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Investigating the Effect of Expiratory Time Constant on Outcome in Intubated Patients with Acute Respiratory Failure Caused by COVID-19 in Critical Care Unit: A Research Study

Fatemeh Eghtedari [1], Shahnaz Fooladi [1], Ali Mohammadian Erdi [1], Atefeh Shadman [2] and Mahzad Yousefian [1, *]

[1] Department of Anesthesiology, School of Medicine, Adabil University of Medical Scienes, Ardabil, Iran
[2] Determinations of Health Research Center, School of Medicine, Adabil University of Medical Scienes, Ardabil, Iran

[*] *Corresponding author*: Department of Anesthesiology, School of Medicine, Adabil University of Medical Scienes, Ardabil, Iran. Email: dr_mahzad@yahoo.com

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Abstract

Background: The coronavirus disease 2019 (COVID-19) has a high prevalence and mortality worldwide. Thousands of patients with acute respiratory failure caused by COVID-19 are daily hospitalized in intensive care units (ICUs) around the world. Many of these patients require full mechanical respiratory support and long-term ventilator use. Using different ventilators and calculating important variables can be helpful in meeting therapeutic needs of patients.
Objectives: The aim of present study was to investigate the effect of expiratory time constant (RCEXP) on the course of treatment and duration of mechanical ventilation in patients with acute respiratory failure hospitalized in ICU.
Methods: The present cross-sectional study was conducted on 60 patients with acute respiratory failure who were hospitalized in the ICU and underwent mechanical ventilation due to COVID-19 in the first six months of 2020. The variables of RCEXP, lung compliance and lung resistance in all patients were recorded daily and analyzed. Then, based on clinical outcome, the patients were divided into two groups: the patients with wean outcome (N = 40) and those with death outcome (N = 20).
Results: The mean ± SD of lung compliance in patients who were separated from ventilator and patients with death outcome were 74.73 (18.58) mL/cm H_2O and 36.92 (10.56) mL/cm H_2O, respectively, which was statistically significant (P = 0.001). The mean ± SD of lung resistance in patients who were separated from ventilator and patients with death outcome were calculated at 9.25 (4.62) and 14 (6.5), respectively, which was statistically significant (P = 0.015). Also, there was a statistically significant difference between the two groups in terms of mean ± SD of RCEXP (0.67 (0.23) vs. 0.49 (0.19), P = 0.010).
Conclusions: According to the results of this study, there was a significant difference between high resistance, low compliance, RCEXP, and weaning success of intubation in patients hospitalized in the ICU.

Keywords: Compliance, Resistance, RCEXP, Mechanical Ventilation

1. Background

The coronavirus disease 2019 (COVID-19), as an epidemic disease that might lead to death, has become a major global concern (1). Human life has been impressed by the advent of this disease, both personally and professionally. e.g., in critical care of residents and physicians' lives, compared to the previous coronavirus epidemics of severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS)) (2, 3). The virus is rapidly spread through close contact, often via small droplets produced by coughing, sneezing, or talking. Due to the examinations and close contact of the physicians and health care workers with the head and neck region and airways, they are particularly at high risk of infection from aerosol and droplet contamination (4). However, about 15 - 20% of the cases are believed to be severe, and many cases are asymptomatic (5). Hemodynamic changes are not significant with normal mechanical ventilation via spontaneous respiration. However, the patient's hemodynamics are greatly affected in several pathological conditions, such as hypovolemia, asthmatic status, pneumothorax, and respiration (6).

Despite the beneficial effects of mechanical ventilation on the pathophysiology of acute pulmonary insufficiency, it is associated with complications such as increased risk of sinusitis, airway injury, thromboembolism, gastrointestinal bleeding, pneumonia, ventilator dependence, pul-

monary barotrauma, and lung injury caused (7). As the need for mechanical respiration ends, the patient should be separated from the ventilator as soon as possible (8). Due to shortage of beds in the intensive care units (ICUs) and lack of mechanical ventilation equipment in hospitals, finding the methods to shorten hospitalization time and reduce ventilator dependence can help reduce the cost of treatment, as well as the complications of mechanical ventilation (9). Hence, timely, rapid, uncomplicated, and successful separation by shortening the mechanical ventilation period reduces ventilation complications (e.g., decreased cardiac output and infections caused by artificial ventilation), hyperventilation and hypoventilation, atelectasis, oxygen poisoning, barotrauma, and psychological ventilator dependence. Furthermore, unnecessary prolonged mechanical ventilation is associated with increased mortality (10-12).

Hypoxia is often the main cause of critically ill patients who need to be transferred to the ICU (13), acute diffuse lung injury, inflammatory lung injury leading to increased pulmonary vascular permeability, increased lung weight, and lung tissue loss (14).

Separating the patient from the ventilator merely based on clinical criteria is usually an incorrect issue which leads to early and unsuccessful separation (15). Furthermore, physiological tests should be considered as a predictor of separation results.

Separation often fails due to the existence of several influential factors. One of the reasons for failure in separation is the existence of several influential factors. Thus, the indicators and criteria that consider a pathophysiological mechanism are not valid and accurate enough. Meanwhile, the indicators that consider multiple mechanisms have higher accuracy (16). There is a higher tendency to determine specific, measurable indicators to predict separation outcomes. However, a single indicator that provides successful outcomes in this prediction has not been identified yet (8).

Expiratory time constant (RCEXP) enables us to assess the respiratory mechanics. The RCEXP less than 0.5 seconds indicates a decrease in lung compliance. In acute respiratory distress syndrome (ARDS) patients, the RCEXP is usually 0.4 to 0.6 seconds, and in individuals with more severe ARDS, this value is shorter, indicating the low compliance of lung. In patients with pulmonary fibrosis or chest wall stiffness, such as kyphoscoliosis, RCEXP is usually very short, ranging from 0.15 to 0.25 seconds. RCEXP more than 0.7 seconds indicates an increase in lung resistance, which may be associated with increased compliance in chronic obstructive pulmonary disease (COPD) patients with pulmonary emphysema. Prolonged RCEXP is common in patients with COPD and asthma. For example, in patients with severe bronchospasm, RCEXP can be up to 3 seconds. If the patient does not have COPD or asthma, prolonged RCEXP may indicate incorrect position or endotracheal contraction (17). There is a wide variety of factors for determining the weaning process time and extubating. Although RCEXP can be used as a factor for successful prediction of weaning, currently there is no study on determining the weaning process time. Considering the importance of predicting successful weaning time in patients with COVID-19 and untimely separation of patients, in this study, we surveyed the effects of these factors on weaning time.

2. Objectives

We aimed to investigate the effect of expiratory time constant on the course of treatment and duration of mechanical ventilation in patients with acute respiratory failure caused by COVID-19 in ICU.

3. Methods

3.1. Patients and Data Collection

The present cross-sectional research was conducted on 60 patients hospitalized in the ICU of Imam Khomeini Hospital of Ardabil University of Medical Sciences, Iran, due to respiratory failure caused by COVID-19, who underwent mechanical ventilation in the first six months of 2020. The variables of RCEXP, lung compliance and lung resistance in all patients were recorded daily and analyzed. Then, based on clinical outcome, the patients were divided into two groups: the patients with wean outcome (N = 40) and those with death outcome (N = 20). The exclusion criteria were hospitalization due to non-pulmonary reasons and hospitalization time less than 48 hours. Data were collected using a checklist, including demographic information extracted from the patients' hospital records. All patients who were hospitalized and intubated due to pulmonary problems and underwent ventilator for more than 48 hours were included. The spontaneous awakening trial (SAT) and spontaneous breathing trial (SBT) protocols were used to separate patients from the ventilator. The following formula was used to calculate lung compliance:

Lung compliance (C) = Changes in lung volume (V)/Change in transpulmonary pressure [Alvoelar pressure (Palv)-Pleural pressure (Ppl)] (18).

Also, body-plethysmography has been demonstrated to calculate the airway resistance (Raw) as a ratio of driving alveolar pressure to airflow (19). RCEXP is a mechanical respiratory measurement using Hamilton ventilators. Since RCEXP is a product of lung capacity and resistance, this variable enables us to assess respiratory mechanics.

It is very useful for diagnosing lung disease and its severity, ventilator settings, monitoring of susceptible position, and understanding some respiratory events. In a patient with normal ventilation and normal lungs, the normal RCEXP is between 0.5 and 0.7 seconds. However, it is important to check that the lung capacity and resistance values are in the normal range. Since lung disease reduces lung capacity and increases lung resistance, it may lead to false normalization of RCEXP (17).

3.2. Ethical Statement

This study was approved by the Ethics Committee of Ardabil University of Medical Sciences, Iran (code: IR.ARUMS. RE1398.322).

3.3. Statistical Analysis

After recording the data and completing the checklist containing such information as lung compliance, lung resistance, RCEXP and age, gender, and underlying disease, statistical analysis was performed using SPSS software version 16. The mean ± SD were reported for quantitative variables, and percentage and frequency were reported for qualitative variables. The t-test and chi-square test were used to compare the two groups. P-value less than 5% was considered as statistically significant.

4. Results

The present study was conducted on 60 patients (age range: 15 - 90 years) referred to Imam Khomeini Hospital in Ardabil, Iran due to COVID-19 disease. According to the results, 40 (66.7%) patients were separated from the ventilator, and 20 (33.3%) patients died. The mean age of participants was 54.98 years, with a standard deviation of 19.74. The mean age and standard deviation in patients who were separated from the ventilator and those who had death outcome were 48.48 ± 18.24 and 68 ± 16.12 years, respectively, which was statistically significant (P = 0.001) (Table 1).

In the present study, 32 (53.3%) participants were male, and 28 (46.7%) were female. The outcome between the two genders did not show a statistically significant difference. Statistical tests showed that out of 40 patients, 18 cases had a history of underlying disease. This difference between the two groups was not statistically significant (P = 0.714).

The mean ± SD of lung compliance in patients who were separated from ventilator and patients with death outcome were 74.73 (18.58) and 36.92 (10.56), respectively, which was statistically significant (P = 0.001). Also, the mean ± SD of lung resistance in patients who were separated from ventilator and those with death outcome were calculated at 9.25 (4.62) and 14 (6.5), respectively, which was statistically significant (P = 0.001). There was a statistically significant difference between the two groups in terms of RCEXP (P = 0.010) (Table 2). Finally, there was an inverse relationship between high resistance, low compliance, and the RCEXP levels and the result of successful weaning.

5. Discussion

In the present study, we investigated the effect of expiratory time constant on the course of treatment and duration of mechanical ventilation in COVID-19 patients admitted to the ICU. According to the results, 66.7% of the patients were separated from mechanical ventilation system, and 33.3% of them died. There was a statistically significant difference in the age of patients between the two groups. Also, 53.3% of the participants were male, and 46.7% were female, and the outcome between the two genders did not show a statistically significant difference. In a similar study conducted on clinical features and prognosis of invasive ventilation in patients who were hospitalized with COVID-19, a large number of critically ill patients admitted to ICU were older males with poor outcomes and a high mortality rate (20). Furthermore, a very high mortality rate of critically ill patients with COVID-19 was reported; since these patients had dyspnea and required mechanical ventilation, they were at a higher risk for death (21). The results of an observational study evaluating the effects of body mass index (BMI) on the mortality of critically ill patients demonstrated that regardless of age and gender, BMI could increase the risk of mortality (22). According to Mahmoodpoor et al., almost 60% of the patients underwent mechanical ventilation, 25% underwent non-invasive ventilation, and 15% received supplementary oxygen through facial oxygen masks (23).

In our study, 45% of patients had a history of underlying disease. In patients who underwent mechanical ventilation with normal lungs, the normal RCEXP was between 0.5 and 0.7 seconds. It is important to check that lung capacity and resistance values are within the normal range. Since lung disease decreases lung capacity and increases lung resistance, and also measuring lung volumes and airway resistance is often important to provide an adequate characterization of the pattern of lung disease (24), it may lead to false normalization of RCEXP. To the best of our knowledge, based on the available data within the first hours of hospitalization, predicting the need for mechanical ventilation, a risk score has been developed that should be validated to determine its further applicability in other populations (25).

Furthermore, controlled modes in COVID-19 (26) and positive end-expiratory pressure (PEEP) application are

Table 1. The Quantitative and Qualitative Variables of the Intubated Patients with Acute Respiratory Failure Caused by COVID-19 in ICU

Variable	Total (N = 40)	Weaning (N=40)	Death (N = 20)	P-Value
Age	120 ± 30	48.48 ± 18.24	68 ± 16.12	0.01
Gender				0.714
Male	32 (5.3)	22 (68.8)	10 (31.3)	
Female	28 (46.7)	18 (64.3)	10 (35.7)	
Respiratory disease				0.714
Yes	17 (28.3)	18 (64.3)	10 (35.7)	
No	43 (71.7)	22 (68.8)	10 (31.2)	
Underlying disease				0.714
Yes	28 (46.7)	5 (29.4)	12 (70.6)	
No	32 (3.53)	35 (81/4)	8 (18/6)	

Table 2. The Mean ± SD of the Resistance, Compliance, and RCEXP [a]

Variable	Weaning	Death	P-Value
Resistance	9.25 ± 4.62	14 ± 6.5	0.015
Compliance	74.73 ± 18.58	36.92 ± 10.56	0.001
RCEXP	0.67 ± 0.23	0.47 ± 0.19	0.01

[a] Values are expressed as mean ± SD.

linked to improved arterial blood gas in patients undergoing gynecologic laparoscopy as one of the strategies for improving the respiratory status (27). A previous case report showed that paying attention to happy hypoxemia critically improved the health status of COVID-19 patients (28). Also, dexamethasone was associated with reduced need for mechanical ventilation as observed in another study, by improving compliance and promoting better oxygenation (29). According to the results of a study by Asri et al., dexmedetomidine may improve arterial oxygenation during one-lung ventilation (OLV) in adult patients under the thoracic surgery, and can be a suitable anesthetic factor for thoracic surgery (30). In a previous study, we demonstrated the effect of vitamin D supplements on expediting the weaning process in patients with the stroke (31). Another study found a significant correlation between total and ionized calcium, but this correlation was not significant between corrected and ionized calcium. They proposed hypocalcemia as a predictor of disease severity and mortality (32).

RCEXP less than 0.5 seconds indicates a decrease in lung compliance. In ARDS patients, the RCEXP is usually in the range of 0.4 to 0.6 seconds. In patients with more severe ARDS, it is shorter, indicating low compliance. In patients with pulmonary fibrosis or chest wall stiffness such as kyphoscoliosis, RCEXP is usually very short, ranging from 0.15 to 0.25 seconds. RCEXP more than 0.7 seconds indicates an increase in lung resistance, which may be associated with increased compliance in COPD patients with pulmonary emphysema (17). Prolonged RCEXP is common in patients with COPD and asthma. In patients with severe bronchospasm, RCEXP can be up to 3 seconds. If the patient does not have COPD or asthma, prolonged RCEXP may indicate incorrect position or endotracheal contraction (17). In patients with normal lungs under mechanical ventilation, normal RCEXP is in the range of 0.5 and 0.7 seconds. In ARDS patients, RCEXP is in the range of 0.4 to 0.6 seconds. RCEXP less than 0.5 seconds indicates decreased lung compliance. RCEXP longer than 0.7 seconds indicates increased lung resistance and increased lung compliance, as seen in patients with COPD and asthma.

In this study, we found a significant difference in lung compliance in the patients who were separated from mechanical ventilation compared to those who died. This finding is in line with the results of a recent study conducted on 113 patients with success and non-success extubation groups, indicating successful extubation in 13.1% of patients (33). In another study, P. Candik examined the relationship between the expiratory time constant and ventilator separation parameters in patients hospitalized with respiratory failure. The results showed that RCEXP was associated with ventilator separation and extubation, so that RCEXP was an important parameter for extubation (34).

In the present study, a statistically significant difference was found between the two groups in terms of mean and standard deviation of RCEXP. Thus, our results confirm these findings, indicating a significant difference in RCEXP between the two experimental groups. Okabe et al. reported that lung-thorax compliance is a potential indicator for extubation failure in patients admitted to the ICU, suggesting that lung-thorax compliance measure-

ment can be a good index for extubation failure in the ICU. They also indicated that measurement of this index during a spontaneous breathing trial potentially can be an indicator of extubation failure in postoperative patients (33).

Basiri et al (35). conducted a study on comparison of pressure index (CROP) and rapid shallow breathing index (RSBI) separation indices in predicting the outcome of mechanical ventilation in 80 patients admitted to the ICU. Based on their results, the sensitivity of CROP and RSBI indices was 85% and 98.2%, respectively, and their specificity was 5% and 26%, respectively. The diagnostic accuracy of CROP (85.2%) was higher than that of RSBI index. In this study, CROP (compliance) had the highest diagnostic accuracy with high sensitivity and specificity. According to the requirement of endotracheal intubation and mechanical ventilation in ARDS in COVID-19 patients, some factors, including severe respiratory distress, loss of consciousness, and hypoxia, were the most important reasons for intubation (36).

Al-Rawas et al. evaluated RCEXP as a criterion for determining respiratory system compliance and resistance (37). In this study, 92 patients with acute respiratory failure who underwent mechanical ventilation through different ventilator modes were evaluated. This study concluded that the RCEXP is a good criterion for determining the respiratory system compliance and resistance (37).

We also witnessed a significant difference between successful and unsuccessful extubation groups. This supports the findings by Okabe et al., in which 162 (93.6%) patients were successfully extubated, and 11 (6.4%) patients experienced unsuccessful extubation. The mean lung compliance in the successful and unsuccessful extubation groups was 71.9 $\pm$ 0.23 and 43.3 $\pm$ 14.6, respectively, which was a statistically significant difference ($P < 0.0001$) (33).

Our results support the use of expiratory time constant on the course of treatment and duration of mechanical ventilation in patients with acute respiratory failure in the ICU. The main limitations of this study included a single-center nature of the study and a small sample size.

5.1. Conclusions

Since RCEXP was lower in the group with death outcome and lower level of this criterion is more common in restrictive lung diseases, it can be concluded that most severe lung diseases caused by COVID-19 have ARDS, and there is a significant relationship between low RCEXP and mortality rate. Further studies with larger sample sizes are required to confirm the results.

Footnotes

Authors' Contribution: MY and FE., Study design, Data analysis, Writing - original draft, Writing - review & editing. ASH Data analysis FE. and AMA, Data collection. The author(s) read and approved the final manuscript.

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