The Effect of Variations in Blood pH upon the Electrocardiogram in Man

By J. ALAN REID, M.D., YALE ENSON, M.D., RÉJANE M. HARVEY, M.D., AND M. IRENÉ FERRER, M.D.

The electrocardiographic response in man to acute changes in blood hydrogen ion concentration has not been well defined. Although the effects of an acute alteration in blood pH have been studied in dogs and isolated heart preparations, examinations in man have usually been limited to clinical situations in which disturbances in serum electrolytes occurred along with deviations in hydrogen ion concentration.

The present investigation is concerned with a study of the electrocardiogram in man during infusions of the acidifying and alkalinizing agents hydrochloric acid, the amine buffer trim (hydroxymethyl) aminomethane (THAM), and sodium bicarbonate.

Material and Methods

Thirty-six studies were performed upon 34 subjects. All but three were men. Their ages ranged from 40 to 73 years (mean 56). Thirty-two subjects had chronic pulmonary disease, one had localized pleural thickening of unknown etiology, and one had a bronchogenic carcinoma. Seventeen of those with chronic pulmonary disease had previously demonstrated right ventricular failure, but none was in failure at the time of study; of these 17, 15 were receiving digitalis therapy. No evidence of left ventricular disease was present in any of the subjects.

The experimental protocol, described in a previous publication, was that of a larger study on the pulmonary circulation. Each of the three infusions was given into the right atrium through a cardiac catheter, since peripheral venospasm and pain may occur if the agents used are injected into a vein. An indwelling Cournand needle in a brachial artery was used to obtain blood samples for determination of pH. Each subject was studied in a basal, fasting, and unsedated state. Isotonic saline infusion was maintained during the control period, which varied from 4 to 31 minutes (mean 12). Blood sodium, calcium, and potassium levels were not measured.

In 10 subjects, following the control period, 0.145 to 0.202 ml./Kg./min. (mean 0.185) of 0.3 M hydrochloric acid was infused at a constant rate. The infusion time ranged between 6 and 14 minutes, and averaged 10.5. One-half to 1.5 ml./Kg. (mean 1.1) of 1.2 M THAM was infused into 14 other subjects for periods varying from 5.5 to 13.5 minutes (average 10.5). An additional 12 subjects received 2.6 to 3.5 ml./Kg. (mean 3.0) of 0.9 M sodium bicarbonate for periods ranging from 8 to 16.5 minutes (average 11.5).

Electrocardiograms consisting of the three standard leads and the three unipolar AV leads were obtained by an oscillographic method of recording.* Records were made at the beginning and end of both the control and the infusion period. The usual standardization of 1 mv. producing a deflection of 10 mm. was employed, with a paper speed of 25 mm. per second. With the aid of a magnifying lens, the PR, QRS, and QT intervals were measured to the nearest 0.005 second, and the P- and T-wave amplitude to 0.25 mm. The PR and QRS intervals were measured in lead II, whereas the QT interval was measured in whichever lead showed the greatest QT duration. In all instances, the values from five or more consecutive cardiac cycles were averaged. The QT intervals were corrected (QTc) to a heart rate of 60 by means of the nomogram of Kissin and co-workers, which is derived from the formula of Bazett. The P- and T-wave amplitudes were measured in whichever lead had the greatest

*Electronics for Medicine, White Plains, New York.
inflection. The mean P, QRS, and T frontal plane vectors were estimated according to the method of Grant.11

Arterial blood samples were obtained at approximately the same time as the serial electrocardiographic recordings. The blood samples were analyzed for carbon dioxide content and oxygen content and capacity by the method of Van Slyke and Neil. The arterial blood pH was determined with an Astrup Radiometer or in a few instances by a Cambridge constant-temperature pH meter. Carbon dioxide tension was estimated from the whole blood carbon dioxide content with the line charts of Van Slyke and Sendroy.

Results

The average values for arterial pH, carbon dioxide content and tension (PaCO₂), heart rate, P-wave amplitude, PR interval QRS duration, T-wave amplitude, corrected QT, and the mean P, QRS, and T frontal plane vectors remained unchanged during the control period, which averaged 12 minutes.

Hydrochloric Acid

The control pH averaged 7.43 (range 7.36 to 7.49). Following the hydrochloric acid infusion, which lasted an average of 10.5 minutes in the 10 subjects, the average pH decreased to 7.37 (range 7.30 to 7.41) resulting in a mean decrease in pH of 0.06 unit. The mean carbon dioxide content decreased 7.1 vol. per cent (55.9 to 48.8), and PaCO₂, which ranged between 31 and 58 mm. Hg, did not change (± 3 mm.) significantly. The T wave decreased very slightly (0.2 to 1.8 mm.) in five subjects, increased its height by 0.3 mm. in one, and was unchanged in four. Thus the mean T-wave amplitude decreased 0.5 mm. (from 2.0 to 1.5), which was an insignificant deviation. A slight increase in the mean heart rate (85 to 89) occurred, but this was not considered significant. In addition, no significant changes occurred in the P-wave amplitude, PR interval, QRS duration, corrected QT interval, or the mean P, QRS, and T frontal plane vectors during the infusion.

THAM

The control pH ranged from 7.35 to 7.48 (average 7.44). At the completion of the infusion, which averaged 10.5 minutes for the 14 subjects, the pH varied from 7.41 to 7.64 (average 7.53), representing an average increase of 0.09 pH unit. The mean carbon dioxide content increased 6.9 vol. per cent (52.9 to 59.8 vol. per cent) and PaCO₂, which varied from 30 to 54 mm. Hg, did not change in 11 subjects, fell 7 and 9 mm. in two subjects, and rose 8 mm. in one. The average variation was not significant. A slight increase in the mean heart rate (72 to 78) occurred, but this was not significant. There was no change in any of the electrocardiographic waves, intervals, or vectors.

Sodium Bicarbonate

The average increase in blood pH in the 12 subjects was 0.10 pH unit, from the mean control of 7.41 (range 7.31 to 7.46) to 7.51 (range 7.43 to 7.58). In one subject, discussed below in detail, the pH did not change, while in the others it increased by 0.05 to 0.16 units. The mean carbon dioxide content increased 24.7 vol. per cent (53.3 to 78.2 vol. per cent) and mean PaCO₂ rose 6 mm. (range −2 to +9) from an average of 46 to 52. The height of the T wave decreased very slightly (range 0.5 to 1.7 mm.) in six subjects and showed no change in six others. The mean T-wave amplitude decreased from the control value of 2.5 mm. to 2.0 mm. by the end of the infusion. Since these changes were not considered to be significant, it was concluded that there was no real T-wave alteration.

The control QTc varied from 0.355 to 0.470 second, with a mean of 0.430. Following the infusion, which averaged 11.5 minutes in duration, there was no change in QTc in six individuals (range of plus 0.015 to 0.030 sec.) and four more had borderline increases (0.040 to 0.045 sec.). An increase of more than 0.04 second is necessary before a change may be viewed as significant.5 Only two subjects exceeded this, with increases of 0.050 and 0.065 second, respectively. The mean QTc for the group increased from 0.430 to 0.465 second, a rise of 0.035, which is not significant. It should be noted that this occurred without any change in T-wave amplitude or appearance of U waves.
No difference in response could be found between the six subjects receiving digitalis and the six who were not. No significant relationship was found between the change in pH and the QTc (r = 0.17), or between the carbon dioxide content and the QTc (r = 0.34, p > 0.10). In addition, no relationship was observed between the rate of infusion and the QTc.

One subject (no. 1139, table 1) received the sodium bicarbonate infusion at a time when he was not in a steady state, but rather was hyperventilating as evidenced by a progressively increasing arterial blood pH and simultaneously decreasing pCO2 levels during the control period. He received 2.93 ml./Kg. of 0.9 M sodium bicarbonate over a 16.5-minute period but the blood pH remained unchanged while the carbon dioxide content increased by 16.6 vol. per cent. The decreased ventilation at the time of the infusion caused sufficient carbon dioxide retention to buffer the infused alkali. Hence with no change in pH and a higher carbon dioxide content the QTc increased only 0.028 second from the average control value of 0.425, a deviation which is not significant.

No significant change occurred in the mean heart rate, P-wave amplitude, PR or QRS intervals, or the mean P, QRS, and T frontal plane vectors. No U waves were observed.

**Discussion**

Others have demonstrated that acutely induced acidosis or alkalosis produce electrocardiographic changes which, in some instances, were said to be similar to those of hyperkalemia, or hypokalemia, respectively.1,3,4,12–15 For example, in acutely induced acidosis in dogs, an increase in the T-wave amplitude appears after severe depression of the pH and when the pH is lowered below 7.10 QRS prolongation and obliteration of atrial electrical activity occur.4 Although these changes were considered more likely to be related to the hyperkalemia which accompanied the acidosis than to the hydrogen ion concentration per se, this issue remains unsettled.

In the present study, blood pH was lowered abruptly by the infusion of hydrochloric acid without inducing any electrocardiographic alterations. The average fall in pH was 0.06 unit, the lowest level achieved was a pH of 7.30, a value considerably higher than those achieved in the animal experiments.4,14 Although the human and animal experiments cannot therefore be considered comparable, the lack of electrocardiographic change in this human series is consistent with the observations in animals that a profound decrease in pH (less than 7.10) is necessary before such changes appear.4,14

**Table 1**

Electrocardiographic, Ventilatory, and Blood Gas Findings in a Patient Receiving an Infusion of NaHCO3

<table>
<thead>
<tr>
<th></th>
<th>pHa</th>
<th>V̇E (L. / M.²)</th>
<th>CO₂ content</th>
<th>PaCO₂ (mm.Hg)</th>
<th>QTc (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(min.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7.38</td>
<td>6.24</td>
<td>59.3</td>
<td>53</td>
<td>0.439</td>
</tr>
<tr>
<td>4</td>
<td>7.40</td>
<td>6.17</td>
<td>58.6</td>
<td>50</td>
<td>0.423</td>
</tr>
<tr>
<td>13</td>
<td>7.43</td>
<td>6.17</td>
<td>59.0</td>
<td>47</td>
<td>0.414</td>
</tr>
<tr>
<td>Infusion period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9 M NaHCO3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.9 ml./Kg.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(min.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td>7.41</td>
<td>5.54</td>
<td>68.9</td>
<td>57</td>
<td>0.443</td>
</tr>
<tr>
<td>8.0</td>
<td>7.40</td>
<td>5.14</td>
<td>72.3</td>
<td>61</td>
<td>0.453</td>
</tr>
<tr>
<td>10.5</td>
<td>7.43</td>
<td>5.64</td>
<td>75.6</td>
<td>60</td>
<td>0.453</td>
</tr>
</tbody>
</table>
Sodium bicarbonate infusions in dogs have produced electrocardiographic changes somewhat similar to, but not identical with, those of hypokalemia, notably T-wave depressions.\(^3\) The effect of THAM upon the electrocardiogram, however, has not heretofore been investigated.

In this study, the lack of any electrocardiographic alterations following THAM, as compared to the rare (two of 12 subjects) and very modest prolongation of the QT interval (without T- or U-wave shift) with sodium bicarbonate infusion, despite similar pH increases in both groups (average increases of 0.09 and 0.10 pH units, respectively) suggests that these rare QT changes seen following bicarbonate were not directly related to the hydrogen ion concentration. It is conceivable that electrolyte shifts could be responsible, however, since the serum electrolyte alterations that occur with sodium bicarbonate infusions have been postulated as the possible explanation for certain electrocardiographic changes observed by others.\(^1,16\) However, these electrocardiographic changes were predominantly in T waves and U waves (such as occur in hypokalemia) as well as in QT intervals. The first two changes were not seen in our study, even when QT lengthened. Singer et al.\(^17\) demonstrated a decrease in plasma potassium and an increase in plasma sodium after hypertonic sodium bicarbonate infusion in humans. In the absence of abnormal T and U waves, however, the two cases of prolonged QT, noted in the present investigation cannot be explained by low potassium alone. In contrast to sodium bicarbonate, electrolyte balance studies of the effects of THAM in dogs show a fall in plasma sodium levels, but the plasma potassium concentration remained either unchanged or slightly increased.\(^18-21\)

No electrolyte determinations were obtained in the present study, so one cannot speculate on the possible contribution of electrolyte shifts in the occasional prolongation of the QT interval noted after the sodium bicarbonate infusion.

The fall in arterial oxyhemoglobin saturation occasioned by THAM\(^8\) did not elicit any electrocardiographic changes in this series of patients, even though the level of unsaturation was marked in some instances. The fall in arterial saturation after THAM averaged 12 per cent (from 90 to 78) for the 12 patients, with a range of −2 per cent to −26 per cent and the lowest level achieved was 60 per cent saturation.

**Summary and Conclusions**

In this series of patients who were subjected to short periods (5.5 to 16.5 minutes) of acute acidosis and alkalosis no electrocardiographic alterations of note could be ascribed to changes in pH. The range of pH achieved (7.30 to 7.64) is well within that seen in medical conditions that alter pH, such as diabetic acidosis, uremia, and hyperventilation. Furthermore, these changes in pH are sufficient to cause hemodynamic alterations.\(^8\) Hence it can be concluded that in the usual states of acidosis and alkalosis seen clinically in man, any electrocardiographic abnormalities that appear are not related directly to the immediate variations in hydrogen ion concentration. It may well be that more marked shifts in pH or a longer period of sustained acidosis or alkalosis will yield different results.

**References**

3. **MAGIDA, M. G., AND 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. Circulation Research 1: 214, 1953.
4. **ROBERTS, K. E., AND MAGIDA, M. G.:** Electrocardiographic alterations produced by decrease in plasma pH, bicarbonate and sodium as compared with those produced by increase in potassium. Circulation Research 1: 206, 1953.
5. **DREIFUS, L. S., AND PICK, A.:** Clinical correlative

*Circulation, Volume XXXI, March 1963*

Limitation of Medicine as Applied Science

The conversion of the practical arts into applied sciences is a characteristic and familiar process in modern civilization. The rate at which this change is going on is often the subject of enthusiastic and even excited comment. To the sober realist, however, it is clear that the rule of science in medicine is still not much more than strictly local and much qualified. The cases are very few in which general principles can be applied to the individual instance with the direct precision of an engineer designing a dynamo. The diagnosis and treatment of errors of refraction, certain cases of bacteriological and of chemical diagnosis, and others of physical diagnosis and treatment, with the dietetic deficiencies, make up the examples of nearly pure applied science. Elsewhere methods of precision must be very strictly subject to the art of medicine if they are not to become a mere snare. The affectation of scientific exactitude in circumstances where it has no meaning is perhaps the fallacy of method to which medicine is now most exposed.—The Collected Papers of Wilfred Trotter, F.R.S. London, Oxford University Press, 1946, p. 159.