Gas Exchange of prone positioning in influenza pneumonia-related acute respiratory distress syndrome: A multicenter retrospective cohort study in Taiwan

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Research Article

Keywords: Prone positioning, Acute Respiratory Distress Syndrome, Influenza, Gas exchange, Outcome

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Abstract

Background: Prone positioning has demonstrated decreased mortality in severe acute respiratory distress syndrome (ARDS) patients. The aim of this study was to investigate the effect of prone positioning in patients with influenza pneumonia-related severe ARDS.

Methods: This retrospective study includes eight tertiary referral centers. All the patients with influenza pneumonia induced severe ARDS and receiving prone positioning were enrolled. Demographic data, laboratory data, treatment record, ventilator setting data and outcomes were collected. PaO2 responders were defined as the PaO2/FiO2 ratio increasing by ≥20% or ≥20 mm Hg, while PaCO2 responders were defined as PaCO2 decreasing by ≥1 mm Hg after prone positioning for one day.

Results: Sixty-five patients receiving prone positioning were enrolled, with 37 (57%) were PaO2 responders and 33 (51%) were PaCO2 responders. Mortality rates were not significantly different between responders and non-responders. PaCO2 responder survivors had significantly shortened length of stay at the ICU (21.0 ± 13.5 vs. 31.7 ± 18.5 days, $P = 0.038$) and hospital (30.2 ± 16.6 vs. 43.0 ± 16.3 days, $P = 0.013$) than did non-responders. Multivariate analysis revealed younger age (odds ratio 0.903, 95% confidence interval 0.824-0.989; $P = 0.028$) and higher PaCO2 level before prone positioning (odds ratio 1.121 confidence interval 1.020-1.231; $P = 0.017$) were the predictors of PaCO2 responders.

Conclusions: In this multicenter retrospective cohort study of influenza pneumonia patients with severe ARDS receiving prone positioning, PaCO2 responders had modestly better clinical outcomes. Younger age and higher PaCO2 level before prone positioning were the predictors of PaCO2 responders.

Keywords: Prone positioning, Acute Respiratory Distress Syndrome, Influenza, Gas exchange, Outcome

Background

Severe complicated influenza including pneumonia, myocarditis, and neurological complications is still a burden of intensive care units (ICU) nowadays, especially viral or secondary bacteria pneumonia-induced acute respiratory distress syndrome (ARDS) [1, 2]. Patients with influenza pneumonia who need mechanical ventilation are at high risk of rapid progression to ARDS. In the 2009 pandemic H1N1 virus infection, 49% to 72% of patients admitted to ICUs had complications with ARDS [3, 4].

In patients with severe ARDS and refractory hypoxemia, even there are several rescue therapeutic options to be used [5, 6], but only four of them have been confirmed with survival benefit by previous studies, including high positive end expiratory pressure (PEEP) [7, 8], low tidal volume [9], neuromuscular blocker [10], and prone positioning. Prone positioning was first speculated in 1974 by Bryan *et al* [11]. The survival benefit of prone positioning was confirmed in the PROSEVA study in 2013 [12] showed decreased 28-day and 90-day mortality and increased ventilator-free day only if the patients had fair lung protective strategy and longer prone positioning duration. The mechanisms of improvement oxygenation including

making more homogenous ventilation, decreasing ventilation-perfusion mismatch, avoiding ventilator induced lung injury, and decreasing compression by heart or abdomen [13].

Since the influenza is a common cause of ARDS, few prone positioning studies focused on influenza pneumonia-related severe ARDS patients [14]. Xu et al. [15] studying H7N9 influenza patients with prone positioning, and the result showed that carbon dioxide (CO_2) retention decreased. Moreover, what factors exist that are able to predict the efficacy or response of prone positioning are still unknown [16]. There was an outbreak of influenza A (H1N1) in Taiwan during the winter season in 2016 where a total of 1,735 severe complicated influenza pneumonia subjects were admitted to ICUs according to the data from centers for disease control of Taiwan [17, 18]. In this study, we focused on patients suffering from severe complicated influenza pneumonia-related ARDS with prone positioning to investigate the factors related to gaseous-exchange responses.

Methods

Study patients and data collection

The Taiwan Severe Influenza Research Consortium (TSIRC) which includes eight tertiary referral centers in Taiwan [14], conducted this retrospective study. From 1 January to 31 March in 2016, all of the patients who were admitted to ICUs with virology-proven influenza were screened, and all of these patients who had the diagnosis of ARDS according to the Berlin definition [19] and also receiving prone positioning were enrolled. The demographic data, laboratory data, treatment record, ventilator setting data and outcomes were obtained from electronic medical records, while a standard case report form was used to collect these data. The local Institutional Review Board for Human Research of the involved hospitals approved this study (Linkou and Kaohsiung Chang-Gung Memorial Hospital IRB No. 201600632B0, National Taiwan University Hospital 201605036RIND, Taipei Veterans General Hospital 2016-05-020CC, Tri-Service General Hospital 1-105-05-086, Taichung Veterans General Hospital CE16093A, China Medical University Hospital 105-REC2-053(FR), Kaohsiung Medical University Hospital KUMHIRB-E(I)-20170097) and the need for informed consent was waived due to the retrospective nature of the study.

Diagnosis of influenza

Influenza was proven by more than 1 of the following tests: influenza rapid antigen test, nucleic acid reverse-transcriptase polymerase chain reaction (RT-PCR), or viral culture, or serum antibody serologic test (antibody titers changed more than 4 times from acute to convalescent stage) according to the different patient or different hospital. The rapid antigen test was sampled from nasopharynx swab or throat swab, and the RT-PCR or viral culture might sampled from nasopharynx swab, throat swab, sputum or bronchoalveolar lavage

Laboratory data

We collected the laboratory data when the patient was admitted to the ICU including complete blood count, white blood cell differential count, and biochemistry data. Arterial blood gas data before and 1 day after the prone positioning were collected. We also collected the severity scores on the ICU admission day including Pneumonia Severity Index (PSI) [20], Acute Physiology and Chronic Health Evaluation II (APACHE II) [21], CURB-65 pneumonia severity score [22], and Sequential Organ Failure Assessment (SOFA) score [23].

Mechanical ventilator setting and prone positioning

The ventilator settings were adjusted according to the ARDSnet with lung protective strategy protocol [9], and the setting data such as peak inspiratory pressure, positive end expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), and tidal volume before and 1 day after the prone positioning were all recorded. The pressure control mode was used in all of the patients. The dynamic driving pressure was defined as peak inspiratory pressure minus PEEP, and the compliance was defined as tidal volume divided by dynamic driving pressure. The methods of prone positioning were according to the PROSEVA study [12] that more than 16 hours/day was used in all of the patients. According to the previous studies, the PaO_2 responders were defined as the post-prone positioning PaO_2/FiO_2 ratio increasing by ≥20% or by ≥20 mm Hg compared to pre-prone positioning, while $PaCO_2$ responders were defined as post-prone positioning $PaCO_2$ decreasing by ≥1 mm Hg compared to pre-prone positioning [12, 13, 24-26].

Statistical analyses

Number (percentages) for nominal variables, and means ± standard deviation for continuous variables were presented in this study. Pearson's Chi Square test was used to compare nominal variables, and the independent Student *t*-test was used to compare continuous variables, with the binary logistic regression test used to analyze univariate and multivariate factors. In this study, the two-tailed test was used, and the definition of significance was p value <0.05. Statistical analyses and database management were performed using SPSS version 22.0.0 (SPSS Inc., Chicago, IL).

Results

General data

Three-hundred and thirty-six patients were screened during the study period. Of these 336 patients, 48 patients without mechanical ventilation and 25 patients without ARDS were excluded. Two-hundred and sixty-three patients met the diagnosis of severe influenza pneumonia-related ARDS, and of these patients,

65 (24.7%) receiving prone positioning were enrolled for this study (Fig 1). The average age was 57.5 ± 11.8 years and 40 patients were male. Fifty-two patients were confirmed with influenza A (46 patients were H1N1 influenza A), 4 patients were influenza B, and 9 patients were of indeterminate type. Before prone positioning, the PaO_2/FiO_2 ratio, setting tidal volume and PEEP measures were 95.9 ± 54.5 mm Hg, 7.7 ± 2.0 ml/kgw and 13.7 ± 3.6 cm H_2O (Table 1).

Comparison of PaO_2 and $PaCO_2$ of responders and non-responders

The characteristics of PaO_2 responders and PaO_2 non-responders are shown in Table 1. Of these 65 patients with prone positioning, 37 patients (57%) were PaO2 responders. The PaO_2 responders had significantly lower PaO_2 (68.1 ± 26.9 mm Hg vs. 91.2 ± 41.2 mm Hg, $P = 0.008$), FiO_2 (0.9 ± 0.1 vs. 0.8 ± 0.2, $P = 0.019$), PaO_2/FiO_2 ratio (77.0 ± 37.9 mm Hg vs. 120.8 ± 63.2 mm Hg, $P = 0.002$), and $P(A\text{-}a)O_2$ (549.7 ± 108.0 vs 445.2 ± 161.3 mm Hg, $P = 0.005$) than did PaO_2 non-responders. The 60-day mortality rates of PaO_2 responders and PaO_2 non-responders were 24.3% and 39.3% without statistically significant difference ($P = 0.196$).

The characteristics of $PaCO_2$ responders and $PaCO_2$ non-responders are shown in Table 2. Of these 65 patients with prone positioning, 33 patients (51%) were $PaCO_2$ responders. The $PaCO_2$ responders were significantly younger (54.4 ± 10.7 years vs. 60.6 ± 12.1 years, $P = 0.031$), had higher $PaCO_2$ (57.2 ± 19.4 mm Hg vs. 39.6 ± 9.5 mm Hg, $P = 0.000$), PEEP (15.0 ± 3.4 cm H_2O vs. 12.5 ± 3.4 cm H_2O, $P = 0.014$) and peak airway pressure (32.0 ± 3.9 cm H_2O vs. 29.2 ± 4.1 cm H_2O, $P = 0.02$) than did $PaCO_2$ non-responders. The 60-day mortality rates of $PaCO_2$ responders and $PaCO_2$ non-responders were 27.2% and 34.4% without statistically significant difference ($P = 0.535$).

Fourteen patients had only PaO_2 response, and 10 patients had only $PaCO_2$ response. Twenty-three patients fulfilled both the criteria of being PaO_2 and $PaCO_2$ responders, and 18 patients were both PaO_2 and $PaCO_2$ non-responders. The 60-day mortality rates in both PaO_2 and $PaCO_2$ responders were lower than both PaO_2 and $PaCO_2$ non-responders (25% vs. 38.9%), but there was no significant difference ($P = 0.335$).

Clinical outcomes

Of these 65 patients receiving prone positioning with influenza pneumonia-complicated severe ARDS, the overall 30-day and 60-day mortality rates were 26.2% and 30.8% respectively. There was no statistically significant difference for the duration of prone positioning between PaO_2 or $PaCO_2$ responders and non-responders in survivors (Table 3). Ventilator free days were longer, but not significantly different in PaO_2 or $PaCO_2$ responders than in non-responders. The lengths of ICU and hospital stays were not significantly

different between PaO_2 responders and non-responders. However, the survivors with $PaCO_2$ responders had significantly shorter ICU (21.0 ± 13.5 days vs. 31.7 ± 18.5 days, *P* = 0.038) and hospital stays (30.2 ± 16.6 days vs. 43.0 ± 16.3 days, *P* = 0.013) than did $PaCO_2$ non- responders (Table 3). PaO_2 responders had lower mortality rates than did non-responders in 30-day (21.6% vs. 32.1%, *P*= 0.339) and 60-day periods (24.3% vs. 39.3%, *P* = 0.196), although there were no significant differences. Multivariate analysis revealed that factors predicting $PaCO_2$ responders were age and pre-prone positioning $PaCO_2$ (*P* = 0.033 and 0.011 respectively) (Table 4).

Discussion

In this multicenter retrospective cohort study, we found that in influenza pneumonia patients with severe ARDS treated with prone positioning, the lower PaO_2/FiO_2 ratio before prone positioning seemed to have a higher percentage of PaO2 response to prone positioning. However, the PaO_2 responders did not have better clinical survival outcomes than the PaO_2 non-responders. The $PaCO_2$ responders had modestly better clinical outcomes including shorter length of ICU and hospital stays than the $PaCO_2$ non-responders. Multivariate analysis revealed that younger age and higher $PaCO_2$ level before prone positioning were the predictors of $PaCO_2$ responders.

PaO_2 responders had lower PaO_2 and higher FiO_2 before prone positioning than PaO_2 non-responders. It seemed that patients having lower PaO_2/FiO_2 ratio before prone positioning could obtain more PaO_2/FiO_2 ratio improvement after the intervention. Prone positioning is one of the rescue therapies for refractory hypoxemia in ARDS. A meta-analysis study of prone positioning in ARDS conducted by Sud et al. [27] found that prone positioning reduced the mortality only in patients with PaO_2/FiO_2 ratio less than 100 mm Hg. In another study, prone positioning demonstrated that it could improve survival outcome in patients with ARDS when the PaO_2/FiO_2 ratio was less than 150 mm Hg accompanied with early, prolonged use and lung protective strategy [12]. In our study, the mean PaO_2/FiO_2 ratios were 77 mm Hg in PaO_2 responders and 120 mm Hg in PaO_2 non-responders; both of them being less than 150 mm Hg. It might mean that if lower PaO_2/FiO_2 ratio threshold for prone positioning had been set, better response might have been seen; however, there was no significant survival benefit noted between PaO_2 responders and PaO_2 non-responders. Regarding the role of prone positioning in severe ARDS, it is important to investigate the gap between PaO_2/FiO_2 ratio threshold and survival benefit.

$PaCO_2$ responders had higher $PaCO_2$, PEEP, and peak airway pressure than did $PaCO_2$ non-responders before prone positioning, and the trend of lower tidal volume and poorer dynamic lung compliance were also noted as almost having statistical significance (*P* = 0.053 and 0.060 respectively). In the present study, unlike PaO_2 responders, the $PaCO_2$ responders had better clinical outcomes including shorter duration of ICU and hospital stays. Gattinoni et al. [24] found that better survival at 28 days was only found in $PaCO_2$ responders (defined as $PaCO_2$ decreased ≥1 mm Hg after 6 hours in the first prone positioning) but not PaO_2 responders, and they suggested that the decreased dead space ratio is an

important marker for survival in patients with ARDS. In another study, no relationship was noted between gas exchange improvement and survival [25]. However, the mortality rate revealed no statistically significant difference between these two groups in our study. The reasons might be due to low mortality rate in both groups in our study (27.2% vs 25.0%). In addition, it might also be due to the causes or risk factors of ARDS being different. In this study, the cause of severe ARDS was influenza pneumonia, which is different from most studies of prone positioning in severe ARDS with diverse risk factors [12, 24].

According to our results, age and $PaCO_2$ before prone positioning were the predictors with $PaCO_2$ response and the $PaCO_2$ responders seemed to have modestly better clinical outcome. Younger patients included more $PaCO_2$ responders. Perhaps younger patients have better respiratory system compliance and lower dead space ventilation [28] that induce more decrease of dead space ventilation after prone positioning, although this needs further investigation; hence, hypercapnia may be a factor as to whether we decide to arrange prone positioning for these patients. The improvement of ventilation-perfusion mismatch due to dead space ventilation might be corrected by prone positioning resulting in better clinical outcome. Furthermore, the high $PaCO_2$, high PEEP, and lower tidal volume before prone positioning might imply that permissive hypercapnia with low tidal volume and high PEEP is still the cornerstone of treatment in patients with severe ARDS, even in prone positioning. A meta-analysis [13] also concluded that patients treated with prone positioning with low tidal volume had better long-term mortality outcomes, but the benefit was not shown in high tidal-volume patients.

There are several limitations in this retrospective study. Firstly, since the prone positioning is not a routine procedure in treatment of patients with ARDS, the case number is relatively small in this multicenter retrospective cohort study. Secondly, prone positioning has no standard protocol even globally such as how many hours are used a day, how to perform the treatment, or how to protect the patients. In this study, every patient at least had prone positioning for more than 16 hours a day. Thirdly, in this study, we focused on patients with influenza pneumonia-related ARDS, so whether the results can be extrapolated to other causes of patients with ARDS is unknown. To confirm the benefit of prone positioning in clinical practice, further prospective randomized controlled studies are needed with strict standard protocols and patient selection. Finally, the factors predicting mortality rates of prone positioning were not surveyed in this study, so further study is needed to resolve this problem.

Conclusions

The present study demonstrated that in patients with influenza pneumonia-related severe ARDS treated with prone positioning, $PaCO_2$ responders had modest clinically better outcomes, while younger age and higher pre-prone positioning $PaCO_2$ level were predictors of being $PaCO_2$ responders. The lower oxygenation including PaO_2/FiO_2 seemed to have a higher percentage of PaO_2 response; however, the PaO_2 response level was not related to clinical survival outcomes. The factors predicting mortality rates of patients with severe ARDS receiving prone positioning were not surveyed in this study and further prospective randomized controlled studies are required to resolve this problem.

Abbreviations

TSIRC: Taiwan Severe Influenza Research Consortium

ARDS: acute respiratory distress syndrome

ICU: intensive care units

PEEP: positive end expiratory pressure

CO_2: carbon dioxide

RT-PCR: reverse-transcriptase polymerase chain reaction

PSI: Pneumonia Severity Index

APACHE II: Acute Physiology and Chronic Health Evaluation II

SOFA: Sequential Organ Failure Assessment

FiO_2: fraction of inspired oxygen

Declarations

Ethics approval and consent to participate

The local Institutional Review Board for Human Research of the involved hospitals approved this study (Linkou Chang-Gung Memorial Hospital IRB No. 201600632B0, Taichung Veterans General Hospital CE16093A, National Taiwan University Hospital 201605036RIND, Taipei Veterans General Hospital 2016-05-020CC, Tri-Service General Hospital 1-105-05-086, China Medical University Hospital 105-REC2-053(FR), Kaohsiung Medical University Hospital KUMHIRB-E(I)-20170097, Kaohsiung Chang-Gung Memorial Hospital 201600988B0) and the need for informed consent was waived due to the retrospective nature of the study.

Consent for publication

not applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: No

Funding: No

Authors' contributions

KWC drafted the manuscript. KCK revised the manuscript and conceived of this study and was responsible for coordination. KWC, MCC, HCH, LCC, WCC, YMC, MJT, and YCC helped with data curation. SWL, LPC, MJT, SJL, HCW, YCC, and WCP helped with formal analysis. KYY, HCH, WCC, WFF, YMC, and CCS helped with validation. All authors critically revised the manuscript. All authors have seen and approved the final draft of the manuscript.

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Tables

Due to technical limiatations, the Tables have been placed in the Supplementary Files section below.

Figures

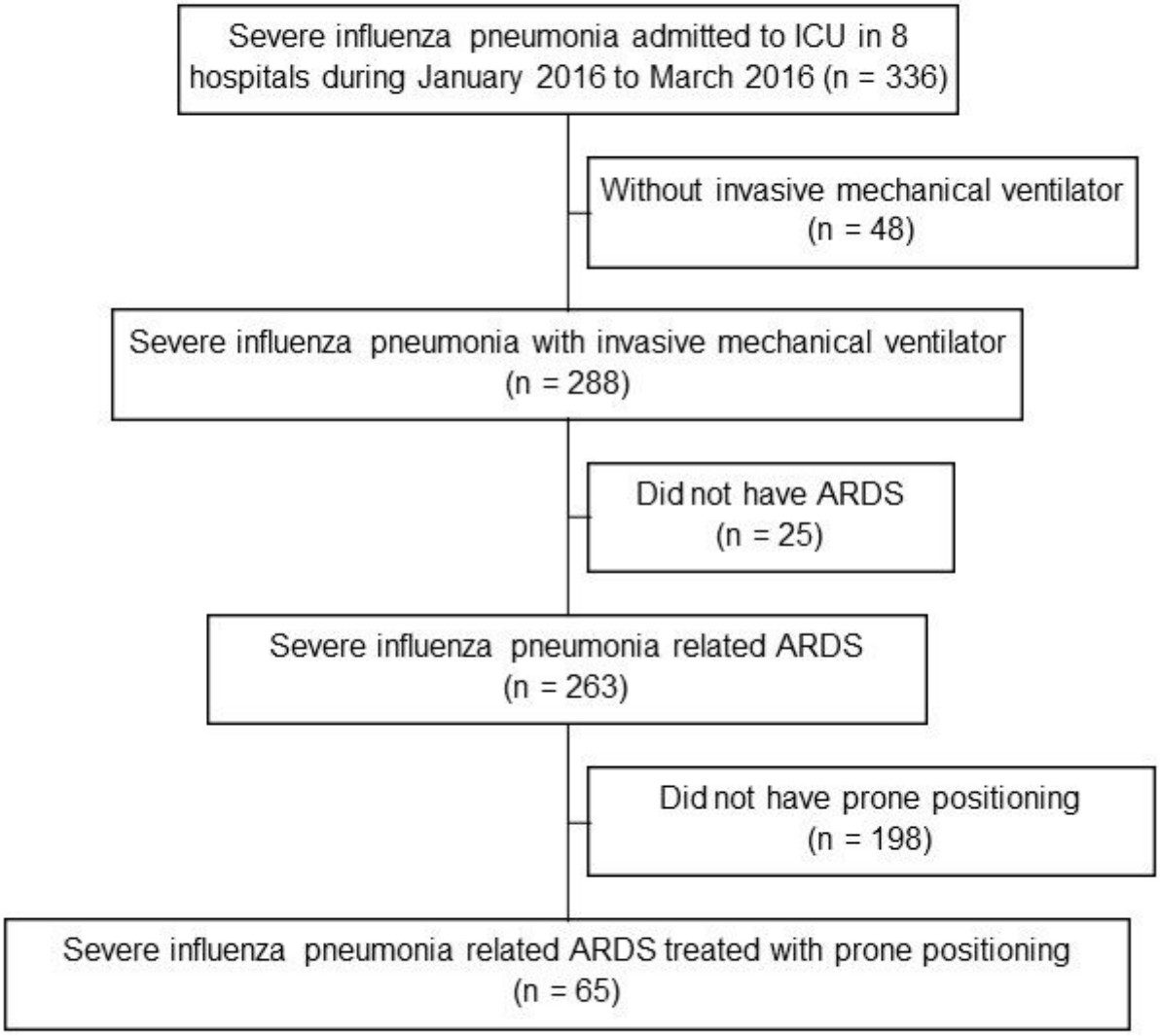

Figure 1

Flow chart for patients' enrollment in the study. ICU: intensive care unit; ARDS: acute respiratory distress syndrome.

Supplementary Files

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