THE RELATION OF HYPERKALEMIA TO THE ELECTROCARDIOGRAPHIC CHANGES CAUSED BY ACIDEMIA

TAKAO WADA, M. D., FUYUHIKO HIGASHI, M. D.,
EIICHI KATO, M. D., AND SEIICHI ASANO, M. D.

Acidemia was induced in normal dogs by CO₂ administration. Plasma electrolyte concentration showed a rise of sodium and potassium and a fall of chloride. Electrocardiograms recorded at the same time showed T-wave changes which resembled those induced by KCl infusion in the same animals. Besides, QTc tended to decrease at that time to the same degree as in KCl infusion. However, the degree of hyperkalemia induced by the acidemia was much less remarkable than those by KCl infusion when both conditions were compared on the same level of T-wave changes. When the acidemia was suppressed with a solution of Tris-buffer (THAM) containing potassium, T-wave changes were also suppressed in spite of the rise of plasma potassium level. These findings suggest that some factors other than hyperkalemia caused the above electrocardiographic changes. Judging from the plasma electrolyte changes seen in the acidemia and from another observation that hypertonic NaCl or NaHCO₃ also causes similar electrocardiographic changes, it is concluded that the changes in gradients across cell membranes of multiple electrolytes, including potassium, sodium, hydrogen ion and so forth, are responsible for the electrocardiographic changes seen in acidemia.

IT HAS been repeatedly demonstrated that the acutely induced increase (acidemia) or decrease (alkalemia) in blood hydrogen ion concentration produces electrocardiographic alterations similar to those seen in hyperkalemia or hypokalemia, respectively.¹⁻⁶ However, since the changes in blood hydrogen ion are usually associated with those in the concentration of plasma potassium, the effect of hydrogen ion per se still remains to be determined.^{7,8} In the present study it was undertaken to dissociate the effect of hydrogen ion changes from that of plasma potassium changes on electrocardiograms.

Key Words:

Electrocardiogram
Acidemia
Hyperkalemia
Hydrogen Ion
Plasma Electrolytes

MATERIALS AND METHODS

Experiments were performed on ten mongrel dogs ranging in weight from 10.5 to 15.0 kg. Anesthesia was induced and maintained by sodium pentobarbital given intravenously. Blood was obtained from a needle indwelling in a femoral artery. The whole blood pH was measured by Radiometer and total carbon dioxide (CO₂) of the plasma by the method of Natelson. PaCO₂ was calculated from these values using the Henderson-Hasselbalch equation. Sodium and potassium were measured by flame photometry, chloride by Schales & Schales method.

Respiratory acidosis was produced by the administration of carbon dioxide-oxygen (CO₂-O₂) mixtures delivered by Palmer pump at rates of 8 to 10 liters per minute. After the control period in the room air, the CO₂ was increased in

(Received for publication: September 1, 1972)

Department of Internal Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo Japan.

Fig.1. The relationship between the change of blood hydrogen ion concentration ($\Delta[\text{H}^+]$) and that of plasma sodium concentration ($\Delta[\text{Na}^+]$). The cross marks represent the dog #4 which showed a special tendency. Although there was no significant correlation between the two parameters ($r=0.05$), most points fell on or above the zero line.

Fig.2. The relationship between the change of blood hydrogen ion concentration ($\Delta[\text{H}^+]$) and that of plasma potassium concentration ($\Delta[\text{K}^+]$). The correlation between the two parameters was significant ($r=0.66$). The cross marks represent the dog #4.

Fig.3. The relationship between the change of blood hydrogen ion concentration ($\Delta[\text{H}^+]$) and that of plasma chloride concentration ($\Delta[\text{Cl}^-]$). Although the chloride concentration tended to fall with increasing acidemia, there was no significant correlation between the two parameters ($r=-0.36$). The cross marks represent the dog #4.

Fig.4. The relationship between the change of blood hydrogen ion concentration ($\Delta[\text{H}^+]$) and that of T-wave amplitude (ΔT). There was a highly significant correlation between the two parameters ($r=0.90$). The cross marks represent the dog #4.

stepwise fashion usually beginning with 5% and terminating with 20%. Thereafter, in four out of

eight animals $\text{O}_2\text{-CO}_2$ mixtures were changed to room air. When the animals returned to the

Fig.5. The plasma potassium changes ($\Delta[K^+]$) induced by CO_2 administration (open circles) and by KCl infusion (closed circles). The both conditions were compared on the same level of T-wave changes (ΔT). None of the points belonging to the latter group did not fall in the range of standard deviation (indicated by thin lines) of the former group.

Fig.6. The relationship between the change of T-wave amplitude (ΔT) and that of QTc (ΔQTc). Open circles represent the experiments of CO_2 administration and closed ones represent those of KCl infusion. Neither groups showed a significant correlation between the two parameters ($r = -0.15$ and $r = -0.40$, respectively).

control state, 15 mEq/l KCl in isotonic saline solution was infused into an antecubital vein at a rate of 0.33 ml/kg/min. In other four animals,

maintaining the maximum respiratory acidosis 8 ml/kg of THAM-E, containing THAM 3.6 g/dl, Na 30 mEq/l, K 5 mEq/l and Cl 35 mEq/l,

Fig.7. The effect of suppression of acidemia by THAM while maintaining plasma potassium level. Note that the decrease of blood hydrogen concentration accompanies the decrease of T-wave amplitude in spite of an increase of plasma potassium concentration.

(Abbott Laboratories, North Chicago Ill.) was administered intravenously in 5 minutes. In the remaining two animals 20 ml of 10% NaCl was injected and after a while the same amount of 10% NaHCO₃ was injected intravenously to examine and compare their effects on electrocardiograms.

Every time the concentration of CO₂ administered was changed fifteen minutes were allowed to pass in order to wait for animals to reach a new equilibrium state, and then blood samples and electrocardiographic recordings were obtained simultaneously. In a preliminary study it had been confirmed that the plasma concentration of hydrogen ion and electrolytes reach equilibrium in 10 minutes after the concentration of CO₂ is changed.

The position of the electrode was chosen so as to give the highest T waves in the area equivalent to V₂ to V₄ in man. The animals were maintained in a fixed position and care was taken to avoid shift of electrodes. The usual standardi-

zation of 1 mV producing a deflection of 10 mm was employed with a paper speed of 25 mm per second. The QT intervals were corrected (QTc) to a heart rate of 60 by means of the formula of Bazett.⁹ Throughout this paper the degree of acidity is expressed directly as hydrogen ion concentration (H⁺ in nanoequivalents per liter, nEq/l) in stead of pH. Precordial leads were used to assess the changes of T waves and QT intervals.

RESULTS

Fig. 1–3 show the changes of plasma electrolytes (ΔNa^+ , ΔK^+ , and ΔCl^-) of eight dogs in relation to the change of whole blood hydrogen ion concentration (ΔH^+). Although the concentration of sodium tended to increase ($\Delta\text{Na}^+ > 0$) and that of chloride tended to decrease ($\Delta\text{Cl}^- < 0$) in all except in the dog #4, there was no quantitative correlation between ΔNa^+ or ΔCl^- and ΔH^+ (Fig. 1 & 3). On the other hand, ΔK^+ had a significant correlation to ΔH^+ (Fig. 2)

Fig.8. The effect of hypertonic NaCl and NaHCO₃ on electrocardiograms. Both of them caused tented T-waves.

($r=0.66$). However, it does not necessarily mean that there is a causal relationship between those two parameters.

An interesting thing is that the data of the dog #4 showed a quite opposite tendency as compared to the other animals as far as the plasma sodium and chloride concentration is concerned. Namely, in that particular dog, in contrast to the others, the concentration of sodium tended to decrease and that of chloride tended to increase when acidemia was induced. The inference that this animal had a special tendency is also endorsed with the abrupt change in the amplitude of T-waves (ΔT) in relation to ΔH^+ (Fig. 4).

Therefore, this animal was not included in the statistical analysis.

In the other animals ΔH^+ is highly significantly correlated with ΔT (Fig. 4) ($r=0.90$).

The increase of plasma potassium in relation to T wave changes were compared between CO₂ administration and KCl infusion. Although the general form of T-waves did not help to differentiate those two conditions, the amplitude of T-waves showed a different attitude between those two (Fig. 5). None of the points representing the latter group fall in the range of standard deviation of the former group. This may suggest that the rise of plasma potassium in respiratory

acidosis is too small to explain the T-wave changes at that time.

QTc tended more to decrease than to increase ($QTc < 0$) after KCl infusion and CO_2 administration, although there was no significant correlation between the ΔQTc and ΔT (Fig. 6).

In order to dissociate the effect of blood hydrogen ion concentration from that of plasma potassium on electrocardiograms, the suppression of acidemia was tried while increasing plasma potassium level. As shown in Fig. 7, intravenous injection of THAM-E reduced the blood hydrogen ion level and the amplitude of T-waves in spite of the elevation of plasma potassium level.

The effect of 10% NaCl and of 10% $NaHCO_3$ on electrocardiograms was examined in two dogs. Since these two animals responded similarly, only one experiment is presented in Fig. 8. It is clearly demonstrated that both the NaCl and the $NaHCO_3$ caused T-wave changes similar to those due to hyperkalemia.

DISCUSSION

Roberts and Magida suggested that the electrocardiographic changes usually ascribed to hyperkalemia may be produced in acidemia with or without hyperkalemia.³ However, this view has been questioned since, as long as plasma potassium level progressively rises with acidemia and falls with alkalemia, one cannot positively exclude the change of plasma potassium level as a cause of electrocardiographic changes on that occasion.^{7,8} Therefore, more critical studies were necessary.

In the present study CO_2 administration was chosen to produce acidemia, since in this form of acidemia it is possible rapidly to return the animals to the control state and to compare the effect of acidemia with that of KCl infusion in the same animal in the same experimental condition.

The present data show that the general form of T-waves (tented T) and the pattern of QTc changes do not help to differentiate the electrocardiographic changes seen in acidemia from those due to hyperkalemia. However, as shown in Fig. 6, the degree of hyperkalemia seen in the acidemia is far less than that caused by KCl infusion when compared on the same degree of T-wave changes. This observation alone may be taken to indicate that the acidemia has increased the sensitivity of cardiac muscles to hyperkalemia. However, when the acidemia was suppressed with THAM infusion, the tented T-waves

tended to subside in spite of the elevation of plasma potassium level at that time (Fig. 7). Accordingly, these findings should be ascribed to some factors other than hyperkalemia.

Our findings with respect to the plasma electrolytes are consistent with those of Giebisch, Berger and Pitts¹⁰ who found a rise of sodium and a fall of chloride (Fig. 2 & 3).

It is probable that all of these changes of plasma electrolytes are in some way related to the electrocardiographic changes in acidemia. In this regard it is to be noted that one dog (#4) showed a peculiar tendency. In this animal, when the acidemia was induced the amplitude of T-waves increased much more markedly than in the other animals and the plasma sodium and chloride tended to decrease rather than to increase. This suggests that the changes of T-waves are associated with the movement of these electrolytes across the cell membranes. It has been suggested that hypernatremia induced by hypertonic saline can cause electrocardiographic changes similar to those due to hyperkalemia.¹¹ However, it may have been due to dilution acidosis caused by saline solution.¹²⁻¹⁴ In order to elucidate this respect the effect of 10% NaCl was compared with that of 10% $NaHCO_3$. As shown in Fig. 8 both of them caused tented T-waves. Therefore, these changes appear to be related to the movement of sodium per se across the cell membranes.

In summary the present data are consistent with the view that electrocardiographic changes induced by acidemia are due to the changes in concentration gradients across the cell membranes, not absolute plasma levels, of multiple electrolytes including potassium, sodium, hydrogen ion and so forth.

REFERENCES

1. ABRAMS, W. B., LEWIS, D. W., & BELLET, S.: The effect of acidosis and alkalosis on the plasma potassium concentration and the electrocardiogram of normal and potassium depleted dogs. *Amer J. Med. Sci.* 222: 506-515, 1951.
2. MAGIDA, M. G. & ROBERTS, K. E.: Electrocardiographic alterations produced by an increase in plasma pH, bicarbonate and sodium as compared with those seen with a decrease in potassium. *Circ. Res.* 1: 214-218, 1953.
3. ROBERTS, K. E. & MAGIDA, M. G.: Electrocardiographic alterations produced by a decrease in plasma pH, bicarbonate and sodium as compared with those produced by an increase in potassium. *Circ. Res.* 1: 206-213, 1953.
4. BARKER, P. S., SHRODER, E. L., & RONZONI, E.: The effects of alkalosis and of acidosis upon the

- human electrocardiogram. *Amer. Heart J.* 17: 169–186, 1939.
5. BELLET, S., GUZMAN, S. V., WEST, J. W. et al.: The effect of molar sodium-lactate on cardiac function: an experimental study in dogs. *Amer. J. Med. Sci.* 233: 286–295, 1957.
 6. TRETHERWIE, E. R. & HODGKINSON, M. M.: The influence of carbon dioxide and pH on the electrocardiogram of the isolated perfused heart. *Quart. J. Exp. Physiol.* 40: 1–11, 1955.
 7. REID, A., ENSON, Y., HARVEY, R. M. et al.: The effect of variations in blood pH upon the electrocardiogram in man. *Circulation* 31: 369–373, 1965.
 8. SURAWICZ, B.: Relationship between electrocardiogram and electrolytes. *Amer. Heart J.* 73: 814–834, 1967.
 9. BAZETT, H. C.: An analysis of the time relationship of the electrocardiogram. *Heart* 7: 353–357, 1920.
 10. GIEBISCH, G., BERGER, L., & PITTS, R. F.: The extrarenal response to acute acid-base disturbances of respiratory origin. *J. Clin. Invest* 34: 231–245, 1955.
 11. SMITH, R. F., HARTHERNE, J. W., & SANDERS, C. A.: Vectorcardiographic changes during selective coronary artery injection. *Circulation (Supple III)* 34: 218, 1966 (Abstract)
 12. SHIRES, G. T. & HOLMAN, J.: Dilution acidosis. *Ann. Intern. Med.* 28: 557–559, 1948.
 13. ASANO, S., KATO, E., YAMAUCHI, M. et al.: The mechanism of acidosis caused by infusion of saline solution. *Lancet* 1: 1245–1246, 1966.
 14. WADA, T.: Role of chloride in metabolic acidosis. *Keio J. Med.* 17: 27–37, 1968.