

## Effect of Chronic Furosemide Administration on Acid-base Balance in Patients with Chronic Hypercapnic Respiratory Failure

Tetsuya URANO, Tetsuri KONDO, Kei-ichi OH-HORI\*, Miho KUMAGAI, Akira MIYAIRI\* and Yasuyo OHTA

*Department of Medicine, Tokai University School of Medicine,*  
*\*Department of Medicine, Kyoundo-Hiratsuka Hospital*

(Received August 19, 1998; Accepted August 20, 1998)

We quantitatively analyzed the effect of long-term administration of oral furosemide on the PaCO<sub>2</sub> - H<sup>+</sup> relationship in patients with chronic hypercapnic respiratory failure. In this study we measured arterial blood gases of eighteen outpatients (mean duration of visits, 7.6 years; mean rise of PaCO<sub>2</sub>, 15.4 mmHg). We obtained linear regression lines for PaCO<sub>2</sub> - H<sup>+</sup>, and determined their Y-axis intercepts and slopes. The results indicated that an increase in the administered dose of furosemide decreased linearly the Y-axis intercept of the regression line [(Y-intercept) = -6.9(dose of furosemide) + 30.9, r = 0.81], and increased linearly the slope of the regression line [(slope) = 0.094(dose of furosemide) + 0.22, r = 0.74]. Thus, the regression line of the PaCO<sub>2</sub> - H<sup>+</sup> relationship moved downward and became steeper at higher doses of furosemide. The regression lines for each dose of furosemide crossed at a PaCO<sub>2</sub> of 75 mmHg. We concluded that there is a mutual interaction between the renal and respiratory mechanisms for acid-base balance in chronic hypercapnia and the effect of furosemide on the PaCO<sub>2</sub> - H<sup>+</sup> relationship is negligible in severe hypercapnia.

**Key words :** Chronic hypercapnia, Arterial blood gas, PaCO<sub>2</sub> - H<sup>+</sup> relationship

### INTRODUCTION

Acid-base balance in acute and chronic respiratory acidosis has been intensively investigated both in experimental animals [6] and in patients with chronic respiratory failure [8]. Although the pH of arterial blood is ameliorated in chronic respiratory acidosis by increases in bicarbonate and other buffer bases, such renal compensation is not achieved in chronic respiratory failure [6, 8]. Many of the patients with chronic respiratory failure are administered oral furosemide [5] which may produce metabolic alkalosis [2]. When we encounter a patient with chronic hypercapnic respiratory failure who has been prescribed oral furosemide, quantitative prediction of arterial H<sup>+</sup> is difficult.

In experimental animals, the PaCO<sub>2</sub> - H<sup>+</sup> relationship in chronic hypercapnia is obtained by inhalation of CO<sub>2</sub>-rich gas with stepwise increases every few weeks [6]. In contrast, in clinical investigations, the PaCO<sub>2</sub>

- H<sup>+</sup> relationship has been obtained by collection of arterial blood gas data from hundreds of patients [3, 8]. We measured arterial blood gases of patients with chronic respiratory failure, whose prescription had not been changed, whose body weight had been stable and whose PaCO<sub>2</sub> had risen gradually over several years. This situation was quite similar to the animal study.

### SUBJECTS AND METHODS

Patients who satisfied the following criteria were collected from the clinical records of Kyoundo-Hiratsuka Hospital: 1) the patient had regularly visited the outpatient clinic for at least 2.5 years, 2) if furosemide had been prescribed in this period, its dose had not been changed, 3) arterial blood gases had been analyzed regularly, 4) PaCO<sub>2</sub> had increased by at least 8 mmHg during the study period, 5) PaO<sub>2</sub> was between 60 and 105 mmHg in each sample, and 6) serum creatinine was within normal range.

We found records of eighteen patients satisfying these criteria. For each of the patients, a linear regression line of the PaCO<sub>2</sub> - H<sup>+</sup> relationship was obtained using the arterial blood gas data.

## RESULTS

Table 1 shows the patient characteristics. The underlying disorders of chronic respiratory failure were pleural adhesion due to tuberculosis (n=8), pulmonary emphysema (n=7) and bronchiectasis (n=3). Furosemide had been chronically prescribed to ten patients and no furosemide had been prescribed in eight patients. The mean study period was 7.6 years (range: 2.5 - 17 years) and the mean frequency of blood gas analysis was 68 times (range: 21 - 133 times). The mean PaCO<sub>2</sub> at the onset of the study was 47.1 ± 4.7 (mean ± SD) mmHg and that at the end of the study was 62.5 ± 5.8 mmHg. We obtained eighteen linear regression lines of the PaCO<sub>2</sub> - H<sup>+</sup> relationship of the subjects and determined Y-axis intercepts and the slopes of the regression lines. Mean serum K<sup>+</sup> was lower in furosemide patients (mean, 4.0 mEq/l) but it was not significantly different from that of furosemide-free patients (mean, 4.2 mEq/l).

Fig. 1 shows Y-axis intercepts (Fig. 1A) and slopes (Fig. 1B) of the regression lines with respect to the prescribed doses of

furosemide (mg/kg). The Y-axis intercept decreased linearly with increases in the prescribed furosemide dose (Fig. 1A) [(Y-intercept) = -6.9(dose of furosemide) + 30.9, r = 0.81, P < 0.0001]. The slope of the regression lines increased with an increase in the dose of furosemide (Fig. 1B) [(slope) = 0.094(dose of furosemide) + 0.22, r = 0.74, P < 0.0001]. These findings suggest that the linear regression line representing the PaCO<sub>2</sub> - H<sup>+</sup> relationship moves downward and becomes steeper at higher doses of oral furosemide.

Fig. 2 shows the PaCO<sub>2</sub> - H<sup>+</sup> relationship calculated from the parameters in Fig. 1. Arterial H<sup>+</sup> at a PaCO<sub>2</sub> of 40 mmHg is estimated to be 38.9 nmol/l if furosemide is not prescribed, and it is 31.6 nmol/l if the patient is treated with 1.0 mg/kg furosemide. This indicates that long term furosemide administration causes mild metabolic alkalosis. In severe hypercapnia, e.g., PaCO<sub>2</sub> = 75 mmHg, the difference between H<sup>+</sup> of the furosemide treatment period and that of the furosemide-free period becomes almost the same. In other words, metabolic alkalosis produced by long-term furosemide therapy is negligible in severe hypercapnia.

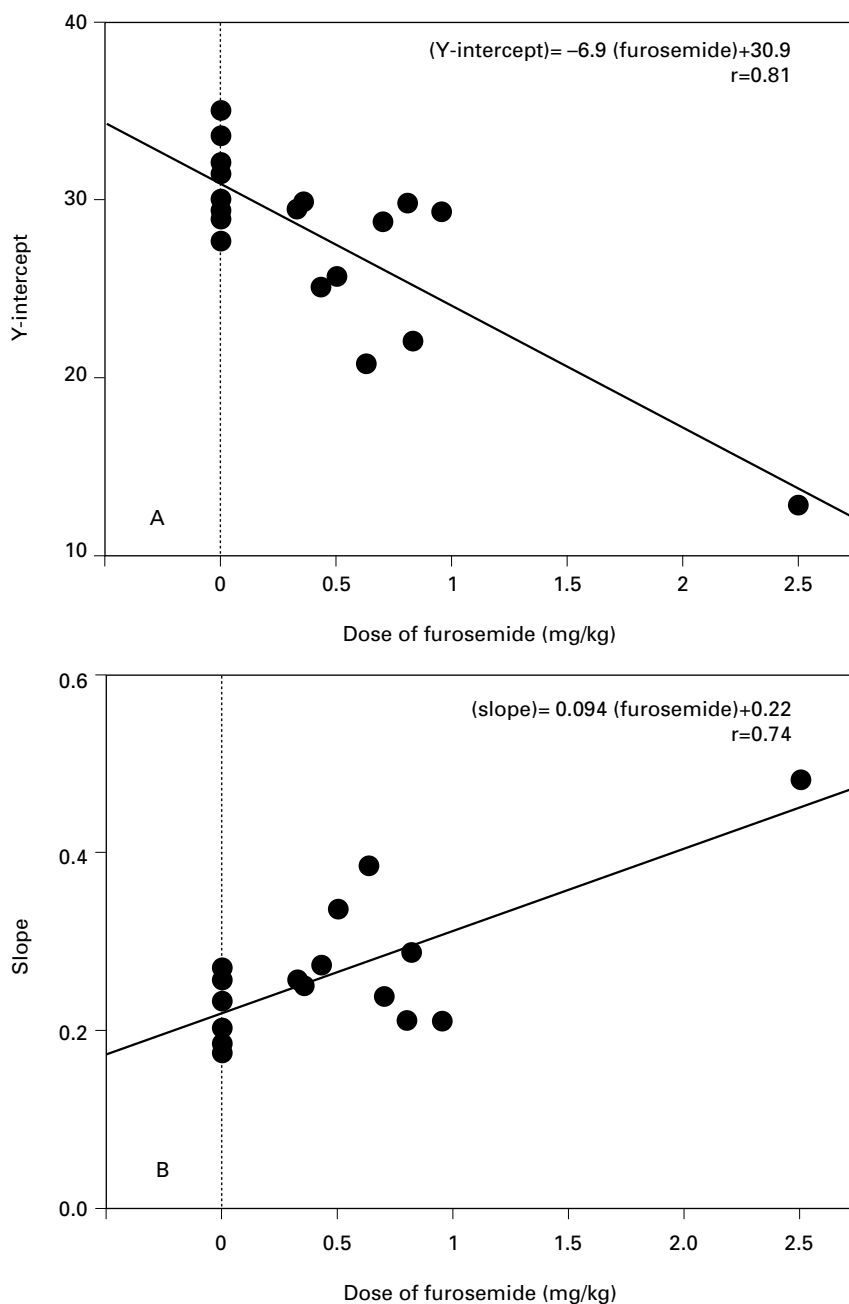
## DISCUSSION

We quantitatively analyzed the effect of long-term furosemide administration on the linear regression line of the PaCO<sub>2</sub> - H<sup>+</sup> rela-

**Table 1** Characteristics of the subjects expressed by mean values (SD)

	furosemide (n=10)	furosemide-free (n=8)
Age (y.o.)	66.3 (12.4)	63.0 (9.4)
Study period (yr)	7.3 (3.6)	9.9 (5.7)
Blood samples (times)	71.9 (26.0)	60.6 (46.9)
Na (mEq/l)	140.1 (1.6)	140.3 (2.6)
K (mEq/l)	4.1 (0.4)	4.2 (0.4)
Cl (mEq/l)	93.9 (4.9)	98.1 (4.5)
Creatinine (mg/dl)	0.91 (0.17)	0.69 (0.17)
Start *-PaCO <sub>2</sub> (mmHg)	48.8 (3.5)	44.7 (5.3)
End **-PaCO <sub>2</sub> (mmHg)	63.9 (5.6)	60.4 (5.9)

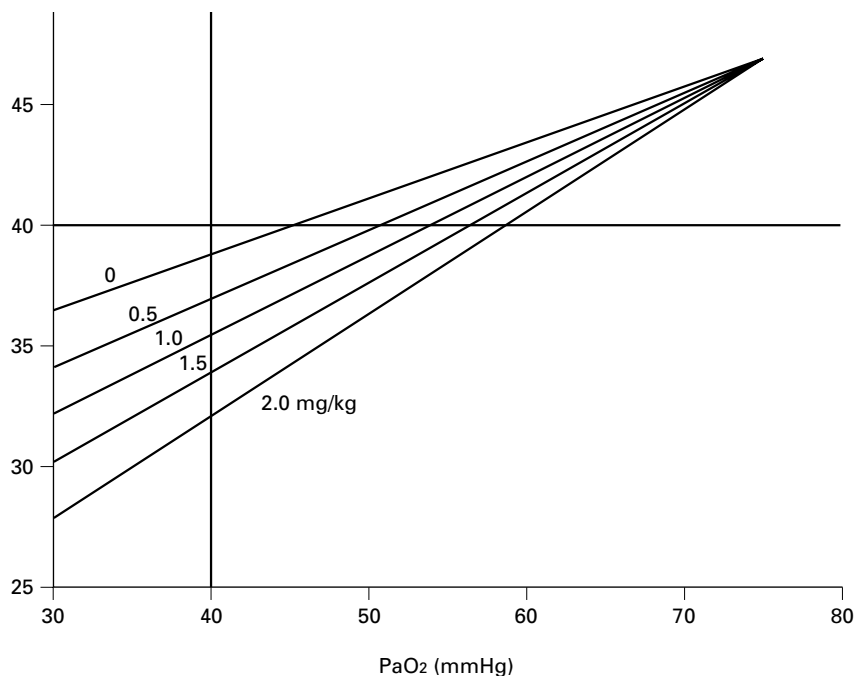
\* Start: start of study period, \*\* End: end of study period



**Fig. 1** (A) Relationship between Y-axis intercepts of the linear regression lines of the PaCO<sub>2</sub> - H<sup>+</sup> relationship and the prescribed doses of furosemide (mg/kg). (B) Relationship between slopes of the linear regression lines of the PaCO<sub>2</sub> - H<sup>+</sup> relationship and the prescribed doses of furosemide (mg/kg).

tionship. We found that the regression line was not shifted in parallel by furosemide administration but its slope was changed. This finding suggests that there is mutual

interaction between the renal and respiratory mechanisms for acid-base compensation. Chronic respiratory acidosis changes renal excretion of HCO<sub>3</sub><sup>-</sup> [6]. On the other hand,



**Fig. 2** A computer simulation of the  $\text{PaCO}_2$  -  $\text{H}^+$  relationship at different doses (0, 0.5, 1.0, 1.5, 2.0 mg/kg) of furosemide. The parameters for simulation were obtained from the regression lines in each patient.

Madias *et al.* [4] reported that minute ventilation in the dog with chronic metabolic alkalosis decreased in proportion to increases in arterial  $\text{HCO}_3^-$ . When the dose of the prescribed furosemide is higher, the induced metabolic alkalosis becomes severer and may reduce ventilation. The reduced ventilation may cause a secondary increase in arterial  $\text{H}^+$  which makes the slope of the  $\text{PaCO}_2$  -  $\text{H}^+$  relationship become steeper. Furosemide may induce metabolic alkalosis by several other mechanisms such as extracellular fluid depletion or electrolyte imbalance [7]. However, extracellular fluid depletion has a significant role only in rapid excretion of edematous fluid. Electrolyte imbalance may not be significant in our study. Aquino and Luke [1] reported that respiratory compensation for metabolic alkalosis was the same when alkalosis was induced by selective  $\text{K}^+$  depletion or  $\text{Cl}^-$  depletion in rats.

The  $\text{PaCO}_2$  -  $\text{H}^+$  relationship in furosemide-free subjects (i.e.,  $\text{H}^+ = 0.22\text{PaCO}_2 + 30.9$ ) obtained from this longitudinal human study was similar to that obtained from a longitudinal animal study (Schwartz

[6],  $\text{H}^+ = 0.32\text{PaCO}_2 + 26.9$ ) or another study on human subjects (Ypersele [8],  $\text{H}^+ = 0.30\text{PaCO}_2 + 26.8$ ; and Engel [3],  $\text{H}^+ = 0.126\text{PaCO}_2 + 35.2$ ). With increases in the prescribed dose of furosemide the regression line move downward and became steeper. As a result, the downward shift was less in severe hypercapnia, when long-term furosemide had no effect on the  $\text{PaCO}_2$  -  $\text{H}^+$  relationship.

In conclusion, the  $\text{PaCO}_2$  -  $\text{H}^+$  relationship in chronic hypercapnic respiratory failure may be modified by long-term administration of furosemide, but its effect can be disregarded in severe hypercapnia.

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