VALUE OF CARBON DIOXIDE COMBINING POWER/POTASSIUM RATIO IN THE ETIOLOGICAL DIAGNOSIS OF CUSHING’S SYNDROME

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ABSTRACT

Introduction: There is currently no easy way to differentiate Cushing’s disease from the ectopic adrenocorticotropic hormone (ACTH) syndrome. Aim of this study was to evaluate value of carbon dioxide combining power/potassium (CO2CP/K) ratio in etiological diagnosis of Cushing’s syndrome.

Materials and methods: 226 patients with histologically confirmed Cushing’s syndrome were enrolled, and 100 people without any diseases were enrolled for comparison. All the clinical and laboratory data were collected by reviewing the electronic database in our hospital and were investigated. The receiver operating characteristic (ROC) curve was analyzed.

Results: Patients with Cushing’s disease had older age, longer disease courses and greater diastolic pressure than those with ectopic ACTH syndrome (P<0.05). Compared with ACTH independent syndrome, ACTH dependent syndrome had significantly (P<0.05) lower potassium (3.30±0.68 vs 3.58±0.62mmol/L) and chloride (101.8±5.2 vs. 104.3±4.2 mmol/L) but significantly (P<0.05) greater pH value, bicarbonate radicals, base excess, and CO2CP/K ratio (9.3±4.6 vs 7.5±2.4). Compared with patients with Cushing’s disease, patients with ectopic ACTH syndrome had significantly (P<0.05) lower potassium (2.33±0.54 vs. 3.42±0.59) and chloride (97.3±6.4 vs. 102.5±4.6 mmol/L) but significantly (P<0.05) greater pH value, bicarbonate radical, base excess, and CO2CP/K ratio (15.98±7.6 vs. 8.1±2.6). Analysis of the ROC curve with the ACTH dependent vs. independent syndrome demonstrated good diagnosis, with the cutoff point of the CO2CP/K ratio being 8.79, sensitivity of 0.46, specificity of 0.87 and AUC of 0.61. Analysis of the ROC curve with the ectopic ACTH syndrome vs. Cushing’s disease revealed good diagnosis, with the cutoff point of CO2CP/K ratio being 12.45, sensitivity of 0.65, specificity of 0.95 and AUC of 0.82.

Conclusion: Analysis of clinical and laboratory data of patients with Cushing’s syndrome and normal control subjects demonstrates that the CO2CP/K ratio is useful in differentiating Cushing’s disease from the ectopic ACTH syndrome with good sensitivity and specificity.

Keywords: Cushing’s syndrome, Hypokalemia, Etiology, Diagnosis, Adrenal gland neoplasms.

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Introduction

The clinical characteristics of Cushing’s syndrome are centripetal fat distribution, purple striae, proximal myopathy, hypertension, osteoporosis, hypokalemia and reduced linear growth with continued gain in weight in children1, 2. As a rare but severe disease, Cushing’s syndrome can cause significant morbidity and mortality if untreated or improperly addressed because of cardiovascular, metabolic and infectious complications3, 4. This syndrome is brought about by either excessive secretion of adrenocorticotropic hormone (ACTH, ACTH-dependent) or primary adrenal hypersecretion of glucocorticoids (ACTH-independent)5. About 85% of the Cushing’s syndrome are ACTH dependent (syndrome of ectopic adrenocorticotropic or pituitary adenoma) while approximately 15% are ACTH independent caused by presence of adrenal lesions (adenoma or carcinoma) or by primary bilateral adrenal cortical hyperplasia. The clinical presentation is greatly variable. Although the diagnosis can be straightforward in some obvious cases, setting up the correct diagnosis can be challenging in patients with mild hypercortisolism and
subtle clinical characteristics, especially in cases of symptom overlap in patients with and without the syndrome. For etiological diagnosis of the syndrome, it is even more difficult and usually involves biochemical, medical imaging and gene techniques which have many limitations in daily practice, thus necessitating simplified approaches clinically. Patients with Cushing’s syndrome usually have hypokalemia, however, the incidence of hypokalemia is different with different subtypes of the syndrome, with marked metabolic alkalosis of hypokalemia in ectopic ACTH-dependent syndrome and adrenal carcinoma. The characteristics of hypokalemic alkalosis are increased carbon dioxide combining power (CO\textsubscript{2}CP) and decreased blood potassium. Patients with different subtypes of Cushing’s syndrome have varied blood levels of potassium and CO\textsubscript{2}CP, and because the electrolyte examination is easy and can be performed in all hospitals, it is assumed that the ratio of CO\textsubscript{2}CP/blood potassium can be used to assist the etiological diagnosis of Cushing’s syndrome. In this study, we performed a retrospective analysis and comparison of patients with Cushing’s syndrome in our hospital for the evaluation of the role of the CO\textsubscript{2}CP/blood potassium ratio in the etiological diagnosis of Cushing’s syndrome.

Materials and methods

Subjects
A total of 226 patients with Cushing’s syndrome who had definite postsurgical or pathological diagnosis and complete laboratory data were enrolled in this study, including 52 male and 174 female patients with a mean age of 42.3±12.4 years. There were 85 cases of ACTH independent Cushing’s syndrome (ACTH independent group), including 67 (78.8%) cases with adrenocortical adenoma, 16 (18.8%) cases of large nodular adrenal hyperplasia, and 2 (2.4%) cases of adrenocortical adenocarcinoma. The rest 141 cases were ACTH dependent (ACTH dependent group), including 124 (87.9%) cases of Cushing’s disease and 17 (12.1%) cases of ectopic ACTH syndrome (EAS group). At the same period, 100 people without any diseases were also enrolled for comparison, including 50 males and 50 females with a mean age of 43.8±9.3 years. The age was matched between the patients with Cushing’s syndrome and the normal control people. The clinical data and laboratory data were collected by reviewing the electronic database of all the subjects and subsequently analyzed. This study was approved by the ethics committee of our hospital with written informed consent obtained from all patients.

Statistical analysis
The statistical analysis was performed by using the SPSS 17.0 software (IBM, Chicago, IL, USA) with all continuous data being expressed as mean ± standard deviation (SD). The student t test was used for comparison between the two groups. Receiver operating characteristic (ROC) curve analyses were performed to determine the sensitivity and specificity of the CO\textsubscript{2}CP/blood potassium ratio in the etiological diagnosis of Cushing’s syndrome. The statistical significance was set at P<0.05.

Results
No significant difference (P>0.05) existed in the clinical data between the ACTH dependent and independent groups (Table 1). Patients with Cushing’s disease had older age, longer disease courses and greater diastolic blood pressure than those with ectopic ACTH syndrome (P<0.05), but no significant difference (P>0.05) existed in the rest data (Table 2).

Compared with patients with ACTH independent syndrome, those with ACTH dependent syndrome had significantly (P<0.05) lower blood potassium (3.30±0.68 mmol/L vs 3.58±0.62 mmol/L) and chloride (101.8±5.2 vs. 104.3±4.2 mmol/L) but significantly (P<0.05) greater pH value (7.44±0.05 vs. 7.41±0.04), bicarbonate radical (27.6±5.7 vs. 25.2±3.1 mmol/L), base excess (1.20 vs. 0.70 mmol/L), and CO\textsubscript{2}CP/blood potassium ratio (9.3±4.6 vs 7.5±2.4) (Table 3).

In comparison with patients with Cushing’s disease, patients with ectopic ACTH syndrome had significantly (P<0.05) lower blood potassium (2.33±0.54 vs. 3.42±0.59) and chloride (97.3±6.4 vs. 102.5±4.6 mmol/L) but significantly (P<0.05) greater pH value (7.47±0.07 vs. 7.43±0.04), bicarbonate radical (30.5±9.3 vs. 26.8±4.3 mmol/L), base excess (5.00 vs. 0.80 mmol/L), and CO\textsubscript{2}CP/blood potassium ratio (15.98±7.6 vs. 8.1±2.6) (Table 3).

Analysis of the ROC curve with the ACTH dependent patients as the disease group and the ACTH independent patients as the control demonstrated good diagnosis, with the cutoff point of the CO\textsubscript{2}CP/blood potassium ratio being 8.79, a sensitivity of 0.46, a specificity of 0.87 and the area under curve (AUC) of 0.61 (Table 4 and Fig.1). Analysis of the ROC curve with the ectopic ACTH patients as the disease group and the Cushing’s disease patients as the control revealed good diagnosis, with the point of tangency of CO\textsubscript{2}CP/blood potassium ratio being 12.45, a sensitivity of 0.65, a specificity of 0.95 and the AUC of 0.82 (Table 4 and Fig.1).
Table 1: Clinical characteristics of 226 patients with ACTH dependent and independent Cushing’s syndrome (mean±standard deviation).

<table>
<thead>
<tr>
<th>Group</th>
<th>No.(M/F)</th>
<th>Age(y)</th>
<th>BMI(kg/m²)</th>
<th>SBP(mmHg)</th>
<th>DBP(mmHg)</th>
<th>FBG(mmol/L)</th>
<th>HbA1c (%)</th>
<th>TC(mmol/L)</th>
<th>TG(mmol/L)</th>
<th>HDL(mmol/L)</th>
<th>LDL(mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH independent</td>
<td>21/64</td>
<td>42.3±11.7</td>
<td>26.5±3.8</td>
<td>143±4.9</td>
<td>9.3±1.5</td>
<td>5.8±3.2</td>
<td>6.7±1.8</td>
<td>5.5±1.3</td>
<td>1.7±1.0</td>
<td>1.77±0.77</td>
<td>3.5±0.97</td>
</tr>
<tr>
<td>ACTH dependent</td>
<td>41/190</td>
<td>42.6±12.8</td>
<td>26.8±3.6</td>
<td>143±13.2</td>
<td>9.4±4.2</td>
<td>6.5±3.1</td>
<td>6.9±1.9</td>
<td>5.5±1.3</td>
<td>1.8±1.2</td>
<td>1.4±0.37</td>
<td>3.2±0.99</td>
</tr>
</tbody>
</table>

Note: ACTH, adrenocorticotropic hormone independent; ACTHD, adrenocorticotropic hormone dependent; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2: Clinical characteristics of 141 patients with ACTH dependent Cushing’s syndrome (mean±standard deviation).

<table>
<thead>
<tr>
<th>Group</th>
<th>No.(M/F)</th>
<th>Age(y)</th>
<th>BMI(kg/m²)</th>
<th>Course(m)</th>
<th>SBP(mmHg)</th>
<th>DBP(mmHg)</th>
<th>FBG(mmol/L)</th>
<th>HbA1c (%)</th>
<th>TC(mmol/L)</th>
<th>TG(mmol/L)</th>
<th>HDL(mmol/L)</th>
<th>LDL(mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>31/93</td>
<td>40.4±11.6</td>
<td>26.7±3.4</td>
<td>24(9.5, 46.0)</td>
<td>150±23</td>
<td>95±14</td>
<td>6.3±3.1</td>
<td>6.8±1.9</td>
<td>5.5±1.1</td>
<td>1.8±1.3</td>
<td>1.4±0.37</td>
<td>3.2±0.74</td>
</tr>
<tr>
<td>EAS</td>
<td>107</td>
<td>53.4±16.1</td>
<td>25.9±5.5</td>
<td>3(1.0, 16.0)</td>
<td>146±22</td>
<td>87±13</td>
<td>7.6±2.4</td>
<td>7.3±1.7</td>
<td>5.5±2.0</td>
<td>2.0±1.2</td>
<td>1.3±0.35</td>
<td>3.3±1.78</td>
</tr>
</tbody>
</table>

Note: CD, Cushing’s disease; EAS, ectopic ACTH syndrome; ACTH, adrenocorticotropic hormone; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 3: Electrolyte comparison of patients with ACTH dependent and independent Cushing’s syndrome (mean ± standard deviation).

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Potassium(mmol/L)</th>
<th>serum sodium (mmol/L)</th>
<th>Chloride (mmol/L)</th>
<th>CO₂CP(mmol/L)</th>
<th>pH</th>
<th>Bicarbonate radical(mmol/L)</th>
<th>BE*(mmol/L)</th>
<th>CO₂CP/K</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH independent</td>
<td>85</td>
<td>3.58±0.62(2.0-4.9)</td>
<td>144.1±3.3</td>
<td>104.3±4.2</td>
<td>27.6±3.2(22.0-44.2)</td>
<td>7.41±0.04</td>
<td>25.2±3.1</td>
<td>0.79±(1.20-2.50)</td>
<td>7.5±2.4(4.0-22.3)</td>
</tr>
<tr>
<td>ACTH dependent</td>
<td>141</td>
<td>3.3±0.68(1.4-5.2)</td>
<td>143.3±4.4</td>
<td>101.8±5.2</td>
<td>28.7±5.4(13.1-53.0)</td>
<td>7.44±0.05</td>
<td>27.6±5.7</td>
<td>1.20(0.73-5.03)</td>
<td>9.3±6.2(8.3-30.8)</td>
</tr>
</tbody>
</table>

Note: ACTH, adrenocorticotropic hormone; CD, Cushing’s disease; EAS, ectopic ACTH syndrome; ACTH, adrenocorticotropic hormone; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 4: Comparison of the point of tangency of the CO₂CP/K ratio with the ACTH dependent and EAS patients as the disease group.

<table>
<thead>
<tr>
<th>Disease group</th>
<th>CO₂CP/K point of tangency</th>
<th>AUC</th>
<th>95% CI</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Misdiagnosis rate</th>
<th>False negative rate</th>
<th>Youden index</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH independent vs dependent</td>
<td>8.79</td>
<td>0.61</td>
<td>0.52-0.70</td>
<td>0.46</td>
<td>0.87</td>
<td>12.9%</td>
<td>54.3%</td>
<td>0.33</td>
</tr>
<tr>
<td>CD vs EAS</td>
<td>12.45</td>
<td>0.82</td>
<td>0.68-0.95</td>
<td>0.65</td>
<td>0.95</td>
<td>4.7%</td>
<td>35.3%</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Note: ACTH, adrenocorticotropic hormone; CD, Cushing’s disease; EAS, ectopic adrenocorticotropic hormone syndrome; CO₂CP/K, carbon dioxide combining power/potassium; AUC, area under the receiver operating characteristic curve; CI, confidence interval.
Analysis of the data of patients with Cushing’s syndrome and normal control people demonstrated that the \( \text{CO}_2 \text{CP/blood potassium} \) ratio was significantly (\( P=0.000 \)) greater in patients with Cushing’s syndrome than the normal control people, with the reference range of the \( \text{CO}_2 \text{CP/blood potassium} \) ratio being 3.98-8.51 for healthy individuals but 2.8-30.8 for patients with Cushing’s syndrome (Table 3). The reference range of the \( \text{CO}_2 \text{CP/blood potassium} \) ratio was 4.9-22.3 for ACTH independent Cushing’s disease, 2.8-17.3 for ACTH dependent Cushing’s disease, and 3.7-30.8 for ACTH dependent ectopic ACTH syndrome.

Discussion

The annual incidence of Cushing’s syndrome in Europe is 2/million to 3/million, with a male to female ratio of 1:3\(^1\). Cushing’s syndrome is defined as a group of clinical signs and symptoms caused by hypercortisolism\(^9\). Cortisol excess may be exogenous or endogenous, with the commonest exogenous cause of glucocorticoid therapy over physiological doses used in various diseases\(^6\). Clinical diagnosis, evaluation and treatment of endogenous Cushing’s syndrome are a significant endocrine concern. Traditionally, endogenous Cushing’s syndrome is divided into ACTH dependent and independent syndrome. For the ACTH dependent Cushing’s syndrome, the commonest cause is an ACTH secreting pituitary adenoma which is defined as Cushing’s disease, probably causing approximately 70% of endogenous cases of the Cushing’s syndrome, and the second most common cause is ectopic ACTH syndrome which is caused by ectopic ACTH secretion by benign or malignant tumors, accounting for about 15%-20% of cases\(^4, 9, 10\). Small-cell carcinomas of the lung or pulmonary carcinoid tumors are most frequently the source of ectopic ACTH secretion, whereas other sources may include pancreatic and thymic neuroendocrine tumors, medullary thyroid cancer and pheochromocytoma\(^11\). ACTH-independent syndrome accounts for 15%-20% of endogenous Cushing’s syndrome with 90% of cases being unilateral adrenal tumors. Of the adrenal tumors, adenomas are the commonest cause (80%), whereas other causes are adrenocortical carcinoma in addition to some rare adrenal causes of Cushing’s syndrome including macronodular adrenal hyperplasia, primary pigmented nodular adrenal disease and McCune-Albright syndrome\(^12, 13\).

Diagnostic testing should be performed in patients suspected of Cushing’s syndrome, including screening in patients with other characteristics of the syndrome. It is also extremely important to differentiate pathological hypercortisolism of endogenous syndrome from those associated with pregnancy, glucocorticoid resistance and other pseudo-Cushing’s states including alcoholism, obesity, depression, bulimia and anorexia nervosa. The basic characteristics of elevated endogenous secretion of cortisol, loss of normal feedback of the hypothalamic-pituitary-adrenal axis, and loss of normal cortisol circadian rhythm are the bases for laboratory tests in this syndrome. The 2008 Endocrine Society guidelines stated that the following tests should be performed for the diagnosis of Cushing’s syndrome: 24-hour urinary free cortisol, late-night salivary cortisol, and/or a low-dose dexamethasone-suppression test\(^14\). However, none of these tests have 100% diagnostic accuracy, and multiple tests are needed to set up the correct diagnosis. Medical imaging is also necessary for correct diagnosis of tumors in different parts of the body including the pituitary and adrenal glands, the lung, pancreas, thyroid glands, etc.

A hallmark of the ectopic ACTH syndrome is hypokalemic alkalosis which may occur in more than 90% of the cases compared with 10% of the cases in other forms of Cushing’s syndrome\(^15, 16\). It has been reported that hypertension occurs in 80% of patients with Cushing’s syndrome and 95% of patients with ectopic ACTH syndrome\(^15, 16\). Hypokalemic alkalosis was found in 84.4%-100% of patients with ectopic ACTH syndrome\(^16, 17\). A study from China found that the incidence of hypokalemia was 44.9%, 32.3% and 100% in Cushing’s disease, adrenocortical ade-
noma and ectopic ACTH syndrome, respectively\(^{(18)}\). Hypokalemic alkalosis was severe in ectopic ACTH syndrome than in Cushing’s disease\(^{(15)}\). Our study was in consistent with the literature report. The mechanism of hypokalemic alkalosis was probably caused by high concentration of cortisol which saturated 11 ß-hydroxysteroid dehydrogenase (11-HSD)\(^{(16)}\). The relative insufficiency of 11-HSD and high concentration of ACTH inhibited 11-HSD, which causes combination of cortisol and mineralocorticoid to promote exchange of sodium and potassium at the distal convoluted renal tubule, finally resulting in hypokalemia and hypertension. Besides, different reaction of the renin-angiotensin-aldosterone system may also play a role in subtypes of Cushing’s syndrome\(^{(19)}\).

CO\(_2\)CP and serum potassium are the frequently tested parameters in clinical biochemistry, and our study revealed that the CO\(_2\)CP and serum potassium were different in different subtypes of Cushing’s syndrome. Compared with ACTH independent patients, the ACTH dependent patients had significantly lower serum potassium but higher CO\(_2\)CP/potassium ratio. However, the AUC was only 0.61, which limits the value of the CO\(_2\)CP/potassium ratio in differentiating diagnosis between ACTH dependent and independent Cushing’s syndrome.

Ectopic ACTH syndrome and Cushing’s disease are important elements of the ACTH dependent syndrome and have clinical symptoms difficult to differentiate, with a high risk of hypokalaeemia, especially for ectopic ACTH syndrome. Although the CO\(_2\)CP/potassium ratio was overlapped between health and diseased populations of Cushing’s syndrome, this ratio was valuable in differentiating ectopic ACTH syndrome and Cushing’s disease. The CO\(_2\)CP/potassium ratio was 15.98±7.6 (3.7-30.8) for ectopic ACTH syndrome, significantly (P=0.000) greater than 8.1±2.6 (2.8-17.3) for ACTH dependent Cushing’s disease. ROC analysis revealed that the cutoff point of the CO\(_2\)CP/potassium ratio was 12.45 which had the greatest Youden index and AUC of 0.82 close to 0.9, with the sensitivity of 0.65 and specificity of 0.95, suggesting a value of this cutoff point of CO\(_2\)CP/potassium ratio in differentiating diagnosis between ACTH dependent and independent Cushing’s syndrome.

Patients with Cushing’s syndrome frequently have hypopotassemia, but different subtypes of Cushing’s syndrome have different incidences of hypopotassemia, with a greater incidence of hypokalemic alkalosis in patients with ectopic ACTH syndrome or adrenal cortical adenocarcinoma. Hypokalemic alkalosis is characterized by increased CO\(_2\)CP and decreased blood potassium. Clinically, we found that different subtypes of Cushing’s syndrome have different blood potassium and CO\(_2\)CP. Thus, we made a hypothesis to use the ratio of CO\(_2\)CP/potassium for assisting diagnosis of Cushing’s syndrome. This ratio combines two parameters of CO\(_2\)CP and blood potassium and is better than either parameter. Moreover, electrolyte examination is easy to be performed in any hospitals, and CO\(_2\)CP/potassium ratio can be readily tested to differentiate Cushing’s disease from ectopic ACTH syndrome for many hospitals which cannot perform ACTH test, blood test from the inferior petrosal sinus and corticotropin releasing hormone stimulation test.

In summary, the carbon dioxide combining power/potassium ratio is useful in differentiating Cushing’s disease from ectopic ACTH syndrome with a good sensitivity and specificity.

\section*{References}


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