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Prognostic Value of Plateau Pressure Below 30 cm H_2O in Septic Patients With Acute Respiratory Failure

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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 H_2O 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_{plat} < 30 cm H_2O 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_{plat} > 25 cm H_2O 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 H_2O in septic patients with acute respiratory failure. *Key words: acute respiratory distress syndrome (ARDS); plateau pressure; respiratory failure; sepsis.* [Respir Care 2015;60(1):1–•. © 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 pressure 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 H_2O is associated with increased ICU mortality.[9] A recent study also demonstrated that limiting P_{plat} to

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< 30 cm H_2O is significantly associated with increased survival.[10] Current guidelines recommend limiting P_{plat} with an initial ceiling of < 30 cm H_2O when applying mechanical ventilation to septic patients with ARDS.[11,12] However, the guidelines also suggest limiting P_{plat} to < 20 cm H_2O in patients with normal lung function in the ICU or undergoing major abdominal surgery with high risk of complications.[13] Thus, it is unclear if lowering P_{plat} further below 30 cm H_2O 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 H_2O is associated with better outcome for patients admitted to an ICU for severe sepsis or septic shock with acute respiratory failure (ARF).

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 H_2O. 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 H_2O, 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.

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, 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 H_2O, 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 $V_T/(P_{plat} - \text{PEEP})$. V_T (mL/kg) was normalized to ideal body weight: male, (height [in cm] $-$ 80) $\times$ 0.7; and female, (height $-$ 70) $\times$ 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 conducted 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 def-

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inition.[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_{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 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

Table 1. Demographic Data

Characteristics	Values
Subjects, *n*	220
Median age, y (range)	76 (22–94)
Gender, *n* (%)	
Male	188 (85.5)
Female	32 (14.5)
APACHE II score, mean ± SD	25.0 ± 6.5
Comorbidities, *n* (%)*	
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, *n* (%)	
Pneumonia	188 (85.5)
Non-pneumonia	32 (14.5)
Rate of resuscitation goals reached, *n* (%)	121 (55.0)
ICU mortality, *n* (%)	65 (29.5)
Hospital mortality, *n* (%)	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

evaluate the power of outcome prediction of P_{plat}. In the ARDS group (baseline $P_{aO_2}/F_{IO_2} < 300$, $n = 191$), 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 $P_{aO_2}/F_{IO_2} \geq 300$, $n = 29$), 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 admission (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).

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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_{aO_2}/F_{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_2O	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	.049
Serum creatinine (mean ± SD), mg/dL	1.9 ± 1.5	1.9 ± 1.2	.90
Compliance at 24 h (mean ± SD), mL/cm H_2O	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

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 H_2O, 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 H_2O 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, underlying diabetes, and goals of urine output and central venous pressure at 6 h after admission for hospital mortality, P_{plat}-24 > 25 cm H_2O 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 ± 36.0 mL/cm H_2O) had better calculated lung com-

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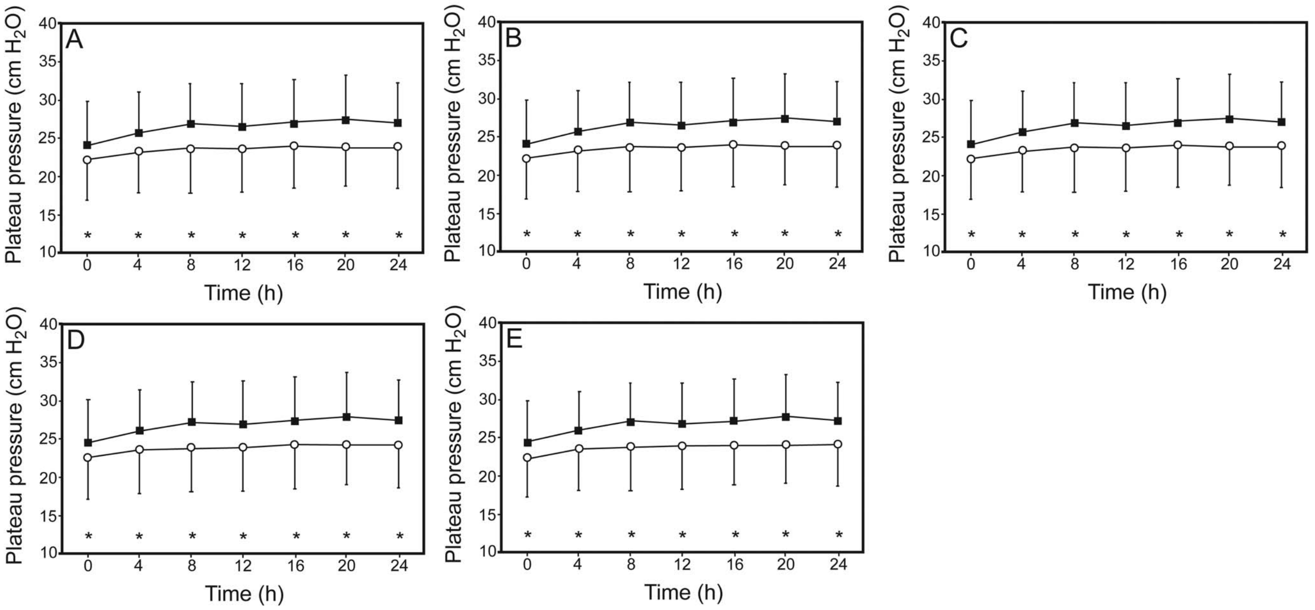

Fig. 1. Plateau pressure (P_{plat}) within 24 h of ICU admission and outcomes. Survivors had lower P_{plat} during the first 24 h of ICU admission both overall (A) and in subgroups (B: $P_{aO_2}/F_{IO_2} < < 300$; C: $P_{aO_2}/F_{IO_2} < \geq 300$; D: extrapulmonary sepsis; and E: pulmonary sepsis). * $P < .05$, survival versus mortality.

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

	Hospital Survival		
	Survivors	Nonsurvivors	*P*
P_{plat} (mean ± SD), cm H_2O			
At ICU admission	22.2 ± 5.3	24.1 ± 5.6	.01
At 4 h after ICU admission	23.3 ± 5.5	25.7 ± 5.3	.002
At 8 h after ICU admission	23.6 ± 5.8	26.8 ± 5.3	< .001
At 12 h after ICU admission	23.6 ± 5.7	26.5 ± 5.6	< .001
At 16 h after ICU admission	24.0 ± 5.6	26.9 ± 5.7	< .001
At 20 h after ICU admission	23.9 ± 5.2	27.4 ± 5.8	< .001
At 24 h after ICU admission	23.9 ± 5.5	27.0 ± 5.2	< .001
V_T (mean ± SD), mL/kg			
At ICU admission	9.2 ± 1.3	8.7 ± 1.9	.02
At 4 h after ICU admission	8.6 ± 1.6	8.2 ± 1.8	.09
At 8 h after ICU admission	8.5 ± 1.6	7.9 ± 1.7	.02
At 12 h after ICU admission	8.4 ± 1.6	7.8 ± 1.7	.004
At 16 h after ICU admission	8.4 ± 1.6	7.7 ± 1.7	.006
At 20 h after ICU admission	8.4 ± 1.6	7.6 ± 1.7	.002
At 24 h after ICU admission	8.4 ± 1.6	7.6 ± 1.7	.001
PEEP (mean ± SD), cm H_2O			
At ICU admission	6.7 ± 2.9	7.6 ± 3.4	.060
At 4 h after ICU admission	8.2 ± 3.9	9.1 ± 3.7	.10
At 8 h after ICU admission	8.4 ± 4.2	9.6 ± 3.9	.02
At 12 h after ICU admission	8.7 ± 4.3	10.0 ± 4.0	.03
At 16 h after ICU admission	8.7 ± 4.1	10.3 ± 4.0	.005
At 20 h after ICU admission	8.7 ± 3.9	10.6 ± 4.2	.001
At 24 h after ICU admission	8.7 ± 3.9	10.6 ± 4.1	.001

For hospital survival, the mean difference in P_{plat} between 24 h and baseline was 2.91 ± 5.4 in nonsurvivors and 1.72 ± 5.4 in survivors ($P = .11$).
P_{plat} = plateau pressure
V_T = tidal volume.

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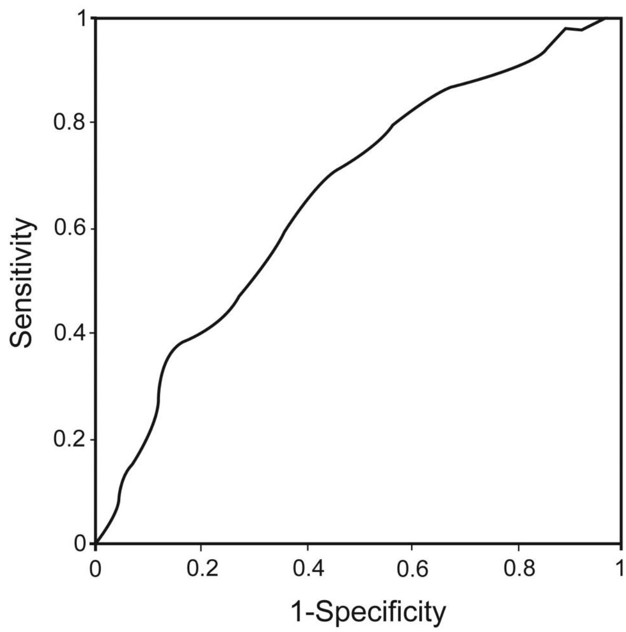

Fig. 2. Receiver operating characteristic curves for various cutoff values of plateau pressure (P_{plat}) in differentiating hospital survival and mortality. The area under the receiver operating characteristic was 0.668 for hospital mortality. Using a cutoff level of 24.5 cm H_2O, P_{plat} had 69.8%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

$P_{plat} > 25$ cm H_2O	Odds Ratio	95% CI	*P*
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

pliance at 24 h after admission than nonsurvivors (28.1 ± 9.0 mL/cm H_2O, $P = .02$).

Subjects were also grouped based on P_{plat}-24 ≤ 20, 21–25, and 26–30 cm H_2O and ≥ 30 cm H_2O. Both lower P_{plat} at admission (P_{plat}-0) and P_{plat}-24 were associated with lower mortality rates even when < 30 cm H_2O (Fig. 3 [linear-by-linear association], panel A, chi-square value of 9.5 and $P = .002$ for P_{plat}-0; and panel B, chi-square value 16.1 and $P < .001$ for P_{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 $P_{plat} < 30$ cm H_2O is associated with increased survival.[10] In this study, as determined by multivariate analysis, $P_{plat} \geq 25$ cm H_2O 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 $P_{plat} < 25$ cm H_2O 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 < 30–35 cm H_2O 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 al[19] demonstrated that subjects ventilated with lower V_T had lower mortality rates even when P_{plat} was < 30 cm H_2O. In our study, most of the subjects had $P_{plat} < 30$ cm H_2O, and lower P_{plat}-0 and P_{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 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 pro-

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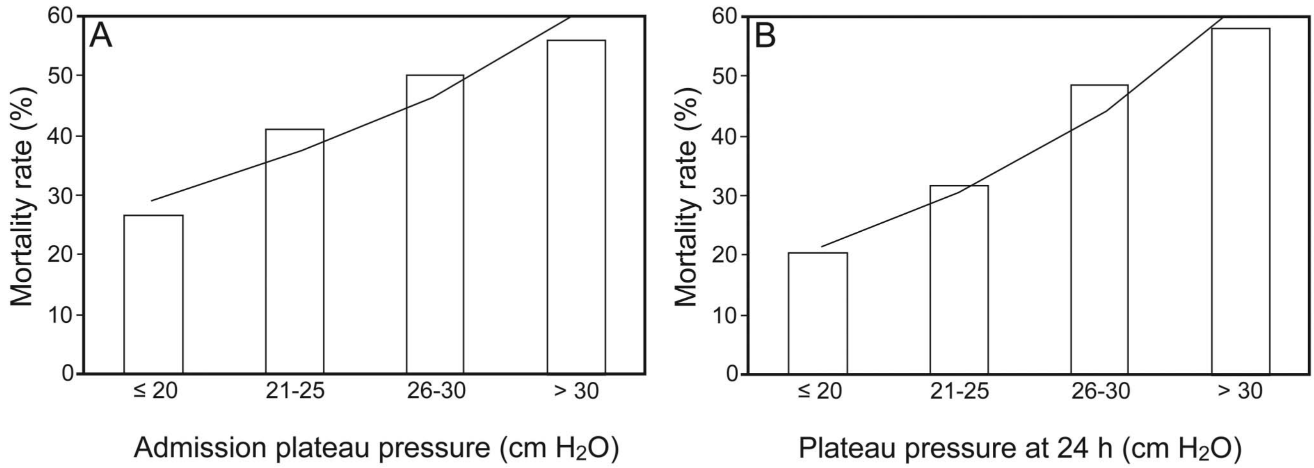

Fig. 3. Lower plateau pressure (P_{plat}) is associated with lower mortality. Subjects were divided into 4 groups ($P_{plat} \leq 20$, 21–25, and 26–30 cm H_2O and > 30 cm H_2O) according to A: P_{plat} at admission (P = .002) and B: P_{plat} at 24 h after admission (P < .001).

tective 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 injury[1] 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 $P_{aO_2}/F_{IO_2} \geq 300$, 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 Matthay[34] 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.

RESPIRATORY CARE Paper in Press. Published on September 23, 2014 as DOI: 10.4187/respcare.03138

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.

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RESPIRATORY CARE Paper in Press. Published on September 23, 2014 as DOI: 10.4187/respcare.03138

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