The Effect of Positive Pressure Ventilation on Aldosterone Level in Critically Ill Patients; Correlation with Renal Function and the Length of Stay in ICU

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Abstract

Background: Positive pressure ventilation has been shown to alter a variety of neurohormonal systems including sympathetic outflow, the renin-angiotensin axis, nonosmotic vasopressin (ADH) release and atrial natriuretic peptide (ANP) production. The end result of all of these neurohormonal pathways is diminished renal blood flow, decreased GFR, and fluid retention (salt and water) with oliguria.

Aim of Study: To investigate the effect of positive pressure mechanical ventilator on aldosterone and to study its prognostic value.

Patients and Methods: This study was conducted on 50 patients admitted to the intensive care unit (ICU) and needed mechanical ventilation and did not meet any of exclusion criteria and 25 control (critically ill patients who did not need mechanical ventilator). The patients were divided into 2 equal groups; group I with high PEEP (10-15) and group II with physiological PEEP (3-5). Aldosterone level was measured for these patients on first day of using PPV (aldosterone 1) then after 72h (aldosterone 2).

Results: Aldosterone levels were increased with use mechanical ventilation and were significantly higher with higher level of PEEP. There were correlations between aldosterone 2 with urea and Creatinine levels and with length of ICU stay only in patient group (p<0.001).

Conclusion: Mechanical ventilation caused elevation of aldosterone levels. Aldosterone levels in mechanically ventilated patients correlated with kidney function test (urea and Creatinine) and with length of ICU stay.

Key Words: PPV – Aldosterone – Mechanical ventilation.

Introduction

MECHANICAL ventilation can be lifesaving but it is also associated with numerous complications. The incidence of some complications increases with duration of mechanical ventilation [1]. There are numerous mechanisms underlying the development of complications in the ventilated patient. Complications may result from the endotracheal tube or tracheotomy tube (or with noninvasive ventilation, the mask), or from the effects of positive-pressure ventilation. Some complications (barotrauma and volutrauma) can result from either the underlying lung disease or the effects of lung overdistension produced by positive-pressure ventilation [2]. Complications may result from therapies or the process of care required by most invasively ventilated patients (e.g., immobility and risk of thromboembolism). Other complications may occur as a manifestation of critical illness or underlying comorbid conditions [3,4].

Physiological consequences of mechanical ventilation on pulmonary and cardiovascular function have been studied extensively, [5] and many investigators have shown that positive-pressure ventilation affects venous return, cardiac pre-load, pulmonary vascular resistance, and cardiac afterload [6,7]. In addition to these direct physiological effects, mechanical ventilation may exacerbate lung injury and cause ventilator-induced lung injury (VILI), resulting in the local and systemic release of inflammatory mediators, organ dysfunction, and increased morbidity and mortality [8].

Although the physiological consequences of mechanical ventilation on pulmonary and cardiovascular function have been extensively studied, its effects on renal function are not as well defined. [9].

The aim of study:

To investigate the effect of positive pressure mechanical ventilator on aldosterone and to study its prognostic value.
**The Effect of Positive Pressure Ventilation on Aldosterone Level in Critically Ill Patients**

**Patients and Methods**

This study was conducted on 50 patients admitted to the intensive care unit (ICU) of Misr University for Science and Technology Teaching Hospital and need mechanical ventilation and 25 control (critically ill patients did not need mechanical ventilation) in the period from 2012 to 2015.

**Patient selection:**

Patients who need mechanical ventilation on ICU admission and did not meet any of the exclusion criteria were selected into the study and they had been followed-up till the day of discharge or demise. Most of patients in this study were traumatic brain injury to fulfill the exclusion criteria.

**Exclusion criteria:**

- Patients with chronic renal impairment.
- Patients with chronic lung disease (e.g. COPD, bronchial asthma, interstitial pulmonary fibrosis).
- Primary pulmonary hypertension.
- Patients with advanced heart failure, acute myocardial infarction and hemodynamically unstable patients.
- Post-arrest patient.
- Patients with severe sepsis or septic shock.
- Patients with liver cirrhosis.
- Patients with terminal malignancy.
- Patient age <18 years old.
- Pregnant female patients.
- Patients with autoimmune disease.

**Patients subdivided into two groups:**

- **Group I:** Patients on mechanical ventilation and need high level of PEEP (10-15cmH₂O), they include 25 patients.
- **Group II:** Patients on mechanical ventilation with lower level of PEEP (5 or less) (i.e. physiological PEEP), they include 25 patients.

**Control group include 25 critically ill patients admitted to ICU and did not need mechanical ventilation.**

The care of patients was directed according to guidelines and was not modified by the study. Generally, the first priority was to stabilize the general condition of the patient and support them with mechanical ventilation according to their requirements.

Routine laboratory investigations were done on study day 1 and subsequently after 3 days to fulfill criteria of APACHE IV.

**Labs specific for this study:**

Plasma aldosterone level were measured immediately after using mechanical ventilator (aldosterone 1) and 3 days later (aldosterone 2). Blood samples were allowed to clot and then centrifuged to separate the serum according to common procedures and were measured using ELIZA technique.

**Principles of the test:**

The principle of the following enzyme immunoassay test followed the typical competitive binding scenario. Competition occurs between an unlabeled antigen (present in standards, controls and samples) and an enzyme-labelled antigen (conjugate) for a limited number of antibody binding sites on the microwell plate. The washing and decanting procedures removed unbound materials. After the washing step, the enzyme substrate was added. The enzymatic reaction was terminated by addition of stopping solution. The absorbance was measured on a microtiter plate reader. The intensity of the colour formed is inversely proportional to the concentration of aldosterone in the sample. A set of standards was used to plot a standard curve from which the amount of aldosterone in samples and controls could be directly read.

**Results**

This study included patients with age ranged from 18-80 years with mean age (47.36 ±16.15). Control group with age ranged from 18-74 with a mean (46.08±1.5.20). There were 31 males (16 in group I and 15 in group II) and 19 females (9 in group I and 10 in group II) and in control group there were 15 males and 10 females.

**Clinical characteristics of enrolled patients:**

**Clinical characteristic of control versus group I and group II:**

In this study, group I had 6 hypertensive patients, 2 diabetic patients and 1 patient with ischemic heart disease. In group II there were 10 hypertensive patients, 3 diabetic patients and 1 patient with ischemic heart disease. In Control group 10 patients were hypertensive, 3 patients were diabetic, and 1 patient had ischemic heart disease. There was no statistically significant difference between group I and group II versus control as regard clinical characteristic (Table 1, Fig. 1).

I- **Aldosterone level in patient versus control:**

The mean aldosterone level for all patients was statistically significantly higher than that in control group. Moreover, serum aldosterone 2 level was...
significantly higher than aldosterone 1 in patients. Group I exhibited significant higher levels of aldosterone (Table 2, Figs. 2,3).

Table (1): Clinical characteristic of control versus group I and group II.

<table>
<thead>
<tr>
<th></th>
<th>Control (N=25)</th>
<th>Group I (N=25)</th>
<th>Group II (N=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN (Y/N)</td>
<td>10/15</td>
<td>6/19</td>
<td>10/15</td>
<td>0.389</td>
</tr>
<tr>
<td>DM (Y/N)</td>
<td>3/22</td>
<td>2/23</td>
<td>3/22</td>
<td>0.869</td>
</tr>
<tr>
<td>IHD (Y/N)</td>
<td>1/24</td>
<td>1/24</td>
<td>2/23</td>
<td>0.767</td>
</tr>
</tbody>
</table>


Table (2): Aldosterone level in patient versus control.

<table>
<thead>
<tr>
<th></th>
<th>Aldosterone 1 (ng/dl)</th>
<th>Aldosterone 2 (ng/dl)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients N=50</td>
<td>196.64±188.74 (50-750)</td>
<td>287.46±216.10 (60-900)</td>
<td>0.027</td>
</tr>
<tr>
<td>Controls N=25</td>
<td>118.32±62.49 (60-300)</td>
<td>124.76±56.58 (50-240)</td>
<td>0.737</td>
</tr>
<tr>
<td>p-value</td>
<td>0.047</td>
<td>0.0005</td>
<td>0.002</td>
</tr>
<tr>
<td>Group I N=25</td>
<td>176.17±167.88 (50-750)</td>
<td>350.40±227.25 (80-900)</td>
<td>0.797</td>
</tr>
<tr>
<td>Group II N=25</td>
<td>225.40±199.93 (70-763)</td>
<td>224.52±188.28 (60-700)</td>
<td>0.987</td>
</tr>
<tr>
<td>p-value</td>
<td>0.063</td>
<td>0.0000</td>
<td>0.002</td>
</tr>
</tbody>
</table>

N: Number. SD: Standard deviation.

II- Aldosterone levels in relation to kidney function test (KFT) (creatinine and urea):
There was significant positive correlation between aldosterone 2 and Creatinine 2 and urea 2 in patients (Table 3).

Table (3): Aldosterone level versus creatinine and urea in patient.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Min Max</th>
<th>Median</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone 1</td>
<td>196.64±188.74</td>
<td>50 750</td>
<td>120</td>
<td>-0.227</td>
<td>0.113</td>
</tr>
<tr>
<td>Creatinine 1</td>
<td>0.822±0.34</td>
<td>0.2 1.5</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone 2</td>
<td>287.46±216.10</td>
<td>60 900</td>
<td>159</td>
<td>0.356</td>
<td>0.011</td>
</tr>
<tr>
<td>Creatinine 2</td>
<td>0.91±0.59</td>
<td>0.1 2.7</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone 1</td>
<td>196.64±188.74</td>
<td>50 750</td>
<td>120</td>
<td>0.014</td>
<td>0.921</td>
</tr>
<tr>
<td>Urea 1</td>
<td>36.92±30.38</td>
<td>5 138</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone 2</td>
<td>287.46±216.10</td>
<td>60 900</td>
<td>159</td>
<td>0.496</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urea 2</td>
<td>35.88±29.04</td>
<td>6 145</td>
<td>26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Min.: Minimum. Max.: Maximum. SD: Standard deviation. 1: Value at first day of mechanical ventilation. 2: Value in third day of mechanical ventilation.
The Effect of Positive Pressure Ventilation on Aldosterone Level in Critically Ill Patients

III- Aldosterone levels in relation to severity of illness during ICU stay:
   a- Correlation between aldosterone levels with length of mechanical ventilation:

   There was no significant correlation between aldosterone level with length of mechanical ventilation (Table 4).

   b- Correlation between aldosterone levels with need for hemodynamic support:

   There was no significant correlation in aldosterone level between patients needed hemodynamic support and those did not need hemodynamic support (Table 5).

   c- Correlation between aldosterone level with length of ICU stay:

   There was significant correlation between length of ICU stay and aldosterone only in patients (Table 6).

IV- Correlation between aldosterone levels with mortality:

   There was no significant difference between aldosterone with mortality either in patients or control (Table 7).

Table (4): Aldosterone versus length of mechanical ventilation (LOMV).

<table>
<thead>
<tr>
<th></th>
<th>Aldosterone 1 (Mean ± SD)</th>
<th>Aldosterone 2 (Mean ± SD)</th>
<th>LOMV (days) (Mean ± SD)</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N=50)</td>
<td>196.64±188.74</td>
<td>287.46±167.88</td>
<td>7.8±216.10</td>
<td>0.725</td>
<td>0.694</td>
</tr>
<tr>
<td>Group I (N=25)</td>
<td>176.17±167.88</td>
<td>350.40±227.25</td>
<td>8.64±225.40</td>
<td>0.016</td>
<td>0.938</td>
</tr>
<tr>
<td>Group II (N=25)</td>
<td>225.4±224.52</td>
<td>225.4±224.52</td>
<td>6.32±224.52</td>
<td>0.363</td>
<td>0.074</td>
</tr>
</tbody>
</table>

N : Number. SD : Standard deviation. LOMV : Length of mechanical ventilation.

Table (5): Correlation between aldosterone with need for hemodynamic support.

<table>
<thead>
<tr>
<th></th>
<th>Aldosterone 1 (Mean ± SD)</th>
<th>Aldosterone 2 (Mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients need HDS (N=7)</td>
<td>274.28±194.75</td>
<td>187.06±183.54</td>
<td>0.286</td>
</tr>
<tr>
<td>Patients not need HDS (N=43)</td>
<td>370.0±235.16</td>
<td>273.79±212.32</td>
<td>0.340</td>
</tr>
</tbody>
</table>

N : Number. SD : Standard deviation. HDS : Hemodynamic support

Table (6): Length of ICU stay (LOS) versus aldosterone in patients and control.

<table>
<thead>
<tr>
<th></th>
<th>LOS (days) (Mean±SD)</th>
<th>Aldosterone 1 r p-value</th>
<th>Aldosterone 2 r p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N=50)</td>
<td>9.3±6.2</td>
<td>169.64±188.74 0.051 0.725</td>
<td>287.46±216.10 0.070 0.630</td>
</tr>
<tr>
<td>Control (N=25)</td>
<td>9.7±5.9</td>
<td>118.32±62.49 0.129 0.538</td>
<td>124.7±56.58 0.036 0.864</td>
</tr>
<tr>
<td>Group I (N=25)</td>
<td>10.8±8.2</td>
<td>176.17±167.88 0.447 0.025</td>
<td>350.4±227.25 0.284 0.168</td>
</tr>
<tr>
<td>Group II (N=25)</td>
<td>8.7±3.9</td>
<td>225.4±199.93 −0.530 0.006</td>
<td>224.52±188.28 −0.348 0.005</td>
</tr>
</tbody>
</table>

N: Number. SD: Standard deviation. LOS: Length of ICU stay.

Table (7): Correlation between aldosterone with mortality.

<table>
<thead>
<tr>
<th></th>
<th>Survivors (N=33) (66%) (Mean±SD)</th>
<th>Non-survivors (N=17) (34%) (Mean±SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone 1 (pts.)</td>
<td>195.67±191.21 212.07±164.57</td>
<td>0.713</td>
<td></td>
</tr>
<tr>
<td>Aldosterone 2 (pts.)</td>
<td>294.83±219.30 266.46±204.33</td>
<td>0.677</td>
<td></td>
</tr>
<tr>
<td>Aldosterone 1 (control)</td>
<td>99.22±34.98 141.77±95.03</td>
<td>0.288</td>
<td></td>
</tr>
<tr>
<td>Aldosterone 2 (control)</td>
<td>116.66±61.64 143.22±49.12</td>
<td>0.343</td>
<td></td>
</tr>
</tbody>
</table>


Discussion

Aldosterone levels increased with the use of mechanical ventilation and were significantly higher with higher level of PEEP. Aldosterone levels were significantly higher in patients than that in control group. Moreover, serum aldosterone 2 level was significantly higher than aldosterone 1. Also aldosterone was significant higher in group I than in group II or control.

Annat G., et al. [11] measured hormonal parameters in seven intensive care patients during three consecutive 60-min periods; one of intermittent positive pressure ventilation (IPPV), one of CPPV (PEEP 10cmH2O), and finally one of IPPV and found that Institution of PEEP led to a significant increase in plasma aldosterone level.

Marius G., et al. [12] who made a study on ten male patients treated postoperatively for 60min using five different ventilation modes, at the end of these periods, hemodynamics, urine production, fractional excretion of sodium (FESo), as well as the hormones [atrial natriuretic peptide (ANP), renin, angiotensin II, aldosterone, and antidiuretic hormone (ADH)] were measured. They found that renin with a positive end-expiratory pressure...
(PEEP) of 15cm H2O and an inspiration/expiration ratio (I:E) of 1:2 revealed significant increases from baseline, However aldosterone, angiotensin II, and antidiuretic hormone (ADH) levels remained within the normal range.

In addition to P Andrivet, et al. [13] who examined the renal and hormonal responses to synthetic human ANF infusion in eight patients during mechanical ventilation with zero PEEP (ZEEP) or 10 cmH2O positive end-expiratory pressure (PEEP). They determined that, compared with ZEEP, MV with PEEP was associated with increase in plasma renin activity (PRA) from 4.83 ± 1.53 to 7.85 ± 3.02 ng.ml-1.l.h-1 (p less than 0.05). Infusion of ANF (5 ng.kg-1.min-1) during PEEP markedly decreased plasma renin activity from 7.85 ± 3.02 to 4.40 ± 1.5 ng.ml-1.min-1 (p less than 0.05). In response to a 10ng.kg-1.min-1 ANF infusion.

On the other hand, JB Thorens, et al. [14] made a study to investigate the haemodynamic and endocrinological effects of noninvasive positive pressure ventilation. Measurements were performed on the fourth day, for 4 hours without noninvasive positive pressure ventilation and 4 hours with noninvasive positive pressure ventilation. They found that plasma renin activity, aldosterone and vasopressin were normal.

Also S. Tanaka, et al. [15] measured responses during Continuous positive pressure ventilation (PEEP = 12mmHg) in 10 male subjects (22.0 ± 6.0 years, 66.8 ± 1.5 kg body weight). The experiments consisted of a 1-hour control, 1h with Continuous positive pressure ventilation, and a 1-h recovery period. Two blood samples were taken during each period for measurements of arginine vasopressin (AVP), plasma aldosterone, plasma renin activity, norepinephrine, and atrial natriuretic peptide. They found that neither plasma renin nor aldosterone levels were changed.

In the current study, aldosterone levels were studied in relation to kidney function test and we demonstrated that there was a significant positive correlation between aldosterone 2 with Creatinine and urea levels only in patients.

We studied aldosterone in relation to severity of illness as; length of mechanical ventilation, length of ICU stay and mortality. This point of our study may not be found in any other equivalent research.

There was no significant correlation between aldosterone with length of mechanical ventilation and mortality.

However, there was a significant negative correlation between length of ICU stay and aldosterone 2.

Conclusion:
Mechanical ventilation caused elevation of aldosterone levels especially with higher levels of PEEP.

We estimated a positive correlation of aldosterone levels in mechanically ventilated patients with kidney function test (urea and Creatinine).

Determination of serum levels of aldosterone may add to the clinical assessment of severity of critical illness in mechanically ventilated patients. Aldosterone 2 levels were correlated with length of ICU stay.

References
The Effect of Positive Pressure Ventilation on Aldosterone Level in Critically Ill Patients


تأثير التهوية الميكانيكية على مستوى الألدوستيرون في مرضى الحالات الحادة

العلاقة مع وظيفة الكلى ومدة الإقامة في العناية المركزة

بعد جهاز التنفس الصناعي أدى الركائز الأساسية في وحدة العناية المركزة حيث يستخدم على نطاق واسع لدعم الجهاز التنفسي لمرضى الحالات الحادة. بالرغم من كون جهاز التنفس الصناعي متفقًا للحياة إلا أنه قد يسبب في العديد من المضاعفات والتي قد تنعكس على المريض. وقد أظهرت بعض الدراسات أن التهوية الميكانيكية بالضغط الإيجابي تثير تأثيرات على كمية البول وأفرار الصوديوم في البول وتصافح الكرياتين.

وقد تثير التهوية الميكانيكية على الكلى من خلال ثلاث آليات: (1) تغيرات في الدورة الدموية وإفراز الناتج القليإ وإعادة توزيع تنفس ADH وANP (الدم الکوى) (2) اضطرابات غازات الدم التأثير على بعض الهرمونات ومنها الرنين الدوستيرون و (3) تغييرات في تقلص ADH وANP والتي تسبب في تقلص الكلى وإنخفاض معدل الترشيح الكبيبي مع قلة البول واحتباس السوائل.

كان الهدف من هذا البحث: دراسة تأثير التهوية بالضغط الإيجابي على الدوستيرون في المرضى على الحالات الحادة الذين يحتاجون لجهاز التنفس الصناعي.

وقد أجريت هذه الدراسة على 100 مريضًا تم حجزه بحجة العناية المركزة ووضعهم على جهاز التنفس الصناعي وقد قسموا إلى ثم سحب عينات الدم الوريدية من مولى المرضى عند وضعهم على جهاز التنفس الصناعي وبعد 22 ساعة من استخدام جهاز التنفس الصناعي. وقد قام تقييم الالدوستيرون باستخدام تقنيات المقاييس الشعاعية الصناعية.

أثبت النتائج: ارتفاع نسبة الالدوستيرون مع استخدام جهاز التنفس الصناعي وخاصة مع مستوى عال من الضغط الإيجابي.

وتلك من صلة ذات دلالة إحصائية بين قيم الالدوستيرون مع وظائف الكلى (اليرييونة والكرياتينيات) في المرضى الذين استخدموا جهاز التنفس الصناعي.

كما أن هناك ارتباط بين الالدوستيرون مع النتائج الأكليتيكية للمرضى مدة الإقامة في الرعاية المركزة.