribution effect and a new balance in V/Q [41].

This study has limitations. First, it represents an exploratory analysis with a small sample size. Second, because of the study design, we could not investigate possible changes in the respiratory mechanics during the time course of patient’s hospital stay, especially for those patients requiring IMV. However, the 3 patients who were intubated showed a higher ΔP_{es} compared to the overall group ($14,5+3,1$ cmH₂O with VM) after the end of the study, even under NIV. Third, some data about respiratory mechanics are missing because 6 patients refused to swallow the esophageal balloon; nevertheless we could record these parameters in the remaining 15, which is the minimum sample size to reach a statistical power of almost 80%. Moreover, in this study it was impossible to measure P_{aw} during the HFNC trial and during VM. For this reason, we assumed an existing reference value as in published literature. However, regardless of the actual absolute value of P_{aw} , it was assumed to be constant during the respiratory cycle and should not modify the $DPL_{D_{yn}}$. Last, the helmet with an integral Venturi flow driver (the

VentuKit) used in this study delivers a flow under the reported experimental conditions. It delivers a flow of approximately 48 L/min, which is not enough to perform a CPAP "high flow" device [42]. Studies [43,44] have shown that the esophageal pressure delta is lower when the device is able to deliver a higher flow and consequently a more stable airway pressure. However, in our study, the advantage of measuring flow and pressure through an external sensor (pneumotacograph mentioned in the article) allowed us to be aware that CPAP flows should not be less than 60 L/min, not only because of the fact that pressure becomes unstable, but also because of the undesirable effect of rebreathing. In addition, the "pressure variations" due to flow or the patient effort were taken into account for all calculations in this study.

In conclusion, our results showed that during the early phase of HARF due to COVID-19 pneumonia, the application of NIV and CPAP ameliorate gas exchange compared to VM, keeping breathing pattern unmodified. NIV can be superior to HFNC and CPAP in reducing the inspiratory effort, maintaining transpulmonary pressure similar to the other NRS devices and within a range of safety, concerning the potential risk of P-SILI or VILI. Further studies are needed to assess the clinical outcomes, the impact of NRS on SILI, and the potential changes in respiratory mechanics in more advanced stages of the disease.

Contributors

GS, LV, SN: study design, experimental procedure, writing and data analysis. LP: study design, experimental procedure, writing. IP: writing and data analysis. VC: experimental procedure and writing and data analysis. Vitt.C: experimental procedure. IB: experimental procedure and data analysis. MZ: data analysis. VMR: writing and data analysis

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.04.012.

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