

Effects of Hyperventilation on Venous-Arterial Bicarbonate Concentration Difference: A Possible Pitfall in Venous Blood Gas Analysis

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ABSTRACT

Objectives: Recent reports on venous blood gas analysis have shown that venous bicarbonate concentration is useful in the evaluation of the body acid-base status. Most of these reports have been based on the Bland-Altman analysis comparing arterial and venous blood gas values. We intended to elucidate any factors that decrease the agreement between venous and arterial bicarbonate concentrations, which might impair the usefulness of venous blood gas analysis. **Methods:** Healthy volunteers and patients with various diseases ($n = 141$) were evaluated by simultaneous arterial and venous blood sampling and Bland-Altman analysis. The venous-arterial bicarbonate concentration difference was compared between healthy volunteers and untreated respiratory alkalosis patients. Intentional hyperventilation (30 or 60 breaths/min, for 3 min) was also performed on 6 healthy volunteers and the venous-arterial bicarbonate concentration difference was evaluated. **Results:** The relative average bias in bicarbonate concentration was 2.00 mEq/l with venous bicarbonate higher than arterial bicarbonate with 95% limits of agreement of ± 4.15 mEq/l. Hyperventilation challenges increased the venous-arterial bicarbonate concentration difference in an intensity-dependent manner. The venous-arterial bicarbonate concentration difference was higher in untreated respiratory alkalosis patients than in healthy volunteers ($P < 0.01$). **Conclusion:** Although venous bicarbonate may be useful to evaluate the body acid-base status, hyperventilation increases the venous-arterial bicarbonate concentration difference. Physicians should keep this phenomenon in mind.

KEYWORDS

Hyperventilation; Bicarbonate; Bland-Altman Analysis; Venous Blood Gas Analysis

1. Introduction

Since the pulse oximeter was invented and it became possible to evaluate the systemic oxygen level by measuring percutaneous oxygen saturation (SpO_2), peripheral venous blood gas analysis (VBGA) with simultaneous SpO_2 measurement has been considered useful as an alternative to arterial blood gas analysis (ABGA) [1-3]. Indeed, physicians are now widely and even routinely performing VBGA with SpO_2 measurement instead of sampl-

ing arterial blood, because VBGA is much easier and less invasive than ABGA especially in the youngest pediatric patients and in an emergency room. The agreement between variables on arterial and venous blood gas analysis has been well reviewed [1]. The usual method to evaluate the agreement has been with the Bland-Altman analysis [4].

Previously we reported that intentional hyperventilation increased venous-arterial partial CO_2 pressure (PCO_2) differences and pH differences [2]. We also reported that underestimation of respiratory alkalosis may occur with the “ SpO_2 plus VBGA” method in untreated

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respiratory alkalosis patients [2]. Here we evaluated the agreement in venous-arterial bicarbonate concentration ($[\text{HCO}_3^-]$) measurements by the Bland-Altman analysis. The effects of intentional hyperventilation on the venous-arterial HCO_3^- difference were also evaluated. In addition, the differences in healthy volunteers and in untreated respiratory alkalosis patients were also compared.

2. Methods

2.1. Subjects

The present study was approved by the Ethics Committees at Ohtawara Red Cross Hospital and the International University of Health and Welfare. 141 subjects (95 males and 46 females, ranging from 16 to 91 years of age) were enrolled in this study after we obtaining their informed consent. Among these 141 subjects, 11 healthy volunteers and 130 patients with various diseases were included. Among these 130 patients, 13 patients with hyperventilation with $\text{PaCO}_2 < 35$ mmHg and arterial pH (pHa) > 7.45 without the treatment such as a paper bag re-breathing maneuver were included.

2.2. Blood Sampling and Gas Analysis

The brachial artery and the median vein were used for the blood sampling. Arterial and venous blood was sampled simultaneously with a small (1 ml) syringe containing heparin, and was immediately analyzed with an automatic blood gas analyzer (Rapidlab 840, Bayer Healthcare, Leverkusen, Germany, or Rapidlab 1265, Siemens Healthcare Diagnostics, Sudbury, United Kingdom). Blood sampling from healthy volunteers was done first at rest and then immediately after hyperventilation. The venous-arterial $[\text{HCO}_3^-]$ difference is hereafter termed $(v-a)[\text{HCO}_3^-]$. End-tidal PCO_2 (P_{ETCO_2}) was measured with a gas analyzer (Respina IH26, NEC San-ei, Tokyo, Japan) [5].

Bicarbonate concentration was calculated by the following equation:

$$[\text{HCO}_3^-] = 0.0307 \times \text{PCO}_2 \times 10^{(\text{pH}-6.105)}$$

2.3. Protocols of Loading Maneuvers

In order to look at the effects of hyperventilation, the subjects breathed room air at a fixed rapid rate for 3 min. The breathing rate was changed from resting (11 - 20 times per min) to 30 and then to 60 times per min. The timing of breathing was announced by a time keeper and the subjects followed his voice. The subjects were requested to keep the same tidal volume so that the P_{ETCO_2}

was 30 ± 2 and 22 ± 2 mmHg during the 30 and 60 breaths/min hyperventilation maneuvers, respectively.

2.4. Statistical Analysis

Values are expressed as mean \pm standard deviation unless indicated. We tested the linear correlation for the bicarbonate difference between ABGA and VBGA by the Spearman rank method, and compared the differences by Bland-Altman analysis [4]. We used an analysis of variance with a Fisher post hoc multiple comparison for the evaluation of repeated measures between resting and intentional hyperventilation. An unpaired *t*-test (two-tail) was used for the comparison between healthy volunteers and patients. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Arterial and Venous Bicarbonate Concentration at Rest

The arterial and venous HCO_3^- data at rest ($n = 141$) are plotted in **Figure 1**. Data for both healthy volunteers and various patients are included. The relationship between the ABGA and VBGA was close for $[\text{HCO}_3^-]$ ($r = 0.897$, $P = 3.85 \times 10^{-51}$, **Figure 1(a)**). Bland-Altman plots are shown in **Figure 1(b)**. The relative average bias of $[\text{HCO}_3^-]$ was 2.00 mEq/l with venous $[\text{HCO}_3^-]$ higher than arterial $[\text{HCO}_3^-]$ and 95% limits of agreement of ± 4.15 mEq/l.

3.2. Effects of Intentional Hyperventilation on Venous-Arterial Bicarbonate Concentration Difference

In the resting condition, $(v-a)[\text{HCO}_3^-]$ was 1.73 ± 1.71 mEq/l ($n = 6$, **Figure 2**). Hyperventilation challenges increased $(v-a)[\text{HCO}_3^-]$ in an intensity-dependent manner.

3.3. Venous-Arterial Bicarbonate Concentration Difference in Patients with Hyperventilation

The $(v-a)[\text{HCO}_3^-]$ data from healthy volunteers and from patients with untreated respiratory alkalosis ($\text{PaCO}_2 < 35$ mmHg and $\text{pH} > 7.45$) are shown in **Figure 3**. It was found that $(v-a)[\text{HCO}_3^-]$ was larger in the untreated patients ($P = 0.0024$).

4. Discussion

A meta-analysis and a review using Bland-Altman analysis reported that venous pH, bicarbonate and base excess

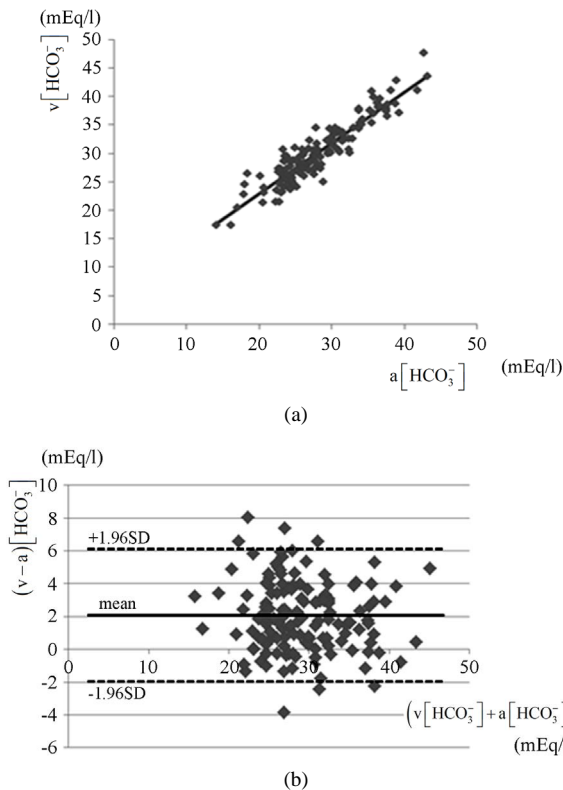


Figure 1. Blood gas data of healthy volunteers and patients with various diseases at rest ($n = 141$). (a) Relationship between arterial bicarbonate concentration ($a[\text{HCO}_3^-]$) and venous bicarbonate concentration ($v[\text{HCO}_3^-]$) is shown. $v[\text{HCO}_3^-] = 0.891 \times a[\text{HCO}_3^-] + 5.08$; $r = 0.897$, $P = 3.85 \times 10^{-51}$. There was a close correlation between $a[\text{HCO}_3^-]$ and $v[\text{HCO}_3^-]$. (b) Bland-Altman plots of $[\text{HCO}_3^-]$ data. Mean differences between arterial and venous data as well as 95% limits of agreement are shown. We cannot clearly say that the 95% limits of agreement are clinically very important, therefore we may be able to use $v[\text{HCO}_3^-]$ and $a[\text{HCO}_3^-]$ interchangeably considering the average difference.

have sufficient agreement to be clinically interchangeable for arterial values for patients in the emergency department [1,3]. On the other hand, agreement between arterial and venous PCO_2 has been reported to be too poor and unpredictable in clinical usage as a one-off test, and PCO_2 might be useful to screen for arterial hypercarbia or monitor trends in PCO_2 for selected patients.

In untreated hyperventilation patients, we reported that the “VBGA plus SpO_2 ” method may lead to underestimation or misdiagnosis of respiratory alkalosis [2]. We speculated that the phenomenon could be attributed to the increase in the differences in venous-arterial PCO_2 and pH in the acute phase of hyperventilation. We also

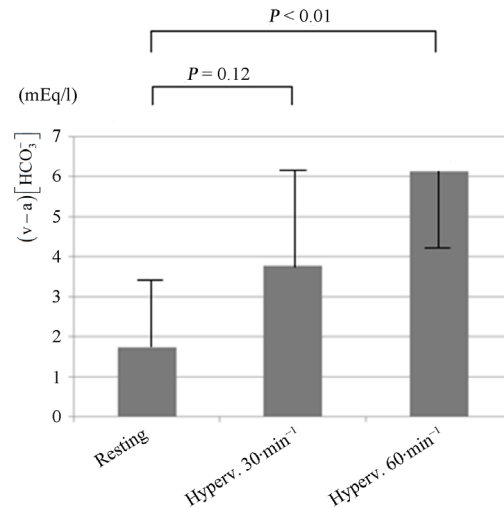


Figure 2. Intensity-response relationship between the level of hyperventilation and the venous-arterial bicarbonate concentration difference ($(v-a)[\text{HCO}_3^-]$). The breathing rate was changed from resting (11 - 20 times per min) to 30 and then to 60 times per min. Hyperventilation (Hyperv.) increased $(v-a)[\text{HCO}_3^-]$ in an intensity-dependent manner ($n = 6$). Error bars: SD.

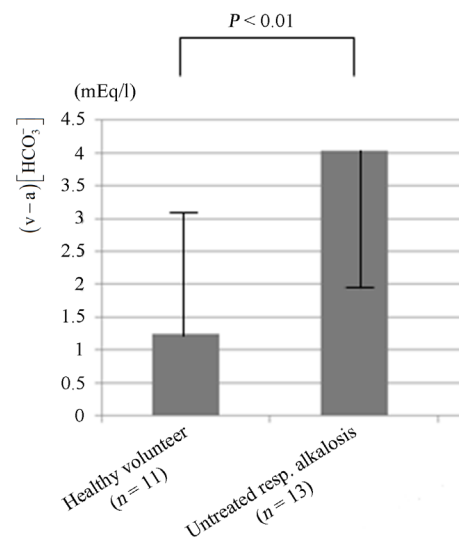


Figure 3. The venous-arterial bicarbonate concentration difference ($(v-a)[\text{HCO}_3^-]$) data in patients with hyperventilation. $(v-a)[\text{HCO}_3^-]$ data were compared between healthy volunteers ($n = 11$) and untreated respiratory alkalosis patients ($n = 13$). In untreated respiratory alkalosis patients, $(v-a)[\text{HCO}_3^-]$ was increased ($P = 0.0024$). Error bars: SD.

speculated that the increases in these differences are due to the reduction of peripheral blood perfusion which was induced by hyperventilation-associated systemic vaso-

constriction. Other reported factors that affect the differences in venous-arterial PCO₂ and pH are finger exercise and hypotension [2,6].

Here we evaluated $(v-a)[\text{HCO}_3^-]$ in hyperventilation and found that $(v-a)[\text{HCO}_3^-]$ increases after the 3 min hyperventilation challenge in an intensity-dependent manner (Figure 2). $(v-a)[\text{HCO}_3^-]$ also increased in untreated respiratory alkalosis patients (Figure 3). The time course of $(v-a)[\text{HCO}_3^-]$ after hyperventilation has not been well studied. Nevertheless, we suppose that $(v-a)[\text{HCO}_3^-]$ is increased in the acute phase of hyperventilation (in the same time of developing respiratory alkalosis), but $(v-a)[\text{HCO}_3^-]$ might decrease more swiftly than the normalization of respiratory alkalosis in arterial blood gas data. We experienced some already treated respiratory alkalosis patients using a paper-bag rebreathing maneuver without an increase in $(v-a)[\text{HCO}_3^-]$ (data not shown). Further investigation is needed to confirm this.

As for the Bland-Altman analysis data, our results for $[\text{HCO}_3^-]$ are similar to previous reports [7-9] (Table 1). The authors wrote that the agreement was acceptably narrow. Nevertheless, we feel that the 95% limits of agreement of ± 5.05 mEq/l [9] are not so narrow. We

Table 1. Previously reported Bland-Altman analysis data comparing arterial and venous $[\text{HCO}_3^-]$.

Authors	The relative average bias of $[\text{HCO}_3^-]$	95% limits of agreement	Subjects	Reference
Kelly <i>et al.</i>	1.2 mEq/l with venous $[\text{HCO}_3^-]$ higher than arterial $[\text{HCO}_3^-]$	± 3.93 mEq/l	Various patients at emergency department	[7]
Herrington <i>et al.</i>	0	± 1.3 mEq/l	Critically ill patients	[8]
Malatesha <i>et al.</i>	0.74 mEq/l with venous $[\text{HCO}_3^-]$ higher than arterial $[\text{HCO}_3^-]$	± 5.05 mEq/l ($\pm 2\text{SD}$)	Various patients at emergency department	[9]
Middleton <i>et al.</i>	0.19 mEq/l with "central" venous $[\text{HCO}_3^-]$ higher than arterial $[\text{HCO}_3^-]$	± 2.08 mEq/l	Intensive care unit patients	[10]

cannot clearly say that our data of 95% limits of agreement of ± 4.15 mEq/l are narrow or not narrow (important or not important). Our feeling is intermediate on this. Anyway, peripheral venous $[\text{HCO}_3^-]$ seems to be useful.

As for the comparison between the arterial blood and "central" venous blood, Middleton *et al.* reported similar data [10] (Table 1).

Our report is the first that addresses how hyperventilation increases the difference between arterial and venous bicarbonate concentration. Physicians should keep this phenomenon in mind when performing venous blood gas analysis.

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