Increased Susceptibility of the Heart to Ventricular Fibrillation During Metabolic Acidosis

By Paul H. Gerst, M.D., William H. Fleming, M.D., and James R. Malm, M.D.

ABSTRACT

Alterations of acid-base balance, clearly defined as metabolic or respiratory in origin, were produced in anesthetized dogs; ventricular fibrillation thresholds were determined during these conditions. During metabolic acidosis, we found that the heart became more susceptible to ventricular fibrillation, as indicated by a decrease in the ventricular fibrillation threshold value. During metabolic alkalosis, the threshold to ventricular fibrillation increased. In contrast, similar variations in pH owing to respiratory acidosis and alkalosis did not affect the ventricular fibrillation threshold. Hyperventilation in dogs with metabolic acidosis, even though resulting in alkaline arterial blood pH, did not protect the hearts from the increased susceptibility to ventricular fibrillation which existed as long as a base deficit was present.

These results indicate that the heart is more susceptible to ventricular fibrillation during acidosis caused by metabolic factors and that primary variations in carbon dioxide tension have no such effect. Our study on dogs, under controlled conditions, provides experimental evidence in support of clinical experience which suggests that metabolic acidosis predisposes the heart to ventricular fibrillation.

ADDITIONAL KEY WORDS respiratory acidosis cardiac arrhythmia cardiac arrest fibrillation threshold metabolic alkalosis respiratory alkalosis anesthetized dogs

The factors which initiate ventricular fibrillation have been studied extensively, but remain poorly understood. Previous investigators have suggested that hypoxia, hypercapnia or electrolyte shifts may play a role in precipitating this arrhythmia. The present report describes the results of an investigation intended to evaluate the effects of acidosis, clearly defined as metabolic or respiratory in origin, upon the susceptibility of the heart to ventricular fibrillation. The data suggest that metabolic acidosis increases the susceptibility to ventricular fibrillation whereas metabolic alkalosis tends to protect the heart against this arrhythmia. Respiratory acidosis and alkalosis, when not associated with other alterations in acid-base balance, seem to have no detectable influence on the vulnerability of the ventricle to fibrillate.

Methods

The susceptibility of the heart of the anesthetized dog to ventricular fibrillation was evaluated quantitatively by determining the threshold for ventricular fibrillation as described by Wiggers and Wegria.1 The ventricular fibrillation threshold is defined as the least amount of electrical energy which, when applied directly to the surface of the heart, will induce ventricular fibrillation.

The electrical system used is illustrated in figure 1. Ventricular fibrillation thresholds were determined by applying single, brief electrical stimuli (2.5 msec in duration) of progressively increasing strength directly to the surface of the right ventricle. The electrodes were 1 cm apart and the area of contact of each electrode with the myocardium was 1.4 mm². A 5,000 ohm resistor was included in one limb of the circuit of the stimu-
FIGURE 1
Diagram of the electrical system used. Single rectangular stimuli from a Grass stimulator, model S4, were applied directly to the surface of the right ventricle through a bipolar electrode. Each stimulus was triggered by an R wave of the electrocardiogram. By means of a variable electrical delay the stimuli were timed so as to arrive in the vulnerable period which occurs during the inscription of the T wave. The strength of the electrical stimuli applied was varied by controlling the output voltage of the stimulator. A 5000 ohm internal resistor was included in one limb of the stimulator circuit in order to minimize the effects of any variations in the electrical resistance of the system.

The animals were anesthetized with pentobarbital (30 mg/kg) given intravenously and were ventilated artificially with a positive pressure respirator that permitted alterations in tidal volume, frequency of ventilation and composition of the inspired gas mixture. The electrocardiogram, femoral arterial blood pressure, and end-tidal carbon dioxide gas tension were monitored continuously. Heating blankets maintained each animal's temperature between 37 and 38°C. Arterial blood samples, obtained just prior to each fibrillation threshold determination, were analyzed for pH, carbon dioxide and oxygen tensions. In all experiments the animals breathed an oxygen-enriched gas mixture which maintained the oxygen tension of the arterial blood at 100 mm Hg or above.

The heart was exposed by a median sternotomy and the pericardium was opened. For each experiment the ventricular fibrillation threshold was first ascertained before any changes in acid-base balance were induced. Three separate determinations were made. These were remarkably constant for each animal and served as the control value. Acid-base alterations were then produced, and ventricular fibrillation thresholds determined after the desired pH variations were achieved. Metabolic acidosis was produced in 16 dogs by infusing either 0.3 M lactic acid (10 dogs) or 0.15 M hydrochloric acid (6 dogs); the blood pH was then restored to normal by the infusion of either 0.3 M sodium bicarbonate or 0.3 M tris-hydroxymethyl-amino-methane (THAM). After the base deficit was fully corrected, the infusion was continued so that a significant metabolic alkalosis resulted; fibrillation threshold was determined again.

Respiratory acidosis and alkalosis were produced in five animals. Respiratory acidosis was induced by decreasing the rate of the respirator while the animal was being ventilated with 100% oxygen; this led to carbon dioxide retention without hypoxia. Respiratory alkalosis was achieved by hyperventilation.

Results

Figure 2 and table 1 summarize the data from all experiments involving respiratory disturbances in acid-base balance. The minimal stimulus that would result in ventricular fibrillation, under normal conditions of acid-base balance, is indicated by the zero on the ordinate. The points plotted show the deviation from this control value during respiratory acidosis and alkalosis. It can be seen that over a pH range from 6.990 to 7.690, equivalent to arterial carbon dioxide tensions of 115 mm Hg and 13 mm Hg respectively, with the exception of two points, the ventricular fibrillation threshold varied ± 1 milliampere from that required to produce ventricular fibrilla-
tion at normal blood pH and pCO₂. Since the stimuli were varied in 1 milliampere increments, a change of this magnitude, which represents a deviation of only one increment, is not significant.

Figure 3 and table 2 summarize the data from the experiments in which metabolic acidosis and alkalosis were produced. The ventricular fibrillation threshold decreased during acidosis and increased during alkalosis.

The relationship between metabolic acidosis and ventricular fibrillation threshold was the same, whether the acidosis was produced by lactic acid or by hydrochloric acid. Similarly, the effects of metabolic alkalosis produced by sodium bicarbonate were the same as those associated with the THAM infusion.

Figure 4 shows the ventricular fibrillation threshold values obtained during an experiment in which the low pH resulting from

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**TABLE 1**

<table>
<thead>
<tr>
<th>Condition and exp. no.</th>
<th>pH</th>
<th>pCO₂ mm Hg</th>
<th>Base deficit mEq/liter</th>
<th>Stimulator output (volts)</th>
<th>Current applied (milliamperes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.378</td>
<td>37.6</td>
<td>3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory acidosis 1</td>
<td>7.284</td>
<td>49.6</td>
<td>3.5</td>
<td>32</td>
<td>6.4</td>
</tr>
<tr>
<td>Respiratory acidosis 2</td>
<td>7.182</td>
<td>71.4</td>
<td>3.0</td>
<td>30</td>
<td>6.0</td>
</tr>
<tr>
<td>Respiratory acidosis 3</td>
<td>7.051</td>
<td>96.2</td>
<td>4.5</td>
<td>33</td>
<td>6.6</td>
</tr>
<tr>
<td>Respiratory alkalosis 1</td>
<td>7.451</td>
<td>31.4</td>
<td>2.2</td>
<td>31</td>
<td>6.2</td>
</tr>
<tr>
<td>Respiratory alkalosis 2</td>
<td>7.558</td>
<td>22.0</td>
<td>2.6</td>
<td>31</td>
<td>6.2</td>
</tr>
<tr>
<td>Respiratory alkalosis 3</td>
<td>7.649</td>
<td>15.4</td>
<td>3.0</td>
<td>30</td>
<td>6.0</td>
</tr>
<tr>
<td>Recovery</td>
<td>7.395</td>
<td>35.4</td>
<td>3.0</td>
<td>30</td>
<td>6.0</td>
</tr>
</tbody>
</table>
metabolic acidosis was increased to the alkaline range by a superimposed respiratory alkalosis. Changes in the acid-base status of the blood, as determined from analysis of sequential blood samples, are plotted on the nomogram proposed by Davenport. While a state of metabolic acidosis was induced by infusion of lactic acid the arterial carbon dioxide tension was kept in the range of 35 to 38 mm Hg by adjustments of the respirator. As metabolic acidosis increased, the ventricular fibrillation threshold declined progressively, from a control value of 9 milliamperes at pH of 7.420, to 8 milliamperes at pH of 7.300, and to 6 milliamperes at pH of 7.210. Respiratory alkalosis was then superimposed by increasing the rate of the respirator. The carbon dioxide tension of the arterial blood fell to 12 mm Hg and the pH rose to 7.640. The base deficit, however, persisted and the ventricular fibrillation threshold remained at 6 milliamperes. Further addition of acid lowered the fibrillation threshold to 5 milliamperes. When the respiratory frequency was then decreased to the rate which existed prior to the period of induced hyperventilation,

| Table 2 |
| Mean Threshold Values for Ventricular Fibrillation During Metabolic Acidosis and Alkalosis* |
| Condition and exp. no. | pH | pCO₂ | Base Deficit | Excess | Stimulator output | Current applied to heart |
| Lactic acid and sodium bicarbonate |
| Control | 7.384 | 40.4 | 2.2 | 5 | 45 | 9.0 |
| Met. acidosis 1 | 7.227 | 40.3 | 11.0 | 37 | 7.4 |
| 2 | 7.061 | 39.5 | 20.2 | 27 | 5.4 |
| Met. alkalosis 1 | 7.573 | 41.5 | 15.9 | 55 | 11.0 |
| 2 | 7.523 | 40.8 | 21.0 | 65 | 13.0 |
| Recovery | 7.409 | 41.0 | 15.0 | 47 | 9.4 |
| Lactic acid and THAM |
| Control | 7.417 | 35.5 | 1.8 | 50 | 10.0 |
| Met. acidosis 1 | 7.190 | 37.0 | 14.9 | 41 | 8.2 |
| 2 | 7.076 | 42.8 | 18.6 | 34 | 6.6 |
| Met. alkalosis 1 | 7.512 | 37.8 | 7.8 | 62 | 12.4 |
| 2 | 7.594 | 38.5 | 16.0 | 70 | 14.0 |
| Recovery | 7.418 | 37.8 | 1.2 | 52 | 10.5 |
| Hydrochloric acid and sodium bicarbonate |
| Control | 7.398 | 40.7 | 0.2 | 60 | 12.0 |
| Met. acidosis 1 | 7.248 | 41.0 | 10.4 | 48 | 9.6 |
| 2 | 7.141 | 40.5 | 16.0 | 41 | 8.2 |
| Met. alkalosis 1 | 7.505 | 40.0 | 9.2 | 72 | 14.4 |
| 2 | 7.583 | 39.0 | 15.8 | 80 | 16.0 |
| Recovery | 7.411 | 45.0 | 3.6 | 58 | 11.6 |
| Hydrochloric acid and THAM |
| Control | 7.371 | 39.7 | 2.1 | 48 | 9.6 |
| Met. acidosis 1 | 7.223 | 37.0 | 13.0 | 38 | 7.2 |
| 2 | 7.063 | 38.7 | 19.2 | 30 | 6.0 |
| Met. alkalosis 1 | 7.518 | 41.0 | 10.4 | 61 | 12.2 |
| 2 | 7.581 | 40.0 | 18.2 | 70 | 14.0 |
| Recovery | 7.408 | 43.0 | 2.2 | 50 | 10.0 |

*These alterations were induced by infusion of lactic acid followed by sodium bicarbonate (five animals), lactic acid followed by THAM (five animals), hydrochloric acid followed by sodium bicarbonate (three animals) and hydrochloric acid followed by THAM (three animals).
Ventricular fibrillation threshold determinations during an experiment in which pH changes were induced by metabolic and respiratory factors. Control point is indicated by the encircled dot (point 1). It shows that during normal acid-base balance, ventricular fibrillation threshold (VFT) was 9 milliamperes. With progressive metabolic acidosis the VFT declined, first to 8 milliamperes (point 2) and then to 6 milliamperes (point 3). Respiratory alkalosis was then superimposed by increasing the rate of the respirator (point 4). Although pH became alkaline, VFT did not change. Increasing the underlying metabolic acidosis (point 5) was associated with a further decrease of VFT. When the respiratory rate prevailing before hyperventilation was restored (point 6) the pH again became acid but the VFT remained unchanged from the preceding value. With infusion of sodium bicarbonate the base deficit was corrected and the VFT returned to its control level of 9 milliamperes (point 7).

...the state of uncompensated metabolic acidosis was restored. The fibrillation threshold remained at 5 milliamperes. When sodium bicarbonate was subsequently infused to correct the base deficit, the pH of the arterial blood returned to the normal range and the ventricular fibrillation threshold rose to its control value of 9 milliamperes.

This experiment demonstrates that, in the face of an existing metabolic acidosis, merely raising the pH by superimposing a respiratory alkalosis does not return the lowered fibrillation threshold to normal even though the pH of the blood may become alkaline. In order to restore the fibrillation threshold to the control value the base deficit associated with the metabolic disturbance must be corrected. From these data it is apparent that, under the conditions of these experiments, acute metabolic acidosis is associated with a decrease in the ventricular fibrillation threshold, whereas during metabolic alkalosis, the threshold to ventricular fibrillation is increased. Changes in pH produced by respiratory variations alone appear to have no significant effect upon the ventricular fibrillation threshold.

**Discussion**

The explanation for the findings described above is not apparent at this time. Hypoxia was not a factor in these studies. Hypercapnia and hypocapnia did not influence the ventricular fibrillation threshold detectably. Since the bio-electric properties of cells are known to be affected by the partition of ions be-
tween the intracellular and extracellular phases, it seems reasonable to suggest that the demonstrated alterations in cardiac excitability may be related to variations in transmembrane ionic gradients.

Calcium and potassium are known to affect cardiac function and the relationship between these ions and cardiac excitability has been emphasized. Our data do not point to any significant correlation between the plasma potassium concentration and ventricular fibrillation threshold during either respiratory or metabolic acid-base disturbances (table 3). This is consistent with the results obtained by Han et al., as well as by Wexler and Pat. These investigators were unable to detect any changes in ventricular vulnerability during hyperkalemia induced by infusion of potassium. Moreover, Brown and Miller, and Young et al. found an increase in the plasma potassium concentration during respiratory acidosis in the dog, but ventricular fibrillation did not develop in these animals during the period of hypercapnia. The arrhythmia did occur, however, in the immediate posthypercapnic period if the carbon dioxide tension was lowered suddenly to normal. This information suggests that a change in the plasma potassium concentration, when it occurs in the course of acid-base imbalance, is merely one factor in the metabolic disturbance but, per se, is not responsible for precipitating ventricular fibrillation. The role of calcium is less clear. Although we know that the concentration of ionized calcium in the blood will change as the pH shifts between 7.0 and 7.7, little significant information is available at this time which would help clarify the specific role of calcium in the phenomenon we have noted.

The concentration of free hydrogen ions in the extracellular fluid normally is such that its pH is approximately 7.4; the pH of the intracellular fluid is estimated to be in the range of 6.8 to 7.0. Thus, there is normally a significant hydrogen ion concentration gradient across the cellular membranes. Because of the slow transmembrane diffusion of ions, this gradient is undoubtedly influenced by alterations in acid-base balance due to metabolic factors. In contrast, since carbon dioxide diffuses readily across biological membranes, acid-base disturbances due to respiratory variations are unlikely to alter the threshold of cellular excitability. Until more is known of the distribution and concentration of ions within the myocardial cells and their specific changes in response to metabolic and respiratory acidosis, little progress can be expected in elucidating the mechanisms responsible for the changes in ventricular excitability.

Although it may not be justifiable to extrapolate conclusions derived from an experimental study such as this to human physiology, documented clinical experience, as reflected by several reports in the current literature, appears to be consistent with the results obtained by us in the laboratory. These reports emphasize that attempts to resuscitate the fibrillating human heart in the presence of severe metabolic acidosis are not likely to be successful. The arrhythmia recurs rapidly even in those instances in which it has been reverted briefly. Harden et al. failed, on three occasions, to defibrillate, with electric countershock, the heart of a patient in ventricular fibrillation, but normal sinus rhythm reappeared shortly after the administration of sodium bicarbonate. A similar case was described by Stewart et al. Brooks and Feldman reported two instances of ventricular fibrillation in patients with metabolic acidosis whose hearts could not be defibrillated successfully until the acidosis was corrected by infusion of sodium bicarbonate. Furthermore, the onset of ventricular fibrillation shortly after restoring blood flow to large masses of hypoxic tissue, as has been reported following venous inflow occlusion, or after removal of occluding aortic clamps, suggests that the arrhythmia may have been precipitated by perfusion of the heart with blood carrying acidic end-products of anaerobic metabolism from the hypoxic cells. The promptness with which the arrhythmia sometimes occurs after the heart is first perfused with such blood, and the rapid improvement in cardiac func-
## TABLE 3
Serum Potassium Concentrations* in Representative Experiments During Metabolic and Respiratory Acidosis and Alkalosis

<table>
<thead>
<tr>
<th>Condition and exp. no.</th>
<th>Exp. A: Respiratory acidosis and alkalosis</th>
<th>Exp. B: Metabolic acidosis</th>
<th>Exp. C: Metabolic alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>pH 7.367</td>
<td>pH 7.423</td>
<td>pH 7.420</td>
</tr>
<tr>
<td>Resp. acidosis 1</td>
<td>pCO₂ 33 mm Hg</td>
<td>pH 7.423</td>
<td>pH 7.420</td>
</tr>
<tr>
<td>Resp. acidosis 2</td>
<td>pCO₂ 35 mm Hg</td>
<td>pH 7.423</td>
<td>pH 7.420</td>
</tr>
<tr>
<td>Resp. acidosis 3</td>
<td>pCO₂ 35 mm Hg</td>
<td>pH 7.423</td>
<td>pH 7.420</td>
</tr>
<tr>
<td>Resp. alkalosis 1</td>
<td>pCO₂ 35 mm Hg</td>
<td>pH 7.423</td>
<td>pH 7.420</td>
</tr>
<tr>
<td>Resp. alkalosis 2</td>
<td>pCO₂ 35 mm Hg</td>
<td>pH 7.423</td>
<td>pH 7.420</td>
</tr>
<tr>
<td>Resp. alkalosis 3</td>
<td>pCO₂ 35 mm Hg</td>
<td>pH 7.423</td>
<td>pH 7.420</td>
</tr>
<tr>
<td>Recovery</td>
<td>pH 7.423</td>
<td>pH 7.423</td>
<td>pH 7.420</td>
</tr>
</tbody>
</table>

### Table Columns
- **pCO₂**: Partial pressure of carbon dioxide in mm Hg
- **Arterial blood pH**: Measured pH of arterial blood
- **Baseline Serum Potassium**: Baseline serum potassium concentration in mEq/liter
- **Ventricular fibrillation threshold**: Stimulator output in milliamperes

### Data
- **Exp. A**: Respiratory acidosis and alkalosis
  - Control: pH 7.367, pCO₂ 33 mm Hg
  - Resp. acidosis 1: pH 7.423, pCO₂ 35 mm Hg
  - Resp. alkalosis 1: pH 7.423, pCO₂ 35 mm Hg
  - Recovery: pH 7.423, pCO₂ 35 mm Hg
- **Exp. B**: Metabolic acidosis
  - Control: pH 7.423, pCO₂ 35 mm Hg
  - Met. acidosis 1: pH 7.423, pCO₂ 35 mm Hg
  - Met. acidosis 2: pH 7.423, pCO₂ 35 mm Hg
  - Met. acidosis 3: pH 7.423, pCO₂ 35 mm Hg
- **Exp. C**: Metabolic alkalosis
  - Control: pH 7.420, pCO₂ 32 mm Hg
  - Met. alkalosis 1: pH 7.420, pCO₂ 32 mm Hg
  - Met. alkalosis 2: pH 7.420, pCO₂ 32 mm Hg
  - Met. alkalosis 3: pH 7.420, pCO₂ 32 mm Hg

*No apparent correlation between serum potassium level and ventricular fibrillation threshold.*

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tion following correction of metabolic acidosi
by infusion of alkali or buffer solutions, sug
suggests that these changes in cardiac physi
ology may be due to variations in the gradi
ents of hydrogen or other, so far undeter
mined, ions across the membrane of the myoc
ardial cells.

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