Hypoxemic Patients With Bilateral Infiltrates Treated With High-Flow Nasal Cannula Present a Similar Pattern of Biomarkers of Inflammation and Injury to Acute Respiratory Distress Syndrome Patients*

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Objective: To examine whether patients with acute hypoxemia and bilateral opacities treated with high-flow nasal cannula and acute respiratory distress syndrome patients who were directly mechanically ventilated are similar in terms of lung epithelial, endothelial, and inflammatory biomarkers.

Design: Prospective, multicenter study.

Setting: ICUs at three university tertiary hospitals.

Patients: Intubated and nonintubated patients admitted to the ICU with acute hypoxemia ($Pao_2/Fio_2 \leq 300$) and bilateral opacities.

Interventions: None.

Measurements and Main Results: Either high-flow nasal cannula or mechanical ventilation was initiated, at the discretion of the attending physician. We measured plasma biomarkers of lung epithelial injury (receptor for advanced glycation end products and surfactant protein D) and endothelial injury (angiopoietin-2) and inflammation (interleukin-6, interleukin-8, and interleukin-33 and soluble suppression of tumorigenicity-2) within 24 hours of acute respiratory distress syndrome onset. Propensity score matching was performed using six different variables (Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, Pao_2/Fio_2, origin of acute respiratory distress syndrome, steroids, renal failure and need for vasopressors). Nonhypoxemic mechanically ventilated critically ill patients and healthy volunteers served as controls. Of the 170 patients enrolled, 127 (74.7%) were intubated and 43 (25.3%) were treated with high-flow nasal cannula at acute respiratory distress syndrome onset. After propensity score matching (39 high-flow nasal cannula patients vs 39 mechanical ventilation patients), no significant differences were observed in receptor for advanced glycation end products, surfactant protein D, angiopoietin-2, interleukin-6, interleukin-8, interleukin-33, and soluble suppression of tumorigenicity-2 between matched patients who were treated with high-flow nasal cannula and those who were intubated at acute respiratory distress syndrome onset. After matching, no differences in mortality or length of stay were observed. All biomarkers (with the exception of interleukin-33) were higher in both groups of matched acute respiratory distress syndrome patients than in both control groups.

Conclusions: Acute hypoxemic patients with bilateral infiltrates treated with high-flow nasal cannula presented a similar pattern of biomarkers of inflammation and injury to acute respiratory distress

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syndrome patients undergoing direct mechanical ventilation. The results suggest that these high-flow nasal cannula patients should be considered as acute respiratory distress syndrome patients. (*Crit Care Med* 2017; 45:1845–1853)

Key Words: acute respiratory distress syndrome; biomarkers; high-flow nasal cannula

Although most of the patients included in high-flow nasal cannula (HFNC) studies have bilateral infiltrates (1–3), it remains debated whether or not these patients can be considered as having acute respiratory distress syndrome (ARDS). The Berlin definition's oxygenation criteria requires a minimal level of 5 cm H_2O or more positive end-expiratory pressure (PEEP) which can be provided either during invasive or noninvasive mechanical ventilation (MV) (4), thus not including HFNC as an acceptable ventilatory support to fulfill the oxygenation criteria. However, one of the mechanisms by which oxygenation may be improved with HFNC is the generation of a certain degree of positive airway pressure (5, 6). This pressure may exceed 5 cm H_2O in some instances, suggesting that hypoxemic patients with bilateral infiltrates treated with HFNC may be considered as ARDS patients (3, 5, 7).

The study of biomarkers has provided important insights into the mechanisms of lung injury. Higher plasma levels of interleukin (IL)-6 and IL-8 have been found in ARDS patients and correlate with mortality (8). Similarly, higher soluble suppression of tumorigenicity-2 (sST2) concentrations have been associated with worse outcome in ARDS patients (9, 10), and importantly, levels of sST2 can discriminate between ARDS and heart failure (9). Our group has also shown that the use of human adipose tissue–derived mesenchymal stem cells overexpressing sST2-attenuated lung injury in a lipopolysaccharide-induced murine ARDS model (11).

Other studies have identified more specific biomarkers of ARDS. In this regard, high baseline arterial levels of soluble receptor for advanced glycation end products (RAGE) help identify ARDS in mechanically ventilated patients (12), correlate with net alveolar fluid clearance rates (13), and have shown a strong association with worse clinical outcomes (14). Furthermore, increased levels of plasma surfactant proteins (SPs)-D have also been associated with worse clinical outcome (15). Finally, angiopoietin-2 improves the identification of high-risk patients for ARDS (16), and higher angiopoietin-2 levels are strongly associated with mortality (17).

Our aim was thus to examine lung epithelial, endothelial, and inflammatory biomarkers in the plasma of HFNC patients and intubated patients with ARDS to test the hypothesis that these HFNC patients exhibit similar degrees of lung injury and inflammation and could therefore be considered as ARDS patients.

METHODS

Study Design and Patients

We performed a 3-year (2014–2016) multicenter prospective cohort study at three tertiary university hospitals, enrolling patients admitted to the general ICU (medical and surgical) who met the Berlin definition for ARDS (4). Hypoxemic nonintubated patients ($Pao_2/Fio_2 \leq 300$ or pulse oximetry [Spo_2]/$Fio_2 \leq 315$) (18) with bilateral radiographic opacities not fully explained by cardiac failure who were treated with HFNC were also included (19). Nonhypoxemic ($Pao_2/Fio_2 \geq 300$ or $Spo_2/Fio_2 \geq 315$) mechanically ventilated critically ill patients without bilateral infiltrates on chest x-ray and healthy volunteers served as controls ($n = 8$ in each control group). Exclusion criteria were age below 18, current pregnancy, and refusal to give informed consent. The Ethics Committee at each hospital approved the study, and written informed consent was obtained from all patients or their relatives before inclusion.

Data Collection

Baseline-recorded data included demographic characteristics, comorbidities, and the origin and etiology of ARDS. All patients received continuous monitoring during their ICU admission, and general respiratory and hemodynamic variables were also recorded. Severity of illness was assessed with the Acute Physiology and Chronic Health Evaluation (APACHE) II score (20) within 24 hours of ICU admission. Sequential Organ Failure Assessment (SOFA) (21) at ARDS onset was also calculated. Acute renal failure was defined as a serum level of creatinine of 1.2 mg/dL or higher, and shock was diagnosed in the presence of vasopressors (1). Community-acquired and healthcare-associated pneumonia were defined according to the American Thoracic Society/Infectious Diseases Society of America guidelines (22). Immunosuppression was defined as primary immunodeficiency or immunodeficiency secondary to radiation treatment, cytotoxic drugs or steroids (daily doses of >20 mg of prednisolone or the equivalent for >2 wk), AIDS, or malignancy (1).

Blood Sample Analysis

Eight milliliters of blood were collected from each patient in ethylenediamine tetraacetic acid tubes within 24 hours of ARDS onset for MV and the first 24 hours of hypoxemia and bilateral infiltrates in patients who were treated with HFNC. The tubes were immediately centrifuged at 3,000 rpm for 10 minutes, aliquoted and stored at −80°C until the day of the experiments. Plasma biomarkers of lung epithelial (RAGE and SP-D) and endothelial (angiopoietin-2) injury as well as inflammation markers (IL-6, IL-8, IL-33, and sST2) levels were measured using commercially available enzyme-linked immunosorbent assay kits. Analyses were conducted at the Mar Medical Research Institute, Barcelona, Spain.

HFNC Therapy

High flow was provided either with the Optiflow device (MR850 heated humidified RT202 delivery tubing and RT050/051 nasal cannula; Fisher & Paykel Healthcare, Auckland, New Zealand) or with Airvo 2 (Fisher & Paykel Healthcare, Auckland, New Zealand). The device consists of a low resistance nasal cannula that can deliver up to 60 L/min of a totally conditioned (37°C and 100% of relative humidity) gas admixture. HFNC is used

in our ICUs in patients with acute respiratory failure with Spo_2 less than 92% or respiratory rate (RR) greater than 30 rpm with conventional oxygen more than 9 lpm, using Fio_2 greater than 0.5 and flow rate greater than or equal to 40 lpm at its onset. The Fio_2 was titrated targeting a Spo_2 greater than 92%, and flow was adjusted according to the patient's tolerance. HFNC or MV was initiated at the discretion of the attending physician and according to HFNC availability.

Failure of HFNC was defined as the subsequent need for MV. The criteria for intubation and MV were decreased level of consciousness (Glasgow Coma Score < 12), cardiac arrest/arrhythmias and severe hemodynamic instability (norepinephrine > 0.1 μg/kg/min), or persisting or worsening respiratory condition defined as at least two of the following criteria: failure to achieve correct oxygenation (Pao_2 < 60 mm Hg despite HFNC flow ≥ 30 L/min and Fio_2 of 1), respiratory acidosis ($Paco_2$ > 50 mm Hg with pH < 7.25), RR greater than 30 beats/min, or inability to clear secretions.

Statistical Analysis

Data are expressed as means (SD) or medians (interquartile range) when not normally distributed. Biomarker concentrations are presented as means (95% CI). Differences between categorical variables were assessed by chi-square or Fisher exact test when necessary. Continuous variables were compared using the Student *t* test or Mann-Whitney *U* test in overall cohort and the paired samples Student *t* test or Wilcoxon signed-rank test in the matched cohort (23), as appropriate. A two-sided *p* value of 0.05 or less was considered statistically significant.

To reduce the risk of selection bias and confounding due to the differences observed between hypoxemic patients treated with HFNC (HFNC group) and those patients with ARDS who were directly intubated (MV group) and also to strengthen causal conclusions, we performed a propensity score analysis with nearest neighbor one-to-one matching (24, 25). Variables with *p* value less than or equal to 0.1 in the univariate analysis comparing HFNC and MV patients (APACHE II, SOFA, origin of ARDS, shock, renal failure and corticosteroids) and others that have been used to describe ARDS severity, such as Pao_2/Fio_2, were used to create the propensity score. Propensity score–matched patients were compared, ensuring that two populations (HFNC vs MV) were balanced in terms of baseline characteristics and severity. Subsequently, differences in concentration of the various biomarkers were assessed. In addition, the concentration of different biomarkers in the two study populations (HFNC and MV) was also compared with both control groups. Differences of biomarkers concentration that correctly predicted patients who would succeed or fail on HFNC were also assessed. The optimal threshold for need for MV was chosen to maximize the sum of sensitivity and specificity in those biomarkers with significant differences. Finally, multivariate logistic regression was used to study the association between biomarkers that have different concentrations between patients who succeeded and those who fail on HFNC, adjusted for admission APACHE II and SOFA score.

Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY), and propensity score analysis was performed using the MatchIt package (24, 25) of R statistical software (R Development Core Team: R: A language and environment for statistical computing. Vienna, Austria, R Foundation for Statistical Computing, 2008. Available at: http://www.R-project.org.).

RESULTS

Baseline Characteristics, ICU Course, and Outcomes

During a 3-year period, 170 patients were enrolled; 127 (74.7%) underwent direct MV at ARDS onset, whereas 43 (25.3%) hypoxemic patients were initially treated with HFNC. The baseline characteristics and variables recorded during patients' ICU stay are provided in **Table 1** for the entire cohort. On day 1, HFNC was set at a median of 50 lpm (8.55) with an Fio_2 of 1, and MV patients were ventilated using a median tidal volume of 7.48 mL/kg predicted body weight (1.62) and a median PEEP of 10 cm H_2O (3.44) yielding a plateau pressure of 25 cm H_2O (4.72). All MV patients were treated using protective MV.

Twenty-one (48.8%) of the patients treated with HFNC needed to be intubated. However, duration of MV in this subgroup of patients was similar to that of MV patients (8 [5–22] vs 13 [6–33], respectively; $p = 0.15$). ICU and hospital mortality were lower in the HFNC group. Furthermore, the HFNC patients who survived also had shorter ICU length of stay (LOS) than MV survivors.

Propensity Score and Biomarkers

After propensity score matching, 39 pairs of patients were selected. These patients were similar in terms of baseline characteristics and severity, as well as in terms of variables related to their ICU course (**Table 2**). No differences in mortality were observed. No significant differences were observed in lung epithelial (RAGE and SP-D) and endothelial (angiopoietin-2) injury biomarker levels between patients who were treated with HFNC and those who were initially intubated (**Fig. 1** and **Table 3**). Nor were significant differences observed in plasma levels of IL-6, IL-8, IL-33, and ST2 in ARDS patients. Compared with both control groups, levels of all other biomarkers were higher in both populations of hypoxemic patients (Fig. 1). Two exceptions were found: 1) nonsignificant differences IL-33 concentration were found between all groups (excepting MV patients compared with healthy volunteers) and 2) only a trend to have higher angiopoietin-2 levels in HFNC patients were observed when compared with mechanically ventilated patients without lung injury.

Differences between HFNC matched and nonmatched patients are presented in **Supplemental Tables 1** and **2** (Supplemental Digital Content 1, http://links.lww.com/CCM/C781).

HFNC Failure

Nineteen patients (48.7%) in the matched population and 21 patients (48.8%) in the overall cohort failed on HFNC and were subsequently intubated. In the overall cohort, median

TABLE 1. Baseline Characteristics and ICU Course of the Entire Cohort

Variable	MV (*n* = 127)b	High-Flow Nasal Cannula (*n* = 43)	*p*
Age (yr), mean (SD)	57 (14.33)	58 (13.04)	0.71
Sex (male), *n* (%)	86 (67.7)	32 (74.4)	0.45
Comorbidities, *n* (%)			
Arterial hypertension	40 (31.5)	16 (37.2)	0.57
Diabetes	31 (24.4)	11 (25.6)	0.84
Cardiovascular disease	18 (14.2)	6 (14)	1
Immunosuppression	36 (28.3)	17 (39.5)	0.19
Chronic obstructive pulmonary disease	19 (15)	4 (9.3)	0.45
Origin of ARDS (intrapulmonary), *n* (%)	81 (63.8)	37 (86)	< 0.01
Etiology of ARDS, *n* (%)			0.15
Pneumonia	74 (58.3)	32 (74.4)	
Extrapulmonary sepsis	26 (20.5)	4 (9.3)	
Pancreatitis	15 (11.8)	2 (4.7)	
Lung resection	2 (1.6)	0	
Others	10 (7.9)	5 (11.6)	
Acute Physiology and Chronic Health Evaluation II at ICU admission, mean (SD)	25 (7.85)	18 (5.50)	< 0.01
At the time of ARDS diagnosis			
Sequential Organ Failure Assessment, mean (SD)	9 (3.76)	6 (2.41)	< 0.01
Pao_2/Fio_2, mean (SD)	120 (53.58)	105 (40.39)	0.11
Lactate (mmol/L), mean (SD)	2.29 (2.05)	1.50 (0.88)	< 0.01
C-reactive protein (mg/dL), mean (SD)	22.39 (13.21)	22.12 (13.92)	0.92
Leukocytes (× 10E9/L), mean (SD)	13.63 (12.50)	12.18 (8.44)	0.40
Corticosteroids, *n* (%)	16 (12.6)	12 (27.9)	0.03
During ICU stay			
Need for MV, *n* (%)		21 (48.8)	
Days of MV, mean (SD)	21 (20.60)	13 (10.29)	0.01
Shock, *n* (%)	100 (78.7)	23 (53.5)	< 0.01
Renal failure, *n* (%)	87 (68.5)	21 (48.8)	0.03
Outcomes			
Length of stay (d), mean (SD)			
ICU			
All	25 (20.32)	14 (11.58)	< 0.01
Survivors	28 (18.29)	13 (11.59)	< 0.01
Hospital			
All	40 (33.13)	35 (23.06)	0.41
Survivors	49 (38.00)	35 (23.04)	0.06
Mortality, *n* (%)			
ICU	53 (41.7)	7 (16.3)	< 0.01
Hospital	57 (44.9)	10 (23.3)	0.02

ARDS = acute respiratory distress syndrome, MV = mechanical ventilation.
Data are expressed as mean (SD) or frequency (percentage).

TABLE 2. Baseline Characteristics and ICU Course of the Matched Groups

Variable	MV (*n* = 39)	High-Flow Nasal Cannula (*n* = 39)	*p*
Age (yr), mean (SD)	57 (14.26)	58 (12.59)	0.90
Sex (male), *n* (%)	25 (64.1)	29 (74.4)	0.48
Comorbidities, *n* (%)			
Arterial hypertension	15 (38.5)	15 (38.5)	1
Diabetes	8 (20.5)	10 (25.6)	0.63
Cardiovascular disease	4 (10.3)	5 (12.8)	1
Immunosuppression	12 (30.8)	17 (43.6)	0.33
Chronic obstructive pulmonary disease	8 (20.5)	3 (7.7)	0.18
Origin of ARDS (intrapulmonary), *n* (%)	34 (87.2)	34 (87.2)	1
Etiology of ARDS, *n* (%)			0.14
Pneumonia	30 (76.9)	30 (76.9)	
Extrapulmonary sepsis	0	3 (7.7)	
Pancreatitis	5 (12.8)	2 (5.1)	
Lung resection	2 (5.1)	0	
Others	2 (5.1)	4 (10.3)	
Acute Physiology and Chronic Health Evaluation II at ICU admission, mean (SD)	20 (6.44)	18 (5.69)	0.11
At the time of ARDS diagnosis			
Sequential Organ Failure Assessment, mean (SD)	7 (2.93)	6 (2.49)	0.52
Pao_2/Fio_2, mean (SD)	110 (48.96)	104 (40.26)	0.56
Lactate (mmol/L), mean (SD)	1.78 (0.92)	1.44 (0.86)	0.19
C-reactive protein (mg/dL), mean (SD)	22.29 (11.16)	21.47 (13.25)	0.72
Leukocytes (× 10E9/L), mean (SD)	13.07 (11.41)	12.28 (8.61)	0.74
Corticosteroids, *n* (%)	7 (17.9)	12 (30.8)	0.23
During ICU stay			
Need for MV, *n* (%)		19 (48.7)	
Days of MV, mean (SD)	26 (24.09)	14 (10.40)	< 0.01
Shock, *n* (%)	29 (74.4)	21 (53.8)	0.12
Renal failure, *n* (%)	18 (46.2)	19 (48.7)	1
Outcomes			
Length of stay (days), mean (SD)			
ICU			
All	26 (21.33)	14 (11.81)	< 0.01
Survivors	28 (19.90)	13 (11.88)	0.03
Hospital			
All	50 (44.40)	35 (24.23)	0.24
Survivors	58 (49.70)	35 (24.41)	0.75
Mortality, *n* (%)			
ICU	11 (28.2)	7 (17.9)	0.42
Hospital	11 (28.2)	9 (23.1)	0.61

ARDS = acute respiratory distress syndrome, MV = mechanical ventilation.
Data are expressed as mean (SD) or frequency (percentage).

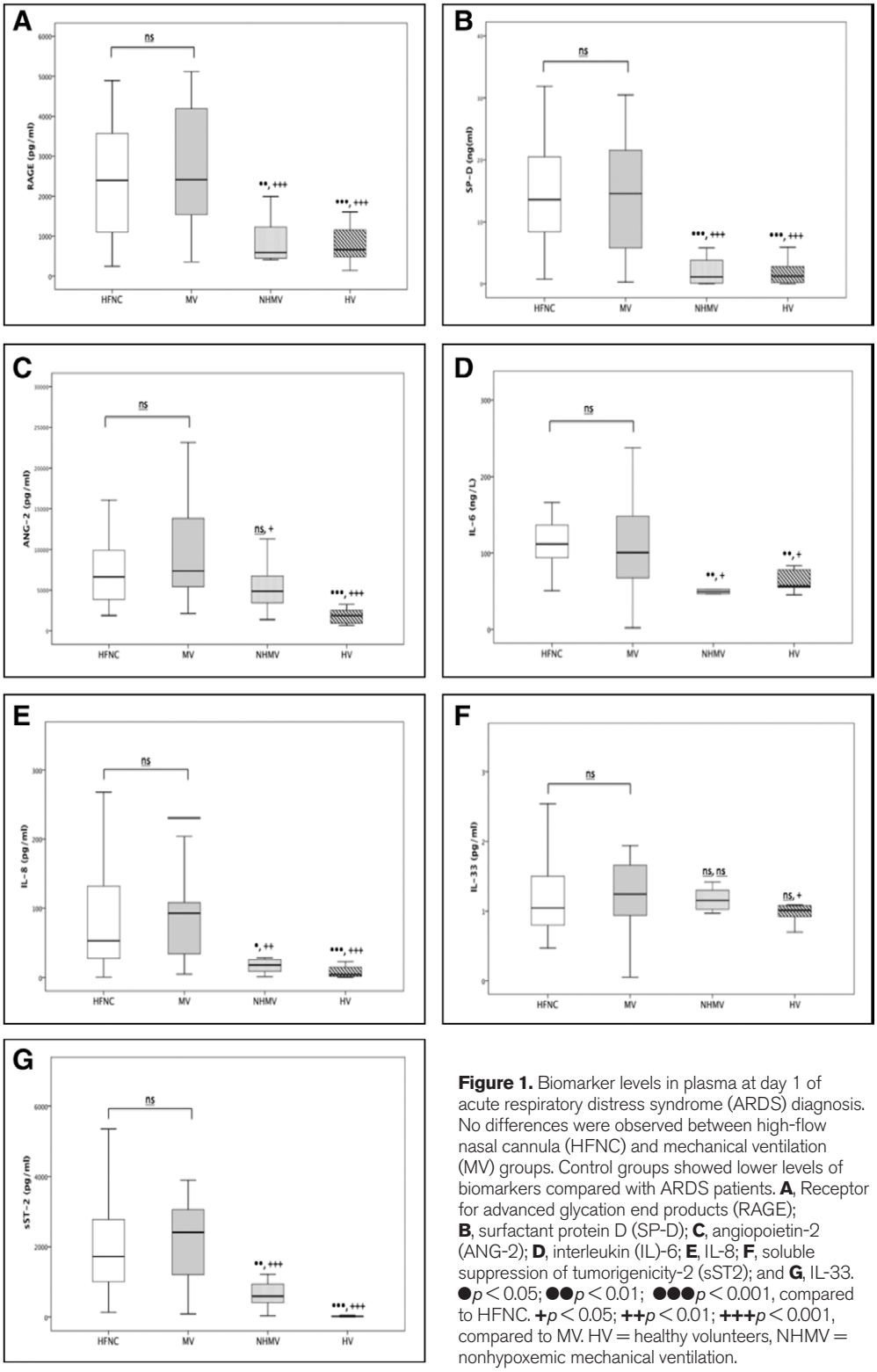

Figure 1. Biomarker levels in plasma at day 1 of acute respiratory distress syndrome (ARDS) diagnosis. No differences were observed between high-flow nasal cannula (HFNC) and mechanical ventilation (MV) groups. Control groups showed lower levels of biomarkers compared with ARDS patients. **A**, Receptor for advanced glycation end products (RAGE); **B**, surfactant protein D (SP-D); **C**, angiopoietin-2 (ANG-2); **D**, interleukin (IL)-6; **E**, IL-8; **F**, soluble suppression of tumorigenicity-2 (sST2); and **G**, IL-33. ●$p < 0.05$; ●●$p < 0.01$; ●●●$p < 0.001$, compared to HFNC. **+**$p < 0.05$; **++**$p < 0.01$; **+++**$p < 0.001$, compared to MV. HV = healthy volunteers, NHMV = nonhypoxemic mechanical ventilation.

Pao_2/Fio_2 ratio of HFNC failure patients 24 hours after MV onset was 113 (93–204). HFNC failure patients showed higher ICU mortality and longer ICU LOS than those who succeeded (**Supplemental Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C781). In contrast, no significant differences in ICU and hospital mortality and ICU and hospital LOS were observed between HFNC failure patients and those who were initially intubated (**Supplemental Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C781). In addition, differences in concentration of the various biomarkers were assessed in the overall HFNC cohort. Interestingly, patients who failed on HFNC had higher plasma concentrations of IL-8 within 24 hours of ARDS onset (**Supplemental Table 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/C781). Furthermore, levels of IL-8 greater than or equal to 67.16 ρg/mL independently predict the need for MV in patients treated with HFNC even after adjusting for severity (**Table 4**).

DISCUSSION

This is the first study to demonstrate that hypoxemic patients with bilateral infiltrates treated with HFNC may present the same levels of plasma biomarkers of epithelial and endothelial injury and biomarkers of inflammation as ARDS patients undergoing direct MV. Furthermore, with the exception of IL-33, all biomarkers were higher in HFNC and MV patients than in both control groups. Thus, hypoxemic patients with bilateral infiltrates treated with HFNC presented similar plasma concentrations of biomarkers of inflammation and lung injury as MV patients with ARDS after matching on clinical variables that are proxies for inflammation (severity of illness APACHE) and lung injury (oxygenation), suggesting that they can be considered both clinically and biologically as ARDS patients.

For obvious reasons, histologic data are absent from the Berlin definition; it has been shown that it does not properly identify patients with diffuse alveolar damage (26). Furthermore, the natural history of ARDS often begins before

TABLE 3. Biomarkers Concentration in the Matched Groups

Biomarker	Mechanical Ventilation ($n = 39$)	High-Flow Nasal Cannula ($n = 39$)	Mean Difference Between Groups (95% CI)	p
Receptor for advanced glycation end products (ρg/mL)	2,653.80 (2,169.80–3,137.81)	2,387.19 (1,972.10–2,802.28)	−280.56 (−969.41 to 408.30)	0.41
Surfactant protein D (ng/mL)	15.07 (12.15–17.99)	14.43 (11.78–17.07)	−1.05 (−4.84 to 2.74)	0.58
Angiopoietin-2 (ρg/mL)	9,885.55 (7,628.81–12,142.29)	7,660.29 (6,213.89–9,106.68)	−2,009.41 (−4,948.72 to 929.89	0.17
IL-6 (ng/L)	122.95 (96.81–149.08)	120.01 (101.67–138.35)	−2.17 (−37.54 to 33.20)	0.90
IL-8 (ρg/mL)	130.89 (91.40–170.38)	90.20 (55.85–124.55)	−40.34 (−95.72 to 15.03)	0.15
IL-33 (ng/mL)	1.48 (1.14–1.82)	1.21 (1.00–1.41)	−0.27 (−0.65 to 0.13)	0.18
Soluble suppression of tumorigenicity-2 (ρg/mL)	3,389.92 (1,789.78–4,990.06)	3,066.77 (1,425.94–4,707.59)	−569.93 (−2,620.75 to 1,480.90)	0.58

IL = interleukin.

Data of mechanical ventilation and high-flow nasal cannula groups are expressed as mean (95% CI).

TABLE 4. Logistic Regression Analysis of Association Between Interleukin-8 Concentrations and Need for Mechanical Ventilation in High-Flow Nasal Cannula Patients

Variable	OR	95% CI	p
Unadjusted association between IL-8 and need for mechanical ventilation			
IL-8 ≥ 67.16 (ρg/mL)	9.21	2.15–39.52	< 0.01
Adjusted analysis by APACHE			
IL-8 ≥ 67.16 (ρg/mL)	8.92	1.94–40.99	< 0.01
APACHE II	1.01	0.88–1.16	0.89
Adjusted analysis by SOFA			
IL-8 ≥ 67.16 (ρg/mL)	17.37	2.66–113.46	< 0.01
SOFA	1.64	1.07–2.51	0.02

APACHE = Acute Physiology and Chronic Health Evaluation, IL = interleukin, OR = odds ratio, SOFA = Sequential Organ Failure Assessment.

intubation and invasive MV onset (19). We should therefore consider other specific criteria in order to better identify patients with ARDS before intubation is required, such as biomarkers. Recently, significant progress has been made in identifying more specific markers for ARDS. Some biomarkers have demonstrated their ability to distinguish between patients with clinical criteria for ARDS and MV controls (12) or patients with heart failure (9). It has been shown that patients with direct ARDS have higher levels of lung epithelial injury biomarkers (RAGE and SP-D) (27); conversely, higher levels of a lung endothelial injury biomarker (angiopoietin-2) were observed in patients with indirect ARDS (28). Additionally, using a latent-class analysis, Calfee et al (29) identified the same two endotypes in two different ARDS cohorts. One of the endotypes was characterized by higher plasma levels of inflammatory biomarkers, a higher prevalence of sepsis, shock and metabolic acidosis, and by worse outcomes. Interestingly, only patients of the more severely inflamed endotype benefited from a higher PEEP strategy although higher PEEP could even cause harm in the noninflamed endotype. Therefore, measuring a panel of biomarkers of epithelial and endothelial injury and inflammation may be a good approach to identify ARDS patients and detect at-risk patients.

By doing so, we found no significant differences in basal plasma levels in patients with HFNC compared with those who were mechanically ventilated. Furthermore, all markers (except IL-33) were higher in both study populations than in the two control groups. These findings show that nonintubated patients treated with HFNC who meet all the Berlin criteria other than PEEP express the same biomarkers of lung injury and should therefore be considered as ARDS patients. This approach is coherent with the findings of Kangelaris et al (19), showing that ARDS is prevalent among nonintubated ICU patients. In addition, this study found that a noticeable number of ARDS patients did not require intubation, in line with recent reports of noninvasive management of ARDS, either with HFNC (3) or noninvasive ventilation (30). However, because late intubation may worsen prognosis (19), biological assessment of lung injury with specific biomarkers as those we used in these patients may help early recognition of those who may require further intubation.

In contrast to sST2, we found nonsignificant differences in plasma IL-33 levels between both study cohorts and both control groups. Indeed, it has been shown that patients with ARDS do not have elevated IL-33 (either in bronchoalveolar lavage or in serum) (31), and this fact strengthens the external validity

of the present study. Interestingly, as previously documented with different ARDS subphenotypes (29), higher levels of IL-8 were significant determinants of HFNC failure in our cohort.

Besides biomarkers, clinical elements may guide physician's decision to intubate patients under HFNC. Although the indication of HFNC was not standardized in our study, physicians based their decisions on known variables that may influence secondary intubation. In this sense, as already suggested, patients with shock were more frequently intubated as they are less likely to respond to HFNC therapy (1, 32, 33). Consistently, use of vasopressors was even an exclusion criteria in the FLORALI study (2). Similarly, as encountered in extrapulmonary sepsis, the presence of other organ failure has been repeatedly associated with a higher HFNC failure rate (3). Judicious timing of intubation is a key issue in patients treated with HFNC because of the impact of delayed intubation on outcome found in a recent study (34). Beyond the important limitations of the study (35), it nonetheless confirms the findings previously seen with NIV that delayed intubation may worsen patients' prognosis. We believe this was not encountered in the present study since no difference in outcomes was observed between patients who failed on HFNC and those who were initially intubated. Therefore, when these conditions are met, HFNC may be a potential therapeutic option to treat severely hypoxemic patients who do not have any other organ failure (36). Physicians may rely on simple clinical variables to detect early predictors for the need of intubation, such as absence of significant decrease in RR, persistence of thoracoabdominal asynchrony (37), or the presence of an additional organ failure (1, 3). More recently, it has been shown that patients with severe pneumonia who after 12 hours of HFNC therapy have a Respiratory rate-OXygenation index (defined as the ratio of Spo_2/Fio_2 to RR) greater than or equal to 4.88 were less likely to be intubated (38).

The current study has some limitations. First, the study may be underpowered for some of the biomarkers used. However, it is a prospective multicenter study including a nonselected population of ARDS patients, using a propensity score–matched population that generated balanced groups. And we have also included two different control groups, and biomarker concentrations observed in the two study groups were similar to those previously reported in larger studies (28). Second, measuring hypoxemia in nonintubated patients is still challenging, and their Pao_2/Fio_2 may not necessarily be comparable to MV patients. However, patients who failed on HFNC still met ARDS oxygenation criteria 24 hours after intubation. Third, we only analyzed plasma levels of seven of the biomarkers, and no sequential measurement was performed; the measurement of other biomarkers in different samples and to know whether they evolve differently in HFNC patients compared with ARDS patients may have added more prognostic information. However, our panel of markers included the most important biomarkers used to date to describe different molecular phenotypes of ARDS (28). In addition, bronchoalveolar lavage may be hazardous and impracticable in hypoxemic patients, especially in those who were not intubated. Fourth, no data prior to intubation in the MV patients were available. And fifth, we have to keep in mind that failing to show statistically significant difference might not be the same that proving equivalence.

In conclusion, the results of the present study demonstrate that acute hypoxemic patients with bilateral infiltrates treated with HFNC may present a similar pattern of biomarkers of inflammation and injury to ARDS patients who undergo direct MV. This suggests that HFNC patients who otherwise meet the Berlin definition criteria may be considered as mild ARDS patients. In addition, biomarker analysis may help identify patients who will fail on HFNC and will need to be intubated. These novel results have important implications both in clinical practice and in research as they provide a rationale for diagnosing and treating ARDS patients in the early stages of the course of critical illness, before MV initiation. Future definitions of ARDS should focus on establishing new criteria that include nonintubated, high-risk ARDS patients.

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