Relationship of Hypoxia to Arrhythmia and Cardiac Conduction Hemorrhage

An Experimental Study

By Richard E. Clark, M.D., M.S., Ignacio Christlieb, M.D., Miguel Sanmarco, M.D., Rodrigo Diaz-Perez, M.D., and J. Francis Dammann, Jr., M.D.

With the technical assistance of Martin E. Zipser

The causal relationship of hypoxia to arrhythmia was established more than 50 years ago. Although acidosis has recently been considered to be the primary cause of cardiac arrhythmias in the postoperative period, the studies of Greene and Gilbert established that hypoxia in the absence of acidosis resulted in arrhythmias. Moreover, oxygen therapy will abolish arrhythmia in some patients in the presence of either mild degrees of acidosis or a normal pH. A recent review noted the correlation of ectopic rhythms with hypoxia, hypercapnia, acidosis, and hyperphosphatemia (all of which were potentiated by vagal stimulation) during operation.

Recent investigations at the University of Virginia have demonstrated the relationship between hypoxia, arrhythmia, and hemorrhage into the conducting system. The clinical evidence for this was threefold. First, 10 of 25 newborn infants who died within a few days had hemorrhage in the atrioventricular (A-V) node and the bundle of His. Of these 10, 7 died of respiratory insufficiency. Second, a histological study of 75 patients who died during or after cardiac operation revealed that hemorrhage was present in 48 per cent. In only 7 of these 75 patients could local trauma be documented. In contrast, only 6 per cent of 50 random postmortem specimens demonstrated similar lesions. Third, a review of the postoperative course of patients who underwent cardiac operation established that in some individuals a drop in arterial oxygen tension below critical levels produced arrhythmias which could be abolished by increasing arterial PO2 without altering any other parameters. Experimental confirmation was obtained from a group of rats subjected to atmospheres of low oxygen concentration in which 60 per cent developed hemorrhage in the area of the conducting system.

The present investigation was undertaken in an attempt to further substantiate the role of hypoxia in producing arrhythmia and conducting system hemorrhage.

Material and Methods

As the first part of this study, 30 albino rats, two days to six weeks old, were placed in a vented plexiglass chamber after being anesthetized with intraperitoneal pentobarbital sodium. They were exposed to low oxygen tensions (5 to 7 per cent at normal atmospheric pressure) for varying periods of time. The electrocardiogram was continuously monitored throughout the experiment and frequent determinations of the ege oxygen tension were made. The rats were sacrificed from 1 to 24 hours after the experiment, and serial sections of the hearts were taken as well as sections of the lungs, kidneys, and livers.

In the second part of the study, different groups of apparently healthy mongrel dogs were exposed to different levels of hypoxia while the electrocardiogram was continuously monitored. All groups consisted of animals weighing from 15 to 29 Kg. Intravenous pentobarbital sodium (26 mg./Kg.) was used for anesthesia. A polyethylene catheter was threaded into the central aorta in order to obtain pressure recordings and/or arterial blood
samples. In some groups, a venous catheter was also inserted to a level just above the diaphragm. After death or sacrifice, sections from the conducting system were obtained according to the method of Lev et al.\textsuperscript{[11]} Hematoxylin-eosin and Masson trichrome stains were used. In addition, control conducting system specimens were obtained from 10 dogs which succumbed from noncardiac causes, and from 5 exsanguinated dogs.

The pathological examination of the specimens and the interpretation of the histological findings were carried out by one of us with no other information than a keyed number. The results were not correlated with the electrocardiographic findings until all formal reports had been submitted.

**Results**

Arrhythmias and hemorrhage of the bundle of His were observed in 66 per cent of rats six weeks of age and in 57 per cent of two-week-old rats. No hemorrhage was present in 15 rats which were two days to one week of age (table I). It is noteworthy that adult rats developed electrocardiographic changes after only 10 minutes of hypoxia and that, in contrast, baby rats submitted to the same degree of hypoxia for periods up to one hour showed no arrhythmias. In the only two animals from the adult group which did not develop arrhythmias, no hemorrhage could be found. The electrocardiographic changes followed a definite pattern in most of the arrhythmic rats. ST-T changes appeared within the first 10 minutes and were followed by sinus bradycardia which promptly progressed to either partial or total A-V block and nodal rhythm; at the end of 18 to 20 minutes, it degenerated into a slow idioventricular rhythm which reverted to normal sinus shortly after the animals were exposed to air.

For the purpose of this study, the dogs were divided into five groups.

**Group I**

Five anesthetized, heparinized (3.3 mg./Kg.) dogs were exsanguinated via the carotid artery. Blood samples for oxygen tension and pH determinations and electrocardiographic tracings were secured prior to the onset of bleeding and immediately after the first changes appeared in the electrocardiogram. The heart was removed as soon as electrical activity had ceased. All five animals in this group showed sinus bradycardia and ST-T changes. Idioventricular rhythm was present in 80 per cent. One dog presented nodal rhythm. In none of the five animals was the pH less than 7.28, and arterial pO\textsubscript{2} was within normal limits in all of them. No hemorrhage was found in this group.

**Group II**

Five anesthetized dogs were intubated and placed on an automatic positive-pressure respirator, using room air at 16 cycles per minute. The trachea was clamped through the open left chest and the dogs were permitted to die by asphyxia. Control arterial blood samples and electrocardiograms were taken, and a second sample was obtained at the end of four minutes. Specific hemorrhage of the conducting system was present in two dogs, one of which showed complete A-V block. The other was one of three animals which had extrasystoles and bygeminal rhythm. Arterial pH was low (7.28) in only one animal.

**Group III**

Twelve experiments were conducted in six dogs: in two dogs, one experiment each; in two dogs, two experiments each; and in two dogs, three experiments each. The animals in the first two subgroups died during or following the first or second experiment. The animals in the last subgroup were sacrificed 24 hours after the third experiment. In each case, the dog was anesthetized, intubated with a cuffed endotracheal tube and placed on a positive-pressure respirator at 16 cycles per minute, using room air. After control arterial and venous blood samples and an electrocardiogram were secured, hypoxia was instituted by supplying the respirator with either an air-nitrogen or an oxygen-nitrogen mixture until the inspired oxygen percentage was decreased to a low limit of 5 per cent. Determinations of arterial and venous pO\textsubscript{2}, pCO\textsubscript{2}, and pH were carried out every 15 minutes. The electrocardiogram was continuously monitored on an oscilloscope, and serial tracings were recorded whenever important changes were observed. Sodium bicarbonate was adminis-
### Table 1

**Summary of Results**

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Species</th>
<th>Average duration hypoxia (min.)</th>
<th>No. of animals</th>
<th>Age</th>
<th>Sinus bradycardia (%)</th>
<th>2 degree A-V block (%)</th>
<th>3 degree A-V block (%)</th>
<th>Nodal rhythm (%)</th>
<th>ST-T change (%)</th>
<th>Bundle-branch block (%)</th>
<th>Idio-ventricular rhythm (%)</th>
<th>PVC* (%)</th>
<th>VF† (%)</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, sealed chamber</td>
<td>Rat</td>
<td>5</td>
<td>48</td>
<td>10</td>
<td>2 days</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>to</td>
<td>Rat</td>
<td>51</td>
<td>7</td>
<td>2 wks.</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Rat</td>
<td>19</td>
<td>9</td>
<td>6 wks.</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respirator, positive pressure</td>
<td>Dog</td>
<td>5</td>
<td>73</td>
<td>6</td>
<td>Young adult</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Exanguination</td>
<td>Dog</td>
<td>20</td>
<td>0</td>
<td>5</td>
<td>Adult</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>Dog</td>
<td>0</td>
<td>8</td>
<td>5</td>
<td>Adult</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total bypass</td>
<td>Dog</td>
<td>100</td>
<td>0</td>
<td>5</td>
<td>Adult</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total bypass</td>
<td>Dog</td>
<td>20</td>
<td>32</td>
<td>5</td>
<td>Adult</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Mitral valve replacement</td>
<td>Dog</td>
<td>100</td>
<td>0</td>
<td>20</td>
<td>Adult</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>5</td>
<td>20</td>
<td>0</td>
<td>2</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

*PVC = premature ventricular contractions.

†VF = ventricular fibrillation.
Electrocardiographic tracings were characterized by striking similarities. The control sinus arrhythmia promptly progressed to sinus tachycardia with the administration of intravenous pentobarbital. The sequence of electrocardiographic changes was delayed and minimized until toward the end of the experiment. This contrasted with the rat experiments where changes occurred early and could persist for a long time without the death of the animal. After the institution of hypoxia, the first electrocardiographic changes were S-T elevation and either peaking or inversion of the T wave. At this point, there was an increase in both pulse rate and arterial pressure. As hypoxia progressed, there was bradycardia associated with a gradual decrease in blood pressure which became significant when arterial pO₂ levels were at or below 25 mm. Hg. Within five minutes from the appearance of these changes, most of the animals developed extrasystoles and an idioventricular rhythm (one dog showed nodal rhythm). A further decrease in blood pressure resulted in ventricular fibrillation in two instances. Those dogs in which ventricular fibrillation did not occur regained a sinus rhythm and normal blood pressure levels within seconds after the administration of 100 per cent oxygen. In three experiments, a brief period of external cardiac massage was needed to initiate effective cardiac action. The three dogs that sustained repeated periods of hypoxia presented symptoms of obvious central nervous system damage at the end of the second or third experiment. Hemorrhage was not found in any of the dogs of this group.

**Group IV**

Five anesthetized and heparinized dogs were submitted to total cardiopulmonary bypass utilizing a disposable bubble oxygenator. The temperature was maintained at 34 to 35 C. Flows varied from 70 to 100 cc./Kg./min. Electrocardiographic tracings and arterial and venous blood samples were taken before perfusion and every 15 minutes after perfusion started. Hypoxia was effected by the use of room air in the oxygenator for 15 to 30 minutes. All animals were on total bypass for one hour. All animals in this group developed extrasystoles during hypoxia, and one developed a nodal rhythm. The arterial oxygen tension ranged from 12 to 40 mm. Hg, depending on the duration of hypoxia. Only two of this group showed hemorrhage in the conducting system. In contrast, five animals undergoing total cardiopulmonary bypass for one hour, utilizing the same system but with 100 per cent oxygen in the oxygenator, had elevated arterial oxygen tensions and did not develop arrhythmias during or after perfusion. No hemorrhage was found in the conducting system of any of these animals.

**Group V**

Total replacement of the mitral valve was carried out in 20 dogs. All animals died within one hour to 13 days after operation. Fifteen of them died of acute pulmonary edema 3 to 10 days after operation; in all of these, acute hemorrhage was present. Of the five without acute hemorrhage, one showed evidence of old hemorrhage by iron stain. Three of the remaining four were the only ones without postoperative arrhythmia.

No hemorrhage was found in any of 10 dogs which died of noncardiac causes and served as a control group.

**Discussion**

The specific physiological effects of hypoxia and ischemia on the canine cardiac conducting system have been studied with endocardial and epicardial electrodes during cardiopulmonary bypass. A marked difference was noted between the sinoatrial and atrioventricular nodes and the distal conducting system. The bundle of His and the Purkinje fibers were moderately depressed by ischemia and not markedly affected by hypoxia. However, since histological examination of the conducting tissue was not performed, the relationship to the presence of hemorrhage could not be determined.
Our experiments implicate hypoxia as the cause for arrhythmias and hemorrhage into the conducting system of rats. It is very significant that 57 per cent of the two-week-old and 66 per cent of the adult rats that were made hypoxic had hemorrhage. This correlates with our previous observation in which 60 per cent of the hypoxic rats developed the same type of lesions. It is also significant that the only two adult rats which had no arrhythmias did not develop hemorrhage. The fact that baby rats were not affected and had no hemorrhage is in keeping with the known ability of all mammalian species to withstand hypoxia during the newborn period. Therefore, the presence of fetal hemoglobin, which shifts the oxygen dissociation curve to the left and thereby enhances the uptake of oxygen, must be suspected as the protective mechanism.

The experimental group in which dogs were placed on the respirator compares electrocardiographically, but not pathologically, with the hypoxic rat experiments. Four dogs in that group had sinus arrest and an idioventricular rhythm which was immediately corrected by the administration of oxygen, and yet demonstrated no hemorrhage in the bundle of His.

The exsanguinated dogs, the asphyxiated group, and those placed on cardiopulmonary bypass using 100 per cent oxygen, served as controls for dogs which underwent hypoxic perfusion. The latter group, in turn, was designed to separate the influence of trauma, which was known to occur during total replacement of the mitral valve, from the role of hypoxia in the development of hemorrhage.

The experimental data are not conclusive. The fact that hemorrhage did occur in perfused hypoxic dogs and in two of five asphyxiated dogs suggests that hypoxia may have been the cause. In contrast, the increased incidence of hemorrhage in the dogs which had mitral valve replacement suggests the importance of trauma. All the canine experiments fail to define the exact sequence of events and the relative roles of hypoxia, hypercapnia, and acidosis. However, since hypoxia was always the initiating factor, and since hypoxic dogs, whether acidotic or not, could be returned to normal by the inhalation of 100 per cent oxygen, hypoxia would appear to be the most important factor. Furthermore, it is a known fact that the most heavily vascularized portion of the heart is the area of the conducting system, and it is also known that hypoxia produces capillary wall changes that increase capillary permeability. Hypoxia, therefore, may be expected to produce selective hemorrhage into the bundle of His with the concomitant arrhythmias.

A species difference with respect to the degree and type of response to hypoxia appears to exist between rats, dogs, and humans. These experiments have demonstrated that specific hemorrhage does appear in the conducting system of a large percentage of rats in response to hypoxia. However, a significantly small percentage of dogs that had been made hypoxic, and with comparable arrhythmias, developed hemorrhage. Previous work has demonstrated that hemorrhage in the human conducting system, and an electrocardiographic pattern similar to that of the hypoxic rat, is a frequent finding following cardiac operation and that, postoperatively, a high level of oxygen tension is necessary to maintain normal cardiac rhythm. Thus, the dog would appear to be more resistant than either rats or humans to the effects of hypoxia, both with respect to the severity of the arrhythmia and to the incidence of hemorrhage. However, in those dogs which underwent successive hypoxic studies, the electrocardiographic changes appeared sooner and with a lesser degree of hypoxia in the second and third experiments. Moreover, progressive electrocardiographic changes of ischemia and necrosis were evident in tracings obtained 24 hours after the experiments, thus suggesting that hypoxia did result in myocardial damage. A series of cats is now being studied in an effort to determine if species, per se, is truly a determinant factor.

**Summary**

The relationship between hypoxia, arrhythmia, and hemorrhage of the conducting system...
was studied in the experimental laboratory by rendering several different groups of rats and dogs hypoxic, and by the histological examination of the area of the atrioventricular node and bundle of His in sections obtained from the hearts of these animals. Sixty-one per cent of rats aged two weeks or older developed arrhythmias and had hemorrhage. None of 10 baby rats presented changes when submitted to the same type of experiment. Hemorrhage was present in only 40 per cent of asphyxiated dogs and in 40 per cent of the dogs that were made hypoxic during cardiopulmonary bypass; 75 per cent of dogs which underwent total mitral valvular replacement and expired in acute pulmonary edema 3 to 10 days postoperatively presented a similar type of lesion. In most cases, the administration of oxygen sufficed to reverse the electrocardiographic changes back to normal.

Hypoxia is suggested as the primary cause for these changes, on the basis of previous clinical and experimental work and the information collected from these experiments. The importance of a possible species difference was suggested when attempts were made to correlate the results in rats, dogs, and humans.

References
Relationship of Hypoxia to Arrhythmia and Cardiac Conduction Hemorrhage: An Experimental Study

RICHARD E. CLARK, IGNACIO CHRISTLIEB, MIGUEL SANMARCO, RODRIGO DIAZ-PEREZ, J. FRANCIS DAMMANN, JR. and Martin E. Zipser

Circulation. 1963;27:742-747
doi: 10.1161/01.CIR.27.4.742

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1963 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/27/4/742

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/