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Early Short-Term Application of High-Frequency Percussive Ventilation Improves Gas Exchange in Hypoxemic Patients

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Key Words
High-frequency percussive ventilation · Hypoxia · Mean airway pressure · Acute lung injury · Short-term therapy

Abstract
Background: Hypoxemia in acute lung injury/acute respiratory distress syndrome (ALI/ARDS) patients represents a common finding in the intensive care unit (ICU) and frequently does not respond to standard ventilatory techniques. ***Objective:*** To study whether the early short-term application of high-frequency percussive ventilation (HFPV) can improve gas exchange in hypoxemic patients with ALI/ARDS or many other conditions in comparison to conventional ventilation (CV) using the same mean airway pressure (P_{aw}), representing the main determinant of oxygenation and hemodynamics, irrespective of the mode of ventilation. ***Methods:*** Thirty-five patients not responding to CV were studied. During the first 12 h after admission to the ICU the patients underwent CV. Thereafter HFPV was applied for 12 h with P_{aw} kept constant. They were then returned to CV. Gas exchange was measured at: 12 h after admission, every 4 h during the HFPV trial, 1 h after the end of HFPV, and 12 h after HFPV. Thirty-five matched patients ventilated with CV served as the control group (CTRL). ***Results:*** Pa_{O_2}/Fi_{O_2} and the arterial alveolar ratio (a/A P_{O_2}) increased during HFPV treatment and a Pa_{O_2}/Fi_{O_2} steady state was reached during the last 12 h of CV, whereas both did not change in CTRL. Pa_{CO_2} decreased during the first 4 h of HFPV, but thereafter it remained unaltered; Pa_{CO_2} did not vary in CTRL. Respiratory system compliance increased after HFPV. ***Conclusions:*** HFPV improved gas exchange in patients who did not respond to conventional treatment. This improvement remained unaltered until 12 h after the end of HFPV.

Introduction

Hypoxemia represents a common finding in the intensive care unit (ICU) and may result from acute lung injury/acute respiratory distress syndrome (ALI/ARDS), trauma, sepsis, and severe postoperative complications among other causes. These patients frequently do not respond to standard ventilatory techniques and, thus, high levels of oxygen, high positive end-expiratory pressure (PEEP), and complementary and intermittent techniques such as prone positioning, recruitment maneuvers, and nitric oxide have been used in an attempt to maintain or increase oxygenation [1–4]. Presently, the comparison be-

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tween the clinical effectiveness of conventional ventilation (CV) and other techniques is warranted almost solely by gas exchange analysis, mortality, and ventilator-free days; commonly, patients are defined as responders if their baseline PaO_2/FiO_2 increases by 10–20% [5, 6]. In patients under diverse mechanical ventilation techniques the information on gas exchange alone may not suffice. Furthermore, another parameter involved in the determination of oxygenation and hemodynamics is the mean airway pressure (P_{aw}) [7], irrespective of the PEEP level and mode of ventilation [8].

Prone positioning has been applied to patients for a short period in order to improve gas exchange; however, this maneuver was used primarily late in the treatment of severe hypoxemic patients. On the other hand, high-frequency percussive ventilation (HFPV) has also been used to improve gas exchange. Previous studies have demonstrated the efficacy of HFPV in the treatment of closed head injury [9], acute respiratory diseases caused by burns and smoke inhalation [10, 11], and obesity [12] and in patients after lung surgery [13]. Moreover, HFPV was found to be effective during chest physiotherapy in cystic fibrosis patients [14]. Recently, HFPV has been compared to the low-tidal volume ventilatory strategy in burned patients with a mean $PaO_2/FiO_2 > 300$ before randomization, and an improvement in gas exchange was found in the HFPV group that reached a maximum value at 24 h of treatment and decreased thereafter [15]. However, to our knowledge, no prospective study has evaluated whether the early 12-hour application of HFPV improves gas exchange in hypoxemic patients with $PaO_2/FiO_2 < 200$. Furthermore, no parameter pertaining to mechanical ventilation has been kept constant when comparing the outcomes of CV and HFPV.

Hence, we hypothesized that HFPV might improve gas exchange in mechanically ventilated patients that did not respond to CV early in the course of the disease. The same P_{aw} used during CV was applied during HFPV to avoid a possible mechanical/gas exchange bias. These patients were compared to those ventilated with CV throughout the study.

Patients and Methods

Study Design

Intubated mechanically ventilated patients (n = 160) who presented hypoxemia at admission were consecutively recruited from the General ICU of Cattinara University Hospital from June 2006 to February 2008. Patients were considered eligible if they met all of the following criteria: PaO_2/FiO_2 of 200 or less during mechanical ventilation; at least 18 years of age, and expected duration of mechanical ventilation longer than 48 h. Patients were excluded from the study if they had evidence of cardiogenic pulmonary edema and chronic obstructive pulmonary disease. All of them had indwelling radial or femoral artery catheters for blood gas collection and hemodynamic monitoring whenever clinically required. The study was approved by the local Ethics Committee and informed consent was obtained.

Methods

After verification of eligibility, patients were allowed a 12-hour period during which their clinical condition could stabilize. During this period clinicians not involved in the study and blinded to the subsequent experimental procedures were free to choose one CV mode (pressure-controlled or volume-controlled), tidal volume amounting to 6–8 ml/kg body weight. PEEP and FiO_2 were selected to obtain arterial oxygen saturation (SaO_2) of 90% or more. Sedative and neuromuscular blocking agents were administered according to the patients' requirements. During these 12-hour periods no additional techniques were used to improve gas exchange.

After the aforementioned stabilization period, arterial blood gas and the arterial alveolar ratio (a/A PO_2) were analyzed (baseline; fig. 1) and the patients that presented PaO_2/FiO_2 of 200 or less or greater than 200 but with an increase below 20% in relation to the admission value were enrolled into the study as nonresponders to conventional mechanical ventilation. The remaining patients (n = 125) were excluded because they were considered responders to conventional therapy, as prescribed by their attending physician. Thus, we prospectively studied 35 patients (26 male) aged between 21 and 77 years with a mean APACHE II equal to 20.5 and a lung injury score (LIS) amounting to 2.25 (median), as seen in table 1. The mean arterial pressure (MAP), tidal volume per predicted body weight (V_T/PBW), respiratory rate (RR), positive end-expiratory pressure (PEEP), respiratory system compliance (C_{rs}), and P_{aw} were also determined.

HFPV was substituted for the conventional one. Inspiratory:expiratory time (I:E) ratios equaled those during CV. To obtain the same previously measured P_{aw}, the following adjustments were made on a volumetric diffusive respirator (VDR-4®; Percussionaire Corporation, Sandpoint, Idaho, USA): during inspiration a pulsatile flow with a percussive frequency of 500 cycles/min and a pulse inspiratory and expiratory ratio (i and e respectively) of 1 was used; during expiration a mean PEEP level similar to that used during CV was obtained by oscillatory PEEP. During the trial, the breathing frequency was adjusted by modifying the I:E ratio, and the oscillating PEEP was varied, if necessary, to maintain normocapnia and the same P_{aw} [16]. During 12 h the patients were ventilated under these conditions and every 4 h blood samples were collected for gas analysis, and MAP and P_{aw} were recorded. At the end of the 12-hour HFPV arterial blood gases were analyzed in order to determine a possible impairment of gas exchange (20% decrease or more in PaO_2/FiO_2), which would yield discharge from the study. Thereafter the patients were returned to CV with the same ventilatory parameters used at the end of the 12-hour stabilization period, and another arterial blood gas analysis was done 1 h later to determine an impairment of gas exchange (20% decrease or more in PaO_2/FiO_2) that would similarly discharge a patient from the study; the MAP was also recorded. After another 12-hour period the last blood sample was

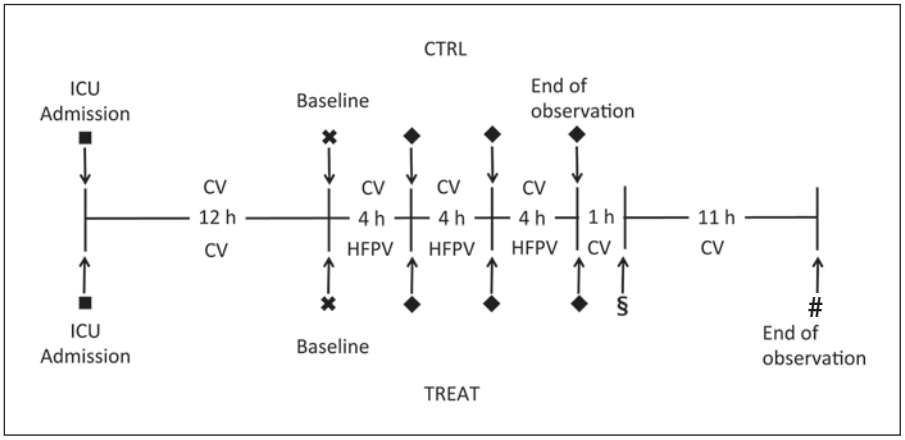

Fig. 1. Experimental timeline. ■ = Measurements: gender, age, weight, pH, $PaCO_2$, PaO_2/FiO_2, acute physiology and chronic health evaluation (APACHE II), and LIS; ✖ = pH, $PaCO_2$, PaO_2/FiO_2, MAP, VT/PBW, respiratory rate, PEEP, C_{rs}, and P_{aw}; ◆ = $PaCO_2$, PaO_2/FiO_2, MAP, and P_{aw}; **§** = $PaCO_2$, PaO_2/FiO_2, MAP, and C_{rs}; **#** = $PaCO_2$, PaO_2/FiO_2, and MAP.

collected, the MAP was measured, and the protocol was ended. The patients were returned to routine ventilatory procedures in the ICU. The static C_{rs} was measured in all patients at baseline and at 25 h after admission as the pressure measured at the end of the end-inspiratory pause minus PEEP divided by the tidal volume. Table 1 details the data gathered in the patients that underwent HFPV (TREAT group). The cardiac index was registered at baseline and after 12 h of HFPV.

The group encompassed patients presenting chest trauma (n = 7), peritonitis (n = 7), sepsis (n = 6), multiple injuries (n = 5), bacterial pneumonia (n = 5), head injury (n = 4), and vasculitis (n = 1).

Another group of 35 patients (historical control, CTRL) were selected from a population of 370 patients admitted to the ICU in the period from January 2003 to May 2006 with ALI/ARDS. They had the same criteria of enrolment as the TREAT group at admission and baseline. For each patient in the HFPV group, one matched control was selected according to the following criteria: age (±5 years of the treated patients), APACHE (±5 points), LIS (±0.5 points), PaO_2/FiO_2 (±25 points), $PaCO_2$ (± 5 mm Hg), and pH (±0.05 units). When matching each patient we based the relative importance of each factor on the coefficients of priority attributed to PaO_2/FiO_2, age, APACHE, LIS, $PaCO_2$, and pH. Table 1 details the CTRL patients' data. These patients were studied during the first 24 h after admission (corresponding to a 12-hour stabilization period plus another 12 h of CV). During this period clinicians were free to choose one CV mode (pressure-controlled or volume-controlled), tidal volume amounting to 6–8 ml/kg body weight. The PEEP and FiO_2 were selected to obtain SaO_2 of 90% or more. Sedation and neuromuscular blockade were pharmacologically controlled according to the patients' requirements. The same variables and timeline pertaining to TREAT patients were considered in the CTRL group (table 1; fig. 1). The group enrolled patients presenting multiple injuries (n = 8), bacterial pneumonia (n = 8), peritonitis, laparotomy (n = 5), sepsis (n = 5), chest trauma (n = 5), and head injury (n = 4).

Analysis

Statistical analysis was performed using open source statistical package R [17]. Normality was assessed using the Shapiro-Wilk test. Descriptive statistics of nonparametric data were provided using median and quartiles. The homogeneity of variances was approached with the Fligner-Killeen test in nonnormal cases. Differences in homoskedastic data were assessed by the Mann-Whitney-Wilcoxon test. Data are expressed as medians (1st to 3rd quartiles). The significance level was assumed to be 5%.

Repeated measures analysis was evaluated by means of mixed-effects modeling [18]. In the HFPV (n = 35) and CTRL (n = 35) groups, we considered the individual time profiles measured in 4 balanced occasions (at 12, 16, 20, and 24 h after admission) as depicted in figure 1. The best model describing the effect of HFPV on PaO_2/FiO_2 was:

$$y_{ij} = \beta_1 + b_{i1} + (\beta_2 + b_{i2})\, x_{ij} + \varepsilon_{ij} \qquad \text{(Equation 1)}$$

where in each group y_{ij} represents the PaO_2/FiO_2 measured at the $12 + j$ hour ($j = \{0, 4, 8, 12\}$) for the $i = 1.35$ subjects per group; β_1 and β_2 are the fixed components; x_{ij} represents the rescaled time for the i subject; b_{i1} and b_{i2} are the random intercept and slope terms for the i subject, which are normally distributed with a mean value equal to zero, and ε_{ij} represents the residuals.

The sample size was calculated targeting PaO_2/FiO_2 as the outcome variable. We decided to achieve a power of 0.80 and chose an alpha equal to 5%. When 16 TREAT patients had been studied the difference between the means (baseline and 24 h) equaled 65.77 and the sum of the two SDs (baseline and 24 h) amounted to 118.66. Based on these values the calculated sample size was 27.5. Considering that the pilot study revealed a nonnormal distribution of PaO_2/FiO_2, we calculated a 25% increase in the sample size and reached the final value of 35.

Mortality between the groups was assessed by Fisher's exact test.

Results

At admission the CTRL and TREAT groups were adequately matched (table 1). At 24 h after admission, no patient in either of the groups presented a decrease of 20% or more in PaO_2/FiO_2. The same applied to the TREAT group at 25 h.

Table 1. Anthropometric, respiratory, and gas exchange

Variables	TREAT		CTRL	p
	CV	HFPV	CV	
Admission				
Gender (M/F)	26/9		26/9	
Age, years	65.0 (48.0–75.0)		64.0 (48.0–72.0)	0.832
Weight, kg	80.0 (73.5–85.0)		76.0 (73.0–84.0)	0.588
pH	7.42 (7.38–7.48)		7.41 (7.38–7.44)	0.169
$PaCO_2$, mm Hg	35.1 (33.6–40.5)		37.9 (36.2–41.1)	0.087
PaO_2/FiO_2	146.0 (116.1–195.0)		148.6 (122.0–171.0)	0.605
APACHE II	21.0 (16.0–24.0)		20.0 (16.0–25.0)	0.915
LIS	2.25 (1.50–2.75)		2.25 (1.75–2.75)	0.613
Baseline, 12 h				
pH	7.41 (7.38–7.45)		7.42 (7.39–7.43)	0.685
$PaCO_2$, mm Hg	37.9 (35.6–41.8)		39.8 (37.5–42.2)	0.084
PaO_2/FiO_2	182.4 (136.0–210.6)		154.1 (139.0–177.9)	0.146
MAP, mm Hg	85.1 (77.2–89.3)		84.0 (80.0–89.0)	0.80
a/A PO_2	0.28 (0.21–0.34)		0.25 (0.21–0.28)	0.163
VT/PBW, ml/kg	7.26 (6.5–8.0)		7.30 (6.9–8.0)	0.773
Respiratory rate, bpm	15.0 (12.3–21.8)		14.0 (12.0–16.0)	0.053
PEEP, cm H_2O	10.0 (7.0–12.0)		9.0 (8.0–10.0)	0.638
C_{rs}, ml/cm H_2O	37.5 (29.7–46.9)		36.3 (32.0–43.8)	0.897
P_{aw}, cm H_2O	13.0 (11.1–16.0)		14.0 (10.0–17.0)	0.864
Baseline, 16 h				
$PaCO_2$, mm Hg		33.2 (31.7–37.5)	38.9 (37.0–42.0)	0.000006
PaO_2/FiO_2		192.0 (161.7–268.4)	152.5 (130.5–183.3)	0.0002
a/A PO_2		0.32 (0.25–0.44)	0.25 (0.21–0.29)	0.001
MAP, mm Hg		82.1 (75.1–86.2)	81.0 (78.0–86.5)	0.67
P_{aw}, cm H_2O		12.8 (10.5–16.1)	13.0 (11.0–18.0)	0.60
Baseline, 20 h				
$PaCO_2$, mm Hg		34.6 (32.2–36.2)	38.0 (35.6–39.7)	0.0002
PaO_2/FiO_2		224.2 (185.8–341.0)	159.0 (127.8–180.3)	<0.000001
a/A PO_2		0.36 (0.29–0.51)	0.26 (0.21–0.28)	<0.00001
MAP, mm Hg		79.3 (74.9–85.8)	82.0 (77.0–85.0)	0.33
P_{aw}, cm H_2O		12.7 (10.9–16.0)	13.0 (11.0–17.0)	0.80
Baseline, 24 h				
$PaCO_2$, mm Hg		36.7 (32.6–37.8)	37.7 (35.2–41.3)	0.026
PaO_2/FiO_2		247.6 (199.3–326.8)	156 (136.2–184.0)	0.000001
a/A PO_2		0.41 (0.31–0.53)	0.27 (0.23–0.30)	<0.00001
MAP, mm Hg		83.3 (77.3–88.4)	81.0 (77.5–87.0)	0.66
P_{aw}, cm H_2O		13.6 (10.2–15.2)	13.0 (11.0–18.0)	0.52
Baseline, 25 h				
$PaCO_2$, mm Hg	34.1 (31.7–37.6)			
PaO_2/FiO_2	261.2 (191.3–303.3)			
MAP, mm Hg	84.8 (78.4–92.9)			
C_{rs}, ml/cm H_2O	40.0 (34.3–46.6)			
Baseline, 36 h				
$PaCO_2$, mm Hg	33.5 (31.9–37.2)			
PaO_2/FiO_2	254.4 (194.5–336.1)			
MAP, mm Hg	81.8 (76.1–88.1)			

TREAT = Patients that received high-frequency percussive ventilation during 12 h; CTRL = patients under conventional ventilation throughout the study; HFPV = high-frequency percussive ventilation; CV = conventional (volume- or pressure-controlled) ventilation; APACHE II = acute physiology and chronic health evaluation; LIS = lung injury score; MAP = mean arterial pressure; VT/PBW = tidal volume per predicted body weight; PEEP = positive end-expiratory pressure; C_{rs} = respiratory system compliance; P_{aw} = mean airway pressure. Data are expressed as median (1st–3rd quartiles).

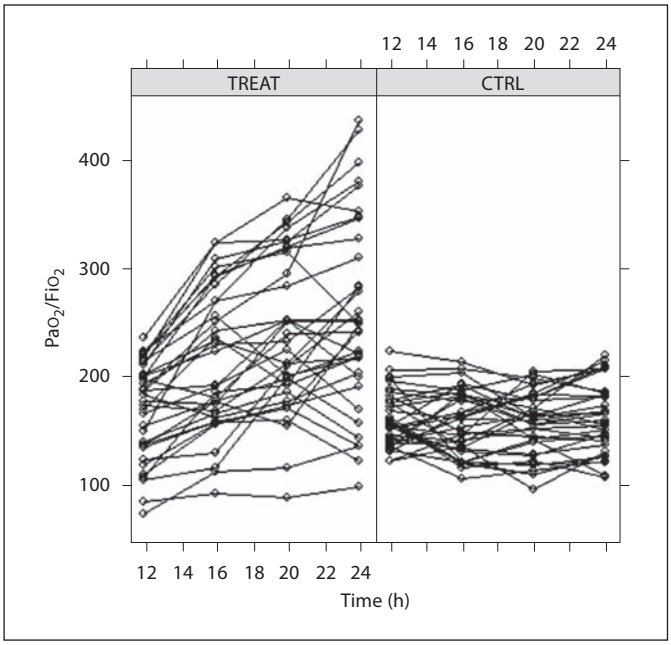

Fig. 2. PaO_2/FiO_2 versus time in hypoxemic patients. At 12 h [baseline, conventional (volume- or pressure-controlled ventilation, CV)] the patients were either switched to HFPV (left panel, n = 35, TREAT group) or left under CV (right panel, n = 35, CTRL group). PaO_2/FiO_2 increased in TREAT patients while it remained unaltered in CTRL.

In the TREAT group P_{aw} values did not show a significant variation from baseline [13.0 (11.1–16.0) cm H_2O] to the end of HFPV [13.6 (10.2–15.2) cm H_2O, p = 0.176]. Table 1 shows arterial blood gases and a/A PO_2 at admission, at 12 h of CV (baseline), and during 12 h of HFPV treatment (measured every 4 h). Arterial blood gases were also collected 1 h after returning to CV and at the end of the experiment. $PaCO_2$ showed a decrease during the first 4 h of HFPV treatment (Wilcoxon test, p = 0.0007), whereas PaO_2/FiO_2 increased ($p < 0.001$), as depicted in figure 2. Thus, HFPV settings were adjusted according to the study design to avoid hypocapnia. In fact, at 8 h of HFPV and thereafter $PaCO_2$ returned to the baseline value. In CTRL patients P_{aw} values also did not show a significant variation from baseline [14.0 (10.0–17.0) cm H_2O] to 24 h after admission [13.0 (11.0–18.0) cm H_2O, p = 0.990]. $PaCO_2$ and PaO_2/FiO_2 remained unaltered during CV (Wilcoxon test, p = 0.610 and p = 0.310, respectively), as listed in table 1.

We modeled the patient-dependent longitudinal measures of PaO_2/FiO_2 obtained during HFPV in TREAT patients and CV in the CTRL group by means of a linear mixed-effects model: PaO_2/FiO_2 increased significantly (t value = 8.7) during HFPV (fig. 2) but remained unaltered in CTRL patients (fig. 2). PaO_2/FiO_2 in TREAT group increased according with Equation 1 with a slope β_2 of 6.9 and an intercept β_1 amounting to 177, as shown in figure 2. In CTRL patients the slope equaled 0.1 while the intercept was 157.6. Additionally, PaO_2/FiO_2 remained unaltered for 12 h after the end of HFPV (p = 0.818) in patients ventilated with CV.

The MAP remained constant in all patients (TREAT and CTRL) throughout the experiment (table 1). The C_{rs} increased significantly (Wilcoxon test, p = 0.0047) between baseline and the end of HFPV (TREAT group; table 1). The CI did not change [baseline = 3.4 (3.0–3.4 l/min/m^2) and 12 h of HFPV = 3.2 (2.9–3.6 l/min/m^2)] in the seven patients with an indwelled Swan-Ganz catheter.

The ventilator-free days were 3 (3–4) and 3 (0–4) in the TREAT and CTRL groups, respectively (p = 0.315). The length of stay in the ICU amounted to 20 (16–31) days in the TREAT group and 15 (8–27) days in CTRL patients (p = 0.015). Seven of the 35 TREAT patients died (with a mortality rate of 20%), but none of these deaths could be associated with the use of HFPV. The first death was recorded on the 13th day of stay in the ICU. On the other hand, 13 CTRL patients died (mortality rate of 37%), but none of these deaths could be associated with the use of CV. The first death was recorded on the 4th day of stay in the ICU.

At baseline the measured variables did not differ between CTRL and TREAT patients (table 1). During the 12-hour treatment period, PaO_2/FiO_2 and a/A PO_2 were higher, and $PaCO_2$ was smaller in TREAT patients compared to CTRL patients, respectively (table 1); no other statistically significant difference between the two groups was detected.

Neither respiratory nor acute hemodynamic complications occurred after transitioning to HFPV.

Finally, mortality was not significantly different between the groups (p = 0.185).

Discussion

The mechanical properties of HFPV have been recently described [16]. HFPV was found to be effective in patients with severe gas exchange impairment while CV was demonstrated to be failing [19]. In this line, convection in a high-frequency oscillating system with imbalances of time constants between neighboring lung units

tends to homogenize the conducting airways, serving as a buffer for those lung units that have long time constants. It may also ventilate some alveoli otherwise not reached by the primary tidal volume [20]. We chose a pulsatile frequency of 500 cycles/min because it represents a good compromise between convection of gases at low percussion frequencies (180–240 cycles/min) and gas diffusion at a high oscillation (300–600 cycles/min), a phenomenon that may be linked to the increased kinetics of the oxygen molecules [13]. This high pulsatile frequency does not introduce a bias in the measurement since the P_{aw} is similar to the mean alveolar pressure at frequencies of 5 and 10 Hz [21]. An important clinical limitation of the VDR-4 is related to the absence of a monitor to display the delivered volume [11]; additionally, it is technically difficult to measure volume with an external device [22]. For this reason P_{aw} is the only parameter that allowed a comparison between HFPV and CV at the bedside.

P_{aw} represents a lumped parameter that does not describe the different regional conditions. P_{aw} values were collected directly from the display of the ventilators instead of being measured by an external pressure transducer. We found in vitro (Bland-Altman plots) that recorded pressures were similar to those registered by an external pressure transducer. The physiologic effects of P_{aw} depend on the instantaneous magnitude of pressure and its duration. For this reason P_{aw} is computed by dividing the area under the pressure curve by the respiratory cycle period. Many factors, such as peak airway pressure, tidal volume, inspiratory time, application of end-inspiratory pause or PEEP, presence of auto-PEEP, and increasing respiratory frequency, influence the values of P_{aw} [7]. In an animal study and in adult patients a positive relationship between P_{aw} and oxygenation was found [23, 24]. Furthermore, the same behavior was observed during high frequency jet ventilation [25]. Based on these reports we decided to keep P_{aw} unaltered in the TREAT group. CTRL patients showed the same behavior.

At admission our patients were not hypercapnic but were hypoxemic (table 1). The overall treatment increased gas exchange in both CTRL and TREAT groups to the same extent. Clinical studies determining P_{aw} have demonstrated an important increment in gas exchange during HFPV in comparison with CV [9, 26–28]. To our knowledge this is the first prospective clinical study comparing gas exchange before and after HFPV under the same P_{aw}. Furthermore, a short and early application of HFPV to improve gas exchange had not been tested before. A PaO_2/FiO_2 increment of 0.28/h of treatment with HFPV in ARDS patients was described [27]. In their study HFPV was preceded by 48 h of CV, and the main rise in PaO_2/FiO_2 took place in the first hour under HFPV (from 111 to 163); during the remaining 47 h PaO_2/FiO_2 reached 193, but this change was not significant. However, P_{aw} incresed significantly from 19.2 to 26.5 cm H_2O from the beginning of CV to the end of HFPV [27]. Additionally, MAP remained unaltered. These results suggest that: (1) HFPV would be effective even during a short time span, and (2) the effect of changing P_{aw} cannot be ruled out as a possible determinant of a better gas exchange in a stable hemodynamic condition. A similar gas exchange improvement was reported in adult post-traumatic respiratory insufficiency patients after being switched from CV to HFPV delivered at a lower peak inspiratory pressure than under CV [9]. Moreover, HFPV improved oxygenation with a concomitant decrement in intracranial pressure (ICP) in head injury patients with acute respiratory failure [29]. Similar results were obtained in ICP management after 16 h of HFPV and constant P_{aw} in ARDS patients conventionally mechanically ventilated [26]. In trauma patients with ARDS that failed CV, 8–12 h of HFPV increased PaO_2/FiO_2, whereas P_{aw} remained unchanged; thereafter oxygenation did not change for up to 12–24 h [26]. Recently, a randomized control trial in burned patients demonstrated that HFPV improved PaO_2/FiO_2 compared with CV in the first 24 h of treatment at the same measured P_{aw} [15]. It should be pointed out that in their study PaO_2/FiO_2 was >300 before randomization, i.e. the patients were different from ours [15]. Indeed, P_{aw} represents the main determinant of oxygenation and hemodynamics, irrespective of the PEEP level and ventilatory pattern [8].

We addressed the rate of rise in PaO_2/FiO_2 as a function of HFPV duration. Table 1 shows that PaO_2/FiO_2 increased 65.2 points. The same behavior has been previously described [27, 28]. We also found that the increase in PaO_2/FiO_2 could be fitted by a straight line with a slope significantly different from zero. Additionally, PaO_2/FiO_2 remained unaltered during the 12 h after the end of HFPV, as previously found [28]. It should be stressed that our patients were under CV during this period. CTRL patients did not present a significant change in PaO_2/FiO_2 from baseline until 24 h after admission. Thus, the two groups behaved differently, as depicted in figure 2. The improvement in PaO_2/FiO_2 could be explained by three findings: (a) respiratory system compliance increased between baseline and 1 h after HFPV, possibly indicating an improvement in respiratory mechanics, which could suggest a certain degree of lung recruitment and improved ventilation/perfusion relationship (from the mechanical

point of view HFPV has been reported to increase the C_{rs} and decrease the work of breathing [30]); (b) our group described an increased lung secretion clearance, which was prolonged after the end of treatment [13], and (c) HFPV accommodates volume distribution without overinflating compartments with low time constants, thus presenting a potential beneficial behavior in mechanically heterogeneous lungs [31].

Patients were considered responders if a 10–20% increase in their PaO_2/FiO_2 was detected [3, 5]. In our case, if the threshold is set at 20%, at the end of HFPV and 1 h thereafter, 29 and 31 TREAT patients, respectively, were considered responders to the treatment (in relation to the baseline value). Indeed, we found a positive HFPV response in 83% of TREAT patients, while a 71% positive prone position response (another alternative treatment in hypoxemic patients) with respect to the supine value was reported [3]. At the end of the protocol 28 out of 35 patients were still considered responders. These 7 patients that did not respond to the treatment started off with a low baseline PaO_2/FiO_2 (below 200) and 4 died of causes unrelated to the protocol. Finally, we found a significant positive dependence of the rate of rise in PaO_2/FiO_2 on its value at the beginning of HFPV (table 1), which had not been previously reported. In the CTRL group only 7 patients could be considered responders. We calculated the a/A ratio instead of the A-a gradient because, unlike the gradient, the ratio is relatively unaffected by FiO_2 and less dependent on the patient's age [32, 33]. The arterial alveolar oxygenation ratio demonstrated an increment of 44.4% at 12 h of HFPV in relation to baseline, while the CTRL group increased by only 9.5% (table 1) indicating that HFPV produced better oxygen diffusion than CV. A possible explanation could be the diffusive characteristic of the former as a result of a higher kinetic energy imposed on the oxygen molecules during high-frequency pulsatile flow.

We did not find a significant overall mortality between CTRL and TREAT groups, as previously reported under similar experimental conditions in burn patients [15], confirming that the two groups were well matched. However, the length of stay in the ICU was significantly shorter in CTRL. This finding is probably due to the high number of early deaths in CTRL that, nevertheless, did not affect the mortality rate.

In conclusion, HFPV applied during 12 h to severe hypoxemic patients with different pulmonary diseases was able to significantly increase their gas exchange. Furthermore, this finding remained unaltered from the cessation of HFPV until 12 h under subsequent CV when the study ended. No deleterious pulmonary and cardiovascular effects were detected during the protocol.

Study Limitations

Our study presents some limitations. First of all, our approach represents a rescue measure to correct gas exchange exclusively, and so a randomized prospective study in this area is warranted. Indeed, our control group was gathered retrospectively. Moreover, for the same tidal volume alveolar pressure may be unevenly distributed in different alveoli depending on the type of disease [34]. Finally, we cannot exclude that our results could partially depend on different etiologies of lung injury. The clinical message of this study should be addressed bearing in mind all of the aforementioned limitations.

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