Role of Magnesium Ion in the Initiation of Ventricular Fibrillation Produced by Acute Coronary Occlusion

By NORMAN L. CARDEN, B.S. AND JOHN E. STEINHAUS, M.D.

The incidence of ventricular fibrillation following acute coronary occlusion in dogs was reduced by perfusing the ischemic area of the myocardium with Locke-Ringer's solution and solutions of magnesium ion in physiological saline. In contrast, normal serum concentrations of magnesium in 5 per cent dextrose appeared to induce ventricular fibrillation in these circumstances. The results suggest that changes in the concentration of magnesium and sodium ion in extracellular fluid may initiate ventricular fibrillation in the ischemic heart.

THE lack of success in the prevention of ventricular fibrillation with quinidine and related drugs following acute coronary occlusion led the authors to the investigation of the physiologic factors involved in the initiation of this process. Wiggers, Wogria and Pinera reported an increase in myocardial irritability in the ischemic heart. Brofman, Leighninger and Beck propose that coronary occlusion produces an electric instability of the heart and that the current of oxygen differential is an important factor in the onset of fibrillation. Since ischemia and circulatory stasis are the primary events resulting from the interruption of the arterial blood supply it has been suggested that abnormal metabolic products or pH changes might explain the myocardial changes which lead to ventricular fibrillation. An approach to this problem was made by perfusing various test solutions into an ischemic area of the heart and observing the incidence of ventricular fibrillation.

METHOD

Dogs weighing between 6 and 15 Kg. were anesthetized with pentobarbital, 30 mg./Kg. The chest was opened, artificial respiration was instituted, the heart was exposed and a loose ligature was placed around the left circumflex coronary artery. Femoral arterial blood pressures were recorded by means of a pressure transducer. Electrocardiograms were taken using lead II of the standard limb leads. The left circumflex coronary artery was cannulated distal to the level of the ligature with a cannula made from the shank of a no. 22 needle connected to a short length of fine bore plastic tubing. An atraumatic forceps was used to occlude the isolated coronary artery for a period of 7 min. after which time it was removed.

Except for the control series, 2.5 ml. of the test solution was injected into the cannulated artery within a period of 30 sec. at 2, 4, and 6½ min. following occlusion of the artery. The test solutions included 0.9 per cent NaCl, 5 per cent dextrose, Ringer's solution, Locke-Ringer's USP XI and XIV. All solutions were heated to remove all dissolved oxygen, adjusted to pH 7.7-7.4 and administered at a temperature of 37°C. The electrolyte components of the Locke-Ringer's solutions were tested in various combinations with special emphasis on the magnesium ion. These solutions included: magnesium 0.05 mEq. (the concentration in Locke-Ringer's USP XI) in 5 per cent dextrose and 0.9 sodium chloride and magnesium 2.0 mEq. (the concentration in Locke-Ringer's USP XIV) in 5 per cent dextrose and in 0.9 per cent sodium chloride. Magnesium 0.05 mEq. was also combined with 3.2 mEq. of calcium and 5.6 mEq. of potassium in 5 per cent dextrose. The effect of magnesium 2.0 mEq. in 5 per cent dextrose was determined in the absence of marked hypoxia by perfusing the solution though the occluded artery 15 sec. after the clamp was applied and releasing the clamp at 45 sec. before significant hypoxia developed.

Constant perfusions of these solutions into an ischemic area of the heart were also performed. A perfusion fluid was injected into the circumflex artery 2 min. following the occlusion at a continuous rate of 5 ml./min. for 5 min. The clamp on the artery was released at the end of 7 min. by which time a total of 25 ml. of fluid had been perfused. In this series of experiments the solutions employed were 0.9 per cent sodium chloride, magnesium 0.05 mEq. in 5 per cent dextrose and 0.9 per cent sodium chloride, magnesium 2.0 mEq. in 5 per cent dextrose and 0.9 per cent sodium chloride and Locke-Ringer's USP XI.

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ROLE OF MAGNESIUM ION IN INITIATION OF FIBRILLATION

Table 1.—Intermittent Perfusion of Ischemic Myocardium

<table>
<thead>
<tr>
<th>Solutions of magnesium</th>
<th>Number of dogs</th>
<th>Number of ventricular fibrillations</th>
<th>Per cent of fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>Locke-Ringer’s USP XIV</td>
<td>11</td>
<td>3·</td>
<td>27</td>
</tr>
<tr>
<td>Locke-Ringer’s USP XI</td>
<td>40</td>
<td>8·</td>
<td>20</td>
</tr>
<tr>
<td>5 per cent dextrose</td>
<td>5</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>0.9 per cent sodium chloride</td>
<td>5</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>Ringer’s solution</td>
<td>5</td>
<td>4</td>
<td>80</td>
</tr>
</tbody>
</table>

* Significant difference (p < .025) as compared to control.
† Highly significant difference (p < .005) as compared to control.

Table 2.—Effect of Magnesium Ions in Ischemic Myocardium

<table>
<thead>
<tr>
<th>Solutions of magnesium</th>
<th>Number of dogs</th>
<th>Number of ventricular fibrillations</th>
<th>Per cent of fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05 mEq. in 5 per cent dextrose</td>
<td>11</td>
<td>2·</td>
<td>18</td>
</tr>
<tr>
<td>0.05 mEq. in 0.9 per cent sodium chloride</td>
<td>21</td>
<td>3·</td>
<td>10</td>
</tr>
<tr>
<td>2.0 mEq. in 5 per cent dextrose</td>
<td>20</td>
<td>20†</td>
<td>100</td>
</tr>
<tr>
<td>2.0 mEq. in 0.9 per cent sodium chloride</td>
<td>24</td>
<td>2†</td>
<td>8</td>
</tr>
</tbody>
</table>

* p < .005 compared to controls.
† Highly significant difference p < .005.

RESULTS

The effects of serial perfusion of various solutions into an ischemic myocardium are revealed in table 1. Both Locke-Ringer’s USP IX and USP XIV reduced the incidence of fibrillation significantly when compared to the control group (p < .005 and < .025 respectively). However, 5 per cent dextrose and 0.9 per cent sodium chloride perfusions did not materially alter the incidence of fibrillation. It is interesting to note that Ringer’s solution which contains the electrolytes found in Locke-Ringer’s, except for magnesium, likewise did not reduce the incidence of this phenomena.

The results of the experiments with magnesium in the perfusion solution are given in table 2. When 0.05 mEq./L. of magnesium was added to either 0.9 per cent sodium chloride or 5 per cent dextrose there was a reduction in the incidence of ventricular fibrillation equal to that produced by Locke-Ringer’s solution. Magnesium in a concentration of 2.0 mEq./L. added to 0.9 per cent sodium chloride was equally effective in reducing the proportion of fibrillations. If magnesium was added to 5 per cent dextrose in a concentration of 2.0 mEq./L., however, ventricular fibrillation developed in 100 per cent of the perfusions. Although the high incidence of fibrillation in the controls made it difficult to demonstrate an increase in this phenomena, the onset of fibrillation with the perfusion of this latter solution occurred within 30 to 60 sec. which suggested that this solution actually induced fibrillation. The electrocardiogram and blood pressure tracing demonstrated a typical elevation in the T wave and S-T segment and the abrupt onset of ventricular fibrillation following the perfusion of 2.0 mEq./L. of magnesium in 5 per cent dextrose. The effect of perfusing this solution of magnesium into the myocardium before marked hypoxia developed was tested in 13 dogs. Ventricular fibrillation did not occur in a single instance and there were very minimal changes in the electrocardiogram.

In a series of ten dogs, 15 mEq./L. of potassium ion in a 5 per cent dextrose perfused into the ischemic myocardium did not produce any discernible increase in the incidence of ventricular fibrillation and there was no immediate onset of fibrillation as seen with the magnesium and dextrose solution. The results obtained
with the other solutions tested did not differ significantly from the control series.

Constant perfusions produced results similar to those obtained with the intermittent perfusions except for 0.05 mEq./L. of magnesium in 5 per cent dextrose. In table 3 the results reveal that all of the dogs fibrillated when 0.05 mEq. of magnesium in 5 per cent dextrose was perfused into the ischemic myocardium just as they did with the 2.0 mEq. of magnesium in dextrose in both intermittent and constant perfusions. Both concentrations of magnesium in 0.9 per cent sodium chloride solution prevented fibrillation in a high percentage of cases and there was a highly significant difference between magnesium in the 5 per cent dextrose and the sodium chloride solutions.

**DISCUSSION**

Harris has suggested that metabolites such as histamine may initiate fibrillation; these perfusion experiments were designed to test this hypothesis. The circumflex branch of the left coronary was selected for clamping and perfusion because it produced a relatively high incidence of ventricular fibrillation. This experience is in agreement with the findings of Allen and Landt. Harris and Rojas reported that if fibrillation were to occur it would appear within the first 10 min. after the occlusion of a coronary artery. The 7 min. period of occlusion used in this study produced essentially the same results.

The mechanical removal of metabolites from the ischemic area of the myocardium was attempted with serial perfusion 2 min. following the occlusion of the artery. Locke-Ringer's solution was selected for the initial test because it most nearly duplicated the electrolytes of the plasma. As indicated in the results, these preliminary studies reduced the incidence of fibrillation. The failure to inhibit the onset of ventricular fibrillation with perfusions of 0.9 per cent sodium chloride and 5 per cent dextrose indicated that simple mechanical removal of metabolites was not an important factor. A similar lack of success with Ringer's solution focused attention upon magnesium ion as the important electrolyte in this process.

When solutions containing 0.05 mEq. of magnesium and 5 per cent dextrose were tested they appeared to be as effective as the Locke-Ringer's solution in the inhibition of ventricular fibrillation. The complexity of this problem was demonstrated when the higher concentration of magnesium (2.0 mEq./L.) was perfused in 5 per cent dextrose and the results were essentially reversed. This higher concentration of magnesium used with 0.9 per cent sodium chloride, however, inhibited fibrillation and the importance of sodium ion was revealed. The contrast between the effects of this latter concentration of magnesium in sodium chloride solution compared to its effect when added to 5 per cent dextrose was the most marked of any results which were obtained. Inhibition of fibrillation with the intermittent perfusion of the lower concentration of magnesium in dextrose solution apparently must be explained by some fortuitous balance of magnesium and sodium ions in the ischemic myocardium. This is borne out by the results of the constant perfusions in which the lower concentration of magnesium in dextrose solution gave very similar results to the 2.0 mEq./L. concentration. It is obvious that the constant perfusion would reduce the sodium ion more markedly than the intermittent since 25 ml. was perfused in the former compared to 7.5 ml. in the latter.

The importance of magnesium ion in the production of ventricular fibrillation in the hypoxic myocardium is further suggested by consistent fibrillation produced by the perfusions with magnesium in dextrose. These effects were all the more remarkable when one considers the fact that this concentration of magnesium ion is within the normal range found in plasma. The lack of fibrillation in the absence of marked hypoxia demonstrates that this effect of magnesium is related to oxygen lack. Histamine solution did not produce ventricular fibrillation in this manner nor did potassium even in a concentration of 15 mEq./L.

It is not possible to exclude other factors such as pH, changes of potassium or calcium ion which may be related directly or indirectly to this process. However, it does appear that the concentration of magnesium and sodium in
the extracellular fluid is of greater importance than the other ions.

**Summary**

An ischemic area of the heart, produced by occluding the left circumflex coronary artery, was perfused with various physiologic solutions and the effect on the onset of ventricular fibrillation was determined. Locke-Ringer's solution significantly reduced the incidence of fibrillation whereas 5 per cent glucose, 0.9 per cent sodium chloride and Ringer's solution were ineffective. The normal serum concentration of magnesium in 0.9 per cent sodium chloride solution markedly inhibited fibrillation, whereas, the same concentration in 5 per cent dextrose appeared to induce this phenomena in the ischemic myocardium. These results suggest the great importance of magnesium ion and also implicate sodium.

**Summario in Interlingua**

Un area ischemic del corde, producite per le occlusion experimental del sinistre arteria coro-nari circumfiexe, esseva perfusionate con varie solutiones physiologic, e le effecto super le declaration del fibrillation ventricular esseva determinate. Le solution de Locke-Ringer reduceva le incidentia del fibrillation significativevmente, durante que 5 pro cento de glucosa, 0,9 pro cento de chloruro de natrium, e le solution de Ringer esseva inefficace. Magnesium in le solution de 0,9 pro cento de chloruro de natrium—in le concentration trovate in sero normal—resultava in un marcate inhibition del fibrillation, durante que magnesium in 5 pro cento de dextrose—in le mesme concentration—resultava in le production de fibrillation in le myocardio ischemic. Iste resultatos indica le grande importantia de iones de magnesium e le facto que etiam natrium es implicate in iste processos.

**REFERENCES**

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