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Aeration changes induced by high flow nasal cannula are more homogeneous than those generated by non-invasive ventilation in healthy subjects

Purificación Pérez-Terán [a,b,*,1], Judith Marin-Corral [a,b,1], Irene Dot [a], Sergio Sans [b], Rosana Muñoz-Bermúdez [a], Raquel Bosch [a], Clara Vila [a], Joan Ramon Masclans [a,b,c]

[a] Critical Care Department, Hospital del Mar. GREPAC – IMIM, Barcelona, Spain
[b] UAB/UPF School of Medicine, Barcelona, Spain
[c] HISpaFlow (Grupo Español Multidiscipinar de Terapia de Soporte con Alto Flujo en Adultos), Spain

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ABSTRACT

Background: Non-invasive mechanical ventilation (NIV) is a standard respiratory support technique used in intensive care units. High-Flow Nasal Cannula (HFNC) has emerged as an alternative, but further evidence is needed. The lung aeration and diaphragm changes achieved with these two strategies in healthy subjects have not been compared to date.

Methods: Twenty healthy subjects were recruited. Ten were ventilated with NIV and ten underwent HFNC. Lung impedance and diaphragmatic ultrasound measurements were performed before and after 30 min of respiratory support. The Mar-index was defined as the ratio of the diaphragm excursion-time index to the respiratory rate.

Results: Both groups showed significant decreases in respiratory rate (NIV: 14.4 (4.1) vs 10.4 (1.6), $p = 0.009$; HFNC: 13.6 (4.3) vs 7.9 (1.5) bpm, $p = 0.002$) and significant increases in the end-expiratory lung impedance (EELI) (NIV: 66,348(10,761) vs. 73,697 (6858), $p = 0.005$; HFNC: 66,252 (9793) vs 69,869 (9135), $p = 0.012$). NIV subjects showed a significant increase in non-dependent silent spaces (4.13 (2.25) vs 5.81 (1.49)%, $p = 0.037$) while the increase was more homogeneous with HFNC. The variation in EELI tended to be higher in NIV than in HFNC (8137.08 (6152.04) vs 3616.94 (3623.03), $p = 0.077$). The Mar-index was higher in HFNC group (13.15 vs 5.27 cm-sec^2/bpm, $p = 0.02$).

Conclusions: NIV and HFNC increased EELI in healthy subjects, suggesting an increase in the functional residual capacity. The EELI increase may be higher in NIV, but HFNC produced a more homogeneous change in lung ventilation. HFNC group has a higher MAR-index that could reflect a different ventilatory system adaptation.

1. Introduction

In recent years, non-invasive mechanical ventilation (NIV) has become a widespread technique for ventilatory support in the Intensive Care Unit (ICU) [1]. NIV is a standard care therapy in exacerbated obstructive pulmonary disease, cardiogenic pulmonary edema, and acute respiratory failure (ARF) in immunodepressed patients. Furthermore, it has been successfully used to avoid reintubation in other ARF patients including those with postextubation respiratory failure and community-acquired pneumonia [1].

In recent decades, high-flow nasal cannula (HFNC) has been described as an effective non-invasive respiratory support technique. HFNC achieves better aeration as well as oxygenation since it flushes the dead space of the nasopharyngeal cavity [2-6] and reduces inspiratory work of breathing [3]; it reduces the metabolic cost of gas conditioning as it delivers warmed and humidified air at up to 60 L/min[3] and can generate a certain degree of positive airway pressure [4-10]. Its high tolerability, even among patients with ARF [11-15], makes it an excellent non-invasive oxygen delivery technique in both adults and children [16-20]. Although the intrinsic mechanisms of HFNC have been discussed [3,18], further studies are needed to assess its effects on lung volume and to determine its clinical applications, especially in adults [3,6,14,18,20,21].

Both NIV and HFNC have been proved to induce changes lung aeration, work of breathing and oxygenation in both healthy subjects and patients [4,12,20,22-25]. Currently, a number of non-invasive techniques are available to assess all these variables at the bedside. First,

* Corresponding author at: Critical Care Department, Hospital del Mar, Ps. Marítim, 25-29, 08003 Barcelona, Spain.
E-mail address: pperez@psmar.cat (P. Pérez-Terán).
[1] Both authors have contributed to the work to the same extent, and so both appear as first authors.

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electrical impedance tomography (EIT) is a non-ionizing, non-invasive method for monitoring lung ventilation at the bedside. The technique generates cross-sectional images of the subject by applying high frequency and low amplitude electrical currents. Using a reconstruction algorithm, impedance images are obtained from the resulting potential differences measured in the electrodes on the surface of the thorax. EIT is capable of tracking regional ventilation, as a change in impedance correlates with tidal volume (TV) variations [22,26,27]. Among the applications of EIT are: monitoring during mechanical ventilation, optimal setting of mechanical ventilation parameters, detecting changes in lung mechanics secondary to frequent maneuvers, and detecting changes in regional ventilation after a change in the patient's position [22,26,27].

Second, lung ultrasound (LUS) allows regional and global visualization of the lung since it can detect loss of aeration and its cause, but it is not able to detect overdistention. Further, ultrasound is a good method for determining diaphragm structure and function parameters, by measuring variations in the thickness and excursion during the inspiration-expiration cycle [28-30] in both healthy and critical care patients [31,32]. Diaphragmatic excursion (DE) can be used to measure the ventilatory functionality in spontaneously breathing patients [30] while the variation in diaphragmatic thickness, also known as the diaphragm thickening fraction (TFdi), is an indicator of the diaphragm's capacity for generating pressure [31,32], and is thus an indicator of diaphragmatic failure [33]. Its limitations are the inter- and intraobserver variability and the lack of correlation between DE and diaphragmatic function in controlled mechanical ventilation [30,34,35]. A preliminary study comparing NIV and HFNC diaphragmatic and LUS measurements in ARF patients [36] reported that NIV induced a significant reduction in TFdi and LUS scores and a significant increase in DE compared to standard oxygen therapy and HFNC (while HFNC did not differ significantly from standard oxygen therapy). However, the main limitation of that study was that ultrasound cannot provide evidence of overdistension. Moreover, Palkar et al. [37] described the diaphragm excursion-time index (*E*-T index) as a new parameter to predict weaning outcome by means of diaphragm ultrasounds suggesting that the prolongation of the time until reaching the maximum excursion peak (Ti) may indicate an appropriate adaptation of the ventilatory apparatus to reduce the work of breathing. On the other hand, previous studies have shown that a significant decrease in the respiratory rate may be an indicator of successful HNFC [4,12-14,38]. In present study, we therefore introduced a variation of this index in an attempt to obtain an additive effect (Mar-index).

The present study tested the hypothesis that non-invasive respiratory support techniques such as NIV or HFNC may generate changes in pulmonary aeration or diaphragm mechanics in healthy subjects that can be detected by impedance and/or ultrasounds. The aim was to compare the differences in pulmonary aeration and diaphragm function generated by these two respiratory support strategies, NIV and HFNC, using EIT and ultrasound measurements in healthy subjects. Assessing these possible changes in healthy volunteers might help to predict their effects on patients with ARF, and might therefore provide key information for the design of future studies.

2. Material and methods

This original single-center prospective interventionist cohort study was conducted at the Critical Care Department of the Hospital del Mar in Barcelona. It was led by the research group (Critical Illness Research Group, GREPAC) at the Hospital del Mar's Institute of Medical Investigations (IMIM). The Ethics and Research Studies Committee approved the study on November 12, 2015 (IRB: 2015/6444/I) and written informed consent was obtained from all subjects prior to their recruitment. The paper was written in accordance with the STROBE recommendations.

2.1. Subjects

Twenty healthy subjects similar for age, sex and weight were recruited and randomized by blocs to (1) NIV vs (2) HFNC, and then consecutively included in the study depending on their group (first NIV and then HFNC). A loss of aeration evidenced by LUS at baseline was considered grounds for exclusion from the study.

2.2. Study procedures

Age, sex, body mass index (BMI) and smoking habit were registered. We allowed the breathing patterns to vary. However, before the baseline measurements all subjects rested for 5–10 min in order to reach a physiological steady state. Afterwards, they were ventilated and the same measurements were made after 30 min of each technique. Systolic blood pressure (BP), diastolic BP, mean BP, hearth rate (HR), respiratory rate (RR) and peripheral capillary oxygen saturation (SpO_2) were registered at baseline and at 30 min. TV was recorded in NIV group. EIT, LUS measurements and diaphragmatic ultrasound were made at baseline and at 30 min.

2.3. Application of NIV

Conditioned room air (F_IO_2 0.21) was delivered with the Respironics V60® device (Philips, Amsterdam, Netherlands) through an oronasal interface at an Inspired Positive Airway Pressure (IPAP) of 10 cmH_2O and an Expired Positive Airway Pressure (EPAP) of 6 cmH_2O throughout the procedure. The IPAP value was set to the minimum value to compensate for the resistance of the respiratory support circuit and thus ensure an acceptable TV. The EPAP value was set to match the continuous positive airway pressure generated with the HFNC, as in Parke's study [9]. The subjects were in a semi-recumbent position at 45° during the test.

2.4. Application of HFNC

Conditioned room air (F_IO_2 0.21) was delivered with the Optiflow® device (Fisher & Paykel healthcare, Auckland, New Zealand) at a constant flow of 60 L/min during 30 min. The humidifier (AIRVO®2, Fisher & Paykel Healthcare, Auckland, New Zealand) temperature was set to 37 °C, and the air was delivered by silicon nasal cannula (RT050/051®, Fisher & Paykel Healthcare, Auckland, New Zealand). The subjects were in a semi-recumbent position at 45° during the test, and breathed with their mouth closed.

2.5. Lung aeration measurements

1. **Electrical impedance tomography:** EIT was measured with the Swisstom BB^2® device (Swisstom, Landquart, Switzerland). The inner surface of the belt containing the 32 electrodes (SensorBelt®, Swisstom, Landquart, Switzerland). The belt was placed around the chest along the sixth intercostal space. EIT data were continuously recorded and later analysed on a personal computer using Swisstom's EIT Data Analyser (ibeX 1.1, Swisstom, Landquart, Switzerland). An example interface image is displayed in Fig. 1. The following EIT-derived parameters were measured at baseline and 30 min as the average of 30 consecutive breaths:
   - Region of interest (ROI). The tidal ventilation distribution was analysed by dividing the lung into three horizontal parallel regions (ROI) within the chest contour: ventral, central and dorsal. The software summed the ROIs and calculated their proportion to each other.
   - Centre of ventilation (COV). This was the geometrical focal point of the overall ventilation expressed as a percentage of the ventral-dorsal and right-left extension of the identified lung region, where 0% refers to ventilation occurring in the most ventral lung region and 100% in the most dorsal part. The same applies for the

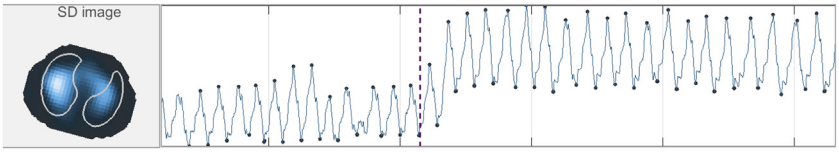

Fig. 1. Impedance changes produced by non-invasive ventilation (NIV). Note the sudden increase in arbitrary units (vertical axis) when NIV is applied.

right-left extension (0% refers to the most-right and 100% to the most left).
- Dependent and non-dependent silent spaces (DSS and NSS). The silent spaces were defined as the smallest impedance changes (<10%) of the maximal impedance change measured. They were classified into DSS and NSS by a virtual line perpendicular to the COV. Their analysis provides information about lung areas that receive less air during tidal breathing and are thus hypoventilated. If they are located on the dorsal half of the lungs (dependent areas), it is very likely that these areas will be collapsed, filled with fluid or closed; if they are located on the ventral half of the lungs (non-dependent areas), they are more likely to be distended or overdistended. The amount of silent spaces was expressed as a percentage of the entire ROI.
- End-expiratory lung impedance (EELI). EIT values at the end of the expiration (EELI) were correlated with end-expiratory lung volume (EELV), and thus with residual functional capacity and lung aeration [22,26,27]. Relative impedance values were measured in arbitrary units.
- EELI variation (ΔEELI). An increase in EELI has been associated with an increase in TV [22,26,27]. We calculated the difference between baseline and 30-min EELI.

2. **Lung ultrasound:** For the ultrasound measurements we used the Vivid I® ultrasound device (General Electric, Fairfield, CT, USA). The LUS measurements were performed with a 3.5–5 MHz probe. Four quadrants of each hemithorax were examined (anterior superior, anterior inferior, lateral superior and lateral inferior) and each one was rated according to the aeration evidenced: 0 = normal aeration (A lines or < 3 B lines); 1 = moderate loss of aeration (multiple B lines); 2 = severe loss of aeration (confluent B lines); 3 = alveolar consolidation (tissue pattern). The LUS score, ranging from 0 to 24, was calculated by adding together all the quadrant rates.

2.6. Diaphragmatic function measurements

With the subject angled at 45°, DE and TFdi were measured in all subjects at baseline and at 30 min. The same experienced observer performed all the measurements and later the blind image analysis. For the DE measurement, each individual was examined with a 3.5–5 MHz probe under the right costal ridge at the level of the middle clavicle line. Using the ultrasound device's M-mode, we calculated the mean of three measurements. For the diaphragm thickness measurements we used a 10–12 MHz probe and placed it over the 9th–10th intercostal space at the level of the anterior axillary line. The M-mode was also used to perform three measures of inspiration and three of expiration. The average values were calculated, and then the TFdi was calculated using the following formula: [(end-of-inspiration thickness - end-of-expiration thickness)/end-of-expiration thickness] per 100. An explanatory image is provided in Fig. 2.

2.7. The Mar-index

The *E*-T index was calculated as the product of DE and Ti as previously described [37]. The new Mar-index was calculated as E-T index × 100/RR.

Palkar et al. [37] described the diaphragm excursion-time index (E-T index) as a new parameter to predict weaning outcome by means of diaphragm ultrasounds. The E-T index was calculated as the product of DE and the time until reaching the maximum excursion peak (Ti). The authors suggested that the prolongation of Ti might indicate an appropriate adaptation of the ventilatory apparatus to reduce the work of breathing. On the other hand, previous studies have shown that a significant decrease in the respiratory rate may be an indicator of successful HNFC [4,12-14,38]. We therefore introduced a variation of this index in an attempt to obtain an additive effect. We named the *E*-T index × 100/RR the Mar-index (ie., defined by the Hospital del Mar team).

2.8. Statistical analysis

Sample size was obtained using the ARCSINUS approximation. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 10 subjects were required in the first group and 10 in the second group to detect a statistically significant difference in EELI between the two proportions, assuming a proportion of 0.40 in the NIV group and 0.1 in the HFNC group. A rate of 0% losses to follow-up was estimated.

Following the results of the Kolmogorov-Smirnoff test, the categorical variables were expressed as frequencies and percentages and the continuous variables as means and standard deviation (SD) when the data followed a normal distribution, or as medians and interquartile range (IR,25–75%) otherwise. The differences between the groups were analysed with the chi-square test ($\chi 2$) for categorical variables and the Student's *t*-test or the Mann-Whitney *U* test for continuous variables. For the comparison between variables in the baseline situation and at 30 min of respiratory support, t-test for paired data or the Wilcoxon test were used as necessary. Statistical significance was established at $p < 0.05$. The data were analysed using the statistical package for social sciences 15.0 (IBM® SPSS Stadystics®, Chicago, IL, USA) for Windows.

3. Results

Twenty healthy subjects were included, 10 of whom were ventilated with NIV and 10 with HFNC. There were no differences in age (32.5 (6.5) vs 34.8 (10.6) years), sex (60% females vs 40% males) or BMI (22.78 (3.40) vs 23.39 (3.60) kg/m^2) between subjects included in the two groups ($p > 0.05$). Individuals who underwent HFNC presented a decrease in diastolic BP, though it was not clinically significant (Table 1). TV in the NIV group was 890 ml (179).

EIT results are shown in Table 1 and Figs. 3 and 4. Briefly, both techniques produced a significant decrease in RR and a significant increase in EELI. NIV also induced a significant increase in NSS after 30 min of respiratory support. Furthermore, significant decreases in left central ROI were observed in the NIV group. HFNC produced a greater decrease in RR, but ΔEELI tended to be higher with NIV.

No differences were found in classical LUS or diaphragmatic parameters between baseline and 30 min measurements in either NIV or HFNC (Table 1). A significant increase in the *E*-T index was evidenced in HNFC group without significant changes in the NIV group (Table 1). However, when we calculated the E-T index changes between the two techniques the median (IQ) variation between baseline and 30 min was −0.07 (−0.69–1.10) with NIV compared with 1.27 (0.6–1.74) cm-*sec* ($p = 0.09$) with HFNC. Associating those changes with changes in respiratory rate (E-T index × 100/RR), defined as the Mar-index, we

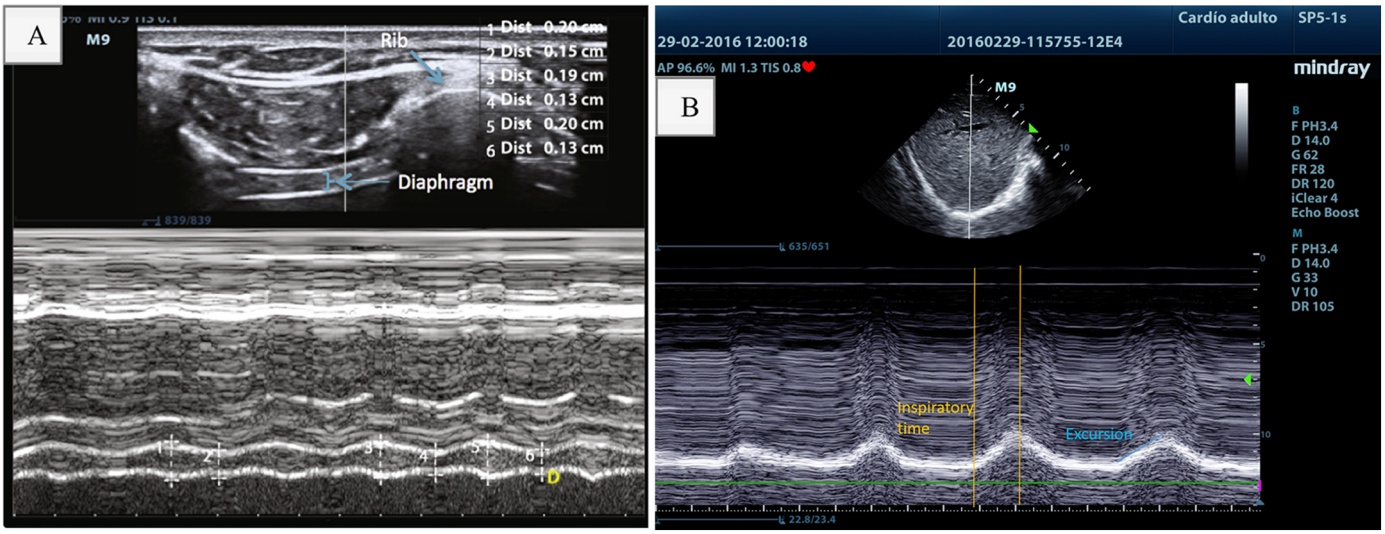

Fig. 2. (A) M-mode measurement of diaphragm thickness variation of the right hemidiaphragm. The diaphragm is seen as 3 parallel lines: 2 hyperechogenic layers and a thicker, central hypoechogenic layer. Number 1 is the inspiratory thickness and number 2 is the expiratory thickness. Diaphragm shortening fraction is the difference between the inspiratory thickness and the expiratory thickness. (B) M-mode measurement of diaphragm excursion during a normal inspiration. The diaphragm can be seen as a hyperechogenic line indicated with an arrow. The excursion is measured as the difference between the end of the inspiration and the end of expiration (cm).

found a change of 5.27 (−2.39–8.80) cm-sec^2/bpm with NIV vs 13.15 (7.36–26.51) cm-sec^2/bpm with HFNC ($p = 0.02$).

4. Discussion

In recent years, HFNC has been shown to be a good method of non-invasive respiratory support in the ICU. However, to our knowledge, this is the first study comparing ventilatory changes between NIV and HFNC in healthy semi-recumbent subjects at rest.

Our results show that both strategies increase EELI in healthy subjects because, as previous studies have demonstrated, they both produce positive airway pressure [2,3,7,9,23]. A good correlation has been described between changes in lung impedance measured by EIT and changes in lung volume [27], suggesting an increase in functional residual capacity. Even though our results were not statistically significant,

Table 1
Clinical data, EIT measurements, diaphragm ultrasound and lung ultrasound results at baseline and 30 min in NIV and HFNC groups.

	NIV			HFNC		
	n = 10			n = 10		
	Baseline	30'	p	Baseline	30'	p
Clinical data						
Systolic BP, mmHg, mean (SD)	115.8 (11.2)	111.5 (14.7)	0.190	112.2 (13.1)	110.5 (13.8)	0.730
Diastolic BP, mmHg, mean (SD)	65.7 (8.6)	64.3 (6.9)	0.473	69.6 (9.4)	63.1 (6.3)	0.021
Mean BP, mmHg, mean (SD)	82.4 (6.7)	80.0 (8.4)	0.185	83.8 (9.5)	78.9 (8.3)	0.091
HR, BPM, mean (SD)	77.6 (11.1)	70.9 (12.0)	0.078	72.5 (15.2)	71.1 (13.2)	0.575
RR, bpm, mean (SD)	14.4 (4.1)	10.4 (1.6)	0.009	13.6 (4.3)	7.9 (1.5)	0.002
SpO_2, %, mean (SD)	98.6 (0.8)	98.8 (1.3)	0.555	98.5 (1.2)	97.9 (1.8)	0.260
EIT measurements						
ROI, right ventral region, %, mean (SD)	7.14 (6.88)	7.13 (4.82)	0.993	4.93 (3.51)	5.54 (4.07)	0.288
ROI, left ventral region, %, mean (SD)	6.10 (2.74)	5.12 (2.71)	0.05	5.76 (3.37)	5.54 (2.38)	0.673
ROI right central region, %, mean (SD)	31.32 (6.34)	33.72 (6.92)	0.165	30.46 (7.00)	30.36 (7.79)	0.943
ROI, left central region, %, mean (SD)	21.57 (4.98)	18.96 (5.80)	0.034	19.51 (8.33)	20.28 (5.98)	0.580
ROI, right dorsal region, % (SD)	20.47 (8.71)	22.55 (8.41)	0.199	25.87 (11.07)	24.20 (7.03)	0.347
ROI, left dorsal region, %, mean (SD)	13.36 (3.53)	12.48 (3.72)	0.445	13.46 (3.44)	14.05 (4.72)	0.650
COV Ventral-Dorsal axis, %, mean (SD)	58.10 (5.08)	58.34 (4.41)	0.819	60.56 (4.67)	60.12 (4.68)	0.455
COV Right-Left axis, %, mean (SD)	46.11 (5.08)	43.41 (6.43)	0.066	44.36 (8.07)	44.93 (5.87)	0.720
DSS, %, mean (SD)	1.71 (2.61)	0.38 (0.91)	0.149	0.55 (0.88)	0.62 (1.14)	0.539
NSS, %, mean (SD)	4.13 (2.25)	5.81 (1.49)	0.037	5.25 (2.19)	4.94 (1.63)	0.533
EELI, AU, mean (SD)	66.348 (10.761)	73.697 (6.858)	0.005	66.252 (9.793)	69.869 (9.135)	0.012
Diaphragm ultrasound						
Right TFdi, %, mean (SD)	46 (18)	50 (19)	0.548	45 (22)	46 (26)	0.868
Left TFdi, %, mean (SD)	56 (38)	40 (18)	0.378	58 (34)	59 (20)	0.338
DE, mm, mean (SD)	22.49 (7.71)	20.20 (6.28)	0.803	20.84 (6.01)	21.18 (7.88)	0.812
ET-index, cm x sec, mean (SD)	3.0 (1.6)	3.1 (1.5)	0.432	2.8 (1.5)	4.2 (2.4)	0.005
Lung ultrasound						
LUS score, median (IR)	0.5 (0.0–1.0)	0.0 (0.0–0.5)	0.438	0.0 (0.0–1.2)	0.0 (0.0–0.2)	0.434

NIV: non-invasive ventilation, **HFNC**: high-flow nasal cannula, **BP**: blood pressure, **mmHg**: millimeter of mercury, **SD**: standard deviation, **ns**: non-statistically significant, **HR**: heart rate, **BPM**: beats per minute, **RR**: respiratory rate, **bpm**: breaths per minute, **SpO_2**: peripheral capillary oxygen saturation, **EIT**: electrical impedance tomography, **ROI**: region of interest, **COV**: center of ventilation, **DSS**: dependent silent spaces, **NSS**: non-dependent silent spaces, **EELI**: end-expiratory lung impedance, **AU**: arbitrary units, **ΔEELI**: end-expiratory lung impedance variation, **TFdi**: diaphragm thickening fraction, **DE**: diaphragm excursion, **ET-index**: diaphragm excursion-time, **LUS score**: lung ultrasound score, **IR**: interquartile range.

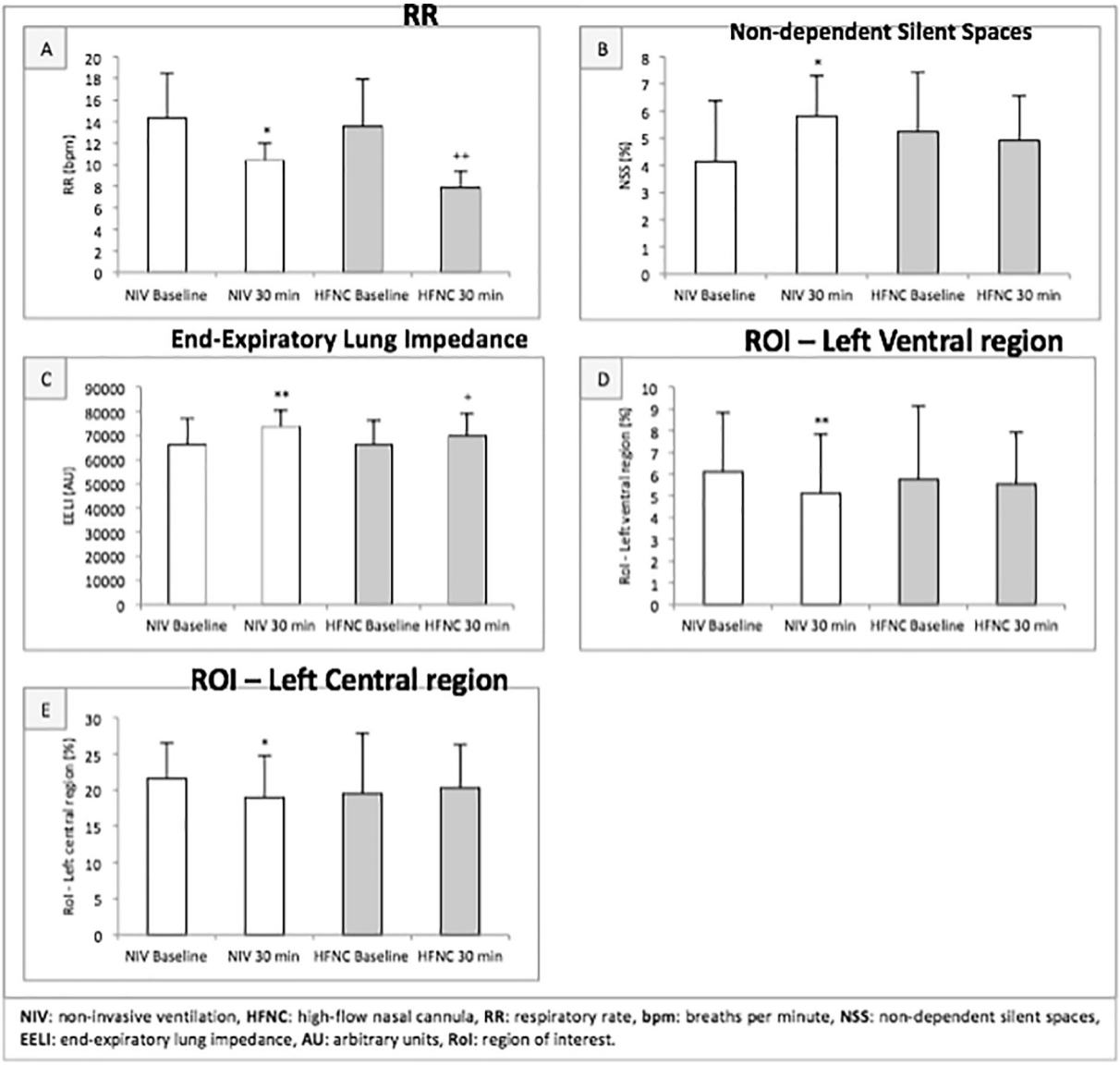

Fig. 3. Significant results between baseline and 30 min: RR (A), NSS (B), EELI (C), ROI - Left ventral region (D) and ROI - Left central region (E).

they suggest that this increase is slightly higher in NIV. However, the ventilation changes produced with HFNC are more homogeneous than with NIV. This is reflected in the significant increase of the non-dependent silent spaces in the NIV group, compared with the absence of any significant changes in the HNFC group. These homogeneous changes have previously been reported in ARF patients undergoing HFNC compared with oxygen facial mask [39]. These results may be relevant for lung injury patients, in whom NIV distribution changes may be more notable and could lead to overdistension. In that sense, Frat et al. [40] showed that HNF achieved lower mortality in the ICU and at 90 days in ARF patients compared with NIV. The authors hypothesized that this increase in mortality in NIV could be related to an increase in the ventilator-induced lung injury due to higher tidal volumes. It is probable that NIV produces this more heterogeneous aeration, and therefore the possibility of overdistension could play a fundamental role in this increase in mortality. As expected, there were no differences in any LUS measurements after NIV or HFNC. As the subjects were healthy, they presented LUS scores of 0 or very close to 0 in the baseline measure before respiratory support. These results are consistent with the preservation of aeration detected by impedance.

There is little information in the literature on the effect of these two strategies on diaphragmatic mechanics [29], probably because of the absence of a simple and accurate method for their assessment in the ICU until the introduction of diaphragm ultrasound. In the present study, no significant differences were found in classical diaphragmatic ultrasound measurements when using either NIV or HFNC. However, when we combined the assessment of the DE with the Ti and the RR to calculate the Mar-index, it was significantly higher in the HFNC group, which probably indicates differences in the adaptation of the ventilatory apparatus. TFdi seems to be the best ultrasound parameter for measuring the diaphragmatic function [33]. However, its measurement may not be easy. What is more, diaphragmatic function is not the only determinant of weaning failure or ARF. Therefore, an index that takes into accounts not just the diaphragmatic function but also adaptive capacity and ventilatory function would be very useful. In this context, the Mar-index combines the information from the *E*-T index with an important clinical

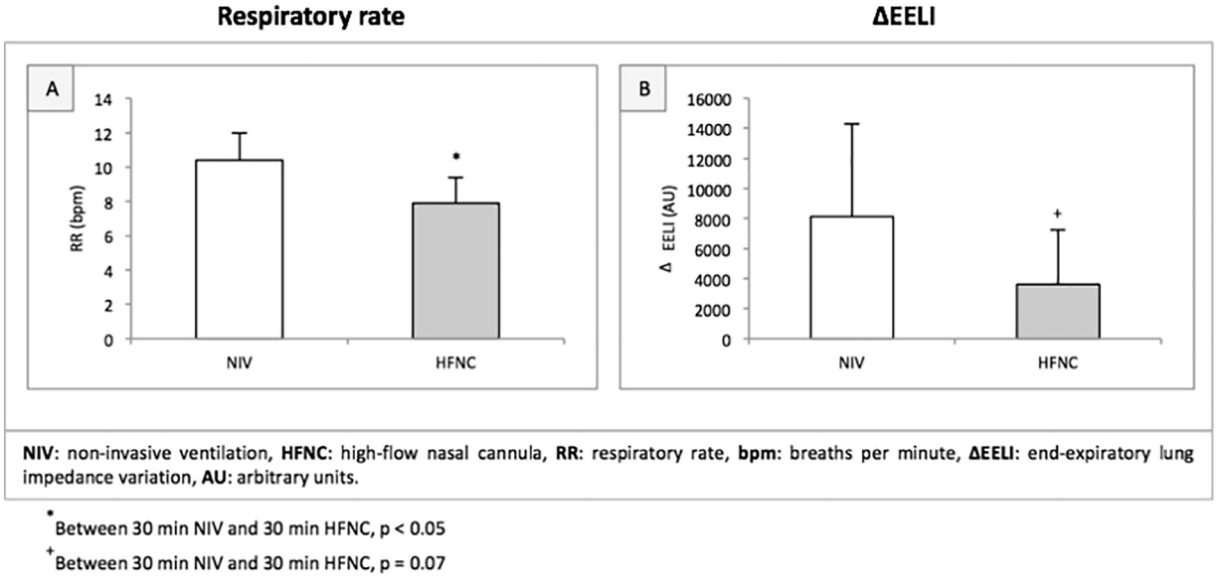

Fig. 4. Most relevant results comparing NIV and HFNC after 30 min of treatment: RR (A) and ΔEELI (B).

predictor like the respiratory rate. Therefore, it would be interesting to analyse this index during the period of weaning from mechanical ventilation or in ARF patients, and its possible relationship with outcomes.

This study has some limitations. First, the EIT only measures a cross-sectional slice of the lung, ignoring the rest of the organ. We could only measure TV directly in subjects undergoing NIV, whereas in HFNC subjects we inferred the TV variations from the EELI values. It is worth noting that several authors have reported a good correlation between variation in TV and in EELI [27]. We did not measure the partial pressure of carbon dioxide (pCO_2) because its non-invasive measurements in mechanically ventilated subjects are hard to apply and assess. Finally, these findings are only applicable to healthy subjects; however, they shed light on the different pathophysiological mechanisms by which these two systems act, and provide a rationale for the design of a study in ARF patients. While acknowledging these limitations, we stress that this is the first study to compare the lung and diaphragmatic effect (aeration and mechanics) of NIV and HFNC in healthy subjects using EIT and ultrasound measurements.

5. Conclusions

Both respiratory support strategies increase the functional residual capacity, as suggested by the RR decrease and EELI increase in our subjects. Ventilation changes produced by HFNC are more homogeneous than those produced by NIV. We also describe the Mar-index a new score that combines ultrasound with clinical changes and that could reflect the degree of the ventilatory system adaptation. This study may help to assess certain differences in aeration between these two non-invasive respiratory support techniques and thus develop new ventilatory support strategies for hypoxemic patients.

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Conflicts of interests

The authors have no conflict of interest to declare.

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References

[1] Esquinas AM, Benhamou MO, Glossop AJ, Mina B. Noninvasive mechanical ventilation in acute ventilatory failure: rationale and current applications. Sleep Med Clin 2017;12:597–606.
[2] Riera J, Pérez P, Cortes J, Roca O, Masclans JR, Rello J. Effect of high-flow nasal cannula and body position on end-expiratory lung volume: a cohort study using electrical impedance tomography. Respir Care 2013;58:589–96.
[3] Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high-flow therapy: mechanisms of action. Respir Med 2009;103:1400–5.
[4] Chatila W, Nugent T, Vance G, Gaughan J, Criner GJ. The effects of high-flow vs low-flow oxygen on exercise in advanced obstructive airways disease. Chest 2004;126:1108–15.
[5] Williams AB, Ritchie JE, Gerard C. Evaluation of a high-flow nasal oxygen delivery system: gas analysis and pharyngeal pressures. Intensive Care Med 2006;32 [Suppl. 219].
[6] Frat JP, Coudroy R, Marjanovic N, Thille AW. High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure. Ann Transl Med 2017;5:297.
[7] Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. Aust Crit Care 2007;20:126–31.
[8] Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? Pediatrics 2008;121:82–8.
[9] Parke RL, McGuinness SP, Eccleston ML. Nasal high-flow therapy delivers low level positive airway pressure. Br J Anaesth 2009;103:886–90.
[10] Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during Nasal high-flow oxygen therapy. Respir Care 2011;56:1151–5.
[11] Tiruvoipati R, Lewis D, Haji K, Botha J. High-flow nasal oxygen vs high-flow face mask: a randomized crossover trial in extubated patients. J Crit Care 2010;25:463–8.
[12] Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. Respir Care 2010;55:408–13.
[13] Sztrymf B, Messika J, Bertrand F, Hurel D, Leon R, Dreyfuss D, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. Intensive Care Med 2011;37:1780–6.
[14] Sztrymf B, Messika J, Mayot T, Lenglet H, Dreyfuss D, Ricard JD. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: a prospective observational study. J Crit Care 2011;27:324.e9–324.e13.
[15] Parke RL, McGuinness SP, Eccleston ML. A preliminary randomized controlled trial to assess effectiveness of nasal high-flow oxygen in intensive care patients. Respir Care 2011;56:265–70.
[16] Holleman-Duray D, Kaupie D, Weiss MG. Heated humidified high-flow nasal cannula: use and a neonatal early extubation protocol. J Perinatol 2007;27:776–81.
[17] Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial. J Perinatol 2006;26:481–5.
[18] Dani C, Pratesi S, Migliori C, Bertini G. High flow nasal cannula therapy as respiratory support in the preterm infant. Pediatr Pulmonol 2009 Jun;44(7):629–34.

[19] Masclans JR, Roca O. High flow oxygen therapy in acute respiratory failure. Clin Pulm Med 2012;19:127–30.
[20] Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. Chest 2015;148:253–61.
[21] Hernández G, Roca O, Colinas L. High-flow nasal cannula support therapy: new insights and improving performance. Crit Care 2017;21:62.
[22] Riera J, Riu PJ, Casan P, Masclans JR. Electrical impedance tomography in acute lung injury. Med Intensiva 2011;35:509–17.
[23] Kallet RH, Diaz J. The physiologic effects of noninvasive ventilation. Respir Care 2009;54:102–15.
[24] Corley A, Caruana LR, Barnett AG, Tronstad O, Fraser JF. Oxygen delivery through high-flow nasal cannulae increase and-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth 2011;107:998–1004.
[25] Perbet S, Betran S, Longere B, Pereira B, Futier E, Constantin JM. Effect of high-flow nasal cannula oxygen on diaphragmatic excursion and lung volumes determined by electrical impedance tomography. Intensive Care Med Exp 2015;3 [Suppl. A165].
[26] Denaï MA, Mahfouf M, Samuri SM, Panoutsos G, Brown BH, Mills GH. Absolute electrical impedance tomography (aEIT) guided ventilation therapy in critical care patients: simulations and future trends. IEEE Trans Inf Technol Biomed 2010;14:641–9.
[27] Hinz J, Hahn G, Neumann P, Sydow M, Mohrenweiser P, Hellige G, et al. End-expiratory lung impedance change enables bed-side monitoring of end-expiratory lung volume change. Intensive Care Med 2003;29:37–43.
[28] Orozco-Levi M, Gayete A, Rodríguez C, Ramírez-Sarmiento A, Méndez R, Tous F, et al. Evaluación funcional no-invasiva de la reserva ante la fatiga y la estructura del diafragma meante ecografía transtorácica en modos B y M. Arch Bronconeumol 2010;46:571–9.
[29] Baldwin CE, Paratz JD, Bersten AD. Diaphragm and peripheral muscle thickness on ultrasound: intra-rater reliability and variability of a methodology using non- standard recumbent positions. Respirology 2011;16:1136–43.
[30] Dot I, Pérez-Terán P, Samper MA, Masclans JR. Diaphragm dysfunction in mechanically ventilated patients. Arch Bronconeumol 2016;53:150–6.
[31] Vivier E, Dessap AM, Dimassi S, Vargas F, Lyazidi A, Thile A, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Med 2012;38:796–803.
[32] Matamis D, Soilemezi E, Tsagourias M, Akoumianaki E, Dimassi S, Boroli F, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Med 2013;39:801–10.
[33] Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, et al. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med 2016;42:853–61.
[34] Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by M-mode ultrasonography. Chest 2009;135:391–400.
[35] Grosu HB, Lee YI, Lee J, Eden E, Eikermann M, Rose KM. Diaphragm muscle thinning in patients who are mechanically ventilated. Chest 2012;142:1455–60.
[36] Schreiber AF, Lu Q, Adam N, Langeron O. High-flow nasal cannula versus noninvasive ventilation on lung re-aeration and diaphragm function [abstract]. European respiratory society international congress; 2017 Sep 9-13. Milan. Sheffield: European Resp Journal; 2017 [Suppl. 61].
[37] Palkar A, Narasimhan M, Greenberg H, Singh K, Koening S, Mayo P, et al. Diaphragm excursion-time index: a new parameter using ultrasonography to predict extubation outcome. Chest 2018;153:1213–20.
[38] Roca O, Messika J, Caralt B, García-de-Acilu M, Sztrymf B, Ricard JD, et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: the utility of the ROX index. J Crit Care 2016;35:200–5.
[39] Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med 2017;195:1207–15.
[40] Frat JP, Thille Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185–96.