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Early View

Original research article

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Title

High-flow oxygen therapy versus non-invasive ventilation: a randomized physiological cross-over study of alveolar recruitment in acute respiratory failure

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Substantial contributions to the conception or design of the work, E. AM., M. B. and C.G.

Acquisition, analysis, or interpretation of data for the work, E. AM., D.B., G.LB., M. B. and C.G.

Drafting the work or revising it critically for important intellectual content, E. AM., M. B. and C.G.

Final approval of the version submitted for publication, all authors.

Accountability 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, E.AM. and C.G.

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Take-home message

We found a potential benefit of HFNC and NIV on alveolar recruitment in patients with hypoxemic ARF. But, NIV also increases lung volumes which may raise to overdistension , reinforcing the concept of patient self-inficted lung injury (P-SILI).

Abstract

High-flow nasal cannula (HFNC) oxygen therapy has recently shown clinical benefits in hypoxemic acute respiratory failure (ARF) patients, while the interest of non-invasive ventilation (NIV) remains debated. The primary endpoint was to compare alveolar recruitment using global end-expiratory electrical lung impedance (EELI) between HFNC and NIV. Secondary endpoints compared regional EELI, lung volumes (global and regional tidal volume variation (TV)), respiratory parameters, hemodynamic tolerance, dyspnea and patient comfort between HFNC and NIV, relative to face mask (FM).

A prospective randomised cross-over physiological study was conducted in patients with hypoxemic ARF due to pneumonia. They received alternately HFNC, NIV and FM.

Sixteen patients were included. Global EELI was 4083 with NIV and 2921 with HFNC (p=0.4). Compared to FM, NIV and HFNC significantly increased global EELI by 1810.5 (95%CI: (857 ; 2646)) and 826 (95%CI: (399.5 ; 2361)) respectively. Global and regional TV increased significantly with NIV compared to HFNC or FM, but not between HFNC and FM. NIV yielded a significantly higher SpO_2/ FiO_2 ratio compared to HFNC (p=0.03). No significant difference was observed between HFNC, NIV and FM for dyspnea. Patient comfort score with FM was not significantly different than with HFNC (p=0.1) but was lower with NIV (p=0.001).

This study suggests a potential benefit of HFNC and NIV on alveolar recruitment in patients with hypoxemic ARF. In contrast with HFNC, NIV increased lung volumes which may contribute to overdistension and its potentially deleterious effect in these patients .

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Keywords: hypoxemic acute respiratory failure, high-flow nasal cannula oxygen therapy, non-invasive ventilation, electrical impedance tomography, alveolar recruitment.

Introduction

During severe hypoxemic acute respiratory failure (ARF), invasive or non-invasive respiratory support allows optimized oxygenation by higher inspired oxygen fraction (FiO_2), and also alveolar recruitment with positive end-expiratory pressure (PEEP).

Although non-invasive ventilation (NIV) is widely used in intensive care units (ICU), it remains controversial in hypoxemic ARF and was not recommended in the last clinical practice guidelines (1). Indeed, it has been suggested that NIV could be potentially deleterious in hypoxemic ARF, even leading to poor outcomes compared to other oxygenation techniques, especially when a high tidal volume (> 9 mL / kg of predicted body weight) are applied (2-4).

High-flow nasal cannula (HFNC) oxygen therapy has been developed more recently in adult ICU patients to overcome pitfalls with conventional oxygen therapy (O_2) (4-5) and, consequently, to optimize oxygenation in severe hypoxemic ARF (4-6). HFNC has been shown to provide a moderate PEEP effect (2 to 5 cmH_2O), depending on the level of gas flow delivered, on whether the mouth opens or not, and on the patient's size and sex (7-11). Nevertheless, the PEEP effect does not guarantee significant distal alveolar recruitment. Furthermore, evaluation of alveolar recruitment remains difficult at the patient's bedside outside invasive mechanical ventilation conditions.

Electrical impedance tomography (EIT), a non-invasive device, allows both dynamic visualization of regional distribution of pulmonary ventilation during each ventilatory cycle (tidal volume variation: TV) and measurement of end-expiratory electrical impedance (EELI), which reflects expiratory lung volume and, thus, indirectly, alveolar end-expiratory recruitment (12). EELI and TV can be measured globally or regionally from predefined lung quadrants. EIT appears, therefore, as an interesting technique for non-invasive alveolar recruitment assessment (EELI) that is both feasible and relevant in patients receiving invasive or non-invasive oxygenation support (13-18).

To our knowledge, no previous study has compared the alveolar recruitment effect by EIT between HFNC and NIV in patients with hypoxemic ARF.

The aim of our study was, therefore, to compare the level of alveolar recruitment between HFNC and NIV in patients with hypoxemic ARF. Secondary objectives were to evaluate the observed difference in regional distribution of TV, respiratory rate and

oxygenation, hemodynamic tolerance, dyspnea and comfort between HFNC and NIV, relative to FM.

Material and Methods

We performed a single-center prospective cross-over physiological study in our medical ICU between February 2016 and February 2018. It was approved by the local ethics committee (CPP-SC 001/2015) and all patients received a written information letter and gave oral consent.

Study population

Eligible patients were those referred for "de novo" hypoxemic ARF due to community acquired pneumonia confirmed by chest X-ray (17), responsible for hypoxemia (PaO2 < 60 mmHg in ambient air), without hypercapnia (PaCO2 < 45 mmHg), requiring more than 6 L/min of O2 on admission with high concentration FM for a pulse oxygen saturation (SpO2) > 94%, and requiring HFNC and NIV in alternately based on the ICU attending physician judgement and current literature (1, 2). Exclusion criteria are detailed in the online supplement.

Experimental protocol

All patients were assessed at bedside in a semi-recumbent position (45°) and alternately received standard O_2, HFNC and NIV according to the study protocol (Figure S1). The first patient included received NIV in period 1 followed by HFNC in period 2. Then, the following patients received HFNC and NIV in the reverse order of the previous patient and so on. In fact, a randomization by alternate plan was determined by the sequences order applied to the first patient. To minimize the residual effect from period 1 ("carry-over effect"), patients received FM between the 2 periods.

Oxygenation was delivered during at least 15 minutes and all measurements recorded after a breathing stabilization period of 5 minutes were analyzed.

Standard O_2 was delivered through a FM at a maximum flow rate of 15 L/min for a SpO_2 > 94% (before HFNC and NIV treatment periods).

HFNC oxygen therapy (OptiFlow®, Fisher & Paykel Healthcare, Auckland, New Zealand) was delivered at a constant flow rate of 50 L/min. The size of HFNC cannulae was chosen to maximize congruence with patients' nostrils. Patients were asked to keep their mouth closed

during HFNC periods for maximum PEEP effect. NIV was delivered with an ICU ventilator in pressure support (PS) mode. The NIV interface was a commercially available naso-buccal mask (Ultra Mirage ^{TM} NV, ResMed, Martinsried, Germany) individually fitted in order to reduce air leaks. The PS level was adjusted individually to achieve an expired tidal volume between 6-9 mL/kg of ideal body weight and an external PEEP of 5 cmH_2O was applied. FiO_2 was adjusted for a SpO_2 > 94% with both techniques.

For ethical reasons we did not perform arterial blood gas in each oxygenation condition and chose, as previously reported (19, 20), the SpO_2/FiO_2 ratio to compare the quality of oxygenation between devices. For FM, FiO_2 was estimated using the following standardized formula: $FiO_2 = 0.21 + oxygen\ flow\ rate \times 0.03$ (19).

EIT measurements (global and regional EELI and TV values) were performed with the Pulmovista® device (Dräger, Lübeck, Germany). Measurements are detailed in the online supplement as well as other data collected.

Statistical analysis

The sample size was based on previous similar physiological studies in this field (17-18, 21-22). Patients' characteristics were described using median, first and third quartiles $[Q1\ ;\ Q3]$ for quantitative variables and absolute numbers with their percentage for categorical variables. The median difference between HFNC and NIV, and its 95% confidence interval (CI), were estimated using the Wilcoxon signed rank test or the sign test (23).

In absence of evidence for an interaction and a residual effect (Tables S1 and S2), secondary aims were to compare the results observed with HFNC and NIV, relative to those observed with FM. These comparisons were carried out as described above for HFNC and NIV.

A p value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, USA).

Results

Study population

Sixteen consecutive patients were included (7 women and 9 men); 8 received NIV first and 8 HFNC first. Patient characteristics and their main outcome data are reported in table 1. Median FiO_2 was 60% [48;70] with a constant flow rate of 50 L/min with HFNC. Median

values for FiO_2 and PS level were 55% [48;70], and 8 cmH_2O [8;9], respectively with NIV, with a PEEP level set at 5 cmH_2O for all patients.

Table 1: Patients characteristics and outcome data

Patients	Age (y)	Sex	BMI	SAPSII	SOFA	Localization of lung consolidation *(ROI 1,2,3 or 4)*	Delay between admission and inclusion *(days)*	Intubation *(Y/N)*	ICU length of stay *(days)*	Death *(Y/N)*
1	63	M	25	27	4	3	0	N	6	N
2	22	F	28	25	3	4	3	N	5	N
3	38	M	22	22	4	2	4	N	6	N
4	19	M	17	15	2	1	6	N	10	N
5	55	M	33	31	3	1	3	N	2	N
6	53	M	40	56	9	3	15	N	17	N
7	71	M	26	27	1	3	2	N	3	N
8	86	M	25	47	4	1	2	N	7	N
9	46	F	36	16	3	3	6	N	5	N
10	42	M	21	32	1	4	2	N	6	N
11	27	M	23	12	6	1	2	N	2	N
12	54	F	21	21	5	3	2	Y	17	Y
13	47	F	21	28	2	4	3	N	4	N
14	69	F	22	48	9	3	9	Y	23	N
15	56	F	26	33	2	3	3	N	6	N
16	33	F	46	20	2	4	4	N	5	N
Total or median[Q1 ;Q3]	50 [37;58]	7 Female/ 9 male	25 [22;29]	27 [21;32]	3 [2;4]	4 *ROI1*; 1 *ROI2*; 7 *ROI3*; 4 *ROI4*	3 [2;5]	2 Yes/ 14 No	6 [5;8]	1 Yes/ 15 No

BMI: Body Mass Index (kg/m^2), SAPSII: Simplified Acute Physiology Score II, SOFA: Sepsis Related Organ Failure Assessment, ICU: intensive care unit, ROI: region of interest, Y: yes, N: no, [Q1 ;Q3]: interval covering 1st and 3rd quartile].

Comparison between HFNC and NIV

No significant difference was found for global EELI between NIV (4083 [2928;5134]) and HFNC (2921 [1706;4850]) as the 95%CI for the difference ranged from -1649.5 to +824.0 (p=0.4). Regional analysis of EELI (figure S1) found no significant difference between HFNC and NIV (Table 2), except for ROI1 (95%CI: (-570.5;+110.0); p=0.01). Regarding TV, global TV was significantly higher with NIV (3161 [1884;3805]) than with HFNC (2323 [1497;2891]; p=0.001). Similarly, regional TV was found higher with NIV than with HFNC in ROI1, ROI2, ROI3 and the consolidation area, but there was no difference in ROI4 TV between NIV (444 [318;861]) and HFNC (ROI4 TV NIV vs HFNC: 444 [318;861] vs 450 [286;664]; p=0.06) (Table 2 and Figure 1). The SpO_2/FiO_2 ratio and SpO_2 were significantly higher with NIV than with HFNC (167 [143;200] vs 163 [140;200]; p=0.001 and 100 [98;100] vs 97 [96;100]; p=0.010 respectively). No significant difference was observed between HFNC and NIV for other physiological parameters (Table 2).

Table 2: Comparison between physiological effects of NIV and HFNC

EIT and Clinical data	NIV	HFNC	HFNC-NIV			
	Median	Median	Median	95% CI limits		p-value*
				lower	upper	
TV global (units)	3161[1884 ; 3805]	2323 [1497 ; 2891]	-678.0	-947.5	-322.0	**0.001**
TV ROI1 (units)	887 [657 ; 1033]	590 [464 ; 774]	-204.5	-279.5	-122.0	**0.0007**
TV ROI2 (units)	686 [413 ; 925]	445 [262 ; 656]	-214.0	-309.0	-130.0	**0.0003**
TV ROI3 (units)	743 [498 ; 1008]	589 [271 ; 909]	-118.5	-221.5	0.0	**0.04**
TV ROI4 (units)	444 [318 ; 861]	450 [286 ; 664]	-93.5	-200.0	7.5	0.06
TV consolidation (units)	778 [338 ; 1002]	489 [198 ; 783]	-133.0	-215.0	-53.5	**0.004**
EELI global (units)	4083 [2928 ; 5134]	2921 [1706 ; 4850]	-570.5	-1649.5	824.0	0.4
EELI ROI1 (units)	842 [646 ; 1144]	562 [215 ; 1000]	-329.0	-570.5	-110.0	**0.01**
EELI ROI2 (units)	960 [469 ; 1406]	408 [355 ; 1152]	-174.0	-563.0	79.5	0.1
EELI ROI3 (units)	767 [336 ; 1124]	618 [370 ; 1251]	-101.0	-487.0	476.0	0.5
EELI ROI4 (units)	846 [488 ; 971]	447 [373 ; 738]	-196.0	-491.5	733.0	0.4
EELI consolidation (units)	899 [767 ; 1144]	486 [381 ; 946]	-322.5	-588.5	178.5	0.1
RR (bpm)	24 [22 ; 27]	23 [21 ; 26]	-2	-4	4	0.6
SpO2/FiO2 ratio	167 [143 ; 200]	163 [140 ; 200]	-4.5	-15.5	-2.0	**0.001**
SpO2 (%)	100 [98 ; 100]	97 [96 ; 100]	-2	-3	0	**0.010**
HR (bpm)	84 [68 ; 98]	90 [78 ; 104]	1	-2	5	0.8
SBP (mmHg)	119 [108 ; 131]	125 [113 ; 137]	3	-1	11	0.2
MAP (mmHg)	80 [76 ; 89]	85 [77 ; 94]	2	-3	5	0.6
Dyspnea score (0;10)	5 [0 ; 5]	5 [2 ; 5]	0	-1	1	0.7
Patient comfort score (0;10)	4 [2 ; 5]	5 [4 ; 7]	0	-1	4	0.7

HFNC: high-flow nasal cannula, NIV: non-invasive ventilation, TV: tidal volume variation, EELI end-expiratory lung impedance, RR: respiratory rate, SpO2: pulse oxygen saturation, HR: heart rate, SBP: systolic blood pressure, MAP: mean arterial pressure. All values are expressed as median [Q1 ;Q3]; * := Wilcoxon signed rank test

Comparison between HFNC and FM

Global EELI increased significantly with HFNC compared to FM (1444 [992;3468] vs 2921 [1706;4850]; p<0.0001). Regional EELI was higher with HFNC in ROI3, ROI4 and the consolidation area, but did not differ significantly in ROI1 and ROI2 (Table 3). We did not find any significant difference for global or regional TV between HFNC and FM. Mean arterial pressure (MAP) increased significantly between HFNC and FM. No significant difference was observed for RR, HR, SBP, SpO_2/FiO_2, SpO_2, dyspnea score and patient comfort (Table 3).

Table 3: Comparison between physiological effects of face mask and HFNC

EIT and Clinical data	FM	HFNC	HFNC-FM			
	Median	Median	Median	95% CI limits		p-value*
				lower	upper	
TV global (units)	2240 [1421 ; 2752]	2323 [1497 ; 2891]	-3.0	-138.5	153.5	0.9
TV ROI1 (units)	618 [440 ; 692]	590 [464 ; 774]	-30.0	-96.0	35.0	0.3
TV ROI2 (units)	408 [295 ; 703]	445 [262 ; 656]	-18.5	-63.5	37.0	0.4
TV ROI3 (units)	597 [287 ; 816]	589 [271 ; 909]	14.5	-27.5	113.0	0.5
TV ROI4 (units)	290 [200 ; 708]	450 [286 ; 664]	15.0	-21.0	77.0	0.4
TV consolidation (units)	290 [233 ; 760]	489 [198 ; 783]	2.5	-57.0	40.5	0.9
EELI global (units)	1444 [992 ; 3468]	2921 [1706 ; 4850]	826.0	399.5	2361.0	**<0.0001**
EELI ROI1 (units)	278 [91 ; 634]	562 [215 ; 1000]	161.5	-19.5	322.5	0.05
EELI ROI2 (units)	325 [181 ; 531]	408 [355 ; 1152]	187.5	-31.5	464.0	0.1
EELI ROI3 (units)	378 [125 ; 446]	618 [370 ; 1251]	220.0	57.0	719.0	**0.01**
EELI ROI4 (units)	309 [130; 499]	447 [373 ; 738]	169.5	31.0	1104.0	**0.01**
EELI consolidation (units)	283 [125 ; 477]	486 [381 ; 946]	138.0	24.5	613.0	**0.01**
RR (bpm)	25 [23 ; 28]	23 [21 ; 26]	-3	-6	1	0.2
SpO2/FiO2 ratio	152 [147 ; 152]	163 [140 ; 200]	16.0	-6.0	48.0	0.1
SpO2 (%)	100 [97; 100]	97 [96 ; 100]	0	-2	1	0.5
HR (bpm)	82 [72 ; 102]	90 [78 ; 104]	1	-2	4	0.4
SBP (mmHg)	118 [107 ; 133]	125 [113 ; 137]	6	0	9	0.1
MAP (mmHg)	81 [74 ; 92]	85 [77 ; 94]	2	1	7	**0.01**
Dyspnea score (0;10)	0 [0 ; 5]	5 [2 ; 5]	0	0	3	0.3
Patient comfort score (0;10)	8 [4 ; 9]	5 [4 ; 7]	-2	-4	0	0.1

FM: face mask before HFNC, HFNC: high-flow nasal cannula, TV: tidal volume variation, EELI: end-expiratory lung impedance, RR: respiratory rate, SpO_2: pulse oxygen saturation, HR: heart rate, SBP: systolic blood pressure, MAP: mean arterial pressure. All values are expressed as median [Q1 ;Q3]; * := Wilcoxon signed rank test

Comparison between NIV and FM

Global EELI increased significantly with NIV compared to FM (1999 [764;2779] vs 4083 [2928;5134]; p=0.001). Regional EELI was higher with NIV than with FM in all ROIs (Table 4). Variations in global and regional EELI between NIV and FM are shown in table 4. A significantly higher global and regional TV was observed with NIV than with FM. The SpO_2/FiO_2 ratio was higher with NIV than with FM without any difference in SpO_2. Patient comfort score was significantly lower with NIV than with FM (Table 4).

Table 4: Comparison between physiological effects of face mask and NIV						
EIT and Clinical data	**FM**	**NIV**	**NIV-FM**			
	Median	**Median**	**Median**	**95% CI limits**		**p-value***
				lower	**upper**	
TV global (units)	2402 [1641 ; 3050]	3161 [1884 ; 3805]	606.0	441.5	792.0	**<0.0001**
TV ROI1 (units)	593 [566 ; 737]	887 [657 ; 1033]	182.5	97.0	269.0	**0.001**
TV ROI2 (units)	479 [321 ; 683]	686 [413 ; 925]	182.5	122.5	251.0	**<0.0001**
TV ROI3 (units)	649 [427 ; 836]	743 [498 ; 1008]	132.5	73.5	194.5	**0.0002**
TV ROI4 (units)	383 [259 ; 772]	444 [318 ; 861]	98.5	17.0	178.0	**0.02**
TV consolidation (units)	593 [160 ; 819]	778 [338 ; 1002]	151.0	58.0	215.5	**0.009**
EELI global (units)	1999 [764 ; 2779]	4083 [2928 ; 5134]	1810.5	857.0	2646.0	**0.001**
EELI ROI1 (units)	327 [115 ; 618]	842 [646 ; 1144]	518.0	315.5	779.0	**<0.0001**
EELI ROI2 (units)	361 [135 ; 880]	960 [469 ; 1406]	457.5	130.0	818.0	**0.009**
EELI ROI3 (units)	317 [144 ; 567]	767 [336 ; 1124]	414.0	76.0	678.5	**0.02**
EELI ROI4 (units)	382 [115 ; 572]	846 [488 ; 971]	374.0	108.0	670.5	**0.01**
EELI consolidation (units)	562 [160 ; 776]	899 [767 ; 1144]	404.5	59.0	718.0	**0.02**
RR (bpm)	26 [25 ; 30]	24 [22 ; 27]	-2	-6	2	0.6
SpO2/FiO2 ratio	152 [145 ; 152]	167 [143 ; 200]	21.0	2.5	50.0	**0.03**
SpO2 (%)	100 [96 ; 100]	100 [98 ; 100]	0	0	2	0.3
HR (bpm)	85 [79 ; 103]	84 [68 ; 98]	-1	-3	5	0.8
SBP (mmHg)	122 [109 ; 129]	119 [108 ; 131]	-1	-7	11	1.0
MAP (mmHg)	84 [77 ; 91]	80 [76; 89]	-1	-2	4	1.0
Dyspnea score (0;10)	2 [0 ; 5]	5 [0 ; 5]	0	-1	3	0.5
Patient comfort score (0;10)	8 [5 ; 10]	4 [2 ; 5]	-3	-5	-1	**0.001**

FM: face mask before NIV, NIV: non-invasive ventilation, TV: tidal volume variation, EELI: end-expiratory lung impedance, RR: respiratory rate, SpO_2: pulse oxygen saturation, HR: heart rate, SBP: systolic blood pressure, MAP: mean arterial pressure. All values are expressed as median [Q1 ;Q3]; * := Wilcoxon signed rank test

Discussion

In this study, we have compared the physiological effects of different oxygenation techniques used in the non-invasive management of hypoxemic ARF secondary to pulmonary infection. We found that both HFNC and NIV increased EELI relative to FM, but, unexpectedly, that there was no significant difference in EELI, i.e., alveolar recruitment between HFNC and NIV. Interestingly, we found that NIV increased TV relative to HFNC and FM whereas HFNC did not increase TV relative to FM. Also, better oxygenation (SpO_2/FiO_2) was observed with NIV despite similar FiO_2 levels between HFNC and NIV. Patient comfort was found better with FM, similar to HFNC, but worse with NIV relative to FM.

One previous study showed a close relationship between EELI measured by EIT and end-expiratory lung volume (EELV) measured by an open-circuit, wash-out maneuver during a PEEP titration maneuver from 0 to 15 mBar in 10 patients mechanically ventilated in volume-controlled mode (14). These results suggest that EELI measured with EIT is strongly correlated with EELV and therefore with pulmonary alveolar recruitment or overdistension. Consequently, changes in EELI results observed between the different oxygenation techniques in the present study can be interpreted as changes in EELV, i.e., alveolar recruitment rather than hyperinflation (14, 24).

We found that NIV increased EELI, i.e., alveolar recruitment, both in global lung and all dependent and non-dependent lung areas (ROIs), including the consolidation area, relative to FM. To our knowledge, this is the first comparative analysis of alveolar recruitment between FM and NIV. In obese patients, three preoxygenation techniques were compared before intubation and a significant increase in EELI after intubation was found among those who received preoxygenation with NIV or NIV plus recruitment maneuvers, relative to those receiving preoxygenation with a simple high-concentration FM (25). However, this study did not provide any comparative EELI results between NIV and FM in any patient before intubation.

In parallel with increased EELI, we observed that NIV also increased TV globally throughout the lung and regionally in all dependent or non-dependent ROIs. It has been demonstrated that tidal volume, measured by pneumotachograph, could be increased by nearly 300 mL with NIV in COPD patients with acute exacerbation, relative to standard O_2 (26). However, in contrast with our study, the regional distribution of this volume was not evaluated. The

increase of TV in dependent (ROI3 + ROI4) and non-dependent regions (ROI1 + ROI2) observed in our study could further explain the potentially deleterious effect of NIV in hypoxemic ARF. Indeed, it has been suggested that NIV might increase intubation and mortality rates in more severe hypoxemic ARF (PaO2/FiO2 ≤ 200 mmHg) relative to standard O_2 or HFNC alone (2). This poor NIV outcome has been linked to frequent excessive expiratory tidal volumes in hypoxemic ARF, above 9.5 mL/kg of predicted body weight (3). In fact, as described with invasive mechanical ventilation, NIV could induce lung injury in *de novo* ARF related to increased expiratory tidal volume due to excessive respiratory drive. Finally, these features have led some experts to define the recent concept of patient self-inflicted lung injury (P-SILI) (27). Therefore, our finding could add further knowledge to this new physiopathological concept, suggesting a potential excess and heterogeneity in lung volume distribution with NIV responsible for overdistension in healthy areas in hypoxemic ARF.

Demonstrating a significant increase in EELI with HFNC relative to FM, our study also confirms a potential PEEP effect and alveolar recruitment with HFNC. Such an effect was previously demonstrated in comparison with FM not only in healthy volunteers (27) but also in postoperative patients undergoing cardiac surgery (17), and more recently in hypoxemic ARF patients (21). The increase in EELI observed with HFNC appears in fact proportional to the increase in the HFNC flow rate used in these studies (17, 22, 27). By testing increasing flow rates with HFNC and measuring EELI, TV, inspiratory effort, compliance and oxygenation in 17 hypoxemic ARF patients, Mauri et al. (21) found not only a linear increase in EELI, but also no significant change in TV with HFNC relative to FM. As in our study, EELI significantly increased in global lung and dependent ROIs, but not in non-dependent ROIs. In contrast, we also specifically evaluated EELI changes in the consolidation area. Finally, our results are consistent with those of Mauri et al. (21), demonstrating that, relative to FM, HFNC can significantly increase EELI in global lung as well as dependent ROIs but without any deleterious effect on global or regional TV. Moreover, the absence of increase in TV with HFNC suggests that alveolar recruitment can be achieved without risk of overdistension in healthy as well as pathologic lung areas.

Perez-Teran et al. (28) compared HFNC and NIV effect on EELI in healthy subjects. EELI significantly increased with HFNC and NIV but NIV subjects showed a significant increase in non-dependent regions while the increase was more homogeneous with HFNC. To our

knowledge, our study is the first to compare EELI and TV between HFNC and NIV, relative to FM in patients with hypoxemic ARF. Only one recent study has physiologically compared HFNC with NIV using helmet (29). These results suggested that helmet-NIV could be more effective than HFNC for moderate-to-severe hypoxemic ARF. Nevertheless, TV measurements were not provided to exclude potential regional overdistension during helmet-NIV.

We found no evidence for differences in EELI between techniques, either in global lung or in each ROI including the consolidation area, except in ROI1, a non-dependent lung region. In fact, although we have found a potential similar PEEP effect and alveolar recruitment reflected by EELI with HFNC and NIV, these results should taken into account the different settings applied in our study with these two techniques. Moreover, although NIV did not improve alveolar recruitment relative to HFNC, we found that NIV significantly increased TV by 26% in global lung, by 36% in non-dependent lung regions (ROI1 + 2) and by 17% in dependent lung regions (ROI3 + 4), suggesting a higher risk of overdistension with NIV relative to HFNC. In fact, this increase in TV was observed in our study despite the use of non-aggressive NIV settings, i.e., a PS level for an expiratory tidal volume of 6-9 mL/kg, as previously suggested (3). As mentioned above, this unexpected increase in lung volume associated with an excess in respiratory drive could be responsible for P-SILI (26) and, consequently, for failure and poor outcome with NIV in hypoxemic ARF (2, 3). In our opinion, such a risk with NIV should favor the use of HFNC given the absence of additional alveolar recruitment with NIV. Regarding oxygenation, NIV significantly increased the SpO_2/FiO_2 ratio when compared to HFNC but no difference was observed between NIV and FM, or between HFNC and FM. These results could appear, therefore, somewhat discordant with those of previous studies, as Parke et al. (10) found better oxygenation with HFNC compared to FM. In another study comparing NIV, HFNC and mask with equal FiO_2, NIV allowed the best oxygenation performance relative to HFNC and FM, and HFNC was also found more efficient than FM (30). The population size of these studies (10, 30) was similar to ours, but one explanation for the discrepancy in oxygenation performance could be the fact that we did not perform arterial blood gases but only used the SpO_2/FiO_2 ratio at the end of each experimental period rather than the PaO_2/FiO_2 ratio. The SpO_2/FiO_2 ratio can exhibit, however, some limitations mainly if SpO_2 is over 95% (31).

We also evaluated patients' dyspnea and respiratory comfort. We did not find any difference in dyspnea Borg scale between HFNC, NIV and FM, in contrast with one study reporting an improvement in dyspnea with HFNC compared to NIV or Venturi mask (30). Respiratory comfort was also found similar between HFNC and NIV or HFNC and FM, but less with NIV relative to FM. Respiratory comfort is, however, highly subjective and other authors reported NIV as the least comfortable among the three techniques (7, 30).

Our study has several limitations. First, similarly to previous studies (16, 17), we did not measure lung volumes directly to objectively assess alveolar recruitment and PEEP effect or eliminate pulmonary overdistension. Indeed, EIT being an indirect and incomplete evaluation of pulmonary volumes and recruitment, a concomitant assessment of lung volumes with a pneumotachograph could be useful and relevant to optimize the dynamic evaluation of the ventilatory mechanics (22). Second, it was a physiological study conducted in a short-time span. However, based on previous studies (17, 21), a 15-minute period could be considered as sufficient to obtain a stable effect on lung volumes and gas exchanges. Third, we applied oxygenation and ventilation parameters similar to those used in the FLORALI trial (2) to perform EELI and TV measurements. However we are aware that other settings (PS and PEEP level with NIV, HFNC flow rate) might give rise to other results. Fourth, comparison of a "ventilatory" support effect between HFNC and NIV would have been of additional interest. Indeed, although HFNC is primarily considered as an oxygenation technique, it was recently demonstrated that HFNC could also reduce the work of breathing in hypoxemic ARF patients (21). Fifth, our relative small sample size, although in line with previous physiological studies (15, 19), could have underpowered the study to detect a potential difference between NIV and HFNC on EELI. Sixth, we exclusively included hypoxemic or "*de novo*" ARF patients with pneumonia for pulmonary homogeneity considerations. Most patients had predominant unilateral pulmonary condensation on chest X-ray, but some bilateral infiltrates may have introduced some heterogeneity. Lastly, EIT imaging displays only one horizontal part of the lungs with regard to the electrode belt and, therefore, cannot measure global lung volume changes along the vertical axis. However, previous studies demonstrated good agreement between EIT measurements of lung volume changes and those obtained by other validated methods (spirometry and plethysmography) (32, 33). Futhermore, Hinz J et al. (14) have demonstrated that the cross-sectional lung electrical impedance variation was correlated with end-expiratory lung volumes during PEEP

trial in mechanically ventilated adults. Moreover, the cross-over design of our study might have made the comparison of EIT measures more accurate.

Conclusion

Our physiological study, comparing for the first time HFNC and NIV in hypoxemic ARF, demonstrates an increase in end-expiratory lung volume with both techniques, suggesting a similar potential alveolar recruitment relative to FM. In contrast with HFNC and although NIV improves oxygenation, NIV could also increase lung volumes which may contribute to overdistension and explain its potentially deleterious effect in these hypoxemic ARF patients.

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Online data supplement

High-flow oxygen therapy versus non-invasive ventilation: a randomised physiological cross-over study of alveolar recruitment in acute respiratory failure

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Online data supplement methods:

Study population:

Patients were excluded if they had cardiogenic pulmonary edema, moderate to severe underlying respiratory disease including chronic obstructive pulmonary disease (COPD), contraindication to or failure of previous NIV or HFNC with the need for immediate invasive ventilation, pregnant or breast-feeding women, carriers of an implantable defibrillator or pacemaker, body mass index (BMI) >50 kg/m^2, or with a cutaneous lesion next to the positioning zone of the Pulmovista® belt.

EIT measurements

EIT measurements (EELI, TV) were performed with the Pulmovista® device (Dräger, Lübeck, Germany) which had been calibrated and self-tested according to the manufacturer's instructions. EIT signal was filtered. The electrode belt was placed considering the largest consolidation area highlighted on chest X-ray or CT-scan (Figure S2). We defined 4 standardized quadrants (the same for all patients) in the thorax section: 2 anterior quadrants (ROI1 and 2), non-dependent zone, and 2 posterior quadrants (ROI3 and 4), dependent zone. EELI and TV were recorded continuously during at least 15 minutes in the different oxygenation conditions and their measurements were expressed in arbitrary units. All EIT data were saved in real time in the Pulmovista® hard drive, downloaded into a personal computer for offline analysis with Dräger review software (Dräger EIT Data Analysis Tool v6.1). For each period, after a period of breathing stabilization, EELI and TV values were averaged from data recorded during 5 minutes, and than, analyzed regionally by defining regions of interest (ROIs) according to 4 quadrants and globally (all ROIs together), including the ROI with the largest alveolar consolidation (Figure S2). EELI and TV values were recorded for each patient with HFNC, NIV and FM following an alternate plan (figure S1). We

compared EELI and TV values obtained with NIV and HFNC. For the comparison of HFNC and NIV with FM, we analyzed the FM data recorded just before HFNC or NIV period

Data collection

In addition to EIT measurements (global and regional EELI and TV values), the following data were collected for each patient: age, sex, body mass index, Simplified Acute Physiology Score (SAPS) II and Sepsis Related Organ Failure Assessment (SOFA) score at ICU admission, localization of the main consolidation on chest X-ray, delay between ICU admission and inclusion, respiratory rate (RR), SpO2/FiO2 ratio, heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP), dyspnea with Borg scale, and patient comfort with a 10-point scale (0=least comfort and 10=most comfort), length of ICU stay, need for invasive mechanical ventilation, and ICU mortality.

Statistical analysis

In order to compare patients receiving NIV first with those receiving HFNC first, just before the start of period 1, i.e. at baseline, Freeman-Halton's extension of Fisher's exact test was employed for categorical variables, and Wilcoxon's test for independent samples for quantitative variables (Table S1). The latter test was also used to check for the presence of a treatment order effect, and the trend over time, i.e. the period effect, was examined with the signed rank test for quantitative variables (Table S2).

A p value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, USA).

Figure S1. Study protocol, electrode position of the electrical impedance tomography (EIT) belt and lung volume modelization.

A. Progress of the experiment: after study inclusion, the first patient included received NIV in period 1 followed by HFNC in period 2. Then, the following patient received HFNC and NIV in the reverse order of the previous patient. To minimize the residual effect from period 1, patients received FM between the 2 periods. Oxygenation was delivered during at least 15 minutes. During this time, EIT measures were recorded. Electrical impedance tomography lay out: B. 16 electrodes united within the same belt were placed on the thorax of the patient facing the alveolar zone of condensation. The reference electrode R was placed on the abdomen. C. Functional EIT images in the acquisition zone defined by the belt. D. Subdivision of the acquisition area into 4 standardized quadrants or regions of interest (ROI) numbered from 1 to 4.

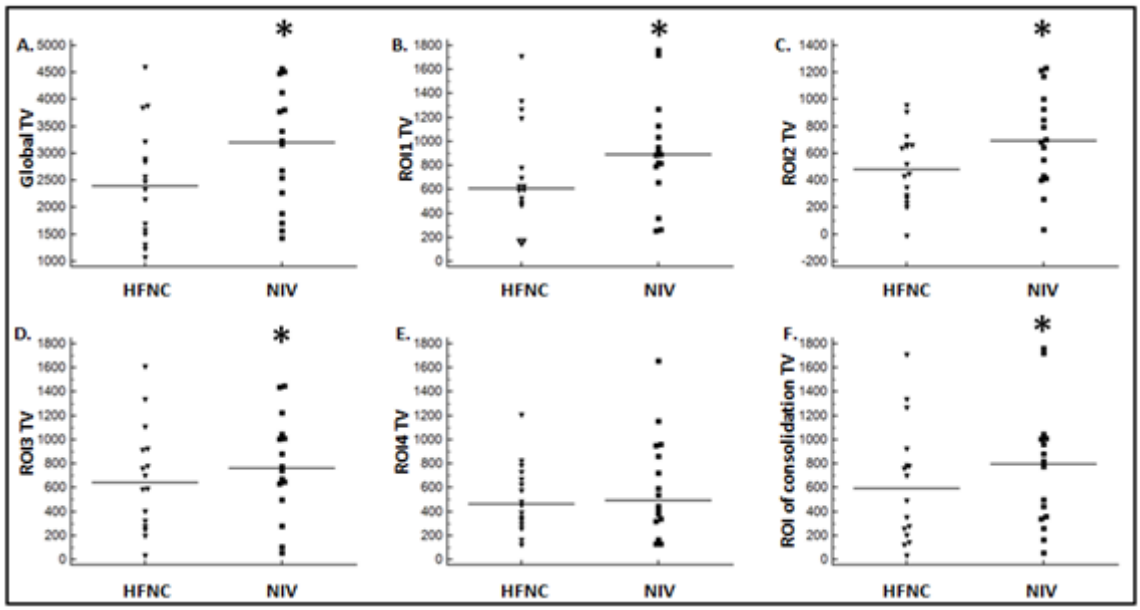

Figure S2. Electrical impedance tomography recordings.
EIT: electrical impedance tomography, A: respiratory rate, global and regional tidal variation (TV) in the four regions of interest (ROI) chosen. End-expiratory lung impedance (EELI) measured by EIT in global lung and in each ROI showing the evolution of EELI between B: face mask (green arrows) and NIV (pink arrows) periods; C: HFNC (red arrows) and face mask (green arrows) periods.

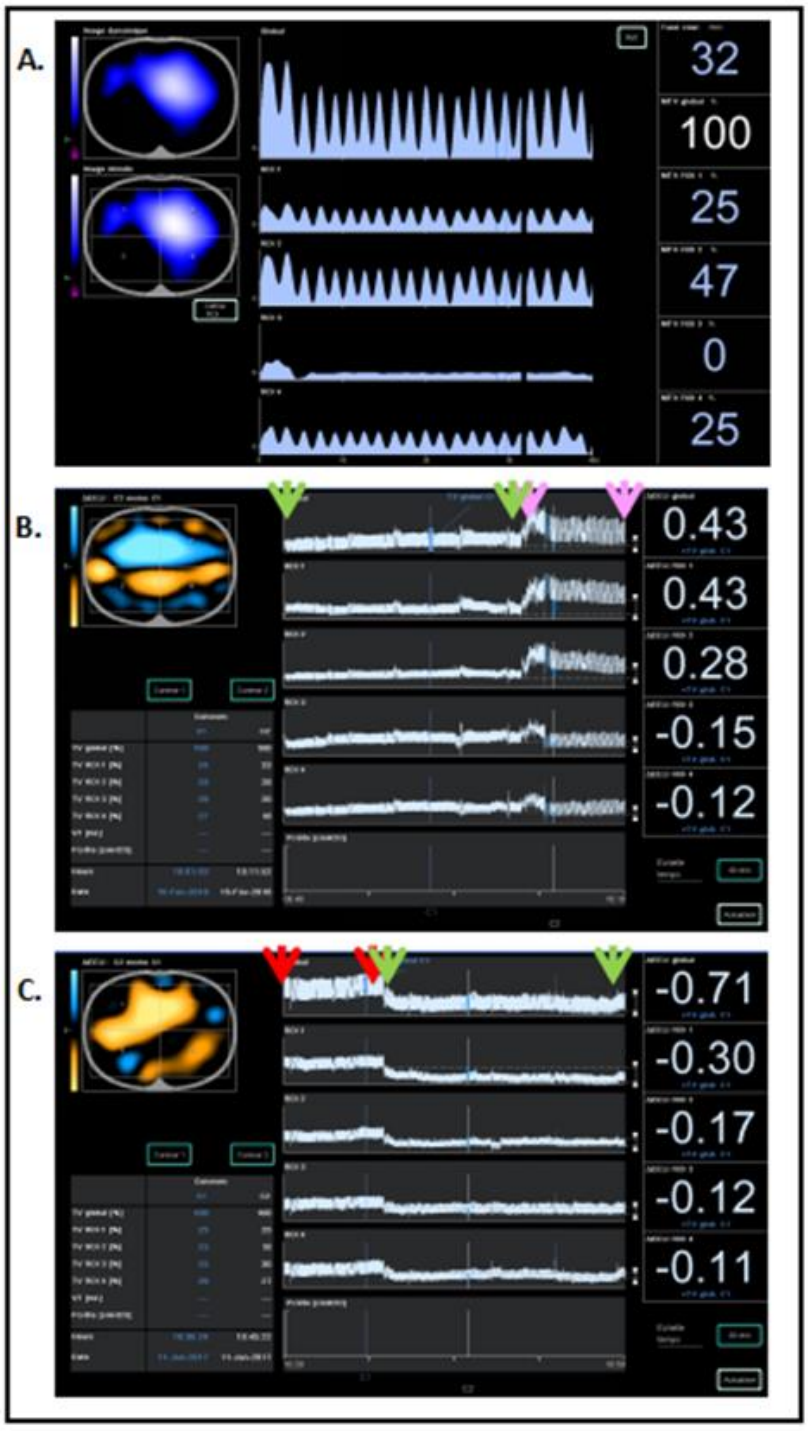

Table S1 : Comparison of patients' characteristics at inclusion by treatment sequence			
EIT and clinical data	**Sequence**		**P -value***
	HFNC then NIV	**NIV then HFNC**	
Age [years]	42 [22;54]	47 [38;56]	0.5
Male	4 (50%)	5 (62%)	1.0**
BMI [kg/m2]	22 [21;28]	25 [22;26]	0.6
SAPSII	25 [20;47]	27 [16;28]	0.4
SOFA	3 [2;5]	3 [2;4]	0.5
ROI of lung condensation	2 (25%)	2 (25%)	0.8**
ROI1			
ROI2	0 (0%)	1 (12%)	
ROI3	3 (37%)	4 (50%)	
ROI4	3 (37%)	1 (12%)	
TV_global during first FM	2583 [1556;3449]	2107 [1186;2480]	0.2
TV ROI1 during first FM	682 [618;1207]	576 [232;625]	0.07
TV ROI2 during first FM	472 [295;703]	476 [93;669]	0.6
TV ROI3 during first FM	816 [310;1057]	573 [84;675]	0.1
TV ROI4 during first FM	220 [189;283]	410 [378;772]	0.2
TV condensation during first FM	283 [233;1057]	593 [93;756]	0.2
EELI_global during first FM	1271 [598;3763]	1719 [764;2645]	1.0
EELI ROI1 during first FM	278 [179;1144]	377 [34;618]	0.8
EELI ROI2 during first FM	306 [98;531]	361 [166;562]	0.5
EELI ROI3 during first FM	385 [54;446]	261 [160;458]	0.9
EELI ROI4 during first FM	201 [93;499]	363 [125;508]	0.7
EELI condensation during first FM	201 [50;477]	398 [160;562]	0.7
RR (bpm)	25 [23;29]	26 [24;30]	0.6
SpO2/FiO2 ratio	152 [138;152]	152 [152;152]	0.7
SpO2 (%)	99 [91;100]	100 [100;100]	0.1
HR (bpm)	80 [71 ;102]	84 [79 ;94]	0.5
SBP (mmHg)	128 [102;136]	119 [106;129]	0.8
MAP (mmHg)	79 [74;89]	82 [78;95]	0.3
Dyspnea score (0-10)	0 [0;5]	3 [0;4]	0.7
Patient comfort score (0-10)	8 [8;10]	6 [3;8]	0.1

HFNC: high-flow nasal cannula, NIV: non-invasive ventilation, BMI: Body Mass Index (kg/m2), SAPSII: Simplified Acute Physiology Score II, SOFA: Sepsis Related Organ Failure Assessment, TV: tidal volume variation, EELI: end-expiratory lung impedance, RR: respiratory rate, SpO2: pulse oxygen saturation, HR: heart rate, SBP: systolic blood pressure, MAP: mean arterial pressure. Categorical variables are expressed as number with column per cent (%), other variables are expressed as median accompanied by 1st and 3rd quartile [Q1;Q3]; *:=Wilcoxon test for 2 independent samples if not stated otherwise, **:= Freeman-Halton's extension of Fisher's exact test.

Table S2: Effect of first treatment on patients' characteristics just before second treatment							
EIT and clinical data		FM2 - FM1				P -value*	
		Patients	Median	Q1	Q3		
TV global (units)	Sequence	8	35	-186	113	0.7	
	HFNC then NIV						
	NIV then HFNC	8	-162	-220	-50	0.1	
	p-value* (sequence)		0.2				
TV ROI1 (units)	Sequence	8	-67	-113	71	0.6	
	HFNC then NIV						
	NIV then HFNC	8	-64	-82	-6	0.1	
	p-value* (sequence)		0.9				
TV ROI2 (units)	Sequence	8	-36	-87	10	0.3	
	HFNC then NIV						
	NIV then HFNC	8	-82	-90	-12	0.1	
	p-value* (sequence)		0.5				
TV ROI3 (units)	Sequence	8	19	-151	117	0.4	
	HFNC then NIV						
	NIV then HFNC	8	-5	-41	22	0.6	
	p-value* (sequence)		0.4				
TV ROI4 (units)	Sequence	8	17	-16	116	0.1	
	HFNC then NIV						
	NIV then HFNC	8	-33	-69	8	0.5	
	p-value* (sequence)		0.1				
TV consolidation (units)	Sequence	8	17	-67	47	0.8	
	HFNC then NIV						
	NIV then HFNC	8	-14	-69	22	0.7	
	p-value* (sequence)		0.5				
EELI global (units)	Sequence	8	159	-3335	2273	0.9	
	HFNC then NIV						
	NIV then HFNC	8	-968	-1059	529	0.6	
	p-value* (sequence)		0.8				
EELI ROI1 (units)	Sequence	8	-158	-839	53	0.4	
	HFNC then NIV						
	NIV then HFNC	8	-220	-286	-49	0.5	
	p-value* (sequence)		1.0				
EELI ROI2 (units)	Sequence	8	-429	-1189	136	0.7	
	HFNC then NIV						
	NIV then HFNC	8	-173	-461	132	0.7	
	p-value* (sequence)		0.6				
EELI ROI3 (units)	Sequence	8	9	-87	464	0.5	
	HFNC then NIV						
	NIV then HFNC	8	-10	-203	68	1.0	
	p-value* (sequence)		0.4				
EELI ROI4 (units)	Sequence	8	52	-942	289	0.6	
	HFNC then NIV						
	NIV then HFNC	8	5	-155	142	0.6	
	p-value* (sequence)		0.9				
EELI consolidation (units)	Sequence	8	95	-368	577	0.3	
	HFNC then NIV						
	NIV then HFNC	8	-80	-191	68	0.6	
	p-value* (sequence)		0,2				
RR (bpm)	Sequence	8	1	-1	1	0.4	
	HFNC then NIV						***
	NIV then HFNC	8	-1	-6	1	1.0	***

	p-value* (sequence)		0.4				
SpO2/FiO2 ratio	**Sequence**	8	-2	-5	0	0.5	
	HFNC then NIV						
	NIV then HFNC	8	0	-5	0	0.2	
	p-value* (sequence)		0.9				
SpO2 (%)	**Sequence**	8	-1	-3	0	0.3	
	HFNC then NIV						***
	NIV then HFNC	8	0	-3	0	0.2	***
	p-value* (sequence)		0.9				
HR (bpm)	**Sequence**	8	3	-4	8	0.7	
	HFNC then NIV						***
	NIV then HFNC	8	-1	-4	3	1.0	***
	p-value* (sequence)		0.5				
SBP (mmHg)	**Sequence**	8	-7	-11	-2	0.2	
	HFNC then NIV						***
	NIV then HFNC	8	-7	-16	4	0.7	***
	p-value* (sequence)		1.0				
MAP (mmHg)	**sequence**	8	-2	-5	-1	0,2	
	HFNC then NIV						***
	NIV then HFNC	8	-2	-7	0	0,2	***
	p-value* (sequence)		0,8				
Dyspnea score (0;10)	**Sequence**	7	0	0	1	0.6	
	HFNC then NIV						***
	NIV then HFNC	8	0	-1	0	1.0	***
	p-value* (sequence)		0.2				
Patient comfort score (0;10)	**Sequence**	7	0	-1	0	1.0	
	HFNC then NIV						***
	NIV then HFNC	8	0	-1	0	0.2	***
	p-value* (sequence)		0.4				

HFNC: high-flow nasal cannula, NIV: non-invasive ventilation, TV: tidal volume variation, EELI: end-expiratory lung impedance, RR: respiratory rate, SpO2: pulse oxygen saturation, HR: heart rate, SBP: systolic blood pressure, MAP: mean arterial pressure. All values are expressed as median accompanied by 1st and 3rd quartile [Q1;Q3]; *:= Wilcoxon test for 2 independent samples, ** := Wilcoxon signed rank test if not stated otherwise, ***:= Sign test.