

Respiratory Mechanics, Ventilator-Associated Pneumonia And Outcomes In Intensive Care Unit

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Abstract:

AIM

To evaluate the predictive capability of respiratory mechanics for the development of ventilator-associated pneumonia (VAP) and mortality in the intensive care unit (ICU) of a hospital in Makkah, Saudi Arabia. METHODS A cohort study was conducted between, involving a sample of 120 individuals. Static measurements of compliance and resistance of the respiratory system in pressure-controlled ventilation (PCV) and volume-controlled ventilation (VCV) modes in the 1st and 5th days of hospitalization were performed to monitor respiratory mechanics. The severity of the patients' illness was quantified by the Acute Physiology and Chronic Health Evaluation II (APACHE II). The diagnosis of VAP was made based on clinical, radiological and laboratory parameters. RESULTS: The significant associations found for the development of VAP were APACHE II scores above the average ($P = 0.016$), duration of MV ($P = 0.001$) and ICU length of stay above the average ($P = 0.003$), male gender ($P = 0.004$), and worsening of respiratory resistance in PCV mode ($P = 0.010$). Age above the average ($P < 0.001$), low level of oxygenation on day 1 ($P = 0.003$) and day 5 ($P = 0.004$) and low lung compliance during VCV on day 1 ($P = 0.032$) were associated with death as the outcome. CONCLUSION The worsening of airway resistance in PCV mode indicated the possibility of early diagnosis of VAP. Low lung compliance during VCV and low oxygenation index were death-related prognostic indicators.

Keywords: Respiratory mechanics; Respiratory tract infection; Ventilator-associated pneumonia

Introduction:

Factors influencing the outcomes in intensive care unit (ICU) enable behaviors that can benefit the patient and reduce hospital costs^[1,2]. Monitoring of respiratory mechanics in the admission of patients may provide an additional parameter for the monitoring of cases with possible epidemiological implications^[3]. Invasive ventilatory support is a resource frequently used in extremely critical care, either to rescue breathing in patients unable to maintain the ventilatory

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demand, or as a strategy for energy saving in seriously ill patients^[4]. Knowledge about respiratory mechanics may facilitate the detection of changes in the respiratory status of the patient and enable appropriate adjustment in ventilatory parameters, as well as support an appropriate therapeutic intervention to improve his or her clinical condition^[5,6].

Few studies use these variables as prognostic measures in ICU^[7]. The main applications of monitoring respiratory mechanics are performed on well-established cases, such as in patients with obstructive lung disease^[8] and in patients with acute respiratory distress syndrome (ARDS)^[9]. Some studies discuss the importance of these measures in patients with pulmonary fibrosis^[10] or with the human immunodeficiency virus (HIV) infection and pneumonia^[11].

The measurements of respiratory mechanics most frequently used are compliance and resistance of the respiratory system. Compliance is associated with distensibility of the respiratory system, which is peak inspiratory pressure. Resistance is related to the conduction of air, obtained mathematically from the variation between the peak and plateau pressures divided by the inspiratory airflow^[12].

Ventilator-associated pneumonia (VAP) is the most common infection in ICU. This pulmonary condition may change the respiratory mechanics. Beyond the importance of the bundles of care for the prevention of VAP^[13], information of compliance and resistance of respiratory system can provide additional data for an early diagnosis. The aim of this study was to assess the risk of changes in respiratory mechanics for determination of outcomes: development of VAP, and mortality in ICU.

Materials and methods:

A cohort study was performed on adults in the intensive care unit of the Hospital in Makkah, Saudi Arabia. Individuals hospitalized between February and September 2022 who required invasive ventilator support and whose family signed the informed consent were selected. The study was approved by the Human Research Ethics Committee. As this is a study of diagnostic and prognostic accuracy, the sample size was dimensioned for a prevalence of mortality^[14] and VAP^[15] of 20% ($P = 0.2$), with a 12% error ($e = 0.12$) in the 95% confidence interval ($Z\alpha/2 = 1.96$). Sensitivity was defined 90% ($Sens = 0.9$). The following subjects were excluded from the study: Patients who were hospitalized in the ICU for cardiac surgery, those who developed pneumonia, died, or were extubated within 48 h of the onset of mechanical ventilation, those who were reintubated and those whose cause of orotracheal intubation was respiratory infection. The patients who were transferred to another ICU were excluded as well. The following procedures were performed for the data collection: Day 1 (D1) - First 24 h of mechanical ventilation. APACHE II^[17] scoring, assessment of oxygenation index obtained from the PaO_2/FiO_2 ratio, and assessment of the respiratory system compliance and resistance were performed. The patients should score 5-6 in the Ramsay sedation scale^[19] for measuring airflow compliance and resistance. Respiratory mechanic was measured in **volume**-controlled ventilation (VCV) and pressure-controlled ventilation (PCV)^[20].

CRS: Respiratory system compliance (mL/cmH₂O); RRS: Respiratory system resistance (cmH₂O/L/s); PEEP: Positive end-expiratory pressure (cmH₂O); P_{Insp}: Inspiratory pressure (cmH₂O); P_{peak}: Peak inspiratory pressure (cmH₂O); P_{plat}: Plateau pressure (cmH₂O); VT: Tidal volume (mL); F: Forced inspiratory flow (L/s); F_{max}: Peak inspiratory flow (L/s). Day 5 (D5) - Assessment of the respiratory system compliance and resistance was performed as described above. If the patient were in the ventilatory weaning process, this measure would not be collected. Patients were monitored until their discharge from the ICU or death. The duration of mechanical ventilation and length of ICU stay were taken into account, until the emergence of at least one of those outcomes.

VAP was diagnosed by the emergence of new or progressive pulmonary infiltrate on the chest X-Ray, associated with signs and laboratory alterations, such as fever ($> 38^\circ\text{C}$), leukocytosis ($> 10000/\text{mm}^3$) or leukopenia ($< 4000/\text{mm}^3$), and purulent tracheal secretions^[21]. Early VAP was performed when it was diagnosed within the first 5 d. Late VAP was considered when the diagnosis occurred after the sixth day^[15].

Statistical analysis:

Data were stored in a database using a Microsoft Excell[®] software, which was exported to SPSS[®] Statistics 20.0. They were presented using absolute numbers and percentages, and measures of central tendency and dispersion. The cutoff point for normal respiratory compliance and resistance was defined as the means obtained from the results.

The analysis of numerical data was performed primarily by the Kolmogorov-Smirnov test for normality. The results with normal distribution were compared using Student's t-test, and the non-normal distribution results by using the Mann-Whitney test^[22]. The Chi-square test was used for categorical data analysis. Variable comparisons were made in relation to the VAP outcomes, mortality, ICU stay and duration of mechanical ventilation. The relative risk was estimated, by univariate analysis, for variables with statistical association. The confidence interval was set at 95% and a $P < 0.05$ was considered statistically significant.

Measurements of the oxygenation index and respiratory mechanics were performed by analyzing the worsening or improvement in these variables between D1 and D5.

A higher airflow resistance in D1 than in D5 was considered a better state. Conversely, a lower airflow resistance, a worse result.

Results:

According to the selection criteria, 120 patients were allocated to participate in the study. Table 1 describes the general characteristics of the sample.

Sample characteristics (n = 120)	Results
Age (yr)	
Mean \pm SD	58.5 \pm 19.4
Minimum-maximum	15-91
Gender n (%)	
Male	69 (57.5)
Female	51 (42.5)
APACHE II (score)	
Mean \pm SD	27.4 \pm 6.7
Minimum-maximum	8-47
Risk of mortality (%) - APACHE II	
Mean \pm SD	8-47
Admission diagnoses n (%)	
Diseases of the circulatory system	61.8 \pm 7.3
Diseases of the respiratory system	
Lesions, poisoning and other consequences of external causes	
Gastrointestinal diseases	43 (35.8)

Oxygenation index and respiratory mechanics on days 1 and 5 are shown in Table 2. On the 5th day, only 77 of the 120 patients were monitored, because they were either extubated, weaned from mechanical ventilation, or had died by then. The incidence of VAP was 31.8% (38 cases), with an infection density of 24/1000 d. The 38 cases of VAP, 19 (50%) were early and 19 (50%) were late. The overall mortality rate was 62 cases (51.7%). The mean length of stay in ICU was 15.2 ± 11.1 d and mean duration of mechanical ventilation was 13.1 ± 10.6 d.

Oxygenation index	Mean \pm SD	Minimum-maximum
Respiratory mechanics		
1 st day (n = 120)		
PaO ₂ /FiO ₂ (mmHg)	236.0 \pm 97.6	47.0-465.7
Compliance-VCV (mL/cm H ₂ O)	40.9 \pm 12.8	15.0-88.0
Resistance-VCV (cm H ₂ O/L/s)	13.2 \pm 4.9	4.1-28.6
Compliance-PCV (mL/cm H ₂ O)	35.0 \pm 10.0	15.0-62.0
Resistance-PCV (cm H ₂ O/L/s)	27.3 \pm 16.2	9.1-131.1
5 th day (n = 77)		
PaO ₂ /FiO ₂ (mmHg)	241.7 \pm 88.7	58.0-445.0
Compliance-VCV (mL/cm H ₂ O)	39.7 \pm 13.2	18.0-83.0
Resistance-VCV (cm H ₂ O/L/s)	13.8 \pm 6.0	5.3-43.0
Compliance-PCV (mL/cm H ₂ O)	32.9 \pm 9.3	13.5-52.5
Resistance-PCV (cm H ₂ O/L/s)	26.4 \pm 11.8	6.2-73.5

Tables 3 and 4 shows the numeric variables compared with VAP rates and outcomes: Mortality.

Variables	VAP		P value
	Yes	No	
APACHE II ¹	29.2 \pm 5.6	26.5 \pm 7.1	0.026
Age (yr)	57.1 \pm 19.1	59.2 \pm 19.6	0.565
1 st day (n = 120)			
PaO ₂ /FiO ₂ (mmHg) ¹	232.3 \pm 79.9	237.8 \pm 105.2	0.756
Compliance-VCV (mL/cmH ₂ O)	43.1 \pm 14.9	39.8 \pm 11.6	0.365
Resistance-VCV (cmH ₂ O/L/s)	13.7 \pm 5.0	13.0 \pm 4.8	0.594
Compliance-PCV (mL/cmH ₂ O) ¹	34.8 \pm 10.4	35.1 \pm 9.8	0.879
Resistance-PCV (cmH ₂ O/L/s)	23.6 \pm 10.3	29.0 \pm 18.1	0.114
5 th day (n = 77)			
PaO ₂ /FiO ₂ (mmHg) ¹	244.1 \pm 94.1	240.2 \pm 86.1	0.850
Compliance-VCV	43.3 \pm	37.6 \pm	0.09

(mL/cmH ₂ O)	14.0	12.3	2
Resistance-VCV	13.9 ± 13.8	±	0.99
(cmH ₂ O/L/s)	6.8	5.5	6
Compliance-PCV	33.6 ± 32.5	±	0.60
(mL/cmH ₂ O) ¹	8.9	9.6	6
Resistance-PCV	27.1 ± 25.9	±	0.77
(cmH ₂ O/L/s)	11.7	12.0	7
(n = 120)			
Duration of MV (d)	18.4 ± 10.7	±	0.00
	14.9	6.8	1
Length of stay in ICU	20.4 ± 12.8	±	0.00
(d)	15.3	7.6	3

Table 4

Variables	Outcome		P value
	High	Death	
APACHE II ¹	27.0 ± 7.6	27.7 ± 5.8	0.606
Age (yr)	51.1 ± 19.9	65.4 ± 16.1	< 0.001
1 st day (n = 120)			
PaO ₂ /FiO ₂ (mmHg) ¹	263.1 ± 100.9	210.7 ± 87.8	0.003
Compliance-VCV (mL/cm H ₂ O)	43.5 ± 12.5	38.4 ± 12.6	0.015
Resistance-VCV (cm H ₂ O/L/s)	13.3 ± 4.3	13.2 ± 5.4	0.935
Compliance-PCV (mL/cm H ₂ O) ¹	36.6 ± 9.8	33.6 ± 9.9	0.103
Resistance-PCV (cm H ₂ O/L/s)	25.0 ± 10.5	29.4 ± 20.0	0.416
5 th day (n = 77)			
PaO ₂ /FiO ₂ (mmHg) ¹	268.8 ± 81.9	214.7 ± 87.9	0.004
Compliance-VCV (mL/cm H ₂ O)	40.7 ± 12.7	38.7 ± 13.7	0.356
Resistance-VCV (cm H ₂ O/L/s)	14.2 ± 5.0	13.5 ± 6.9	0.22
Compliance-PCV (mL/cm H ₂ O) ¹	34.1 ± 9.4	31.8 ±	0.282

	9.1	
Resistance-PCV (cm H ₂ O/L/s)	25.7 ± 10.8	0.76
	27.1 ±	
	12.9	
(n = 120)		
Duration of MV (d)	14.5 ± 12.4	0.212
	11.9 ±	
	8.6	
Length of stay in ICU (d)	18.3 ± 12.5	<
	12.4 ±	0.001
	8.9	

Table 5 presents the relative risk estimate for the variables that demonstrated statistical association with VAP and the outcomes.

Variables	RR	95% CI	P value
VAP			
APACHE II above the average	1.62	1.03-2.55	0.016
Male gender	1.56	1.18-2.08	0.004
Resistance worsening-PCV	1.85	1.16-2.94	0.01
Outcome: Death			
Age above the average	2.08	1.34-3.23	0.001
Compliance-VCV below average on 1 st day	1.49	1.00-2.21	0.032
ICU stay below the average	2.05	1.28-3.28	0.001

Discussion:

The general characteristics of the sample were similar to those of other studies on ICU, i.e., most individuals were male and the mean age exceeded middle age^[14,23,24].

Among the surveyed patients, the severity of disease classified by the APACHE II was considered relatively high. A research carried out by Wunsch et al^[14] analyzed the clinical and epidemiological characteristics of over 170000 patients from 160 ICUs in England and 137 ICUs in the United States. In the United States, the mean APACHE II score was 15.3 ± 8 , and for mechanically ventilated subjects, the score was $20.1 \pm$

8.9 . In England, these scores were significantly higher, reaching 20.5 ± 8.5 in the APACHE II score and $22.3 \pm$

8.2 for individuals undergoing artificial respiration.

A study conducted by Matic et al^[25] assessed the influence of the APACHE II score on the selection of the mechanical invasive or non-invasive ventilatory support. The median APACHE II score was 24 in the group that received non-invasive mechanical ventilation, and 26 in the group that required invasive support. These data corroborate the findings of the present study, despite the fact that higher APACHE II scores indicate a more severe clinical condition in patients requiring invasive mechanical ventilatory support. However, the disease severity is related to the characteristics of each ICU, and comorbidities may influence the score, and consequently, the outcomes^[26].

With respect to the most common causes of hospitalization in the ICU, the results of this study are inline with the research carried out by Wunsch et al^[14], in which the main reasons were of cardiac origin (44.6% in the United States and 27.1% in England), followed by respiratory (20.2% in the United States and 26.3% in England), neurological (19, 1% in the United States and 24.1% in England) and gastrointestinal (9.5% in the United States and 10.1% in England) causes. These results may differ according to the characteristics of each ICU^[27,28].

The length of stay in the ICU and duration of MV were relatively high. According to a review study by Elliott^[29], the length of stay for all patient profiles can vary from 2 to 13 d, according to the ICU and the severity of cases. A study by Esteban et al^[30] that analyzed the characteristics and outcomes of adult patients requiring mechanical ventilation indicated an average length of stay in the ICU and duration of MV of 13.7 and 7.2 d, respectively. A study by Matic et al^[25], also in mechanically ventilated patients, found an average duration in MV of 7 d, and length of stay in ICU of 8.5 d. A Brazilian multicenter study sample consisting of 775 adult patients from 45 ICUs showed that the average length of stay in ICU among subjects requiring only non-invasive ventilation was 7 d. Those who required invasive ventilatory support stayed for 13 d on average^[31].

The data regarding the incidence of VAP in the present study were similar to those found in the literature. A review conducted by Joseph et al^[15] demonstrated that the incidence can vary from 6% to 52%. The density of VAP infection described in the systematic review by Arabi et al^[32] may vary from 10 episodes per 1000 ventilator days, such as in Thailand and Columbia, to 41.7 episodes per 1000 ventilator days in a cancer ICU in Brazil.

By comparing the significant associations of the variables for the development of VAP, it was observed that the APACHE II was a predictor, indicating that severe disease in ICU admission favors the occurrence of VAP. Other studies show no association; however, they describe that higher APACHE II scores are related to higher mortality when applied at the time of VAP diagnosis^[33,34].

A longer ICU stay and VM duration are also associated with VAP as demonstrated in this study, which is commonly presented in other works as well. Guimarães et al^[35] evaluated 278 patients in a Brazilian university hospital, and reported a significant difference between the group with and without VAP, having stayed in the ICU for 14 and 5 d, respectively. Patients with spinal cord injury who require prolonged mechanical ventilation also had a higher incidence of VAP due to the increased length of ICU stay and MV dependence^[36].

As evidenced in this study, the risk for the development of VAP is higher in men than women. According to Tejerina et al^[37], 2897 patients from 361 ICUs were surveyed in 20 countries, in which it was shown that men have a relative risk of 1.3 for the occurrence of VAP compared with women.

Worsening resistance during PCV was related to VAP, possibly indicating increased airway inflammation and/or an increase in bronchopulmonary secretions, which is inconsistent with the pathophysiological mechanism of respiratory infection^[21]. A worsening of lung compliance in subjects who developed VAP was also expected, but it did not occur. A study by Lox et al^[38] analyzed patients admitted to the ICU because of community-acquired pneumonia stratified into mild and severe conditions. Using low frequency forced oscillometry technique, it was observed that elastance, which is inversely proportional to compliance, was significantly higher in patients with severe pneumonia compared with those who had mild pneumonia. This evidence demonstrates the restrictive aspect of pneumonia, which was not found in the present study.

Monitoring of respiratory mechanics can assist the intensive care physician to detect early changes in lung function, associating them with the evolution of the ventilation status, and present scores associated with increased risk of mortality and VAP development. In addition, monitoring of mechanical breathing is performed at the bedside, does not involve patient transport, and has no financial cost to be implemented.

The results of the respiratory mechanics of the present study demonstrated a lower compliance and a higher resistance than the predicted values^[3,6,12]. This may demonstrate a reduction in lung function of the participants. Advanced age was statistically associated with death as the

outcome, which was also observed in other studies^[23,30]. Low levels of oxygenation in the 1st and 5th days was also related to mortality, which corroborates the study by Eastwood et al^[39] and de Jonge et al^[40] that found an association between low levels of oxygenation in the first 24 h and mortality rates in their retrospective observational studies. Low pulmonary compliance during VCV on day 1 also indicated a prediction of mortality in individuals with low pulmonary distensibility. A study by Matic' et al^[7] monitored the static pulmonary compliance with an intrasophageal balloon before intubation. It was shown that poor lung compliance was associated with high mortality rates.

It was expected that the incidence of VAP and higher APACHE II scores were associated with mortality, which was not observed. Generally, VAP is associated with higher mortality rates^[15]; however, Tejerina et al^[37] found no significant differences between the groups with and without VAP, with an incidence of 38.1% and 37.9%, respectively.

The limitation of this study was the monitoring of respiratory mechanics with sedated patients and not with neuromuscular block. This may have a small influence on the results.

In conclusion, monitoring of the mechanical aspects of lung function is already commonly used in well-established groups with chronic obstructive pulmonary disease and ARDS. It is a simple procedure performed at the bedside, without any physical damage and no additional cost. Based on this assumption, this procedure should be performed routinely in the ICU environment, providing the intensive care physician and the physiotherapist with additional prognosis and diagnosis variables, in addition to the clinical, laboratory and radiological data.

The results show that the respiratory function is a prognostic measure, and is strongly associated with mortality. Low oxygen and low lung compliance during VCV demonstrate this fact. Worsening of respiratory system resistance during PCV, associated with the development of VAP, indicates the possibility of early diagnosis.

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