Delayed Development of Ventricular Ectopic Rhythms following Experimental Coronary Occlusion

By A. Sidney Harris, Ph.D.

Following aseptic occlusion of the anterior descending artery of the dog's heart ectopic ventricular tachycardia develops after a latency of four and one-half to eight hours, and persists for two to four days. Large gross infarcts are found in all hearts. The duration of latency of onset of major ectopic activity approximates the minimal period of ischemia required to produce histologic signs of necrosis. It is suspected that products or processes of necrosis have excitatory effects on tissues bounding the ischemic zone. Evidences concerning various possible excitatory factors are briefly reviewed.

Previous experimental studies on ventricular ectopic activity following coronary occlusion, with few exceptions, have been confined to observations made within a brief acute period after occlusion, though both experimental and clinical reports have shown that ventricular arrhythmias may develop after periods of many hours and even days after obstruction of the artery. The scarcity of experimental studies upon the delayed development of ventricular arrhythmias and fibrillation perhaps is attributable in part to the high rate of early mortality via ventricular fibrillation, which results from abrupt occlusion of one of the two major rami of the left coronary artery, and perhaps in part to the observation that in hearts that survive the first few minutes, ectopic activity ceases or nearly ceases within ten to twenty minutes, and observations were terminated because continuation seemed useless.

In experiments preliminary to this study a method was discovered whereby the loss of animals by ventricular fibrillation during the immediate period of danger could be prevented in all cases. Ectopic activity which arose later could then be recorded and analyzed without the obstacle of high early mortality. This study is devoted to recording and analysis of the delayed ectopic ventricular activity following coronary occlusion.

The early development of ectopic ventricular discharges and ventricular fibrillation which often follows the experimental abrupt occlusion of a large coronary artery in the dog has been analyzed in some detail in previous reports. It was observed that the period of susceptibility to early ventricular fibrillation was brief, and that each fibrillation was initiated by a paroxysm of ventricular ectopic systoles accelerating in frequency. Fibrillation did not occur later than the tenth minute of occlusion though in some of the nonfibrillating trials the occlusion was maintained for thirty minutes before release of the artery. The frequency of ventricular premature systoles was at its maximum during the period from about the fifth to the eighth minute, after which it slowly declined. In some trials the ventricular premature systoles ceased entirely after ten to twenty minutes, and in others the ectopic frequency continued at a slow rate of about 1 to 5 per minute.

A causal relationship between ventricular premature systoles and the initiation of ventricular fibrillation has been demonstrated and the mechanism explained in a series of papers. The problem of the genesis of ventricular fibrillation, in a fundamental sense, contains the problem of ventricular ectopic discharges.

**Procedures**

Male dogs weighing 10 to 22 Kg. were used in all experiments. In the first series of animals, morphine (about 2 mg. per Kg.) and the minimal dose of barbital sodium necessary for surgery (180 mg. per Kg. intravenously) were used. If extra morphine was needed after awakening, it was given. Pentothal sodium and pentobarbital sodium have been used
in later experiments for comparison of possible effects of changed duration of anesthesia upon the
time of development of delayed ectopic activity.

During the preliminary acute experiments the chest was opened by a midline incision of the sternum. The anterior descending artery was dissected free for a few millimeters near the distal edge of the left auricular appendage and ligated there. After three of the first four hearts developed ventricular fibrillation within a few minutes of ligation, two-stage occlusion was tried. A double ligature of sufficient length was passed under the freed artery by a small curved forceps or a small aneurysm needle. The double ligature was cut, thus becoming two ligatures. The first ligature was drawn snugly but not tightly around the artery together with a 20-gage hypodermic needle. The needle was withdrawn immediately, leaving the artery constricted but still permitting some blood to pass. The second ligature was tightened one hour after the first in early experiments. Later the waiting period was shortened to thirty minutes. The second ligature completely and permanently compressed the artery.

This method was successful to such a degree that its use in three other experiments and in more than 60 aseptic occlusions through a small opening in the thoracic wall has produced only one early ventricular fibrillation. In that one case the first ligature was too tight. It indented the arterial walls so deeply that the lumen remained occluded after the needle was removed. Only a few ventricular premature systoles have been seen following partial occlusion in any other experiment after the first ligature, or in the first few minutes following the subsequent total occlusion.

After the procedure of two-stage occlusion was developed, aseptic methods were employed in all operations. The ligatures were applied through a small opening in the fourth interspace. The wounds were closed in layers and the animals were kept for periods varying up to forty-six days, though almost all of them were sacrificed or died within two weeks after the operation.

Results

Following the tightening of the second ligature, i.e., the completion of the occlusion, electrocardiograms were made at frequent intervals, and observations of the electrocardiographic deflections for movements indicative of ventricular ectopic beats which might not be included in brief records were made even more frequently and often continued for many minutes at a time.

The records in figure 1 illustrate the electrocardiographic (Lead II) findings during the development of ectopic activity. The control record was made shortly after the administration of the anesthetic. The animal was asleep, but not fully anesthetized. The record shows normal complexes, a relatively slow rate, a normal sinus arrhythmia. Four hours and thirty minutes after occlusion, the rate was faster but there were no premature ventricular beats. At five hours and twenty minutes complexes of ectopic ventricular origin had begun, and at times were fairly numerous, though their rate was not yet rapid. After eight hours the ectopic activity was dominant. It was difficult to find a normally initiated beat in long strips of record. None are contained in the piece shown. The discharges were multifocal. The rate was about 160 per minute. In some other experiments the maximal ectopic rate has been as high as 250 per minute.

A chart to illustrate more quantitatively and over a longer time the rate of development and subsidence of ventricular ectopic activity in an experiment in which morphone–barbital sodium anesthesia was employed is reproduced in figure 2. This is a plot of data from the first animal of the aseptic series. During the first four hours following occlusion there were occasional ectopic ventricular beats. Sometimes there were 1 to 3 per minute. At other times there were none during many minutes of observation.

Between the ends of the fourth and sixth hours, the ectopic ventricular frequency increased sharply. By the end of the eighth hour all beats were of idioventricular origin. This completely ectopic ventricular rhythm continued from about the eighth hour of occlusion until sometime between the fifty-first and sixty-ninth hours. During the third postoperative day ventricular ectopic beats persisted at a frequency of about one-half the total heart rate. No ectopic beats were observed on the fourth day. The maximal frequency of the abnormal complexes in this experiment (250 per minute) was recorded at twenty-one hours. There was a slight diminution to 230 at thirty hours and to 160 on the second day (forty-eight hours). This general pattern of rise and decline was found to be characteristic of the series, but with the time of beginning of the rapid rise in frequency of ectopic complexes
VENTRICULAR ECCOTIC RHYTHMS

varying in a large majority of experiments between four and one-half and eight hours, and the duration of ectopic activity varying between two and five days.

The maximal rate of ectopic activity was reached in all experiments by the thirtieth rate estimates. During the early part of the delayed rise there were periods of three or four minutes when no ectopic beats were seen. Then two or three might appear in succession or within a few seconds. Even with ectopic beats averaging 30 to 40 per minute, as many as 10

![Electrocardiograms](http://circ.ahajournals.org/)

**FIG. 1.—Electrocardiograms illustrating development of ventricular ectopic activity following coronary occlusion.** Control record was made with dog under morphine-Pentothal sodium anesthesia before operation. Other records were made four hours thirty minutes, five hours twenty minutes, and eight hours after total occlusion.

hour. In the usual case it was reached within ten to twenty hours, and persisted at a high level throughout the first postoperative day.

During the period of occasional or developing ectopic activity, it was necessary to observe the electrocardiographic deflections for minutes at a time and to count in order to make accurate or 15 consecutive normally initiated complexes sometimes were observed. Interspersed with such successions were periods when almost all beats were from ventricular pacemakers. It appeared that a ventricular focus (often more than one) with a frequency of impulse formation almost equal to that of the S-A node was
alternately gaining and losing dominance of the cardiac rhythm. Such interplay between the S-A node and subordinate pacemakers has been well described.\textsuperscript{13}

With further increase in ectopic activity normal complexes became fewer and eventually were completely or almost completely supplanted by ectopic forms. At the height of ectopic activity the rate of the idioventricular discharges usually did not vary greatly. Only exceptional experiments showed significant variations in ectopic activity on the first post-barbital anesthesia might be a governing factor. A series of operations were then performed using Pentothal sodium, pentobarbital sodium, and ether anesthesia. Ether was used in the smallest number of experiments, four. The animals awoke from each of these anesthetics more rapidly than from morphine and barbital. The animals given Pentothal sodium were quite active within two to three hours after the completion of the operation. When they moved themselves about vigorously on their hammocks, showing excitement in their partly nar-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Chart showing heart rate (normal beats plus ventricular premature systoles) and frequency of premature beats as they changed with time after occlusion of the artery. Lower curve, rectal temperature. Operation performed under morphine–barbital sodium anesthesia.}
\end{figure}

operative day when the excitatory drive (of whatever kind) of the ectopic pacemakers was most intense.

During the subsidence of ectopic activity on later days alternating periods of dominance by the normal and ectopic pacemakers apparently similar to those seen during the time of development of ectopic discharges reappeared.

\textit{Relation to the Anesthetic.} The consistent repetition of the four and one-half to eight hour latency before the onset of the rapid rise of activity in ventricular foci led to a suspicion that the lessening of effect of the morphine–barbital sodium, 15 mg. per Kg., and barbital sodium, 60 mg. per Kg., were tried in different experiments.
The animals operated under ether exhibited no significant increase in early ectopic activity over that of the first four and one-half hours following occlusion under morphine and barbital sodium. Following pentobarbital sodium there were moderate increases between three and four and one-half hours after occlusion, but as in the Pentothal sodium experiments they were easily controlled until the main rise made its appearance, after which half anesthetic doses of pentobarbital and the resulting deep sleep made no observable change in the steep rise in ectopic frequency.

The evidence indicates that the usual latent period of four and one-half to eight hours between occlusion and the onset of the steep rise of ectopic activity is not due to the time required for awakening from anesthesia.

Relation to Temperature Changes. The charts almost consistently show a rising rectal temperature during the period of increasing ectopic activity. In two experiments, however, the main increase in temperature occurred during the two hours just preceding the detection of any rise of ectopic activity. In three experiments the temperature showed a downward fluctuation while the ectopic frequency was rising. On the second or third postoperative day it was not uncommon to find ectopic activity subsiding while the temperature held a level near its maximum. In many experiments there was a striking parallelism between temperature and ectopic frequency. It is possible that both are related to tissue changes that resulted from ischemia of the myocardium. In some experiments the temperatures fell postoperatively to levels significantly below the control readings of 37 to 38°C. Recovery from the low temperature in these experiments fused with the rise which occurred after a few hours in all experiments. The presence or absence of an initial fall in temperature bore no consistent relation to the maximum temperature eventually reached, nor to the intensity of ectopic activity attained. The highest temperature observed was 40.2°C. The delayed rise in ectopic ventricular activity is independent of the rise in temperature, though they sometimes follow parallel courses. It is probable that there are common predisposing factors.

Level of Occlusion. The distances of the ligatures from the ostia of the left coronary arteries were measured in all of the first 36 hearts of the aseptic series after preservation in formalin. These distances, together with associated mortality rates (seventy-two hours) and the number and percentage of animals in the different ligature-distance groups that developed rapid ventricular tachycardia within the usual time range are summarized in table 1.

Of a total of 10 animals in the group with ligatures nearest the ostia, 4 died during drug tests and therefore are excluded from the mortality table. Of the remaining 6, 5 died at periods varying from two hours fifty-five minutes to seventeen hours after ligation. Only one of these 5 animals that died developed more than an occasional ectopic beat at any time. All were very weak and dyspneic. It is probable that all of them died of myocardial failure leading eventually to cessation of pacemaker action. The 4 animals that were killed in drug tests had developed rapid ventricular ectopic rhythms and did not appear so weak as did the previously described group. Throughout the study it was observed that the animals that appeared very weak and ill usually produced few ectopic discharges, though there were exceptions.

In the 30 animals with ligatures between 1.5 and 3.0 cm. from the ostia, the mortality rates ranged from 25 to 33 per cent in the various subdivisions. The percentage of animals that developed rapid ectopic ventricular tachycardia was significantly higher in those hearts with the ligatures 2 to 3 cm. from the ostia than in those with more proximal ligatures. Ligatures placed within this distance range offer the highest probability of yielding surviving animals with rapid ectopic discharges for purposes of investigations upon this phenomenon. As a surgical guide ligatures should be placed 5 to 8 mm. distal to the edge of the left auricular appendage.

Infarction. No animals were sacrificed earlier than six days after operation, though some died earlier. A report on the first 25 dogs of the series will fairly present the gross observations on infarction. Twenty-one of these dogs were sacrificed at periods varying from six to twenty-five
days after the occlusion. Two others died at eighteen and one-half and twenty hours following occlusion after developing ectopic ventricular tachycardia in the typical manner. One died two hours and another three hours after occlusion. Gross infarcts with approximately normal thickness of the wall were clearly apparent in 16 of the 21 hearts that survived long enough to produce them. The infarcted muscle was stiffened in some hearts, and in others it was very soft, approaching liquefaction. The epicardial surface of the infarcted area of some hearts was rough.

The line of demarcation between necrotic and normal myocardium usually was very sharp. This was particularly true upon viewing the endocardial surface and cuts across the boundary region within the muscle.

The other five hearts of dogs that were sacrificed after a period sufficiently long to produce infarction were found to have greatly thinned anterior left ventricular walls (to about 2 mm.) and the color of the remaining tissue in this area was a paler more grayish-yellow color than the muscle of other areas. Usually it was very tough and fibrous, though the epicardial surface bore the appearance of muscle. It was evident that much tissue had been removed from these thinned walls, and that, like the hearts with obvious thick infarcts, the anterior wall of the left ventricle had suffered severe necrosis. In these five it appeared that the outer layer of muscle had survived and that fibrous tissue had been added, leaving a thin but strong tough scar. In these hearts the durations of occlusion were 11, 12, 14, 20 and 21 days. In some of the other hearts with similar durations of occlusion (one twenty-five days) the infarcts were hard, not thinned, and were without evidence of processes of softening or dissolution. In these, and in other hearts with infarcts undergoing liquefaction, the necrosis often extended through the entire wall except a very thin, not easily detected, endocardial layer. Liquefaction and canalization extended almost through the walls of two hearts, but there were no ruptures.

Microscopic studies of tissues from the ischemic or infarcted areas have been made from hearts of animals that survived coronary occlusion for periods varying from two hours to twenty-five days. The findings were similar to those reported by others.14, 15, 16

Tissues from ischemic areas of hearts of animals that died two and three hours after occlusion appeared normal on microscopic examination. Definite changes were seen in sections from animals that died six hours thirty-five minutes, nine hours forty minutes and ten hours after occlusion. Among the changes observed in these specimens were leukostasis, leukocytic infiltration, hyaline changes in the muscle fibers, fragmentation of muscle, changes in staining properties, vacuolation and changes in the nuclei.15 Mallory and co-workers have reported that histological evidence of necrosis can be detected within five or six hours after occlusion.15

**DISCUSSION**

The discovery that by two-stage occlusion the immediate loss of animals by ventricular fibrillation could be circumvented has been of the greatest value in facilitating the study of delayed ectopic ventricular activity. The reason why protection against immediate ventricular ectopic rhythms and ventricular fibril-

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**TABLE 1.—Relation of Early Mortality (72 Hours) and of Development of Ectopic Discharges to Distance of Ligature from Ostium of Left Coronary Artery.**

<table>
<thead>
<tr>
<th>Distance of Ligature</th>
<th>No. of Animals</th>
<th>Mortality in 72 Hours</th>
<th>Rapid Ectopic Systoles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No. of Animals</td>
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<td>Cm.</td>
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<tr>
<td>1.1-1.5</td>
<td>6*</td>
<td>5 83</td>
<td>2 (6 of 10)*</td>
</tr>
<tr>
<td>1.6-2.0</td>
<td>15</td>
<td>5 33</td>
<td>9</td>
</tr>
<tr>
<td>2.1-2.5</td>
<td>11</td>
<td>3 27</td>
<td>9 (10 of 12)*</td>
</tr>
<tr>
<td>2.6-3.0</td>
<td>4</td>
<td>1 25</td>
<td>4</td>
</tr>
</tbody>
</table>

* Animals that were killed in the process of drug testing during the first 72 hours could not be included in the mortality table. There were 4 such animals in the 1.1-1.5 cm. group and 1 in the 2.1-2.5 cm. group. The inclusion of these animals in the data on development of rapid ventricular ectopic systoles produced the figures given in parentheses.
lation (first ten minutes) results from partial occlusion for thirty minutes before total occlusion has not been determined. Others who have cited a preliminary report on this finding have assumed that the protection results from the development of collateral circulation during the partial occlusion period. It should be remembered however that extensive and severe myocardial necrosis develops in each of these hearts. This seems to be a strong argument against an important development of collateral circulation within so brief a period. Others have reported from experimental observations that a longer period is required to develop a measurable increase in collateral circulation. It is probable that during the thirty minutes of partial occlusion accommodation of the muscle fibers to the kind of excitatory influence that causes the early ectopic activity develops. A few hours later other kinds of excitatory factors apparently arise.

Site of Origin of Ectopic Impulses. Evidence from earlier studies on excitability changes in moderate and severe anoxia in heart muscle and from local lead recording of time of activation in different regions of the ventricular surfaces during coronary occlusion indicates that ectopic discharges that arise within a few minutes after sudden occlusion originate in the partially ischemic boundary between the fully ischemic and normally circulated areas of muscle. Observations in chronic experiments of severe necrosis in the region of infarction and of the entirely normal appearance of muscle outside of the infarct in animals sacrificed after five to twelve days indicate also, by elimination, that the boundary zone is the probable site of pacemakers in delayed ectopic activity. This boundary is extensive. It is made up of (1) a thin band of tissue forming a circumference around the fully ischemic area and extending in a majority of hearts from the epicardium to within a fraction of a millimeter of the endocardium; (2) a thin sheet of tissue between the ischemic muscle and the endocardial layer; and (3) in some hearts a thin sheet of tissue between the ischemic muscle and a spared external (epicardial) layer. The circumferential band is complicated in that the infarct extends onto the septum including the anterior third or fourth of it from the level of the liga-
ture to a distal limit near the apex. The boundary, therefore, divides the septum. It also extends along the edge of the right ventricle.

The form of the electrocardiographic deflections during low frequency ectopic activity often indicates a predominant single focus. As the activity becomes more frequent, i.e., as the intensity of the ectopic excitatory drive becomes greater, the form of the complexes shows many variations indicating multifocal origins.

Factors in Ectopic Excitation. Moderately anoxic heart muscle has been shown to be hyperexcitable by measurement of its threshold to electric stimuli. This hyperexcitability exists when the whole heart is subjected to the same degree of anoxia; therefore it cannot be attributed to an injury potential, though in regional ischemia the injury potential undoubtedly adds another factor of excitation (see next paragraph). Within a very thin sheet of boundary cells between ischemic and nonischemic muscle there is a transition from adequately circulated cells to cells that are ischemic to a degree sufficient to produce complete inactivation followed by necrosis. Within the transition sheet there are cells in all stages of ischemic hypoxia and anoxia; therefore some cells will be within the range that produces hyperexcitability. However, anoxia alone when produced slowly by rendering the whole animal anoxic does not cause ectopic impulses. It may be inferred then that some other excitatory factor or factors must act upon these border cells made hyperexcitable by partial anoxia or ischemia to evoke discharges. Some of the possible additional factors are injury potentials, sympato-adrenal stimulation, histamine, and possibly other excitatory products liberated from tissues.

 Injury Potentials. From neurophysiology it is known that the region of nerve near an injury is hyperexcitable and that it may discharge impulses spontaneously or respond to stimuli that would be subthreshold to a region of nerve farther from the injury. Hyperexcitability near an injured area of nerve extends 10 to 12 mm. from the injury, diminishing with distance. This distance corresponds almost identically with the length of nerve adjacent to an
injury from which injury potentials of significant intensity have been recorded. This hyperexcitability is attributable to the injury potential which produces a state of catelectrotonus and partial depolarization of the cell membranes within the region.

An ischemic area of heart muscle becomes electrically negative with respect to the normally circulated muscle within about one and one-half minutes after obstruction of the artery. The diastolic negativity of injured heart muscle is found in all parts of the injury and is said to have a sharp boundary coinciding with the boundary of the injured zone. Strong catelectrotonic effects of the injury potential undoubtedly exist in the boundary region. Injury potential, therefore, can be regarded as a probable contributing factor in ectopic ventricular excitation after coronary occlusion.

**Sympatho-Adrenal Stimulation.** Sympathetic impulses to the heart and injected epinephrine facilitate the production of ectopic ventricular beats. Excision of the adrenal glands and stellate ganglia markedly reduced the ectopic activity and probability of ventricular fibrillation in experimental acute benzo poisoning in cats and monkeys. The removal of the stellate and upper five thoracic ganglia has been reported to diminish markedly the occurrence of premature systoles, ventricular tachycardia and fibrillation immediately after sudden occlusion of a coronary artery. Many studies, recently reviewed by Raab, have shown that heart muscle contains high concentrations of epinephrine and epinephrine-like catechols.

All of these observations are consistent with the view that sympahto-adrenal excitation may be a factor which contributes to the production of ventricular ectopic rhythms following coronary occlusion.

**Histamine** is present in the tissues of the body in quantities which are toxic when liberated. When added to fluid bathing non-rhythmic heart tissues, histamine has induced rhythmic activity. Cardiac muscle releases histamine-like substance continuously. The amount is increased by increasing the work of the heart, by anoxia and by increased carbon dioxide. Blood histamine is increased by slow intravenous injection of epinephrine. There is evidence that histamine, tyramine, and possibly other amino acid derivatives present in tissue extracts sensitize heart tissues to epinephrine.

It appears possible, therefore, that in regional ischemia histamine and other products liberated from proteins in the ischemic muscle could diffuse to the hyperexcitable cells and there become factors in the discharging of ectopic impulses.

**Correlation of Postulated Excitatory Factors to the Immediate, Intermediate and Delayed Phases of Ectopic Activity.** There are three distinct periods which compose a time pattern in the manifestations of ventricular ectopic activity after experimental occlusion of a large coronary artery: (1) an immediate period of intense ectopic activity and danger of ventricular fibrillation within the first ten minutes, followed by (2) an intermediate period of little ectopic activity which lasts four and one-half to eight hours, and then (3) the delayed persistent period of intense ectopic drive begins.

**The Immediate Period and Following Quiescent Hours.** During the crescendo of ectopic beats that occurs within the first ten minutes after occlusion it is obvious that products of necrosis are not involved. Hyperexcitable partially anoxic boundary cells exist and they are subjected to the catelectrotonic effect of the injury potential which probably reaches its maximum by the end of one and one-half minutes and continues. The increasing excitation which produces the rising ectopic frequency for the next few minutes occurs while the animal is under morphine-barbital or other barbiturate anesthesia of surgical depth; therefore it is unlikely that reflex excitation is responsible. It appears more probable that the direct effects of ischemia on the excitable membranes of the cardiac muscle cells produce this excitation and the subsidence which follows. Similar behavior of nerve receptors in ischemic skeletal muscle has been reported.

**Intermediate Period.** During the quiescent period after the subsidence of action of the immediate period (or after the second ligature in two-stage occlusion) and before the delayed rise of ectopic activity, the ischemic-nonische-
mic boundary remains, and the injury potential has been found to be relatively constant at a high level in some recent experiments (as yet unpublished) during these hours. Evidently additional factors are required to produce rapid ectopic discharges, but for a number of hours these are weak or lacking.

Moderate increases in ectopic activity occurred in some animals during excitement periods while awakening from anesthesia, especially Pentothal sodium, two and one-half to four and one-half hours after the occlusion. These premature beats usually subsided when the animal became calm spontaneously and were controllable by sedation. This response to rest and to sedative drugs suggests that sympathto-adrenal excitatory factors may have produced the added excitation required for these moderately increased discharges during the hours prior to the main rise.

Delayed Ectopic Activity. Since the rapid rise of ectopic activity that begins four and one-half to eight hours after occlusion is not prevented nor visibly influenced by normal sleep nor by barbital sodium administered a short time before its beginning, it probably is determined by factors which are not dependent upon nerve impulses. The finding that the four and one-half to eight hour latency approximates the minimal period of ischemia found by pathologists to be necessary for the development of histologic evidence of necrosis may be more than fortuitous coincidence. It is of interest also that the circulation of a dog's limb must be obstructed for about six hours by tourniquet or ischemic compression in order to produce shock by this technic. Recent experiments have indicated the presence of a vasoconstrictor substance with properties of norepinephrine in blood from dogs' limbs that had been ischemic for five hours. It appears probable that processes and products of necrosis are of major significance in producing the intense delayed ectopic excitation that occurs during acute myocardial infarction in the dog's heart.

Possible Influence of a Delayed Increase in Collateral Circulation. In occlusions of the anterior descending artery in acute experiments the ectopic discharge frequency passed through a maximum and then subsided. The sudden release of the occlusion after the decline or cessation of ectopic beats caused a very brief return of high frequency ectopic discharges after about one minute. These quickly produced ventricular fibrillation in a high percentage of trials. In the few trials that did not terminate in fibrillation the rapid ectopic discharges lasted about ten seconds and subsided.

There is some evidence that the small collateral blood flow to the area made ischemic by the occlusion of the anterior descending artery remains relatively unchanged for a few hours and then begins to increase. It has been suggested that the delayed increase of circulation could restore excitability in depressed cells, through a hyperexcitable stage similar in nature to that described on readmission of blood in the acute experiment. This might cause discharging of delayed ectopic impulses. However, this concept appears improbable when the long duration of this activity (two to five days) is considered. Adaptation to the conditions produced by the increased flow, and cessation of the discharge would be expected within a much shorter time. Excitation by products of necrosis appears to be the more probable late developing factor.

Summary

The anterior descending arteries of dogs were ligated aseptically and the resulting ectopic ventricular activity was studied almost continuously by electrocardiographic observations and frequent records.

By occluding the artery in two stages loss of animals by early ventricular fibrillation was prevented.

Following the final stage of occlusion there was a period of four and one-half to eight hours with little or no ectopic activity. After this latency, ectopic impulses developed rapidly, reaching the maximal frequency within ten to twenty-one hours. Typically, a high ectopic rate persisted through the first postoperative day and then subsided slowly, disappearing after two to four days.

The rectal temperature usually rose simultaneously with the rapid increase in ventricular
ectopic frequency, but consistent correlations between temperature and ectopic frequency are lacking.

Large gross infarcts resulted from the occlusions. In some hearts an external layer was spared. A very thin endocardial layer appears to be spared in all hearts. The earliest microscopic signs of necrosis have been found to become visible after a period similar in duration or only slightly longer than the latency for the rapid delayed rise of ectopic activity.

An attempt toward an analysis of the excitatory factors which probably produce ectopic impulses has been made. Cells within the boundary between the ischemic and non-ischemic tissues undoubtedly are rendered hyperexcitable by moderate ischemia, and this hyperexcitability probably is enhanced by catelectrotonus resulting from the injury potential.

Possible additional excitatory factors are sympahto-adrenal substances, histamine, and other substances formed or liberated during necrosis.

The delayed and rapid rise of frequency of ectopic beats which begins after four and one-half hours of occlusion or longer is evidence that new and intense excitatory influences are added after this long latency. This long delay together with the failure of added anesthesia to prevent the delayed rise is considered as evidence that the delayed excitatory factors are produced or released by processes of necrosis.

The possibility that a delayed increase in collateral circulation to the ischemic area may increase excitability and thereby contribute to the delayed ectopic activity is discussed. It is not believed to be an important factor.

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