ADRENAL INSUFFICIENCY IS ASSOCIATED WITH DIFFICULT VENTILATOR WEANING AND INCREASED IN-HOSPITAL MORTALITY IN RESPIRATORY CARE WARD

Wei-Li Lien¹, Huang-Chi Chen², Mei-Fang Chen³

Abstract

Background and Objective: Adrenal insufficiency (AI) is a common disorder in critical ill patients and usually increases difficult ventilator weaning and mortality. However, it is seldom discussed with regards to patients with prolonged mechanical ventilation in respiratory care wards (RCW). The purpose of this study is to examine relationship of adrenal insufficiency, difficult ventilator weaning and in-hospital mortality among patients in RCW.

Methods: We retrospectively collected 102 patients in RCW from September 1, 2008 to November 30, 2009. 48 patients enrolled in the study were under mechanical ventilation for more than 21 days. 19 patients with cortisol ≥25 μg/dl and 29 patients with cortisol < 25 μg/dl were enrolled in the study.

Results: In-hospital mortality was higher in the group of cortisol < 25 μg/dl than the group of cortisol ≥25 μg/dl (44.8% vs. 21.1%, P=0.042). The days of in-hospital mortality after admission were found to be shorter in the group of cortisol < 25 μg/dl than the group of cortisol ≥25 μg/dl (146.92±65.83 vs. 215.0±53.37, P=0.039). The weaning percentage was higher in the group of cortisol ≥25 μg/dl than the group of cortisol < 25 μg/dl (57.9% vs. 31.0%, P=0.036). However, the weaning days between the two groups were shown to be of no statistical significance (P=0.284).

Conclusions: For patients with prolonged mechanical ventilator dependence, AI may be an important risk factor which may associate with a higher in-hospital mortality in RCW. Although the successful weaning days were not associated with AI, higher in-hospital mortality among AI patients might lead to a lower weaning percentage.

Key Words: Adrenal insufficiency, Ventilator weaning, Respiratory care ward, In-hospital mortality

INTRODUCTION

Adrenal insufficiency (AI) is common in intensive care units (ICU), and may occur during severe sepsis.¹-⁴ The overall incidence of AI in critically ill patients is about 30%, with an incidence rate as high as 50-60% in patients with septic shock.⁵ Chronic primary adrenal insufficiency,
as first described by Addison in the mid-1800s, is a rare disease.\textsuperscript{6,7} However, acute adrenal insufficiency is a common and largely unrecognized disorder in critical ill patients. An even minor degree of adrenal insufficiency increases the mortality of critically ill or injured patients.\textsuperscript{8}

Respiratory care ward (RCW) is a long-term acute care facility developed for ventilator-dependent patients in Taiwan. It is a step-down unit after ICU and Respiratory Care Centers (RCC), and is a weaning ward of ventilator-dependent patients. Several studies have discussed the association between adrenal insufficiency and mortality and ventilator weaning in ICU.\textsuperscript{9,10} However, little attention has been given to the long-term outcome of patients in ventilator weaning units about the problems of adrenal insufficiency. Therefore, in this study, we tried to evaluate the relationship between the outcome of patients and adrenal insufficiency in RCW.

**METHODS**

**Patients**

This study was conducted at Kaohsiung Municipal United Hospital, which is a 500-bed, teaching hospital that serves as a tertiary referral center and a primary-care facility in southern Taiwan. The RCW is a 45-bed unit that cares for patients with prolonged mechanical ventilator dependence. From a retrospective review, 102 adult patients detected in the period from September 1, 2008 to November 30, 2009 were selected. All patients enrolled from the ICU of other tertiary teaching facilities or our ICU. All patients enrolled in the study were under mechanical ventilation for more than 21 days at ICU and had a tracheostomy. These patients were hemodynamically stable and had no obvious infection. They must have not received steroid treatment for at least 14 days before the study.\textsuperscript{11} Low albumin level would be ruled out since hypoproteinemia results in lower than expected concentrations of serum total cortisol.\textsuperscript{12,13} Patients without adequate cough reflex or with malignancy were excluded for the low possibility of successful weaning. The study was performed with the approval of the hospital ethics committee.

**Study protocol**

Cortisol concentrations were measured with a competitive immunoassay using direct chemiluminescent technology (ADVIA Centaur Assay, BAYER) in the laboratory of the hospital. The morning cortisol level (between 7 AM and 9 AM) was checked on the second day after admission. Plasma cortisol concentration using a threshold of 25 μg/dL was considered to reflect intact adrenal function or not. The use of a threshold random (stress) serum cortisol of 25 μg/dL for the diagnosis of an adequate cortisol response is supported by the literature.\textsuperscript{5,14} The group of cortisol level below 25 μg/dL were replaced with oral prednisolone 5 mg every morning and 2.5 mg every evening. A flow chart of the study is presented in Figure 1. The rapid shallow breathing index (RSBI),\textsuperscript{15} maximum inspiratory pressure (PImax),\textsuperscript{16,17} albumin level, leukocyte count, hemoglobin and Acute Physiology, Age and Chronic Health Evaluation (APACHE II) score\textsuperscript{18} were recorded for all patients before ventilator weaning was attempted.

Weaning was started for all enrolled patients when they met the weaning criteria. The weaning criteria are listed as follows: cardiovascular stability, adequate cough reflex, FIO\textsubscript{2} ≤ 0.4, PEEP ≤ 5cmH\textsubscript{2}O, SpO\textsubscript{2} ≥ 92%, heart rate ≤ 130 bpm or respiratory rate ≤ 30/min, pressure support mode ventilation with pressure lower than 10 cmH\textsubscript{2}O. Patients meeting the weaning criteria entered a protocol of spontaneous breathing T-piece trial (SBT). The protocols are listed as follows: SBT for two hours on the first day, increase the duration of SBT as the rate of 2 hours per day, starting 24-hours SBT on the next day after SBT up to 8 hours, 24-hours SBT for 3 days was defined successful weaning. The criteria to terminate SBT were: respiratory rate > 35/min for more than 5 minutes, O\textsubscript{2} saturation <90% for more than 30 seconds, heart rate > 140/min or sustained 20% increase in heart rate for more than 5 minutes, systolic blood pressure >180 mmHg or < 90 mmHg at least one minute of repeated measurements, diaphoresis, agitation or anxiety for more than 5 minutes.
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Figure 1. The flow-chart of patients enrolled in the study.
* Hemodynamic unstable represents the patients required vasopressor agent to maintain blood pressure or heart rate \( \geq 140 \).
** Acute infection represents the body temperature higher than 38 degree Celsius or leukocyte counts \( \geq 14000/μL \).

**Statistical analysis**
Descriptive statistics were applied for all variables collected. All demographic data, in-hospital mortality and successful weaning were expressed as mean ± SD or frequency (%) where appropriate and were analyzed with one way analysis of variance tests. Both groups were compared using the student’s t-test. A p value <0.05 was considered to represent statistical significance.

**RESULTS**
During the one-year and three months period of the study, 102 ventilated patients via tracheostomy with Cortisol concentrations measured were admitted to the RCW. The main etiologies of the respiratory failure are shown in Table 1. Among these, 9 patients were excluded for hemodynamic unstable or acute infection when admitted. 93 pa-
tients were evaluated for this study. However, only 48 patients were enrolled in the study after 45 patients were excluded (Figure 1). Following the evaluation of the cortisol level, 19 patients were found to have adequate adrenal function (cortisol $\geq 25 \mu g/dl$) and 29 patients with adrenal insufficiency (cortisol < 25 μg/dl).

Demographic data for the two groups are shown in Table 2. No any statistical differences between the two groups were found including the age, gender, RSBI, PImax, total leukocyte count, hemoglobin, APACHE II score and albumin level.

In Table 3, we found the in-hospital mortality was higher in the group of cortisol < 25 μg/dl than the group of cortisol $\geq 25 \mu g/dl$ (44.8% vs. 21.1%, P=0.042). The days of in-hospital mortality after admission were found to be shorter in the group of cortisol < 25 μg/dl than the group of cortisol $\geq 25 \mu g/dl$ (146.92±65.83 vs. 215.0±53.37, P=0.039). The weaning percentage was higher in the group of cortisol $\geq 25 \mu g/dl$ than the group of cortisol < 25 μg/dl (57.9% vs. 31.0%, P=0.036). However, the weaning days of the two groups were shown to be of no statistical significance (P=0.284). The percentage of mechanical ventilator dependent (MVD) and days of MVD at the endpoint of the study between the two groups were also shown no significance differences.

Table 1. Etiology of respiratory failure

<table>
<thead>
<tr>
<th>Causes of respiratory failure</th>
<th>Cortisol $\geq 25$ (μg/dl)</th>
<th>Cortisol &lt; 25 (μg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Cerebral vascular disease</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Cervical-spine injury</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adult respiratory distress syndrome</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 2. Demographic characteristics of respiratory failure patients

<table>
<thead>
<tr>
<th></th>
<th>Cortisol $\geq 25$ (μg/dl) (n=19)</th>
<th>Cortisol &lt; 25 (μg/dl) (n=29)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.24±11.63</td>
<td>77.34±11.89</td>
<td>0.182</td>
</tr>
<tr>
<td>Gender (male %)</td>
<td>55.6%</td>
<td>51.7%</td>
<td>0.158</td>
</tr>
<tr>
<td>RSBI*</td>
<td>122.89±42.87</td>
<td>138.45±51.47</td>
<td>0.795</td>
</tr>
<tr>
<td>PImax**</td>
<td>-12.06±7.66</td>
<td>-13.69±8.22</td>
<td>0.893</td>
</tr>
<tr>
<td>Total leukocyte (×1000/μL)</td>
<td>9.96±3.81</td>
<td>10.16±3.49</td>
<td>0.965</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.93±1.62</td>
<td>10.15±1.36</td>
<td>0.851</td>
</tr>
<tr>
<td>Albumin(g/dl)</td>
<td>3.15±0.71</td>
<td>2.91±0.54</td>
<td>0.814</td>
</tr>
<tr>
<td>APACHE II score**</td>
<td>19.84±2.41</td>
<td>20.45±2.72</td>
<td>0.209</td>
</tr>
</tbody>
</table>

* RSBI = Rapid shallow breathing index (respiratory rate/tidal volume)
** PImax = Maximum inspiratory pressure
*** APACHE II = Acute Physiology, Age and chronic Health Evaluation
Presently, we demonstrate that patients with low cortisol levels (< 25 μg/dl) with prolonged MVD in RCW have higher in-hospital mortality and lower weaning rate. Many studies have been reported about the deficiency of cortisol being associated with increased morbidity and in-hospital mortality during critical illness.\(^8,19\) However, this study may be the first report to discuss in-hospital mortality and weaning rate with the adrenal insufficiency in RCW.

Although cortisol is one of the most widely studied hormones, it is probably one of the least understood. The definition of AI remains controversial. A cortisol level greater than 25 μg/dl was considered adequate adrenal reserve in many lectures and recent studies. Schroeder et al reported a mean random cortisol level of 19 μg/dl with severe sepsis, with non-survivors having a lower cortisol level than survivors (10 μg/dl vs. 17 μg/dl).\(^{20}\) None of the patients were treated with corticosteroids in this study. However, in our study we found that patients with lower cortisol level still have higher in-hospital mortality in RCW with prolonged MVD despite having corticosteroid treatment. Therefore, we infer that low cortisol level may be an independent risk factor regarding prognosis in RCW patients and is not related to corticosteroid replacement.

Why do the patients with AI have higher in-hospital mortality at RCW? We think that in response to the stress (like respiratory distress with prolonged MVD), the neuronally stimulated corticotropin release of corticotropin-releasing factor from the hypothalamus induces an increase in ACTH secretion by the anterior pituitary gland. The adrenal cortex responds to ACTH by increasing cortisol secretion, but prolonged elevation of serum cortisol triggers a negative feedback inhibition loop that results in subsequent decreases in ACTH and cortisol release.\(^{21}\) Cortisol is a major stress response hormone that has metabolic, catabolic and anti-inflammatory effects. The cortisol also mediates maintenance of peripheral vasomotor tone by facilitating catecholamine-induced vasoconstriction and has a permissive effect on the synthesis of catecholamines and vasoactive peptides.\(^{22,23}\) Thus, decrease cortisol release and a deranged interaction between catecholamines, adrenergic receptors, and corticosteroids would lead to adrenergic hyporesponsiveness. This desensitization or down-regulation of \(\alpha\)- and \(\beta\)-adrenergic receptors may result in vascular hyporesponsiveness and myocardial depression.\(^{24,25}\) All of these adverse effects might explain why the AI group would have the higher in-hospital mortality.

Although the weaning rate was lower in the group of cortisol < 25 μg/dl than the group of cortisol ≥25 μg/dl, the duration of weaning days between the two groups were no significance differences. The duration of weaning days in the group of cortisol ≥25 μg/dl were 116.45±101.14 and the group of cortisol < 25 μg/dl were 94.44...
±42.42 (P= 0.284). Interestingly, we can find the duration of weaning days varied more markedly in the group of cortisol ≥25 μg/dl than the group of cortisol < 25 μg/dl. Therefore, we suggest the higher weaning rate may be due to the lower in-hospital mortality and longer survival in the group of cortisol ≥25 μg/dl than the group of cortisol < 25 μg/dl. In other words, if the patients could survive for a longer period, than they could have a higher possibility to try weaning and then wean successfully.

Huang et al.26 ever performed a prospective, randomized, placebo-controlled, double-blinded study about the association of adrenal insufficiency and ventilator weaning in ICU. For patients with respiratory failure, early identification of adrenal insufficiency and appropriate supplementation with stress dose hydrocortisone increase the success of ventilator weaning and shortens the weaning period. However, we can not find the benefit of corticosteroid replacement for ventilator weaning in RCW. Despite the aforementioned explanations, the given-doses of corticosteroid for adrenal insufficiency are much different. 50 mg intravenous hydrocortisone every 6 h during the weaning period was given in the former study but only oral prednisolone 5 mg every morning and 2.5 mg every evening in our study. Besides, we don’t use a high-dose adrenocorticotropic (ACTH) stimulation test to confirm AI, which was defined by an increase in serum cortisol of less than 9 μg/dl after a 250-μg intramuscular cosyntropin injection with blood samples taken immediately before and 60 min after the test. The limitation of our study is the small patient number in each group. However, the result inspired us to conduct a larger and multicenter study to prove the present finding.

In conclusion, for patients with prolonged mechanical ventilator dependence in RCW, adrenal insufficiency may be an important risk factor which may be associated with a higher in-hospital mortality rate. It also implies that higher in-hospital mortality rate and shorter survival period for weaning may lead to a lower opportunity for weaning successfully and result in a lower weaning rate.

Conflict of Interest Statement: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

REFERENCES

呼吸照護病房腎上腺功能不全與呼吸器脫離困難及死亡率之相關性探討

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摘要

背景與目的：腎上腺功能不全是在重症個案常見的一種障礙，常常會增加個案呼吸器脫離困難與死亡率。然而，在呼吸照護病房卻鮮少探討，故本研究目的為探討呼吸照護病房依賴病患之腎上腺功能不全與呼吸器脫離困難及死亡率之相關性。

方法：採回溯性研究法，從2008年9月1日至2009年11月30日，個案已使用呼吸器超過21天為研究對象，共48名個案參與本研究。其中19名個案cortisol≧25μg/dl，29名個案cortisol<25μg/dl。

結果：在死亡率方面，在cortisol<25μg/dl那組顯著高於cortisol≧25μg/dl那組(44.8% vs. 21.1%, P=0.042)。在住院後至死亡的天數方面，cortisol<25μg/dl那組顯著短於cortisol≧25μg/dl那組(146.92±65.83 vs. 215.0±53.37, P=0.039)。在能呼吸器脫離的百分比，cortisol≧25μg/dl那組高於cortisol<25μg/dl那組。然而，在呼吸器脫離天數方面，cortisol≧25μg/dl與cortisol<25μg/dl兩組間無顯著差異(P=0.284)。

結論：在呼吸照護病房，對呼吸器依賴延長的個案，腎上腺功能不全有較高的死亡率。然而成功呼吸器的脫離天數與腎上腺功能不全無顯著相關，可能是高的死亡率導致較低的脫離百分比。

關鍵詞：腎上腺功能不全，呼吸器脫離，呼吸照護病房，死亡率