Electrolyte Changes in Heart Tissue and Coronary Arterial and Venous Plasma Following Coronary Occlusion

By JOHN E. CUMMINGS, PH.D.

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Biochemical reactions of myocardial cells to infarction are of basic interest in arrhythmia research. The purpose of the present investigation was to measure in the same dogs concentrations of K, Na, Ca, and Mg in coronary sinus and arterial blood before infarction, during a period of ventricular arrhythmia following coronary artery occlusion, and in infarcted and noninfarcted heart tissue. For comparative purposes, similar analyses were made in control, sham-operated animals.

Methods

Myocardial infarction was produced by the method of Harris which consisted of ligating the left anterior descending coronary artery in 2 stages. The resultant ventricular arrhythmia, which begins 5 to 6 hours following occlusion with the appearance of scattered ectopic beats and then develops into a nearly complete ventricular tachycardia 10 to 15 hours postligation, has been described by Clark and Cummings. For controls, similar experiments were carried out on sham-operated animals in which ligatures were placed under but did not occlude the artery. All experiments were performed under pentobarbital anesthesia. Upon left thoracotomy at the fifth intercostal space, artificial respiration with room air was instituted and continued during the course of the observation. Care was taken to maintain uniform body temperature throughout each individual experiment. Electrocardiograms were obtained on a multichannel recorder.

Blood samples for hematocrit and plasma electrolyte determinations were obtained by direct puncture of the coronary sinus and the common carotid artery. At the start of the coronary occlusion and sham-ligation experiments, 2 control plasma samples were collected 30 minutes apart. Then, beginning 8 hours after ligature placement, additional plasma samples were obtained at hourly intervals. An 8 to 11 hour postligation collection period was chosen because ventricular arrhythmias were always in evidence at this time.

Upon collection of the last coronary sinus and arterial blood samples, each animal was sacrificed by quickly removing its heart. Samples of infarcted tissue from the left ventricle (or noninfarcted tissue in the sham-ligation experiments) and of noninfarcted tissue from the right ventricle were then obtained for cardiac tissue electrolyte analysis.

Eighteen mongrel dogs, ranging in weight from 8.5 to 17.0 Kg., were studied; 11 with coronary artery ligation and 7 with sham-ligation in which the ligatures were placed under but did not occlude the artery. All experiments were performed under pentobarbital anesthesia. Upon left thoracotomy at the fifth intercostal space, artificial respiration with room air was instituted and continued during the course of the observation. Care was taken to maintain uniform body temperature throughout each individual experiment. Electrocardiograms were obtained on a multichannel recorder.

Plasma K, Na, and Ca were determined on a Beckman Flame Photometer. Modifications from the supplied data sheets included measurements of high, medium, and low standards for checking on linearity and bracketing the unknown samples and an improved Ca precipitation technic. Plasma Mg was determined by the spectrophotometric method of Levine and Cummings. In the plasma analyses, only nonhemolyzed blood with normal hematocrit was used.

For tissue analysis, replicate 2 Gm. samples of fresh, minced heart muscle, trimmed of visible fat, were dried to constant weight to determine water content. The samples were then placed on a steam bath and wetashed with 8 ml. nitric acid until dryness. A 1 ml. sulfuric-perchloric acid mixture (35 parts conc. H2SO4, 65 parts 60 per cent HClO4) was added next, the temperature raised to 120 C. and, with the addition of several drops of 30 per cent hydrogen peroxide, digestion proceeded until only a moist, white ammonium salt residue remained. Tissue K and Na were determined by flame photometry, using a 1:300 and a 1:100 dilution, respectively. Magnesium was determined by the spectrophotometric method of
Table 1

Electrolyte Concentrations (mEq./l) in Coronary Sinus Plasma Before and Eight to Eleven Hours After Coronary Occlusion During a Period of Ventricular Arrhythmia

<table>
<thead>
<tr>
<th></th>
<th>Potassium</th>
<th>Sodium</th>
<th>Magnesium</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>During arrhythmia</td>
<td>Control</td>
<td>During arrhythmia</td>
</tr>
<tr>
<td></td>
<td>3.81</td>
<td>4.26*</td>
<td>146.3</td>
<td>144.1*</td>
</tr>
<tr>
<td>±0.32</td>
<td>±0.34</td>
<td>±2.6</td>
<td>±2.1</td>
<td>±0.23</td>
</tr>
</tbody>
</table>

*Significantly different from control at the 0.05 probability level.

Because of the acidity of the 1:50 diluted ashed sample, it was necessary to first adjust pH to that of the Mg water standards before addition of the piperidine buffer, alcohol and Eriochrome Black T dye.

Results

Analytical Recovery

The recovery of K, Na and Ca in 20 samples of dog plasma was within 1 to 2 per cent of the amounts added. Each sample was analyzed in duplicate and good agreement was obtained. As mentioned in a previous publication, the average recovery error of known amounts of Mg added to serum was 1.5 per cent. Known concentrations of K, Na, Ca and Mg were carried through the wet ash procedure. Differences between the amounts taken and the amounts found were less than 2 per cent. In 3 out of 6 recovery experiments, the original salt solutions contained 400 mg. of tyrosine. The amount of K and Na in the standard solutions approximated the content in a 2 Gm. wet weight heart sample, while the amounts of Mg and Ca were arbitrarily selected. In analyzing ventricular tissue, it was found that the Mg content was more than 10-fold that of Ca, and under these conditions the error in determining Ca by the simultaneous Eriochrome Black T method of Young et al. amounted to as much as 30 per cent. Currently, the Ca concentration in normal cardiac tissue is determined complexometrically by the procedure of Bachra et al. The precision of the method appears to be satisfactory for tissue analysis, and data on Ca concentrations in normal and infarcted heart muscle will be reported later.

Plasma Electrolyte Patterns

The average coronary sinus plasma electrolyte concentrations before and 8 to 11 hours after total occlusion of the left anterior descending coronary artery are shown in table 1. As may be noted, K and Mg concentrations were elevated and Na and Ca concentrations were decreased at a time when ventricular arrhythmias were being recorded. No significant arteriovenous electrolyte differences were noted during the 8 to 11 hour postligation period. Throughout this 3 hour collection period, there were no significant trends in either coronary sinus or arterial blood samples.

Cation concentrations 8 to 11 hours after coronary artery ligation were compared to cation concentrations 8 to 11 hours after merely placing ligatures under the coronary artery. Statistical analysis of the data using an unpaired t-test revealed that the increases over control in coronary sinus and arterial Mg and K plasma concentrations in the coronary artery ligation experiments were significantly different (p < 0.05) from the plasma concentrations obtained during a comparable time period in the sham ligation experiments. Likewise, the decreases from control in the Na concentrations in coronary sinus and arterial plasma found during a period of ventricular arrhythmia were of a greater magnitude than the corresponding sham experiment values (p < 0.05). The decreases from control in plasma Ca concentrations 8 to 11 hours following coronary occlusion, however, were not remarkably different from concentrations ob-
ELECTROLYTE CHANGES FOLLOWING CORONARY OCCLUSION

Table 2
Changes in Coronary Sinus and Arterial Plasma Electrolyte Concentrations Eight to Eleven Hours After Ligature Placement

<table>
<thead>
<tr>
<th>CATION</th>
<th>CORONARY LIGATION EXPERIMENTS</th>
<th>SHAM LIGATION EXPERIMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average differences from control, mEq./l</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>+0.45**</td>
<td>+0.09</td>
</tr>
<tr>
<td>Na</td>
<td>-2.3†</td>
<td>+0.7</td>
</tr>
<tr>
<td>Mg</td>
<td>+0.44*</td>
<td>-0.02</td>
</tr>
<tr>
<td>Ca</td>
<td>-0.17*</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

Each dog served as its own control.
*Significant at the 0.05 probability level.
**Significant at the 0.01 probability level.

Electrolyte Patterns in Infarcted and Noninfarcted Cardiac Tissue

The cation concentrations in infarcted postmortem heart tissue obtained 8 to 11 hours after coronary ligation were compared with noninfarcted heart tissue concentrations obtained from the same animal and from sham-operated animals. These data are shown in Table 3. Compared to noninfarcted left ventricular tissue, the infarcted left ventricular tissue averaged 121 per cent more Na (5.1 mEq./100 Gm. wet weight), 47 per cent less K (4.0 mEq./100 Gm. wet weight), and 49 per cent less Mg (1.12 mEq./100 Gm. wet weight). As measured by wet weight-dry weight differences, the infarcted tissue was edematous. Tissue Ca concentrations are not reported due to the inaccuracy of the method of Young et al. when adapted to this problem.

Discussion

For the purpose of discussion, the following assumptions will be made: (1) that about 25 Gm. (1/4) of the myocardium was infarcted following ligation of the left anterior descending coronary artery, (2) that the extracellular space was about 1.5 L. and (3) that all of the K and Mg released from the infarcted tissue remained in the extracellular compartment. Using the data presented in Tables 1 and 3, one can now calculate that the cation loss from the infarcted ventricle would have elevated the plasma K 0.7 mEq./L. and the plasma Mg 0.2 mEq./L. These theoretical values, interestingly enough, approximate the increases actually found in the coronary sinus plasma 8 to 11 hours postligation.

Regardless of the absolute validity of the above assumptions, the fact that altered electrolyte patterns in blood and tissue occurred...
Table 3

<table>
<thead>
<tr>
<th>No. dogs</th>
<th>Ventricular tissue</th>
<th>K mEq./100 Gm. wet weight</th>
<th>Mg mEq./100 Gm. wet weight</th>
<th>Na mEq./100 Gm. wet weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samples from coronary ligation preparations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left ventricle (infarcted)</td>
<td>4.5</td>
<td>1.18</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>right ventricle (noninfarcted)</td>
<td>8.3</td>
<td>2.11</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Samples from sham operated preparations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left ventricle (noninfarcted)</td>
<td>8.5</td>
<td>2.30</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>right ventricle (noninfarcted)</td>
<td>8.4</td>
<td>2.26</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

Standard deviation.

following total ligation, whereas none of these alterations took place after sham-ligation, makes it apparent that the changes in K, Mg, Na and perhaps Ca were due to occlusion of the coronary artery. In all probability, tissues other than myocardium were also responsible for the disturbed coronary sinus and plasma electrolyte patterns recorded 8 to 11 hours postligation. The observations of D'Silva, Houssay et al., and Auditore and Holland that epinephrine and norepinephrine cause hepatic loss of K and the findings of Nuzum and Bischoff and Forssman that urinary catechol amines increased following coronary infarction suggest that some of the hyperkalemia recorded in the present myocardial infarction experiments was due to an adrenergic effect on the liver.

Harris and co-workers have reported that 7 minutes after abrupt occlusion of the left anterior descending coronary artery the concentration of K in venous blood in contact with an area of ischemia was twice that found in a vein draining the noninfarcted posterior ventricle. Although not measured, a significant arteriovenous difference undoubtedly existed. In contrast, the lack of A-V differences 8 to 11 hours postligation indicate that the altered electrolyte concentrations were evenly distributed throughout the extracellular compartment at a time when a persistent ventricular arrhythmia became firmly established in the 2-stage coronary ligation preparation.

The literature is replete with references to abnormal electrolyte patterns associated with cardiac irregularities. Of the cations, K has been studied the most extensively in regard to myocardial infarction. The fact that K escapes from the general region of infarction is well documented. In contrast, the magnitude of K increase from control values during a period of ventricular tachycardia (+0.5 mEq./L.) was considerably less than that obtained by Harris and colleagues from "coronary veins draining the ischemia area" (+3.0 mEq./L.). The difference in plasma K content reported by the latter investigators may be explainable on the different site chosen for venous sampling, on a larger area of myocardial infarction, and on a greater release of K following coronary ligation from organs other than the heart. Sham-ligation experiments and the variation in their electrolyte values would have been of interest.

The amount of Mg lost from the infarcted heart tissue was comparable to that found in human autopsy material by Iseri and co-workers. Although an increase in coronary sinus and arterial Mg following coronary infarction has not been previously reported, Garden and Steinhaus have suggested on the basis of coronary artery perfusion studies that an imbalance between extra- and intracellular Mg may be a cause of ventricular fibrillation following acute coronary artery occlusion. Loss of intracellular Mg and K perhaps accounts for the efficacious antiarrhythmic action of these cations when administered to coronary ligation dog preparations.

Soon after coronary ligation, the affected myocardium begins to gain Na and become edematous. Postligation time, therefore, is important in determining the quantitative content of Na. This may explain the difference.
in Na concentration of infarcted tissue found in this investigation with that found by Iseri et al. in human hearts. A trend was found in this study for the Ca concentrations to be reduced in the coronary sinus and arterial plasmas at the time of ventricular tachycardia. If this observation were due to Ca uptake by the myocardium, it would tend to support the thesis of Covino and Hegnauer that small increases in intracellular Ca are associated with augmentation of cellular excitability, thereby contributing to the development of a ventricular arrhythmia.

In conclusion, various data support the hypothesis that alterations in K, Mg, Na and Ca patterns following coronary occlusion are important excitatory factors in the resultant ventricular arrhythmia. The inherent difficulty in separating cause from effect, however, persists as a perplexing problem.

Summary
When coronary sinus and arterial plasma samples obtained during a period of ventricular tachycardia 8 to 11 hours after coronary ligation were analyzed for electrolyte concentrations, it was found that there was an increase in K and Mg and a decrease in Ca and Na. By comparison, when blood samples were taken from sham dogs 8 to 11 hours after the ligatures had simply been placed under the artery, no significant change in plasma cation concentrations over control values was observed. Infarcted ventricular tissue, as compared with noninfarcted tissue, contained an average of 5.1 mEq./100 Gm. wet weight more Na, 4.0 mEq./100 Gm. wet weight less K, and 1.12 mEq./100 Gm. wet weight less Mg.

Acknowledgment
The author gratefully acknowledges the role of Dr. B. B. Clark who helped to initiate this study and gave valuable counsel throughout the investigation. Important assistance in the electrolyte analyses was provided by Mrs. A. F. Krivis and Dr. R. R. Levine.

Summario in Interlingua
Quando specimens de plasma coronario-sinusael e arterial, obtenite durante un periodo de tachycardia ventricular 8 a 11 horas post ligation coronari, esseva analysate con respecto al concentration del electrolytos, un augmento de K e Mg esseva constatate e un reduction de Ca e Na. Del altere latere, quando le specimen esseva obtenite ab canes a ligation fictitie, nulle significative alteraciones del concentrationes cationie in le plasma esseva observe in comparison con le valores de controlo. Tissu ventricular infarcite, comparente con tissu non-infarcite, conteneva al media—per 100 g de peso humido—un augmento de 5,1 mEq de Na, un reduction de 4,0 mEq de K, e un reduction de 1,12 mEq de Mg.

References


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Circ Res. 1960;8:865-870
doi: 10.1161/01.RES.8.4.865

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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