EFFECT OF THE ACUTE ADMINISTRATION OF SODIUM BICARBONATE ON RESPIRATION IN THE PRESENCE OF HYPEROXIA

T. NISHINO, N. HATA, Y. SAKAKIBARA AND Y. HONDA

SUMMARY

The effects of the acute administration of sodium bicarbonate on respiration were studied in 10 normal subjects. Carbon dioxide response curves and tidal volume vs. $P_{CO_2}$ relationships were obtained under hyperoxic conditions using a closed-circuit breathing system. During alkalosis, a decrease in the slope, and a displacement of the response curves to the right, were observed. These findings indicate that metabolic alkalosis, induced acutely by the administration of sodium bicarbonate, alters the respiratory response to carbon dioxide and that sodium bicarbonate may have a depressant effect on respiration.

Although sodium bicarbonate (NaHCO$_3$) is administered commonly to patients with metabolic acidosis to correct the acid–base disturbance, its effect on respiration is far from clear. Mithoefer, Karetzky and Porter (1968) found no ventilatory depression after the i.v. administration of sodium bicarbonate. However, hypoventilation in patients with metabolic alkalosis has been reported recently (Tuller and Mehdi, 1971; Steer et al., 1972; Perez-Guerra, 1974). In order to study adequately the effects of drugs on respiration, the respiratory response to carbon dioxide (CO$_2$) should be assessed. Katsaros and others (1960) reported that the CO$_2$ response curve was shifted to the right during alkalosis, whereas Goldring and others (1968) noted that metabolic alkalosis induced by buffers (sodium bicarbonate, THAM) was associated with alveolar hypoventilation and a diminished ventilatory response to CO$_2$ (decrease in slope and shift of the CO$_2$ response curve). However, such results were obtained during chronic alkalosis and, as there are few reports of the effect of acutely induced metabolic alkalosis, the present study investigated the effect on the CO$_2$ response curve of acutely induced metabolic alkalosis produced by the administration of NaHCO$_3$. Although the ventilatory response to CO$_2$ is considered most often to be essentially linear, the respiratory response to low concentrations of inspired CO$_2$ may be curvilinear in some subjects (Lambertsen et al., 1953). In Goldring's report and that of Katsaros, the number of points of ventilation for varying $P_{CO_2}$ which were plotted to obtain the response curve seem to be insufficient to assess the ventilatory response curve precisely. We believe that many parameters of the curve are necessary. It is necessary also to repeat the test under hyperoxic conditions to exclude any hypoxic respiratory response.

METHOD

Ten normal human subjects (age range 19–49 yr) were studied in the supine position. Their weights ranged from 57 to 72 kg. All were in good health and were free of pulmonary disease. All studies were performed in the morning following overnight starvation. Each subject rested on a chair in the recumbent position for 30 min before the first arterial sample of blood was withdrawn through an indwelling catheter which had been inserted 1 h before the start of the experiment, under local anaesthesia. During cannulation no subject complained of pain, discomfort or anxiety nor was there evidence of hyperventilation. Each subject breathed from a closed-circuit system (fig. 1) incorporating an infra-red carbon dioxide analyser (Capnograph–Godart), a $P_{O_2}$ electrode (Radiometer) and a 9-litre spirometer (Aika). End-tidal air was sampled by a device based on that reported by Severinghaus and Hamilton (1970). The $P_{O_2}$ electrode, which was covered with 6.25-μm Teflon membrane and responded rapidly (95% in 1 s), was inserted in the chamber of the end-tidal sampler. Thus breath-by-breath end-tidal $P_{O_2}$ ($P_{E'O_2}$) was recorded continuously. End-tidal $P_{CO_2}$ ($P_{E'CO_2}$) was recorded continuously also by the infra-red CO$_2$ analyser to which the air in the respiratory valve was sampled at a flow rate of 2–3 litre/min. Equal proportions of oxygen and nitrogen were admitted to the
FIG. 1. The closed circuit. The subject is connected to the closed circuit and the desired value of $P_{E}CO_{2}$ and $P_{E}O_{2}$ is obtained by changing the bypass flow and by controlling the gas flow of $N_{2}$ and $O_{2}$.

circuit. By changing the proportions, it was possible to adjust $P_{E}O_{2}$ accurately. $P_{E}CO_{2}$ was altered by adjusting the valve which controlled the proportion of gas bypassing the $CO_{2}$ absorber in the expiratory line. $P_{E}CO_{2}$ was increased by 0.5-kPa* steps to the limits of the subjects' tolerance. The $PO_{2}$ electrode and infra-red $CO_{2}$ analyser were calibrated several times during each experiment by introducing known concentrations of carbon dioxide and oxygen which had been analysed previously using a Schölander apparatus. To obtain the $CO_{2}$ response curve, $P_{E}CO_{2}$ was controlled by changing the bypass flow in the circuit. After each change of the bypass flow, it usually took 6-10 min to attain a stable $P_{E}CO_{2}$ and steady-state ventilation. The spirogram was then recorded for 2 min; seven graphs of ventilation were recorded for each end-tidal $P_{E}CO_{2}$. After obtaining the control data, sodium bicarbonate 0.3-0.5 mmol/kg orally was administered with orange juice and 20 min later 2 mmol/kg (in 7% solution) was given i.v. over 10 min. A second blood sample was obtained 20 min after completion of this infusion. Immediately after taking the second sample, the subject was connected to the closed circuit and the ventilatory response was measured again. The subject then breathed room air at rest for 10 min and the third blood sample was taken.

On another day a control experiment using a 0.9% saline solution (5 ml/kg) instead of sodium bicarbonate was performed on three of the 10 subjects. During this experiment, four blood samples were taken from each subject through an indwelling catheter: after 30 min rest on a chair (first sample), immediately before the infusion of the saline solution (second

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* 1 kPa = 7.5 mm Hg.
sample), 20 min after completion of the saline infusion (third sample) and 10 min after completion of the CO\textsubscript{2} response test (fourth sample). The total time required to obtain each response curve was approximately 90 min and PE\textsubscript{CO\textsubscript{2}} was maintained in the range 24.0–26.7 kPa throughout this period. Pa\textsubscript{O\textsubscript{2}} and arterial pH were measured by a Radiometer blood-gas analyser (BMS 2 MK2) immediately after sampling. The total plasma CO\textsubscript{2} concentration was measured by the micro Van Slyke method (Van Slyke and Plazin, 1961). Pa\textsubscript{CO\textsubscript{2}} and the bicarbonate concentration (HCO\textsubscript{3}) were calculated by using the conversion factors of Austin from the pH and the total plasma CO\textsubscript{2} concentration (Austin, 1965).

The CO\textsubscript{2} response curve and the P\textsubscript{CO\textsubscript{2}} v. tidal volume curve were obtained by linear regression analyses of the minute volume changes in relation to changes in PE\textsubscript{CO\textsubscript{2}}. The minute volume and the tidal volume are presented as litre/min. m~2~.

Blood-gas analyses

There were no significant changes in pH, Pa\textsubscript{CO\textsubscript{2}}, Pa\textsubscript{O\textsubscript{2}} and HCO\textsubscript{3} before and after the infusion of normal saline. Marked changes were noted after administration of sodium bicarbonate (fig. 2, table I).

In the group receiving sodium bicarbonate the arterial pH of the first blood sample (control) was 7.390 (SD 0.014) and that of the second sample (20 min after NaHCO\textsubscript{3} infusion) was 7.487 (SD 0.016) (P<0.01). pH of the third sample (10 min after completion of the experiment) was 7.477 (SD 0.013) and this was significantly different from the control value (P<0.01), but there was no significant difference between the second and the third samples. Pa\textsubscript{O\textsubscript{2}} decreased slightly in the second and the third samples from the control value and there was a significant difference between the control value and the values during alkalosis (P<0.05), but no significant difference between the second and the third blood samples occurred. Pa\textsubscript{CO\textsubscript{2}} increased after the administration of NaHCO\textsubscript{3} from 4.90 (SD 0.25) kPa (control) to 5.17 (SD 0.28) kPa (the second sample), and 5.53 (SD 0.46) kPa (the third sample). There were significant differences between the control and the second sample (P<0.05), and between the control and the third sample (P<0.01). No significant difference was seen between the second and third samples.

### TABLE I. Blood-gas data before and after administration of NaHCO\textsubscript{3}

<table>
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<tbody>
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<td>Sample 1</td>
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<tr>
<td>pH</td>
<td>7.375</td>
<td>7.379</td>
<td>7.374</td>
<td>7.412</td>
<td>7.388</td>
<td>7.415</td>
<td>7.389</td>
<td>7.386</td>
<td>7.400</td>
<td>7.389</td>
<td>7.390 ± 0.014</td>
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<tr>
<td>P\textsubscript{O\textsubscript{2}} (kPa)</td>
<td>13.10</td>
<td>13.66</td>
<td>12.86</td>
<td>12.77</td>
<td>13.44</td>
<td>13.46</td>
<td>*</td>
<td>12.82</td>
<td>13.24</td>
<td>12.06</td>
<td>13.04 ± 0.48</td>
</tr>
<tr>
<td>P\textsubscript{CO\textsubscript{2}} (kPa)</td>
<td>5.24</td>
<td>4.96</td>
<td>5.10</td>
<td>4.50</td>
<td>4.92</td>
<td>4.68</td>
<td>5.28</td>
<td>4.84</td>
<td>4.76</td>
<td>4.73</td>
<td>4.90 ± 0.25</td>
</tr>
<tr>
<td>HCO\textsubscript{3} (mmol/litre)</td>
<td>22.0</td>
<td>21.0</td>
<td>21.4</td>
<td>21.1</td>
<td>21.2</td>
<td>21.5</td>
<td>23.0</td>
<td>20.9</td>
<td>21.2</td>
<td>20.6</td>
<td>21.4 ± 0.7</td>
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| Sample 2 |       |       |       |       |       |       |       |       |       |       |            |
| pH      | 7.483 | 7.505 | 7.463 | 7.511 | 7.489 | 7.469 | 7.475 | 7.482 | 7.496 | 7.505 | 7.487 ± 0.016 |
| P\textsubscript{O\textsubscript{2}} | 9.80  | 14.44 | 12.33 | 11.22 | 12.70 | 12.05 | 11.64 | 12.37 | 11.58 | 12.65 | 12.07 ± 1.19 |
| P\textsubscript{CO\textsubscript{2}} | 5.50  | 4.70  | 5.52  | 5.09  | 5.04  | 5.02  | 5.53  | 4.94  | 5.33  | 5.12  | 5.17 ± 0.28 |
| HCO\textsubscript{3} | 29.9  | 26.8  | 28.5  | 29.6  | 27.4  | 26.4  | 29.4  | 26.8  | 29.9  | 29.3  | 28.4 ± 1.4 |

| Sample 3 |       |       |       |       |       |       |       |       |       |       |            |
| P\textsubscript{O\textsubscript{2}} | 10.10 | 13.70 | 12.13 | 11.06 | 11.64 | 10.96 | 12.17 | 11.25 | 11.38 | 11.40 | 11.57 ± 0.95 |
| P\textsubscript{CO\textsubscript{2}} | 6.10  | 5.88  | 5.66  | 4.73  | 5.25  | 5.69  | 5.02  | 6.10  | 5.74  | 5.22  | 5.53 ± 0.46 |
| HCO\textsubscript{3} | 33.8  | 32.2  | 28.2  | 26.1  | 27.7  | 30.1  | 27.3  | 32.0  | 30.9  | 29.0  | 29.7 ± 2.5 |

* Not measured.

Sample 1: control; sample 2: 20 min after NaHCO\textsubscript{3} infusion; sample 3: 10 min after the completion of the experiment.
Resting ventilation

Control $PE'_\text{CO}_2$ at rest (hyperoxia; $PE'_\text{O}_2$ 24.0 kPa; no $\text{CO}_2$ loading) was 4.81 (SD 0.36) kPa. Resting $PE'_\text{CO}_2$ after inducing alkalosis was 5.22 (SD 0.53) kPa and this difference was significant ($P<0.05$). The resting minute ventilation (control and after inducing alkalosis) was 4.8 (SD 0.6) and 4.8 (SD 0.8) litre/min.m$^{-2}$, respectively and there was no significant difference between these values. There was a slight decrease in the resting tidal volume from the control value of 298.7 (SD 46.4) ml/m$^2$ to 273.6 (SD 39.9) ml/m$^2$ during induced alkalosis but the difference was not significant.

Carbon dioxide response test

The $CO_2$ response curve and the $PCO_2$-tidal volume curve were obtained by linear regression analyses and these curves included the lowest points of $PCO_2$. The correlation coefficient values ($r$ values) of all these curves were greater than 0.84. Figure 3 shows the $CO_2$ response curve obtained from three subjects in the control experiments using 0.9% saline solution and orange juice. No significant differences in the position and the slope were seen before and after the administration of the saline. The $CO_2$ response curve of one subject after the administration of sodium bicarbonate is shown in figure 4. The $CO_2$ response curves and the tidal volume vs. $PE'_\text{CO}_2$ relationships of all the subjects are shown in figures 5 and 6. The values of $PE'_\text{CO}_2$ for the minute ventilation of 10 litre/m$^2$ and the tidal volume of 500 ml/m$^2$ both in the control situation and during alkalosis are shown in tables II and III. There were significant differences between the values obtained under control conditions and during alkalosis ($P<0.01$).

The mean slope of the control response curve was 5.28 (SD 1.28) and the mean slope of the curve obtained during alkalosis was 4.00 (SD 1.36) litre/min.m$^{-2}$.kPa$^{-1}$. The percentage ratio of the slope of the response curve obtained after administration of
sodium bicarbonate to the slope of the control curve is shown in tables IV and V. Significant decreases in the slopes of both the $PCO_2$-tidal volume curve and the $PCO_2$-ventilation curve were seen during alkalosis ($P < 0.05$).

**DISCUSSION**

Sodium bicarbonate is used often to correct metabolic acidosis. Sometimes metabolic alkalosis is induced because of over-correction. There has been disagreement as to whether or not such metabolic alkalosis causes hypoventilation. However, there are many clinical reports of hypoventilation associated with severe metabolic alkalosis (Alexander et al., 1955; Roberts et al., 1956; Falchuk, Lamb and Tenney, 1966; Mithoefer et al., 1969; Van Ypersele de Strihou and Frans, 1973). There has been disagreement also as to the ventilatory effect of the i.v. sodium bicarbonate to the slope of the control curve is shown in tables IV and V. Significant decreases in the slopes of both the $PCO_2$-tidal volume curve and the $PCO_2$-ventilation curve were seen during alkalosis ($P < 0.05$).

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Continued experiment without alkalosis. During alkalosis the curves were shifted to the right and their slopes were decreased in comparison with the control curves. Neither change in slope nor change in position was seen.

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Neither change in slope nor change in position was seen.

Fig. 3. The CO₂ response curves in control experiments. Neither change in slope nor change in position was seen.

Fig. 4. The CO₂ response curve of subject A. O. A decrease in slope, and displacement of the curve to the right, was seen during alkalosis.

One way of assessing the ventilatory depressant effect of a drug is to compare blood-gas data obtained before and after administration of that drug. Another way is to measure the ventilatory response to carbon dioxide. In our study the control PaₐCO₂ and HCO₃⁻ were relatively small and we are unable to explain this. It may have been a result of fasting (which causes metabolic acidosis) or an inherent metabolic characteristic of the individual, or another unknown cause. Although an increase in PaₐCO₂, and a decrease in PaₐO₂, were seen after the administration of sodium bicarbonate, severe hypventilation, sufficient to overcome the apparent alkalaemia, was not seen.

The CO₂ response test is one of the most reliable tests in an evaluation of effects of drugs on respiration. However, the details of the method are critical, especially when data between different experiments are to be compared. In a recent report Linton and others (1973) concluded that the rebreathing method...
and the steady-state method do not assess similar aspects of the chemical control of breathing. The closed-circuit technique which we used in this study is fundamentally a steady-state technique although the subject breathes part of his own expired air. This technique is easy to perform and permits the rapid adjustment of the CO₂ concentration by controlling the bypass flow. There is minimum discomfort for the subject and the technique permits also the control of the oxygen concentration. In the interpretation of the response curve some workers (Anderton and Harris, 1963; Lloyd and Cunningham, 1964; Bellville and Green, 1965) have discussed the change both in the slope and in the intercept. Others prefer to consider the Pco₂ at a particular level of ventilation as the index of the displacement of the curve insisting that extrapolation of the response curve in a linear fashion is potentially misleading and dangerous (Bülow, 1963; Keats and Telford, 1964; Bellville and Green, 1965). As we agree with the latter workers and we feel that the response curve should be interpreted within the measured range, we chose PE'co₂ at a ventilation of 10 litre/min·m⁻² and at a tidal volume of 500 ml/m² as our index of displacement of the curve. Goldring and others (1968) examined the ventilatory adjustment to induced chronic metabolic alkalosis and reported that metabolic alkalosis induced by sodium bicarbonate was associated with alveolar hypoventilation and that a shift to the right (in addition to a decrease in slope) of the response curve as obtained by the steady-state technique, was seen. Linton and others (1973) found that, using the steady-state technique, there was a shift of the response curve without a change in slope during chronic metabolic alkalosis induced by sodium bicarbonate. Our data show that in the resting state during hyperoxia, the resting ventilation and tidal volume after the induction of alkalosis were not significantly different from the control values even though the values for end-tidal Pco₂ were significantly higher than those of the control values (P < 0.05). This shows that the resting ventilation shifted to the right after the administration of NaHCO₃. During alkalosis the values of PE'CO₂ at a minute volume of 10 litre/m² and a tidal volume of 500 ml/m² were significantly higher than the control values. These data show that the response curve was displaced to the right during induced metabolic alkalosis. The decrease in slope of the response curve was seen during alkalosis and this does not accord with the results of Katsaros and others (1960) and Linton and others (1973), although it is in accord with the results of Goldring and others (1968). Our data show also a consistent decrease in tidal volume at all values of PE'CO₂ during alkalosis and this suggests that the reduction of minute ventilation was affected greatly by the reduced tidal volume. The decrease in slope of the response curve cannot be explained simply on the basis of changes in the sensitivity of the respiratory centre, because many other factors may affect the slope of the response curve. Lung compliance, airway resistance, muscle activity and even peripheral nerve activity affect the slope of the response curve (Bellville and Seed, 1960; Guz et al., 1966), but from the clinical observations noted in this study it seems inconceivable that these factors could have played a considerable role in this experiment. Therefore, we suspect that this decrease in slope is chiefly a result of decreased sensitivity of the respiratory centre.

Disagreement exists as to the cerebrospinal fluid (c.s.f.) acid–base relationships occurring during alkalosis. Some studies have shown that there was little difference in the composition of c.s.f. during alkalosis induced by sodium bicarbonate (Swanson and Rosengren, 1962; Monroe and Kazemi, 1973). Others have reported that small changes occurred in the composition of c.s.f. during alkalosis induced by sodium bicarbonate (Pappenheimer, 1967; Hodson et al., 1968; Lifschitz et al., 1972). We did not study the changes of c.s.f. composition on this occasion, but if it is assumed that the H⁺ concentration of c.s.f. has the chief role in the regulation of respiration, it is conceivable that some changes in c.s.f. occurred to explain the decreased sensitivity of respiration observed in this study. The present study was carried out under hypoxic conditions so that a hypoxic stimulus can be excluded. It is thought that the major factor which affects the peripheral chemoreceptor is oxygen, but it is true also that the CO₂ and hydrogen ion concentrations influence chemoreceptor activity (Saito, Honda and Hasamura, 1960; Mitchell and Singer, 1965). However, it is known that in animals, the effect of CO₂ and H⁺ on the peripheral chemoreceptor nerves diminishes progressively as Po₂ increases (Fitzgerald and Parks, 1971) and that, in man, no response of peripheral chemoreceptors to CO₂ and H⁺ under hyperoxia was seen (Miller et al., 1974). Therefore, under hypoxic conditions the activity of the peripheral chemoreceptor must be neglected.

Cerebral blood flow and changes in cardiac output may affect the sensitivity of the respiratory centre (Bellville et al., 1959; Fencl, Vale and Broch, 1969). In the present study we did not measure either of these and we do not know whether metabolic
alkalosis, induced acutely and as studied in this experiment, changes cerebral blood flow or cardiac output to the point at which they may affect the respiratory centre.

REFERENCES


EFFET DE L'ADMINISTRATION EN FORTES DOSES DE BICARBONATE DE SOUDE SUR LA RESPIRATION EN PRESENCE D'HYPEROXIE

RESUME
On a étudié sur 10 sujets normaux, les effets qu'a sur la respiration l'administration en fortes doses de bicarbonate de soude. On a obtenu des courbes de réaction à l'acide carbonique et des relations du volume courant par rapport au \( P_{CO_2} \) dans des conditions hyperoxiques, à l'aide d'un système de respiration en circuit fermé. On a observé pendant l'alkalose, une diminution de la pente ainsi qu'un déplacement vers la droite des courbes de réaction. Ces découvertes indiquent que l'alkalose métabolique, provoquée d'une manière aiguë par l'administration de bicarbonate de soude, modifie la réaction respiratoire à l'acide carbonique et que le bicarbonate de soude peut avoir un effet modérateur sur la respiration.

WIRKUNG DER AKUTEN VERABREICHUNG VON NATRIUMBICARBONAT AUF DIE ATMUNG BEI EINEM ZU HOHEN SAUERSTOFFGEHALT DES KREISLAUFES

ZUSAMMENFASSUNG
Es wurden in 10 normalen Versuchspersonen die Wirkungen der akuten Verabreichung von Natriumbicarbonat auf die Atmung studiert. Um die Kohlensäurereaktionskurven und die Verhältnisse des Atemvolumens gegenüber dem Kohlensäuredruck \( P_{CO_2} \) zu erhalten, wurde ein geschlossenes Beatmungskreissystem benutzt. Während der Alkalose wurde festgestellt, dass sich die Steigung verringerte und die Reaktionskurven sich nach rechts verschoben. Dieser Befund deutet an, dass die, durch die Verabreichung von Natriumbicarbonat akut herbeigeführte Stoffwechselalkalose die Atmungsreaktion auf Kohlensäure ändert, und dass Natriumbicarbonat eventuell dämpfend auf die Atmung wirkt.

EFECTO DE LA ADMINISTRACIÓN AGUDA DE BICARBONATO SÓDICO SOBRE LA RESPIRACIÓN EN PRESENCIA DE HIPEROXIA

SUMARIO
Los efectos sobre la respiración de la administración aguda de bicarbonato sódico fueron estudiados en 10 sujetos normales. Se obtuvieron las curvas de respuesta del bióxido de carbono y relaciones volumen respiratorio pulmonar vs. \( P_{CO_2} \) bajo condiciones hiperoxicas, empleando un sistema respiratorio de circuito cerrado. Durante la alcalosis se observaron un descenso en la vertiente, y un desplazamiento hacia la derecha, en las curvas de respuesta. Estos hallazgos indican que la alcalosis metabólica, inducida agudamente mediante administración de bicarbonato sódico, altera la respuesta respiratoria al bióxido de carbono, y que el bicarbonato sódico pudiera ejercer un efecto de depresión sobre la respiración.