Journal of Critical Care 53 (2019) 183–185

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Increasing support by nasal high flow acutely modifies the ROX index in hypoxemic patients: A physiologic study

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ARTICLE INFO

Keywords:
Nasal high flow
Acute hypoxemic respiratory failure
Electrical impedance tomography
Monitoring

ABSTRACT

The ROX (Respiratory rate-OXygenation) index is an early predictor of failure of nasal high flow (NHF), with lower values indicating higher risk of intubation. We measured the ROX index at set flow rate of 30 and 60 l/min in 57 hypoxemic patients on NHF. Patients with increased ROX index values at higher flow ($n = 40$) showed worse baseline oxygenation, higher respiratory rate and lower ROX index in comparison to patients with unchanged or decreased ROX index values ($n = 17$). The ROX index variation between flows was correlated with the change in end expiratory lung volume. Set flow rate during NHF might impact the ROX index value.

1. Introduction

Interest in Nasal High Flow (NHF), a non-invasive support for acute hypoxemic respiratory failure (AHRF) patients, is rapidly growing. Compared to conventional oxygen therapy, this technique may improve oxygenation and decrease the respiratory drive, possibly decreasing the need for invasive mechanical ventilation and mortality [1,2]. However, a major clinical challenge during NHF is to avoid delayed intubation by early recognition of patients lacking significant improvement [3]. The ROX (Respiratory rate-OXygenation) index was recently introduced as an early predictor of intubation and mechanical ventilation in patients with AHRF treated with NHF [4]. The ROX index was defined as the ratio of SpO_2/FIO_2 (which has a positive association with NHF success) to respiratory rate (RR, which has an inverse association). The ROX index measured at 12 h showed the best prediction accuracy for NHF success (ROX ≥4.88) or failure (ROX <3.85) in patients with pneumonia [5]. We showed that the set flow rate significantly impacts oxygenation and RR of AHRF patients on NHF [6] and in the present study, we reasoned that the ROX index might be acutely modified by increasing the set flow rate during NHF. Moreover, we hypothesized that improvement of this index at higher flow rate could be associated with more severe baseline condition in comparison to patients with stable values.

2. Material and methods

We performed a new analysis of data collected during two prospective randomized cross-over physiologic studies. [6,7] Fifty-seven non-intubated AHRF patients with $PaO_2/FiO_2 \leq 300$, recent worsening of respiratory failure and pulmonary infiltrates on chest X-ray admitted to the intensive care unit (ICU) of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy were included. Exclusion criteria were: age < 18 years; hemodynamic instability; AHRF only due to cardiac failure; severe chronic obstructive pulmonary disease and altered mental status. The Ethical Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, approved the studies (reference numbers: 628_2015 and 193_2017) and informed consent was obtained from each patient according to local regulations.

Patients were kept in semi-recumbent position without sedation and a calm environment was ensured around the patients throughout

Abbreviations: NHF, Nasal High Flow; AHRF, acute hypoxemic respiratory failure; ROX, Respiratory rate-Oxygenation; RR, respiratory rate; ΔEELV, end expiratory lung volume changes; EIT, electrical impedance tomography.

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https://doi.org/10.1016/j.jcrc.2019.06.020
0883-9441/

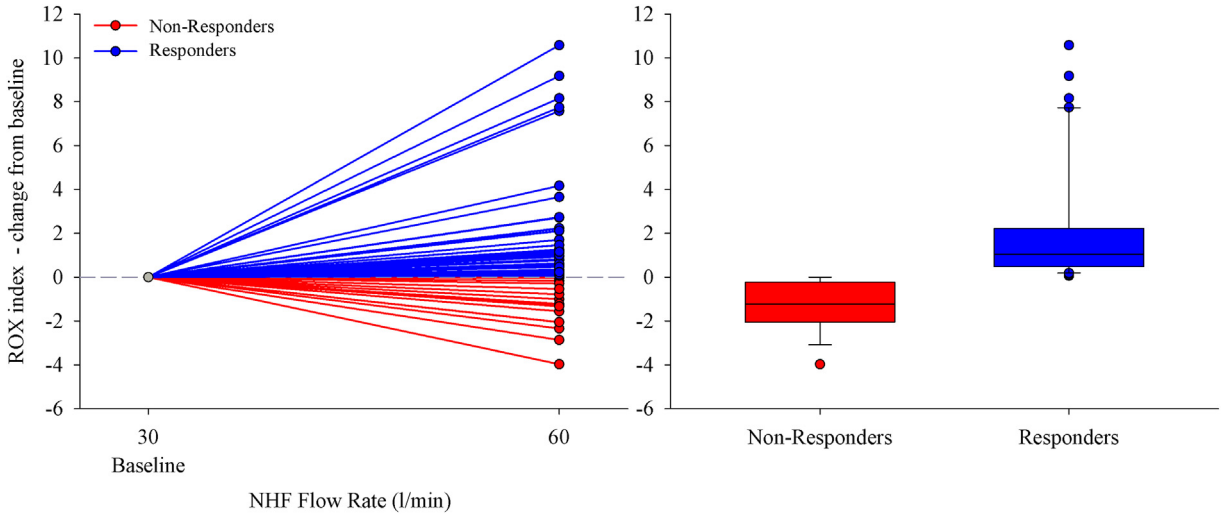

Fig. 1. Absolute change of the ROX index during nasal high flow delivered at 30 l/min (baseline) and 60 l/min. The left panel shows individual patients with unchanged or decreased ROX index (red) and patients with increased ROX index (blue). On the right panel, median values and box plots of the change in the 2 subgroups are represented ($p < .001$, see text for details).

the study. NHF was delivered through specific nasal prongs of medium or large size (AIRVO2, Fisher and Paykel Healthcare, Auckland, New Zealand) to fit the size of the nares. The set FiO_2 was clinically chosen by the attending physician to target a peripheral saturation of 90–96% and was kept constant during all phases. Temperature was set at 37 °C. Patients did not receive any instruction regarding mouth opening or closing.

At enrolment, Demographics, body mass index, presence of bilateral infiltrates, SAPS II at admission and SOFA score were collected.

Then, all patients underwent the following two study phases in computer-generated random order, with each phase lasting 20 min:

1. NHF with gas flow at 30 l/min;
2. NHF with gas flow at 60 l/min.

At the end of each study phase, we collected data on the arterial blood gas analysis, Oxygen saturation ($SatO_2$), FiO_2, respiratory rate, hemodynamics and, in a subset of 17 patients, end expiratory lung volume changes (ΔEELV) by electrical impedance tomography (EIT) [8]. ΔEELV is the change of impedance value at end expiration given a baseline period (i.e., lower set flow rate in this study) calibrated through standard spirometry performed during tidal breathing to obtain volume from impedance change. In the context of higher NHF support, increased ΔEELV signifies increased lung inflation through higher PEEP effect and alveolar recruitment. The ROX index was then calculated as $(SatO_2/FiO_2)/RR$.

Values are reported as means±std. or median [IQR] as appropriate. Comparison between groups were performed by *t*-test, Mann-Whitney Rank Sum Test or Chi-Square Test, as appropriate. A Spearman Rank Order Correlation test was used to assess a correlation between ROX index and lung volume variations (SigmaPlot 11.0, Systat Software Inc., San Jose, CA and SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

Patients were 61 [49–69] years old, 25 (44%) were female. PaO_2/FiO_2 was 199 ± 54, SOFA score 6 [3-8] and SAPSII score was 40 ± 12.

Increasing NHF set flow rate from 30 to 60 l/min led to a small but significant increase of the ROX index (10.21 [7.15–13.33] vs. 11.14 [8.81–13.93], $p = .003$), corresponding to a percentage increase of 7 [−1−20]%.

Forty patients showed an increase in ROX index at flow 60 l/min in comparison to lower flow rate (relative change: 14 [6–32]%), while 17 had unchanged or decreased ROX index at higher flow (relative change: −9 [−15 to −2]%, $p < .001$ vs. patients with increased ROX) (Fig. 1). Tidal volume, as measured by EIT, wasn't changed between the two study phases (437 ± 314 ml vs 429 ± 301 ml, $p = .525$).

The two subgroups showed significant baseline (i.e., at enrolment or during the 30 l/min phase for dynamic respiratory variables) differences in terms of set FiO_2, RR, $SatO_2$, $SatO_2/FiO_2$ and the ROX index, with patients positively responding to the "flow challenge" showing worse condition. Demographics, SAPS II score and hemodynamics, instead were not different between the 2 groups (Table 1).

The ROX index variation from 30 to 60 l/min was correlated with the corresponding ΔEELV change (Coefficient = 0.756, $p < .001$).

4. Discussion

We described that the set flow rate of NHF significantly impacts the ROX index. As this was recently suggested as early predictor of success/failure of NHF under non-protocolized clinical settings, it could be even more relevant to standardize its measurement at the lowest NHF support (i.e., 30 l/min). Interestingly, in our population, more severe patients, characterized by lower $SatO_2/FiO_2$, higher respiratory rate and lower ROX index at 30 l/min, showed larger benefits by increasing NHF flow rate. Hence, the change of ROX index during a 20-minute "flow challenge" might be helpful to identify more severe patients, likely needing closer monitoring. As a reference, absolute increase in ROX index >0 at higher flow rate might deserve shorter follow up. Finally, the finding that change increased ΔEELV was correlated with improvement of the ROX index [9] could suggest: first, that increased lung inflation might be a crucial mechanism for relieving respiratory distress; and, second, that the PEEP effect exerted by NHF support might increase adaptively in more severe patients [6], likely by increased expiratory resistance in patients with rapid shallow breathing and short expiratory time [10].

Our study has several limitations, including the relatively short observation period, the measure of EIT data only in subset of patients and the application of only two flow rates. We studied patients only during 20-minute phases, while, from a clinical perspective, longer observation periods (30–60 min) might obtain more accurate and reliable variations. Moreover, patients enrolled in this study were clinically stable, as indicated by relatively high baseline ROX index values. The effects of increasing NHF support on the ROX index might differ in patients with early unstable AHRF (i.e., the population in which we are concerned about NHF failure). In addition, the randomized crossover design can't exclude carry-over effect between the two study

Table 1
Study Results. Demographic and physiological variables of patients divided according to ROX index change after a "flow challenge" from baseline (30 l/min) to 60 l/min. Values are reported as means ± std. or median [IQR] as appropriate. *p* value refers to *t*-test, Mann-Whitney Rank Sum Test or Chi-Square Test, as appropriate.

Baseline variables	Unchanged/decreased ROX index ($N = 17$)	Increased ROX index (N = 40)	P value
Age (yrs)	56 [52–69]	62 [48–72]	0.688
Sex (N female (%))	8 (47%)	17 (43%)	0.751
SAPS II	39.5 ± 12.6	40.0 ± 11.5	0.889
SOFA	4 [3–6]	6 [3–9]	0.102
Borg dyspnea scale	2 [1–3]	3 [2–6]	0.126
FiO_2	40 [40–40]	50 [40–55]	**0.001**
RR (bpm)	18.0 [18.0–21.0]	23.5 [19.0–30.0]	**0.007**
$SatO_2$	97.0 [96.0–99.0]	96.0 [93.5–97.8]	**0.044**
$SatO_2/FiO_2$	243 [238–248]	195 [171–239]	<**0.001**
ROX index	13.61 [11.43–14.29]	8.64 [6.30–11.61]	<**0.001**
MAP (mmHg)	83 ± 12	82 ± 11	0.846
HR (bpm)	87 ± 18	87 ± 17	0.943

FiO_2 indicates inspired oxygen fraction, RR indicates respiratory rate, $SatO_2$ oxygen saturation, ROX index indicates Respiratory rate-OXygenation index, MAP mean arterial pressure, HR heart rate. Bold highlights significant differences.

phases and a wash-out period could have been performed to decrease this potential physiologic bias.

5. Conclusions

Changing flow rates between extremes of NHF support while measuring the ROX index could be a simple, rapid, bedside addition to the monitoring of AHRF patients and could further help in identifying more severe patients. Whether changes of the ROX index could improve prognostic accuracy remains to be evaluated in prospective adequately powered studies.

Declaration of Competing Interests

None.

Financial disclosure statement

Antonio Pesenti received payment for lectures and service on speaker bureau from Maquet and Novalung; has received consulting honorarium from Maquet and Novalung. All these relationships are outside the submitted work.

Dr. Mauri reports personal fees from Fisher and Paykel, outside the submitted work.

Author's contributions

TM, EC, ES, FDC, JDR, OR conceived and designed the study. TM, EC, ES, CT, FDC, RR, AP, GG participated to acquisition and analysis of data for the study. TM and EC drafted the work. All authors collaborated to interpretation of data, revising the work critically for important intellectual content and approved the version to be published. TM and AP agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sources of support

The present study was supported in part by institutional funding (Ricerca corrente 2019 – "Optimization of respiratory support and clinical management of patients with acute and chronic respiratory failure") of the Department of Anesthesia, Critical Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

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