

Prognostic Value of Plateau Pressure Below 30 cm H₂O in Septic Subjects With Acute Respiratory Failure

Ming-Cheng Chan MD, Jeng-Sen Tseng MD, Jung-Te Chiu MD, Kuo-Hsuan Hsu MD, Sou-Jen Shih RN MSN, Chi-Yuan Yi RN, Chieh-Liang Wu MD PhD, and Yu Ru Kou PhD

BACKGROUND: Ventilation with low tidal volume is recommended for patients with acute lung injury. Current guidelines suggest limiting plateau pressure (P_{plat}) to < 30 cm H₂O for septic patients needing mechanical ventilation. The aim of this study was to determine whether P_{plat} within the first 24 h of ICU admission is predictive of outcome and whether $P_{\text{plat}} < 30$ cm H₂O is associated with lower mortality rates. **METHODS:** This study was a retrospective analysis of prospectively acquired clinical data from an ICU of a tertiary referral hospital in central Taiwan. Subjects were included if they were admitted due to sepsis and respiratory failure requiring mechanical ventilation from April 2008 to November 2009. **RESULTS:** There were 220 subjects (188 males, 32 females) with a median age of 76 y and a mean Acute Physiology and Chronic Health Evaluation II score of 25.0 ± 6.5 . Pneumonia was the major cause of sepsis (85.5%). The hospital mortality rate was 39.1%. P_{plat} was higher throughout the first 24 h of ICU admission in nonsurvivors. Higher P_{plat} was associated with higher mortality rates regardless of acute lung injury. In multivariate regression analysis, $P_{\text{plat}} > 25$ cm H₂O at 24 h after admission was an independent risk factor for mortality (adjusted odds ratio of 2.33, 95% CI 1.10–4.91, $P = .03$ for hospital mortality). **CONCLUSIONS:** P_{plat} within the first 24 h of ICU admission is predictive of outcome, with lower P_{plat} associated with lower mortality rates. There is no safety margin for P_{plat} . Limiting P_{plat} should be considered even at < 30 cm H₂O in septic patients with acute respiratory failure. *Key words:* acute respiratory distress syndrome (ARDS); plateau pressure; respiratory failure; sepsis. [Respir Care 2015;60(1):12–20. © 2015 Daedalus Enterprises]

Introduction

Acute respiratory failure is common in severe sepsis. Patients with severe sepsis have increased risk of developing ARDS,¹ as sepsis is also the leading cause of ARDS.^{2,3} Avoiding ventilator-induced lung injury^{4,5} by limiting pres-

sure and volume can effectively reduce the mortality of ARDS.^{6,7} However, despite recent advances in understanding the mechanism and treatment of ARDS, mortality remains high.⁸

An international survey of adult patients receiving mechanical ventilation showed that plateau pressure (P_{plat}) ≥ 35 cm H₂O is associated with increased ICU mortality.⁹ A recent study also demonstrated that limiting P_{plat} to

Drs Chan and Kou are affiliated with the Institute of Physiology, School of Medicine, National Yang-Ming University, Taipei, Taiwan. Drs Chan, Tseng, and Chiu are affiliated with the Division of Chest Medicine; Drs Hsu and Wu are affiliated with the Division of Critical Care and Respiratory Therapy, Department of Internal Medicine; and Ms Shih and Ms Yi are affiliated with the Department of Nursing, Taichung Veterans General Hospital, Taichung, Taiwan. Dr Chan is also affiliated with the Central Taiwan University of Science and Technology, Taichung, Taiwan. Drs Tseng and Hsu are also affiliated with the Institute of Biomedical Sciences, National Chung Hsing University, Taichung, Taiwan. Dr Wu is also affiliated with the Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Chiayi Branch, Chiayi, Taiwan.

This study was supported by National Science Council of Taiwan Grant NSC 101-2320-B-010-042-MY3 and a grant from Aim for the Top University Plan, Ministry of Education, Taiwan. The authors have disclosed no conflicts of interest.

Correspondence: Yu Ru Kou PhD, Institute of Physiology, School of Medicine, National Yang-Ming University, Taipei 11221, Taiwan. E-mail: yrkou@ym.edu.tw.

DOI: 10.4187/respcare.03138

< 30 cm H₂O is significantly associated with increased survival.¹⁰ Current guidelines recommend limiting P_{plat} with an initial ceiling of < 30 cm H₂O when applying mechanical ventilation to septic patients with ARDS.^{11,12} However, the guidelines also suggest limiting P_{plat} to < 20 cm H₂O in patients with normal lung function in the

SEE THE RELATED EDITORIAL ON PAGE 147

ICU or undergoing major abdominal surgery with high risk of complications.¹³ Thus, it is unclear if lowering P_{plat} further below 30 cm H₂O is beneficial. There are also limited data regarding mechanical ventilation in septic patients without ARDS.

The aim of this retrospective study was to determine whether P_{plat} is a surrogate marker for mortality and if initial P_{plat} lower than < 30 cm H₂O is associated with better outcome for patients admitted to an ICU for severe sepsis or septic shock with acute respiratory failure (ARF).

Methods

Subjects

This study was a retrospective analysis of prospectively acquired data on a cohort of subjects with sepsis and ARF admitted to the 24-bed ICU at Taichung Veterans General Hospital between April 2008 and November 2009. The hospital's ethics committee/institutional review board approved the study protocol, and the requirement for informed consent was waived. Inclusion criteria were severe sepsis or septic shock of either pulmonary or extrapulmonary origin, bundled treatment based on the Surviving Sepsis Campaign Guidelines,^{11,12} and respiratory failure requiring mechanical ventilation. Exclusion criteria were deviation from the treatment protocol for any reason, respiratory failure for causes other than sepsis, use of noninvasive mechanical ventilation, and incomplete data records.

Sepsis Bundle Treatment Protocol and Data Records

A protocol was set up to implement bundle treatment based on the guidelines for managing and monitoring septic patients within the first 24 h of ICU admission. If a subject had a suspected site of infection, 2 or more systemic inflammatory response syndrome criteria, and one or more organ dysfunction criteria, resuscitation procedures were applied. In this protocol, the initial resuscitation bundle included lactate measurement, antibiotic and infection source control, pathogen identification and cultures, hemodynamic stabilization, stress dose steroid use,

QUICK LOOK

Current knowledge

Lung-protective ventilation includes low tidal volume ventilation (6 mL/kg of predicted body weight) and limiting plateau pressure (P_{plat}) to < 30 cm H₂O. Early application of a lung-protective approach may prevent acute lung injury.

What this paper contributes to our knowledge

Lower P_{plat} was associated with a decreased mortality, even at levels below 30 cm H₂O, in subjects with sepsis and respiratory failure. There is no absolute safety margin of P_{plat} in septic patients with ARF, although P_{plat} within the first 24 h after ICU admission is a valuable outcome predictor.

appropriate glycemic control, and limiting inspiratory P_{plat} for ventilated subjects.

Hemodynamic stabilization procedures included fluid resuscitation, blood product transfusion, and inotropic agent use. Fluid resuscitation was done by monitoring and achieving 4 goals: mean arterial pressure > 65 mm Hg, central venous pressure 11–16 cm H₂O, central venous oxygen saturation > 70%, and urine output > 0.5 mL/kg/h.

P_{plat} was recorded at the beginning of the first 24 h of sepsis bundle treatment and every 4 h thereafter. Respiratory mechanics, including tidal volume (V_T), peak inspiratory pressure, P_{plat} , and PEEP, at each time point were also recorded. P_{plat} was recorded by breath-holding at the end of inspiration for 0.5 s while the subject was sedated with muscle relaxant. Lung compliance was calculated as $V_T/(P_{\text{plat}} - \text{PEEP})$. V_T (mL/kg) was normalized to ideal body weight: male, (height [in cm] – 80) × 0.7; and female, (height – 70) × 0.6.

The subjects' demographic and hemodynamic data, diagnosis and indication of sepsis bundle treatment, results of resuscitation goals achieved, and mechanical ventilation parameters were recorded. The degree to which the resuscitation goals were achieved was defined as the percentage of subjects who achieved all 4 goals by 6 h after admission. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated on the day of admission. Chart review and chest radiograph readings were conducted by 2 intensive care physicians.

Statistical Analysis

Subjects were divided into survivor and nonsurvivor groups upon discharge from the hospital. Univariate analyses using Student *t* test and the chi-square test were con-

ducted to compare the demographic, hemodynamic, and laboratory variables and the mechanical ventilation parameters between these 2 groups.

In the subgroup analysis, the cohort was divided into ARDS and non-ARDS groups according to the Berlin definition.¹⁴ Subgroup analysis was also performed based on the cause of sepsis.

A Cochran-Mantel-Haenszel chi-square test was used to compare the relationship between different P_{plat} levels and mortality. Multivariate analyses using a logistic regression model were done to evaluate the power of P_{plat} at 24 h after the start of sepsis bundle treatment ($P_{\text{plat}}-24$) for predicting hospital mortality. It was adjusted by relevant factors that influence P_{plat} measurement (ie, V_T and PEEP) and variables with borderline significance in univariate analysis (defined as $P < .2$). Analysis was performed using SPSS 15.0.0 (SPSS, Chicago, Illinois). Statistical significance was set at $P < .05$ (2-tailed test).

Results

Subjects

A total of 279 subjects with sepsis and respiratory failure were admitted to the respiratory ICU during the study period. Fifteen subjects were excluded due to the use of noninvasive ventilation, 18 subjects were excluded because sepsis was not the main reason for respiratory failure, and another 26 subjects were excluded for deviating from the sepsis bundle treatment protocol. The remaining 220 subjects were enrolled for analysis. Based on their demographic data (Table 1), their median age was 76 y (range of 22–94 y), and 188 subjects (85.5%) were male. Pneumonia was the major cause of sepsis (85.5%), and the mean APACHE II score was 25.0 ± 6.5 . The sepsis bundle goal completion rate was 55.0%. Thirty-four subjects (15.5%) had a history of chronic lung disease, including 2 subjects with asthma, 3 subjects with bronchiectasis, and 29 subjects with COPD. No subject had interstitial lung disease. The ICU and hospital mortality rates were 29.5% and 39.1%, respectively.

Subject Characteristics and Outcomes

Univariate analyses of hospital survival (Table 2) showed that nonsurvivors had significantly higher APACHE II scores than survivors at hospital discharge (26.2 ± 6.8 vs 24.2 ± 6.1 , $P = .02$). At hospital discharge, subjects with diabetes had lower mortality rates (16.3% vs 29.9%, $P = .03$). Baseline hemodynamic and oxygenation status, sepsis bundle goal completion (including central venous oxygen saturation, mean arterial pressure, central venous pressure, and urine output), and cause of sepsis did not significantly correlate with subject outcomes. The mean

Table 1. Demographic Data

Characteristics	Values
Subjects, <i>N</i>	220
Median age, y (range)	76 (22–94)
Gender, <i>n</i> (%)	
Male	188 (85.5)
Female	32 (14.5)
APACHE II score, mean \pm SD	25.0 ± 6.5
Comorbidities, <i>n</i> (%) [*]	
Diabetes mellitus	54 (24.5)
Chronic lung disease	34 (15.5)
Cerebral vascular accident	31 (14.1)
Cardiovascular disease	45 (20.5)
Chronic renal disease	19 (8.6)
Chronic liver disease	14 (6.4)
Cause of sepsis, <i>n</i> (%)	
Pneumonia	188 (85.5)
Non-pneumonia	32 (14.5)
Rate of resuscitation goals reached, <i>n</i> (%)	121 (55.0)
ICU mortality, <i>n</i> (%)	65 (29.5)
Hospital mortality, <i>n</i> (%)	86 (39.1)

^{*} Chronic lung diseases include chronic obstructive lung disease, asthma, and bronchiectasis. Cardiovascular diseases include coronary artery disease, cardiomyopathy, and valvular heart disease. Chronic liver diseases include chronic hepatitis B and C and liver cirrhosis. Chronic renal disease denotes plasma creatinine levels of > 1.5 mg/dL for > 6 months. APACHE II = Acute Physiology and Chronic Health Evaluation II

values of central venous oxygen saturation in both survivor and nonsurvivor groups were higher than the criteria desired according to the Surviving Sepsis Campaign.¹⁵ The subjects were then divided into ARDS and non-ARDS groups according to baseline oxygenation status to evaluate the power of outcome prediction of P_{plat} . In the ARDS group (baseline $P_{\text{aO}_2}/F_{\text{IO}_2} < 300$, $n = 191$), nonsurvivors had significantly higher P_{plat} levels than survivors (Fig. 1B). P values were significant after 4 h of admission for hospital survival. In the non-ARDS group (baseline $P_{\text{aO}_2}/F_{\text{IO}_2} \geq 300$, $n = 29$), nonsurvivors also had significantly higher P_{plat} levels, and their P values were significant at all time points (Fig. 1C).

In subjects with sepsis caused by pneumonia ($n = 188$), nonsurvivors had significantly higher P_{plat} at baseline at all time points within the first 24 h of admission (Fig. 1D). In subjects with extrapulmonary sepsis ($n = 32$), the nonsurvivors seemed to have higher P_{plat} , but this was not statistically significant (Fig. 1E).

P_{plat} and Outcomes

Univariate analyses of P_{plat} and outcomes (Table 3) showed that, for hospital survival in the overall population, nonsurvivors had significantly higher P_{plat} at baseline and at all time points within the first 24 h of ad-

PROGNOSTIC VALUE OF P_{PLAT} IN ACUTE RESPIRATORY FAILURE

Table 2. Univariate Analysis of ICU and Hospital Survival

Characteristics	Hospital Survival		P
	Survivors	Nonsurvivors	
Age (mean ± SD), y	70.6 ± 14.8	73.2 ± 11.6	.15
Gender (male), n (%)	115 (85.8)	73 (84.9)	.85
APACHE II score, mean ± SD	24.2 ± 6.1	26.2 ± 6.8	.02
Comorbidities, n (%)*			
Diabetes mellitus	40 (29.9)	14 (16.3)	.03
Chronic lung disease	22 (16.4)	12 (14.0)	.70
Cerebral vascular accident	22 (16.4)	9 (10.5)	.24
Chronic renal disease	11 (8.2)	8 (9.3)	.81
Cardiovascular disease	30 (22.3)	15 (17.4)	.40
Chronic liver disease	9 (6.7)	5 (5.8)	> .99
Baseline $P_{\text{aO}_2}/F_{\text{IO}_2}$, mean ± SD	188.0 ± 122.5	174.2 ± 87.6	.37
ARDS, %	59.7	69.0	.23
Baseline lactate (mean ± SD), mg/dL	35.0 ± 32.7	31.3 ± 23.3	.34
Baseline S_{cvO_2} (mean ± SD), %	72.5 ± 10.3	72.2 ± 9.6	.83
Baseline central venous pressure (mean ± SD), cm H ₂ O	17.0 ± 6.6	16.3 ± 6.9	.43
Baseline mean arterial pressure (mean ± SD), mm Hg	72.7 ± 15.8	70.0 ± 14.6	.22
Rate of resuscitation goals reached, %			
S_{cvO_2}	72.0	72.9	> .99
Central venous pressure	84.0	92.5	.09
Mean arterial pressure	91.7	89.5	.64
Urine output	95.4	89.4	.12
All completed	52.2	59.3	.33
Fluid administered within first 24 h (mean ± SD), mL	9,781 ± 4,169	10,400 ± 3,785	.26
Urine output within first 24 h (mean ± SD), mL	2,917 ± 2,392	2,491 ± 2,187	.18
Fluid balance within first 24 h (mean ± SD), mL	6,864.4 ± 3,633.7	7,918.4 ± 3,942.9	.05
Serum creatinine (mean ± SD), mg/dL	1.9 ± 1.5	1.9 ± 1.2	.90
Compliance at 24 h (mean ± SD), mL/cm H ₂ O	37.6 ± 36.0	28.1 ± 9.0	.02
Cause of sepsis (pneumonia), %	112 (83.6)	76 (88.4)	.43
Use of neuromuscular blockade, %†	134 (100)	86 (100)	> .99

* Chronic lung diseases include chronic obstructive lung disease, asthma, and bronchiectasis. Cardiovascular diseases include coronary artery disease, cardiomyopathy, and valvular heart disease. Chronic liver diseases include chronic hepatitis B and C and liver cirrhosis. Chronic renal disease denotes plasma creatinine levels of > 1.5 mg/dL for > 6 months.

† Atracurium besylate, dose range of 0.3–0.6 mg/kg/h

APACHE II = Acute Physiology and Chronic Health Evaluation II

S_{cvO_2} = central venous oxygen saturation

mission (Fig. 1A). For factors that might influence P_{plat} measurement, including V_T and PEEP, our analysis showed that nonsurvivors had lower V_T and higher PEEP (Table 3).

The receiver operating characteristic was constructed to evaluate different levels of P_{plat} at 24 h after admission for predicting hospital mortality (Fig. 2). The area under the receiver operating characteristic was 0.668. Using a cutoff level of 24.5 cm H₂O, P_{plat} had 69.8% sensitivity and 56.7% specificity for hospital mortality.

The power of outcome prediction of P_{plat} -24 was further evaluated using a logistic regression model (Table 4). Subjects with P_{plat} -24 > 25 cm H₂O were associated with higher hospital mortality (adjusted odds ratio of 2.89, 95% CI 1.65–5.06, $P < .001$). When the results were adjusted by potential confounders, including V_T , PEEP, age, APACHE II score, underlying diabetes, baseline central venous pressure, goal of urine output at 6 h after admission, and causes of sepsis for ICU mortality as well as V_T , PEEP, age, APACHE II score, under-

PROGNOSTIC VALUE OF P_{PLAT} IN ACUTE RESPIRATORY FAILURE

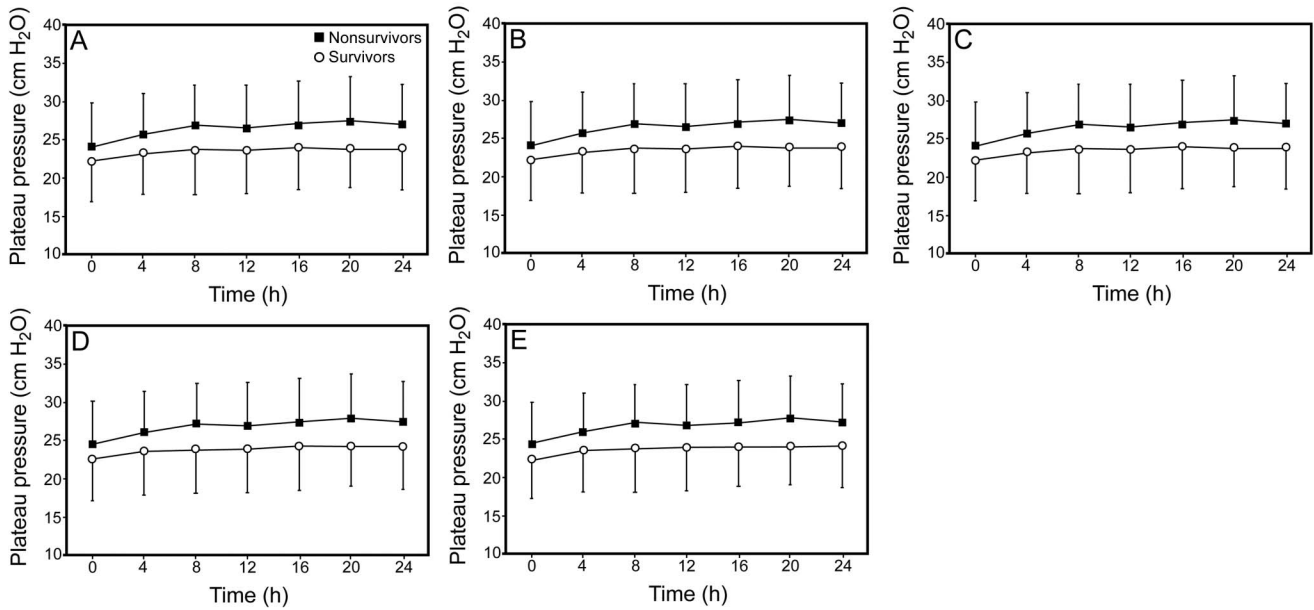


Fig. 1. Plateau pressure (P_{plat}) within 24 h of ICU admission and outcomes. Survivors had lower P_{plat} during the first 24 h of ICU admission both overall (A) and in subgroups (B: $P_{\text{aO}_2}/F_{\text{IO}_2} < 300$; C: $P_{\text{aO}_2}/F_{\text{IO}_2} \geq 300$; D: extrapulmonary sepsis; and E: pulmonary sepsis). All points $P < .05$, survival versus nonsurvivors.

Table 3. P_{plat} , V_T , PEEP, and Outcomes

	Hospital Survival		<i>P</i>
	Survivors	Nonsurvivors	
P_{plat} (mean \pm SD), cm H ₂ O			
At ICU admission	22.2 \pm 5.3	24.1 \pm 5.6	.01
At 4 h after ICU admission	23.3 \pm 5.5	25.7 \pm 5.3	.002
At 8 h after ICU admission	23.6 \pm 5.8	26.8 \pm 5.3	< .001
At 12 h after ICU admission	23.6 \pm 5.7	26.5 \pm 5.6	< .001
At 16 h after ICU admission	24.0 \pm 5.6	26.9 \pm 5.7	< .001
At 20 h after ICU admission	23.9 \pm 5.2	27.4 \pm 5.8	< .001
At 24 h after ICU admission	23.9 \pm 5.5	27.0 \pm 5.2	< .001
V_T (mean \pm SD), mL/kg			
At ICU admission	9.2 \pm 1.3	8.7 \pm 1.9	.02
At 4 h after ICU admission	8.6 \pm 1.6	8.2 \pm 1.8	.09
At 8 h after ICU admission	8.5 \pm 1.6	7.9 \pm 1.7	.02
At 12 h after ICU admission	8.4 \pm 1.6	7.8 \pm 1.7	.004
At 16 h after ICU admission	8.4 \pm 1.6	7.7 \pm 1.7	.006
At 20 h after ICU admission	8.4 \pm 1.6	7.6 \pm 1.7	.002
At 24 h after ICU admission	8.4 \pm 1.6	7.6 \pm 1.7	.001
PEEP (mean \pm SD), cm H ₂ O			
At ICU admission	6.7 \pm 2.9	7.6 \pm 3.4	.06
At 4 h after ICU admission	8.2 \pm 3.9	9.1 \pm 3.7	.10
At 8 h after ICU admission	8.4 \pm 4.2	9.6 \pm 3.9	.02
At 12 h after ICU admission	8.7 \pm 4.3	10.0 \pm 4.0	.03
At 16 h after ICU admission	8.7 \pm 4.1	10.3 \pm 4.0	.005
At 20 h after ICU admission	8.7 \pm 3.9	10.6 \pm 4.2	.001
At 24 h after ICU admission	8.7 \pm 3.9	10.6 \pm 4.1	.001

For hospital survival, the mean difference in P_{plat} between 24 h and baseline was 2.9 \pm 5.4 in nonsurvivors and 1.7 \pm 5.4 in survivors ($P = .11$).

P_{plat} = plateau pressure

V_T = tidal volume.

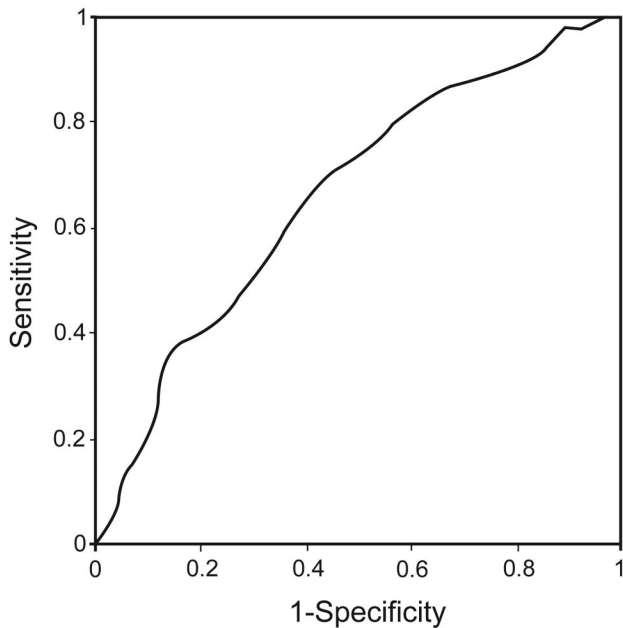


Fig. 2. Receiver operating characteristic curves for various cutoff values of plateau pressure (P_{plat}) in differentiating hospital survival and mortality. The area under the receiver operating characteristic was 0.668 for hospital mortality. Using a cutoff level of 24.5 cm H_2O , P_{plat} had 69.8% sensitivity and 56.7% specificity for hospital mortality.

Table 4. Logistic Regression of P_{plat} at 24 h After ICU Admission in Septic Subjects With Respiratory Failure

$P_{\text{plat}} > 25 \text{ cm H}_2\text{O}$	Odds Ratio	95% CI	<i>P</i>
Hospital mortality			
Unadjusted	2.89	1.65–5.06	< .001
Adjusted*	2.33	1.10–4.91	.03

In the logistic regression model, fluid balance within 24 h significantly correlated with the ICU mortality (adjusted odds ratio of 2.20, 95% CI 1.06–4.56, $P = .034$).

* Adjusted by tidal volume per ideal body weight (mL/kg), PEEP (cm H_2O), age, Acute Physiology and Chronic Health Evaluation II scores, underlying diabetes mellitus, and goals of urine output and central venous pressure (cm H_2O) at 6 h after early goal-directed therapy completion and fluid balance within 24 h

P_{plat} = plateau pressure

lying diabetes, and goals of urine output and central venous pressure at 6 h after admission for hospital mortality, $P_{\text{plat-24}} > 25 \text{ cm H}_2\text{O}$ remained an independent outcome predictor (adjusted odds ratio of 2.33, 95% CI 1.11–4.87, $P = .03$ for hospital mortality). Survivors ($37.6 \pm 36.0 \text{ mL/cm H}_2\text{O}$) had better calculated lung compliance at 24 h after admission than nonsurvivors ($28.1 \pm 9.0 \text{ mL/cm H}_2\text{O}$, $P = .02$).

Subjects were also grouped based on $P_{\text{plat-24}} \leq 20, 21\text{--}25$, and $26\text{--}30 \text{ cm H}_2\text{O}$ and $\geq 30 \text{ cm H}_2\text{O}$. Both lower P_{plat} at admission ($P_{\text{plat-0}}$) and $P_{\text{plat-24}}$ were associated with lower mortality rates even when $< 30 \text{ cm H}_2\text{O}$ (Fig. 3 [linear-by-linear association], panel A, chi-square value of

9.5 and $P = .002$ for $P_{\text{plat-0}}$; and panel B, chi-square value 16.1 and $P < .001$ for $P_{\text{plat-24}}$).

Discussion

This study shows that P_{plat} within 24 h of ICU admission was an independent predictor of outcome in subjects with severe sepsis and ARF. Higher P_{plat} was associated with increased mortality, even in subjects without ARDS. Moreover, lower P_{plat} was associated with decreased mortality rates, even at levels below 30 cm H_2O .

Mechanical ventilation with a protective strategy of limiting pressure and volume to prevent ventilator-induced lung injury is the cornerstone of ARDS management. A recently published retrospective analysis of an international multi-center database showed that the presence of acute lung injury in sepsis is associated with increased mortality, whereas $P_{\text{plat}} < 30 \text{ cm H}_2\text{O}$ is associated with increased survival.¹⁰ In this study, as determined by multivariate analysis, $P_{\text{plat}} \geq 25 \text{ cm H}_2\text{O}$ was an independent risk factor for hospital mortality (see Table 4). Furthermore, the increase in P_{plat} over the first 24 h was not related to the magnitude of mortality risk (see Table 3). Although this demonstrates that P_{plat} is an independent predictor of outcome in septic patients with ARF, it does not necessarily mean that $P_{\text{plat}} < 25 \text{ cm H}_2\text{O}$ is safe.

In a previous study, decreased respiratory system compliance was independently associated with increased risk of death.¹⁶ As compliance is calculated from P_{plat} , PEEP, and V_T , these original values can be more representative. However, P_{plat} measurement can be influenced by numerous factors, including PEEP, V_T , and chest wall and abdominal pressure. For better estimation of transpulmonary pressure, measurement of esophageal pressure can help in setting PEEP to achieve better oxygenation and compliance.¹⁷ However, esophageal balloon estimation of pleural pressure can be influenced by several factors, including body position, intra-abdominal pressure, and different lung conditions.¹⁸ Thus, P_{plat} measurement remains important and practical, and its interpretation should take these factors into consideration.

Limiting P_{plat} to $< 30\text{--}35 \text{ cm H}_2\text{O}$ is a commonly accepted concept for management of patients with respiratory failure requiring mechanical ventilation. By analyzing data from the ARDS Network trial with lower versus higher V_T ,⁷ Hager et al¹⁹ demonstrated that subjects ventilated with lower V_T had lower mortality rates even when P_{plat} was $< 30 \text{ cm H}_2\text{O}$. In our study, most of the subjects had $P_{\text{plat}} < 30 \text{ cm H}_2\text{O}$, and lower $P_{\text{plat-0}}$ and $P_{\text{plat-24}}$ were associated with lower mortality rates. During positive-pressure ventilation, low V_T can still augment lung injury when airway pressure is not high.²⁰ In ARDS, because the recruitability of lung tissue is highly variable,²¹ the benefits of higher PEEP and recruitment maneuvers may be

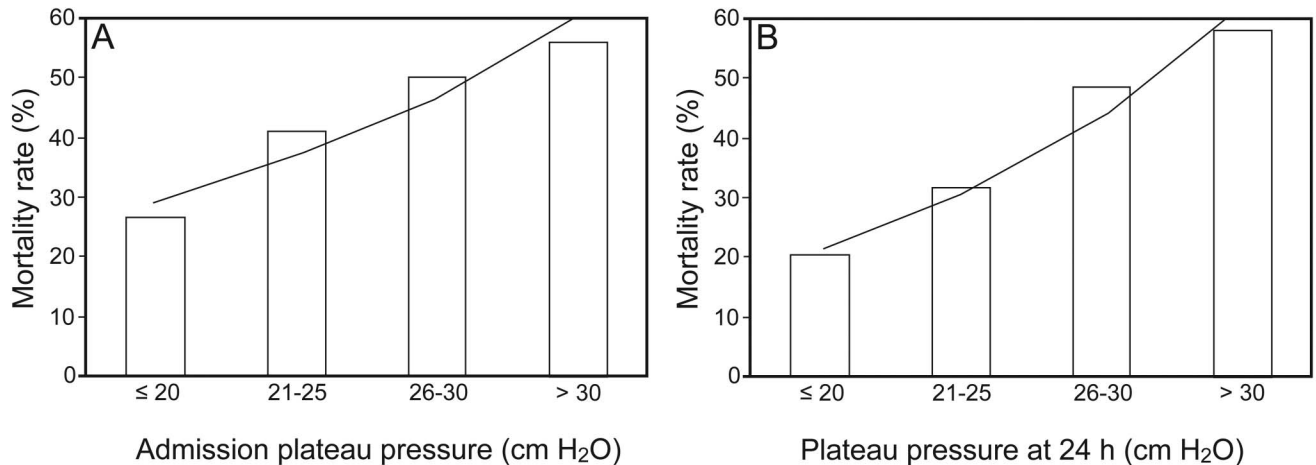


Fig. 3. Lower plateau pressure (P_{plat}) is associated with lower mortality. Subjects were divided into 4 groups ($P_{\text{plat}} \leq 20$, 21–25, and 26–30 cm H₂O and > 30 cm H₂O) according to A: P_{plat} at admission ($P = .002$) and B: P_{plat} at 24 h after admission ($P < .001$).

offset by harm from higher airway pressure.^{22,23} Because there is no absolutely safe level of airway pressure, management of mechanical ventilation in ARDS should aim to minimize ventilator-induced lung injury rather than target a certain P_{plat} level.

Currently, there is no consensus on how to ventilate patients without ARDS. A meta-analysis showed that protective ventilation with lower V_T was associated with better outcomes in subjects without ARDS.²⁴ Using lower V_T and limiting P_{plat} for patients at risk to develop ARDS is suggested.²⁵ Patients with sepsis and ARF are vulnerable and under constant threat of developing acute lung injury¹ because they have a variety of risk factors, such as profound local and systemic inflammation, transfusion,²⁶ mechanical ventilation,²⁷ and massive fluid resuscitation.²⁸ In a recently published study, ventilation with low V_T of anesthetized abdominal surgery patients with high risk of pulmonary complications was associated with improved clinical outcomes.²⁹ In non-ARDS patients, a lung-protective strategy can increase the chance of eligible and harvested lungs in brain-dead donors.³⁰ In contrast, mechanical ventilation with $V_T > 10$ mL/kg is a significant risk for subsequent organ failure and prolonged ICU stay.³¹ In our study, not all of the subjects met the criteria of ARDS, and the results show that even in subjects with $P_{\text{aO}_2}/F_{\text{IO}_2} \geq 300$, the nonsurvivors had higher P_{plat} . To this end, prospective studies are needed to evaluate optimal ventilator strategy for patients without ARDS.

Timely and early intervention to achieve hemodynamic stabilization targeting predefined goals can reduce mortality in patients with severe sepsis.³² In this study, the rate of achieved resuscitation goals was $> 50\%$ that in a large international survey.¹⁵ The rates of resuscitation goals achieved were not different between survivors and nonsurvivors. Moreover, the mean values of central venous

oxygen saturation in both groups were high, fulfilling the criteria of the Surviving Sepsis Campaign.¹⁵ This may be due to the fact that these subjects had already been resuscitated in the emergency room. Several studies have shown that conservative fluid management in subjects with ARDS can improve patient outcomes.³³ Ware and Matthay³⁴ demonstrated that impaired alveolar fluid clearance was associated with increased hospital mortality in ARDS subjects. Our results show that nonsurvivors had more positive fluid balance during the first 24 h after ICU admission. This may reflect worse hemodynamic stability and lead to increased lung edema in ARDS. However, taking fluid balance into consideration, P_{plat} was still an independent factor for determining subject mortality.

An interesting finding is that hospital mortality was lower in subjects with diabetes. Hyperglycemia is common in critically ill patients and is associated with increased morbidity and mortality in a variety of diagnoses.^{35–37} However, in severe sepsis, the presence of diabetes does not influence outcome.³⁸ In contrast, nondiabetic patients who are hyperglycemic on admission have increased mortality rates.³⁹ Furthermore, patients with diabetes are less likely to develop acute lung injury and have better outcomes than nondiabetic patients.^{40,41} Nonetheless, the relationship and mechanism of diabetes in terms of outcome in septic patients with ARDS warrant further studies.

This study has a few limitations. This is a retrospective study without blinding, and pre-specified end points may be biased by known and unknown confounders. We cannot conclude that lowering P_{plat} further would be helpful. P_{plat} may be a marker of severity of underlying illness. However, P_{plat} can serve as an outcome predictor in septic patients with ARF. We noted that V_T was slightly lower in nonsurvivors compared with survivors. This may be because nonsurvivors had worse respiratory conditions, so

we tried to better manage these subjects with regard to maintaining lung-protective ventilation goals. Another issue that should be addressed is the use of neuromuscular blockade for measurement of P_{plat} and management of ARDS. Currently, as it is not a standard of care, the applicability of these medications should be considered.

Conclusions

In summary, lower P_{plat} is associated with decreased mortality rates, even at levels below 30 cm H_2O , in septic patients with respiratory failure. There is no absolute safety margin of P_{plat} in septic patients with ARF, although P_{plat} within the first 24 h after ICU admission is a valuable outcome predictor.

ACKNOWLEDGMENTS

We thank Mr Kuang-His Chang (Department of Medical Education and Research, Taichung Veterans General Hospital, Taichung, Taiwan) for his help with statistical analysis. We are also grateful to Dr Gene Alzona Nisperos (Asia Training Solutions, Taiwan) for his help with language editing.

REFERENCES

- Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multi-center cohort study. *Am J Respir Crit Care Med* 2011;183(4):462-470.
- Rubinfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;353(16):1685-1693.
- Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151(2):293-301.
- Slutsky AS. Basic science in ventilator-induced lung injury: implications for the bedside. *Am J Respir Crit Care Med* 2001;163(3):599-600.
- Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998;157(1):294-323.
- Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338(6):347-354.
- The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301-1308.
- Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, et al. Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med* 2009;179(3):220-227.
- Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002;287(3):345-355.
- Martin-Loeches I, de Haro C, Dellinger RP, Ferrer R, Phillips GS, Levy MM, Artigas A. Effectiveness of an inspiratory pressure-limited approach to mechanical ventilation in septic patients. *Eur Respir J* 2013;41(1):157-164.
- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39(2):165-228.
- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41(2):580-637.
- Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013;369(22):2126-2136.
- Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;38(10):1573-1582.
- Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, et al. *Intensive Care Med* 2010;36(2):222-231.
- Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, Matthay MA. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002;346(17):1281-1286.
- Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008;359(20):2095-2104.
- Cortes GA, Marini JJ. Two steps forward in bedside monitoring of lung mechanics: trans-pulmonary pressure and lung volume. *Crit Care* 2013;17(2):219.
- Hager DN, Krishnan JA, Hayden DL, Brower RG. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005;172(10):1241-1245.
- Muscledere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994;149(5):1327-1334.
- Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006;354(17):1775-1786.
- Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299(6):646-655.
- Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299(6):637-645.
- Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci Mde O, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA* 2012;308(16):1651-1659.
- Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O. What tidal volumes should be used in patients without acute lung injury? *Anesthesiology* 2007;106(6):1226-1231.
- Gajic O, Rana R, Winters JL, Yilmaz M, Mendez JL, Rickman OB, et al. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. *Am J Respir Crit Care Med* 2007;176(9):886-891.
- Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004;32(9):1817-1824.

28. Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009;136(1):102-109.
29. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013;369(5):428-437.
30. Mascia L, Pasero D, Slutsky AS, Arguis MJ, Berardino M, Grasso S, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA* 2010;304(23):2620-2627.
31. Lellouche F, Dionne S, Simard S, Bussi eres J, Dagenais F. High tidal volumes in mechanically ventilated patients increase organ dysfunction after cardiac surgery. *Anesthesiology* 2012;116(5):1072-1082.
32. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early-goal directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345(19):1368-1377.
33. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354(24):2564-2575.
34. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients of acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001;163(6):1376-1383.
35. Gale SC, Sicoutris C, Reilly PM, Schwab CW, Gracias VH. Poor glycemic control is associated with increased mortality in critically ill trauma patients. *Am Surg* 2007;73(5):454-460.
36. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 2001;32(10):2426-2432.
37. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000;355(9206):773-778.
38. Stegenga ME, Vincent JL, Vail GM, Xie J, Haney DJ, Williams MD, et al. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. *Crit Care Med* 2010;38(2):539-545.
39. Schuetz P, Jones AE, Howell MD, Trzeciak S, Ngo L, Younger JG, et al. Diabetes is not associated with increased mortality in emergency department patients with sepsis. *Ann Emerg Med* 2011;58(5):438-444.
40. Moss M, Guidot DM, Steinberg KP, Duhon GF, Treece P, Wolken R, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. *Crit Care Med* 2000;28(7):2187-2192.
41. Frank JA, Nuckton TJ, Matthay MA. Diabetes mellitus: a negative predictor for the development of acute respiratory distress syndrome from septic shock. *Crit Care Med* 2000;28(7):2645-2646.

This article is approved for Continuing Respiratory Care Education credit. For information and to obtain your CRCE (free to AARC members) visit www.rcjournal.com

