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High-frequency percussive ventilation in severe acute respiratory distress syndrome: A single center experience

Herbert Spapen, Marianne Borremans, Marc Diltoer, Viola Van Gorp, Duc Nam Nguyen, and Patrick M Honoré

Department of Intensive Care, University Hospital, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium
Address for correspondence: Prof. Herbert Spapen, Department of Intensive Care, University Hospital, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium. E-mail: herbert.spapen@uzbrussel.be

Abstract

Background:

Few studies have investigated high-frequency percussive ventilation (HFPV) in adult patients with acute respiratory distress syndrome (ARDS).

Materials and Methods:

We retrospectively analyzed data from critically ill-patients with moderate and severe ARDS who received HFPV. Ventilation and oxygenation were governed according to a predefined protocol. HFPV was continued until patients could be switched to conventional ventilation.

Results:

A total of 42 patients (20 with pneumonia-related ARDS and 22 non-septic ARDS cases) were evaluable. Baseline demographic characteristics, severity of illness, lung injury score; pH and respiratory variables were comparable between pneumonia and non-sepsis-related ARDS. Within 24 h, HFPV restored normal pH and $PaCO_2$ and considerably improved oxygenation. Oxygenation improved more in non-septic than in pneumonia-related ARDS. Patients with pneumonia-induced ARDS also remained longer HFPV-dependent (7.0 vs. 4.9 days; $P < 0.05$). Mortality at 30 days was significantly higher in pneumonia-related than in non-sepsis-related ARDS (50% vs. 18%; $P = 0.01$).

Conclusions:

HFPV caused rapid and sustained improvement of oxygenation and ventilation in patients with moderate to severe ARDS. Less improved oxygenation, longer ventilator dependency and worse survival were observed in pneumonia-related ARDS.

Keywords: Acute respiratory distress syndrome, high-frequency percussive ventilation, pneumonia

Introduction

The acute respiratory distress syndrome (ARDS) remains a matter of high concern in critically ill-patients. Mortality of the syndrome in the intensive care unit (ICU) and in-hospital still fluctuates around 40%.[1] Treatment of ARDS involves adequate control of the underlying disease, mechanical ventilation with application of positive end-expiratory pressure (PEEP), judicious fluid management and organ support. However, the only intervention resulting in a mortality benefit has been the introduction of low-tidal volume (i.e., 5-7 mL/kg predicted body weight) ventilation.[2]

High-frequency ventilation (HFV) has been proposed as an alternative to conventional ventilation. Among HFV techniques, high-frequency percussive ventilation (HFPV) has been shown to improve oxygenation and ventilation at a lower peak inspiratory pressure and with minimal effects on hemodynamics. An additional benefit of HFPV is its ability to enhance the recruitment and mobilization of secretions from the lung periphery to the central airways, thus potentially resolving atelectasis and preventing pneumonia.[3] HFPV has shown promising results in neonatal and pediatric ARDS and in adult patients with inhalational lung injury.[3] However, in adult ARDS patients, HFPV is either not recommended or only positioned as a salvage treatment for refractory hypoxemia in some centers.

We report our experience with HFPV in an adult ARDS cohort, particularly regarding the effect of HFPV on respiratory parameters and outcome. In addition, we investigated whether HFPV produced different effects on oxygenation, ventilation and mortality in pneumonia-induced septic versus non-septic ARDS.

Materials and Methods

The study was designed as a historical cohort study (retrospective analysis of prospectively gathered data) and included 59 ARDS patients who had been switched to HFPV within 24 h after initiation of conventional ventilation. The study was approved by the Institutional Review Board and Ethical Committee of The University Hospital Brussels (file n° B.U.N. 143201214502). ARDS was defined according to the recently published "Berlin definition"[4] as respiratory failure not due to cardiac failure or fluid overload, occurring within 1 week after a well-defined clinical insult and characterized by bilateral opacities on chest X-ray not explained by effusions (partial) lung collapse or masses. Moderate (100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg with PEEP ≥ 5 cm H_2O) and severe (PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥ 5 cm H_2O) ARDS were considered. Pneumonia-related ARDS was defined as ARDS complicating a microbiologically documented bacterial pneumonia. Non-septic ARDS was defined as ARDS not related to pneumonia, including distinct forms of direct pulmonary involvement such as inhalational lung injury and lung contusion. Patients were excluded when one of the following criteria were present: Age < 18 years, pregnancy, neuromuscular disease, GOLD (Global initiative for chronic Obstructive Lung Disease) class III chronic respiratory disease, Child-Pugh class B and C liver cirrhosis, bone marrow or lung transplantation, dismal prognosis (i.e., patients with end-stage lung fibrosis or metastatic cancer, documented advanced dementia, or unlikely to survive within the first 24 h following ICU admission) and unwillingness to accept full life support. In addition, no concomitant modalities that could possibly affect ventilation and/or oxygenation (e.g., neuromuscular blockade, nitric oxide inhalation, prone positioning, extracorporeal membrane oxygenation or CO_2 removal, alveolar recruitment maneuvers) were allowed but could be initiated in case patients did not respond to 24 h HFPV treatment. These patients were not evaluable for study endpoints.

All patients were initially ventilated in pressure-controlled modes with tidal volumes of 6 ± 1 mL/kg predicted body weight at plateau pressures below 30 cm H_2O. Patients received standardized analgesic sedation with remifentanyl (up to 0.2 μg/kg/min) and propofol (up to 75 μg/kg/min). Resuscitation aimed to obtain and maintain a mean arterial blood pressure ≥70 mmHg and a $ScvO_2$ >70%. An adequate cardiac output was assured at baseline under transesophageal echocardiographic guidance. To achieve resuscitation goals, patients received colloid and crystalloid infusion and if needed, dobutamine or norepinephrine. All patients received standard routine treatment and care for the disease processes underlying ARDS (i.e., antibiotics, fracture fixation, protocolized glucose control, enteral and/or parenteral nutrition, stress ulcer and deep vein thrombosis prophylaxis and respiratory physiotherapy).

HFPV was initiated at the attending physician's discretion and performed with the VDR-4 Percussionnaire™ (Volumetric Diffusive Respirator, Bird Technologies, Sandpoint, ID). Ventilator starting settings were: High-frequency rate 500/min; pulsatile flow rate to attain a peak inspiratory pressure of maximum 30 cm H_2O; oscillatory PEEP 10 cm H_2O; FiO_2 100%; T_i/T_e = 1.5/1; i/e = 1/1 to 1/2. HFPV goals were: pH 7.35-7.45; $PaCO_2$ 35-45 mmHg and SpO_2 > 95%. Adequate humidification was assured by a high-volume nebulizer incorporated in the ventilator circuit, an external heated humidifier (F and P 850™ System; Fisher and Paykel Health-care, Auckland, NZ) and continuous instillation of 10 mL/h water directly into the endotracheal tube. Blood gases were determined at least every 4 h or when considered as necessary by the attending physician. Ventilation and oxygenation were adapted according to a predefined protocol [Figure 1] under the supervision of a dedicated team of trained physicians and

respiratory therapists. Patients stable on HFPV could be switched at the physician's discretion to conventional pressure-controlled ventilation and subsequently weaned.

SPSS for Windows (IBM™, SPSS™, Statistics for Windows, Version 20.0, IBM Corp., Armonk, NY) was used for statistical analysis. Fisher's exact test and Mann-Whitney U test were performed to evaluate differences in age, gender, mortality and Acute Physiology and Chronic Health Evaluation II score between patients with pneumonia-related or -unrelated ARDS. Respiratory variables and pH between these two ARDS groups were compared by one-way analysis of variance for repeated measurements followed by Bonferroni correction for multiple comparisons. Data were expressed as mean ± standard deviation. Statistical significance was accepted at $P < 0.05$. Kaplan-Meier survival analysis was performed including a log-rank (Mantel-Cox) test.

Results

Patient's selection procedure was depicted in Figure 2. Of the 42 evaluable patients, 20 had pneumonia-induced and 22 had non-sepsis-related ARDS. Baseline demographics, severity of illness, lung injury score, respiratory variables and PEEP levels were comparable between both groups [Table 1]. 22 (52%) of the patients had severe ARDS, including 10 (50%) pneumonia-associated cases and 12 (54%) non-septic subjects.

The evolution of pH, $PaCO_2$ and PaO_2/FiO_2 during HFPV was outlined in Figure 3 (all patients) and Figure 4 (pneumonia vs. non-septic patients). Data collection and comparison between patient groups were relevant for up to 6 days of HFPV treatment. Thereafter, the number of patients remaining on HFPV became too low to allow meaningful statistical evaluation.

All patients taken together, HFPV rapidly restored and maintained normal pH and PaCO2 and significantly improved oxygenation. Both pneumonia-related and non-septic ARDS patients experienced a similar beneficial evolution of pH and PaCO2 during HFPV, but oxygenation improved more in the non-septic subjects, becoming significant from baseline after 48 h of treatment. Patients with pneumonia-related ARDS also spent more days on HFPV than their non-septic counterparts (7.0 vs. 4.9 days, $P < 0.05$).

Overall mortality at 30 days and in-hospital mortality were respectively 33% and 42%. Moderate and severe ARDS patients had a similar 30 days mortality rate (33% vs. 41%; P = NS). However, 30-day mortality was significantly higher in pneumonia-related as compared with non-septic ARDS (50 % vs. 18%; $P = 0.01$) [Figure 5]. Causes of death during HFPV in pneumonia-related ARDS were refractory septic shock ($n = 2$), intractable multi-organ failure ($n = 5$) and cerebral hemorrhage ($n = 1$) whereas, the only patient in the non-septic group died after treatment was withdrawn because of confirmed brain death. At 30 days, most patients had died from uncontrollable or relapsing organ failure except one non-septic patient who succumbed from an acute cardiac event. Hospital mortality was also higher in pneumonia-associated than in non-septic ARDS (60% vs. 27%; $P = 0.03$). Barotrauma was never observed during HFPV. Except for the two patients with pneumonia-induced septic ARDS who developed refractory shock, no significant changes in dose or duration of inotropic or pressure infusions were observed after initiation or during the course of HFPV treatment (data not shown).

Discussion

The landmark ARDSNet trial showed that low tidal volume ventilation (6 mL/kg predicted body weight) substantially reduced absolute mortality when compared with “traditional” ventilation applying tidal volumes of 12 mL/kg. Since then, this so-called protective ventilation strategy ranks as the gold standard for treatment of ARDS.[2] Yet, underuse of lung protective ventilation is common[5] and the inherent “permissive” hypercapnia may be harmful for patients with compromised cardiac function or brain injury. Moreover, Villar *et al*. recently reported an ICU and hospital mortality of respectively 43% and 48% in a large cohort of ARDS patients treated by protective ventilation, which markedly exceeded the 31% of mortality was observed in the ARDSNet trial.[6] This may be explained in part by a changing pattern of ARDS over time. Indeed, patients with ARDS nowadays are older and more severely ill. Furthermore, sepsis-related ARDS is increasing steadily whereas, the number of ARDS cases associated with trauma and transfusion has declined.[7]

HFV comprises any application of mechanical ventilation at respiratory rates exceeding 100 breaths/min. High-frequency oscillatory ventilation (HFOV) is currently the most often used form of HFV in adult critical care. HFOV basically functions by creating a constant high mean airway pressure holding the lungs inflated to maintain oxygenation whilst ventilation is assured by a piston that "oscillates" delivered gas at high frequency around the mean airway pressure. However, two recent multicenter, randomized, controlled trials that compared HFOV with a low tidal volume ventilation strategy in adult patients with moderate to severe ARDS showed no benefit of early application of HFOV on mortality.[8,9] One study found higher need for sedation and neuromuscular blockers, more and prolonged hemodynamic instability and even higher in-hospital mortality in HFOV-treated patients.[8]

In contrast to HFOV, HFPV stepwise inflates the lung to a selected increase in lung volume, before entering an "oscillatory equilibrium," ventilating the lung with continuously programmed percussive sub tidal breaths. A unique feature of HFPV is the presence of a Phasitron™. This piston mechanism situated at the end of the endotracheal tube acts as a sliding Venturi and produces a dynamic airway interface through which pulsatile flow is delivered into the lungs. Percussive frequency, inspiratory (I) and expiratory (E) times, plateau and PEEP and I/E ratio are determinant factors of mean airway pressure and are, either alone or in combination, able to modify gas exchange. An additional benefit is that HFPV generates intrabronchial vibrations, airway turbulence and higher airflow, all of which may enhance mobilization and clearance of airway debris and secretions.[3]

The current study showed that application of HFPV in patients with severe ARDS resulted in rapid improvement of oxygenation and ventilation. This is in accordance with both former[10] and recent[11] studies in adult ARDS patients demonstrating that HFPV significantly improved gas exchange at similar levels of mean airway pressure as in conventional ventilation. This effect occurred already within the 1st h after initiation of HFPV and was sustained during the whole period of ventilation. More importantly, our data showed that HFPV enabled to maintain a stable acid-base balance, did not alter hemodynamics and was not complicated by barotrauma.

Only one prospective randomized study, conducted 25 years ago, compared conventional ventilation with HFPV in patients with acute lung injury.[12] Both groups were ventilated to the same therapeutic endpoints (pH > 7.35, $PaCO_2$ 35-45 mmHg and PaO_2/FiO_2 > 225). In patients with documented ARDS, HFPV provided comparable oxygenation and ventilation at a lower peak, mean and end-expiratory pressures as compared with conventional ventilation. However, this study does not match current standards of care since it compared the now obsolete intermittent mandatory ventilation mode with HFPV delivered by a non-commercialized VDR device. Subsequent observational studies evaluating HFPV in critically ill-patients with ARDS mainly included surgical and trauma patients and used HFPV as a non-protocolized rescue therapy for intractable hypoxemia.[13,14,15,16] In general, these studies confirmed significant improvement of oxygenation after 16-48 h of treatment.[13,14,15,16] In head-injured patients, HFPV resulted in a dramatic decrease in intracranial pressure.[16]

Our study results suggested that patients whose ARDS was pneumonia-based may respond differently to HFPV than patients with non-septic ARDS. We observed a similar pattern of normalization and stabilization of pH and $PaCO_2$ in both patient groups. However, significant improvement of oxygenation was observed in the non-septic ARDS group only. During HFPV, the latter also displayed better, though not significantly, oxygenation than pneumonia patients developing ARDS. Non-septic patients had more HFPV-free days, suggesting better tolerance of this ventilation mode. This diverging response of pneumonia-related versus non-sepsis associated ARDS to HFPV remains unexplained. However, sepsis- and non-sepsis-related ARDS are thought to be different entities with regard to pathophysiology, clinical features and outcome.[17] Septic ARDS patients indeed present more acute inflammation and a higher degree of endothelial cell and coagulation activation than their non-septic counterparts. Clinically, sepsis-related ARDS is linked to a higher mortality, a lower successful extubation rate and fewer ventilator-free and ICU-free days.[17]

Whole group overall 30-day and hospital mortality in our study were in-line or even lower than reported during conventional protective[6] or prone position[18] ventilation. Yet, a more striking observation was the much higher 30-day and hospital mortality in pneumonia-related when compared with sepsis-naive ARDS. Moreover, most deaths in the pneumonia group were related to refractory septic shock and multi-organ failure. Thus, although highly speculative, it is conceivable that HFPV adversely propagated

reactive pathways in pneumonia-related ARDS that promoted or enhanced local and/or remote inflammation and subsequent organ damage. Our results cannot be compared with the existing literature on HFPV use in ARDS since published data predominantly relate to trauma patients. Nonetheless, the few described medical ARDS patients, most of whom suffering pneumonia, had an ICU mortality approaching 65%.[13,14] Further research is needed to elucidate why HFPV offers no outcome benefit in pneumonia-related ARDS.

Our study has several major shortcomings. First, despite being the largest observational study to date, our patient sample size is still much too low to allow any concrete positioning of HFPV in current management of adult ARDS. Second, it is not known what the course and outcome of ARDS in our study population would have been if patients had been continued on protective conventional ventilation. This issue can only be solved by a large prospective randomized study comparing both types of ventilation within the constraints of a strict ventilation protocol. Third, the retrospective nature of our study precluded to retrieve and to compare data regarding respiratory mechanics, airway pressures and hemodynamic variables, all of which being potentially relevant to ventilation and patient outcomes. Finally, HFPV requires the use of a ventilator that is not available in all ICUs. Though more user-friendly than its predecessors, the VDR-4 Percussionaire remains difficult to handle. This was reflected by the high number of protocol violations. The success of HFPV remains directly proportional to the enthusiasm and commitment of respiratory therapist(s) and ICU staff. Insufficient knowledge of the ventilator, untimely adaptation of ventilatory settings, or non-adherence to an established ventilation protocol will all preclude obtaining adequate results and risk to turn HFPV into a frustrating experience.

Conclusions

The application of HFPV in moderate and severe ARDS resulted in rapid and sustained improvement in oxygenation and ventilation. Pneumonia-related ARDS patients submitted to HFPV have less improved oxygenation, longer ventilation dependency and worse survival than non-sepsis-related ARDS patients. Whether this is due to a HFPV-induced triggering of injurious local and/or systemic inflammatory processes remain to be established.

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Footnotes

Source of Support: Nil

Conflict of Interest: None declared.

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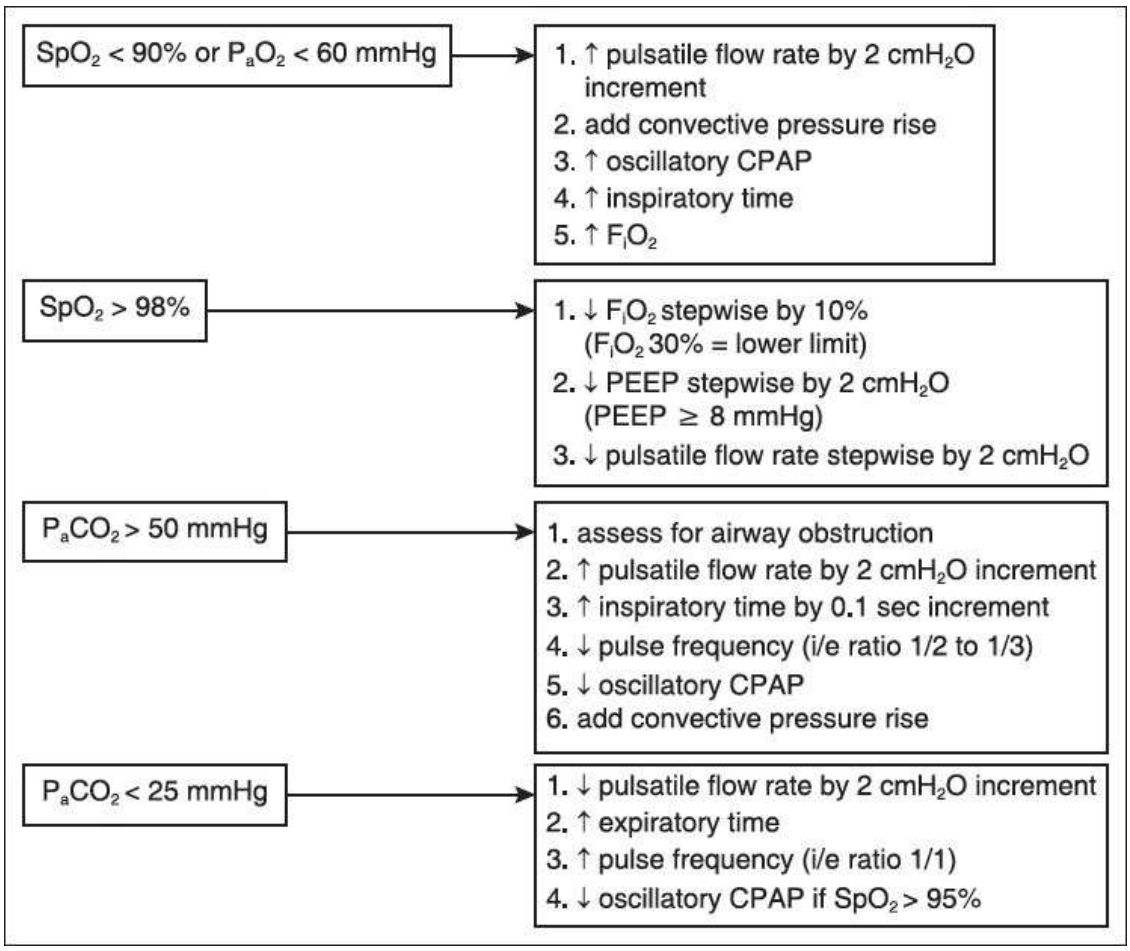
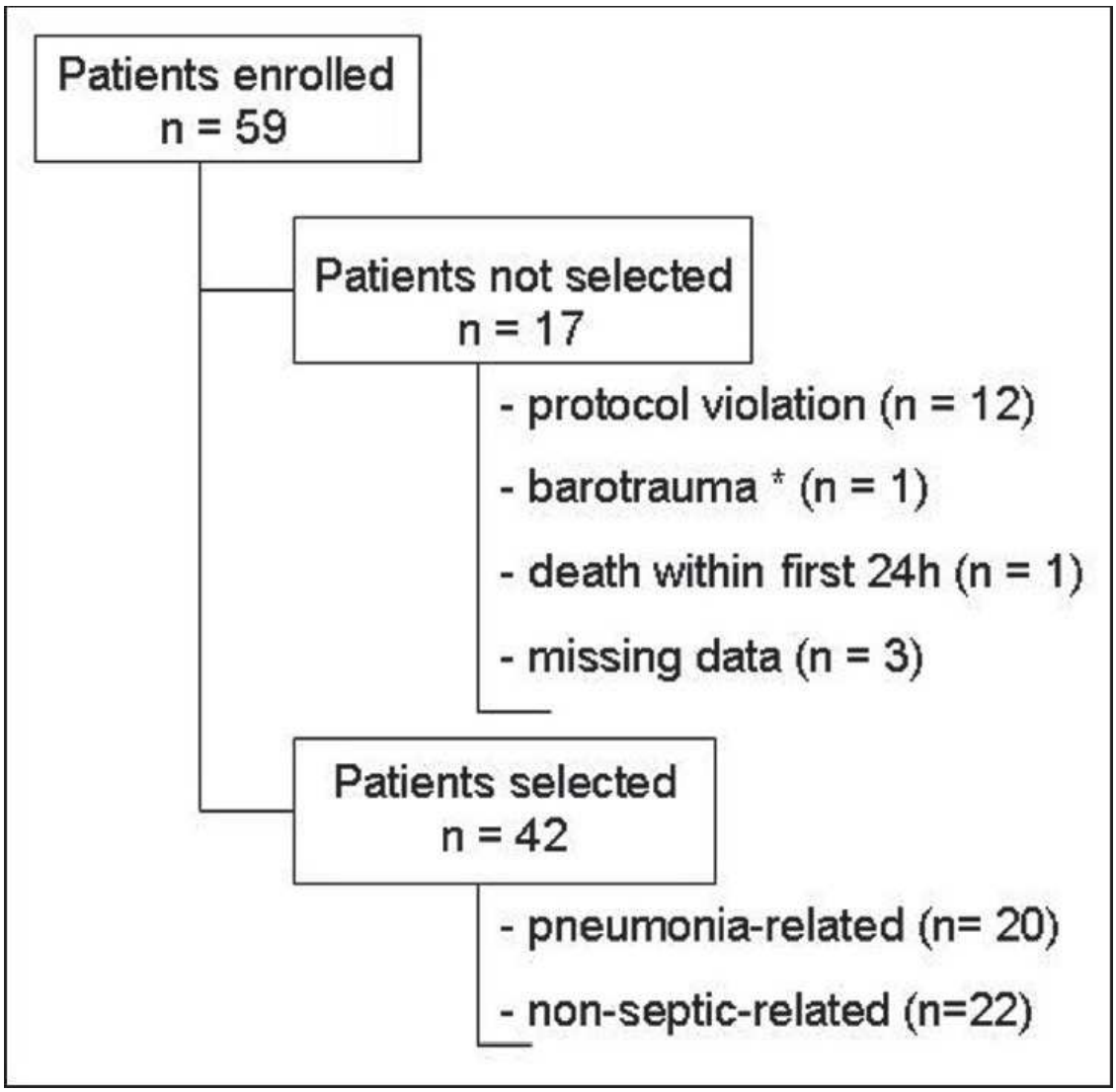
Figures and Tables

Figure 1



High-frequency percussive ventilation protocol

Figure 2



Patient selection. *Barotrauma diagnosed prior to start high-frequency percussive ventilation

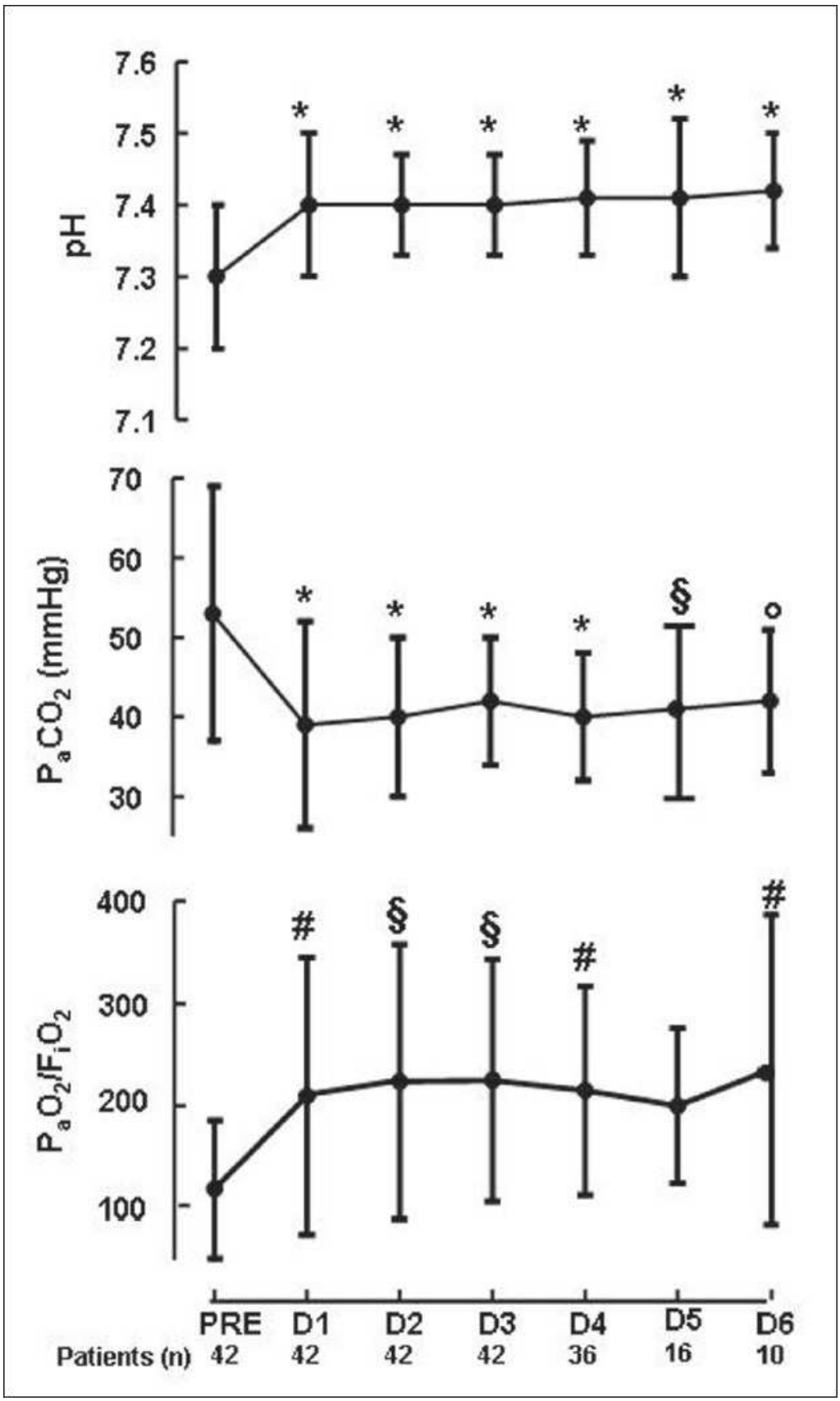
Table 1

Variable	PR ARDS (n = 20)	NSR ARDS (n = 22)	P
Age, years	57±19	58±17	0.51
Gender, male	12	13	0.90
APACHE II	25±11	24±10	0.77
Lung injury score*	3.7±0.5	3.6±0.5	0.87
Arterial pH	7.28±0.10	7.31±0.11	0.52
$PaCO_2$, mmHg	56±20	50±12	0.21
PaO_2/FiO_2	109±46	127±82	0.46
PEEP, cm H_2O	11±3	10±3	0.24
Cause of ARDS (n)			
Pneumonia	20	—	
Aspiration	—	5	
Trauma	—	6	
Polytransfusion	—	5	
Others#	—	6	

*Data are presented as mean ± SD. APACHE = Acute physiology and chronic health evaluation, PR ARDS = Pneumonia-related acute respiratory distress syndrome, NSR ARDS = Non-sepsis-related acute respiratory distress syndrome, SD = Standard deviation, ARDS = Acute respiratory distress syndrome, PEEP = Positive end-expiratory pressure. #Acute pancreatitis (n = 1), post-cardiopulmonary bypass (n = 2), inhalational lung injury (n = 1), lung contusion (n = 2). *All patients had alveolar consolidation in all 4 lung quadrants*

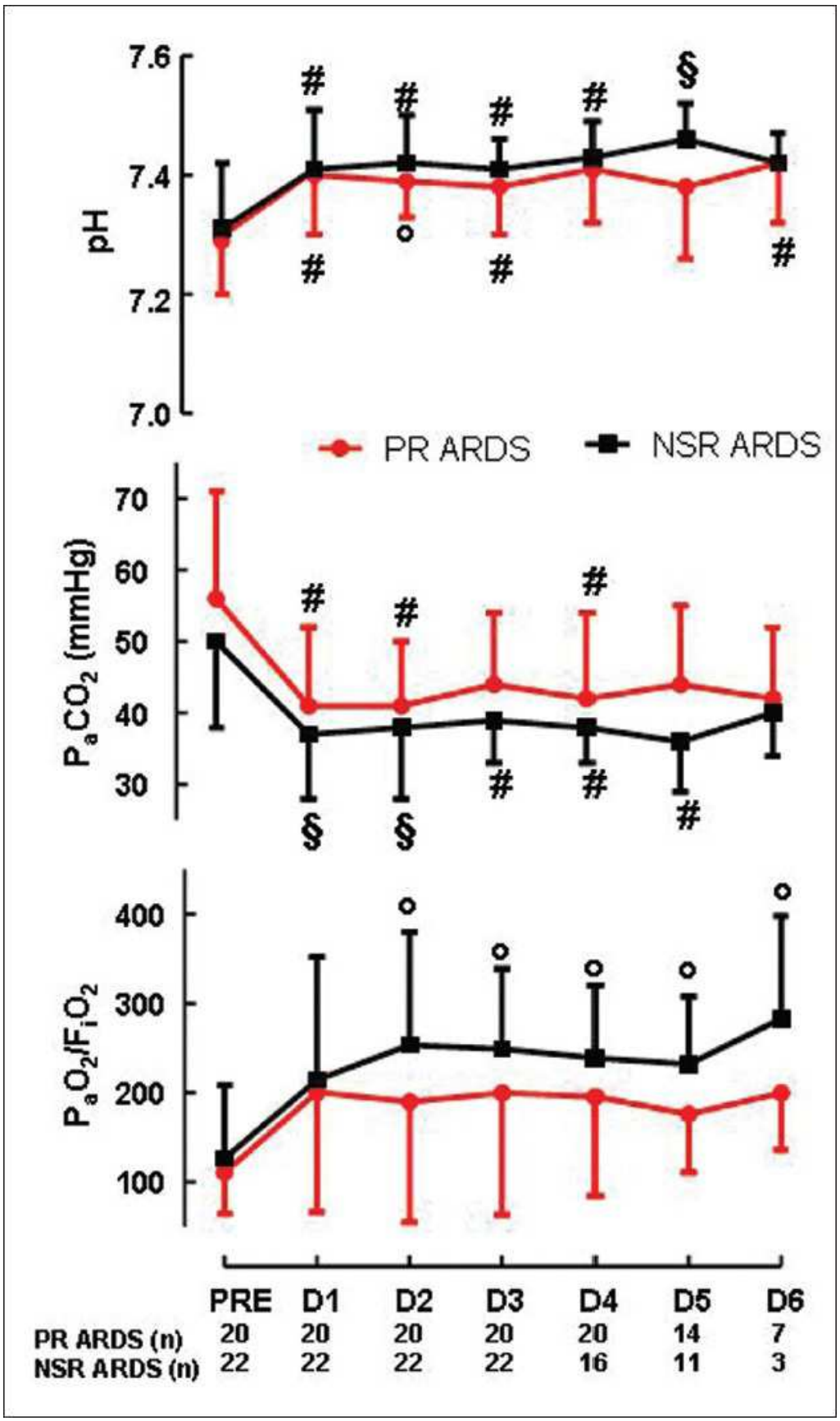
Patient characteristics at baseline and primary cause of ARDS

Figure 3



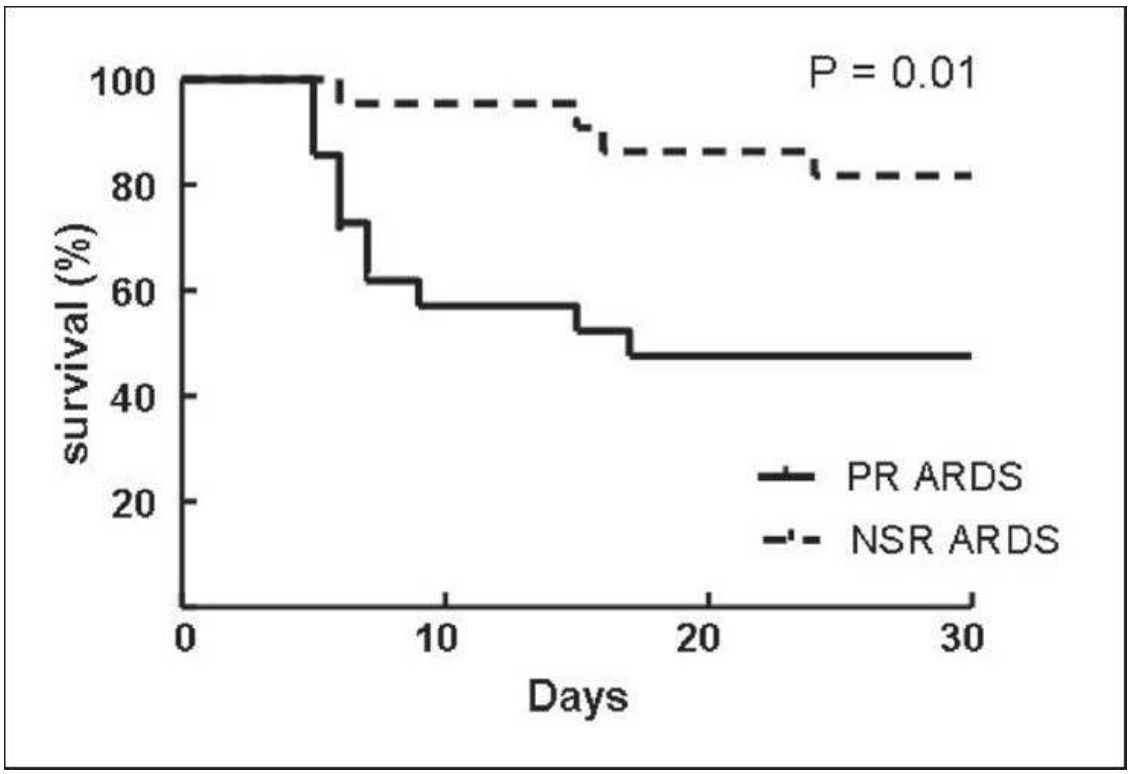
Evolution of pH, $PaCO_2$ and PaO_2/FiO_2 during high-frequency percussive ventilation treatment in all patients. $^{*}P < 0.0001$;$^{\S}P < 0.001$;$^{\#}P < 0.01$;$^{\circ}P < 0.05$

Figure 4



Evolution of pH, $PaCO_2$ and PaO_2/FiO_2 during high-frequency percussive ventilation treatment in patients with pneumonia-related acute respiratory distress syndrome (PR ARDS; red line) and patients with non-sepsis-related ARDS (NSR ARDS; black line). $^{\S}P < 0.001$;$^{\#}P < 0.01$;$^{\circ}P < 0.05$

Figure 5



Kaplan-Meier curve for 30-day survival between patients with pneumonia-related acute respiratory distress syndrome (PR ARDS) and patients with non-sepsis-related ARDS (NSR ARDS). *P* value was obtained by log-rank test