Ventricular Reentry and Automaticity in Myocardial Infarction*

Effect of Size of Injury

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The effects of the size of acute myocardial infarction on ventricular reentry and automaticity were studied in 36 mongrel dogs. Large transmural myocardial infarctions were produced by ligation of the left anterior descending coronary artery (major ligation; diameter of infarction above 4.0 cm), and small subendocardial or intramural infarctions were produced by ligation a small diagonal branch of the left anterior descending coronary artery (minor ligation; diameter of infarction less than 1.5 cm). Reentrant arrhythmias were induced by rapid ventricular stimulation, and ventricular automaticity was determined during vagal stimulation. Ventricular automaticity became enhanced only 30 to 45 minutes after both major and minor coronary arterial ligations; however, the animals with major ligations attained a higher level of increased automaticity. While automaticity became enhanced in both groups, reentrant arrhythmias could never be produced artificially (or observed spontaneously) in the animals with small myocardial infarctions. The dependence of the so-called reentrant arrhythmias on the size of the infarction is a major support for the theory of reentry as the basis for these arrhythmias.

Detailed analysis of the mode of death from acute myocardial infarction reveals that 40 to 60 percent of the deaths occur before the patients ever reach the hospital. Ninety percent of these are due to ventricular fibrillation, which becomes, therefore, the prime cause of death from acute myocardial infarction. While ventricular fibrillation denotes sudden death, it is now clear that it is closely related to ventricular premature beats and ventricular tachycardia. The study of ventricular arrhythmias in acute myocardial infarction becomes, therefore, of primary importance.

Acute infarction in the canine heart results in a reproducible sequence of ventricular arrhythmias. In the acute phase (2 to 20 minutes after ligation), these arrhythmias are the result of reentry, as shown in several studies which demonstrated delayed propagation of electrical impulses in the ischemic areas. Reentrant arrhythmias are the result of sufficient delay of the wave front of activation in or around the ischemic zone (or both); these arrhythmias should be dependent, among other factors, upon the dimensions of the injured area. On the other hand, the increased automaticity, being a cellular phenomenon, would be independent of the size of the infarction.

In the present experimental study, we have investigated the course of time for the development of both reentrant arrhythmias (spontaneous and stimulation-induced) and the phenomena of increased automaticity following acute myocardial infarction and their dependence on the size of the infarction.

Materials and Methods

The study was performed on mongrel dogs weighing 15 to 30 kg (33 to 66 lb). The operations and studies of stimulation were performed under anesthesia with intravenously administered pentobarbital sodium (25 mg/kg of body weight).
Experimentally Produced Acute Myocardial Infarction

Coronary arterial ligation was performed as follows: after anesthesia the dogs were intubated and ventilated with a constant-infusion pump (Harvard). The chest was opened through the fourth intercostal space, and the anterolateral aspect of the heart was exposed. The left anterior descending coronary artery was dissected and ligated 2.0 cm distal to its origin by the two-stage procedure (major ligation). In several experiments (as will be indicated), the artery was ligated in one stage. This procedure ordinarily results in infarction of about 15 to 30 percent of the left ventricle. The electrocardiogram was monitored throughout the procedure of ligation and was recorded later (when applicable). In another set of experiments, only a small left diagonal branch of the left anterior descending coronary artery was ligated in one stage (minor ligation).

Procedures of Stimulation

The effect of rapid direct ventricular stimulation (for vulnerability to reentry) was studied as follows: a No. 5 French bipolar electrode catheter (U.S.C.I.) was introduced through the right external jugular vein and was placed in the apex of the right ventricle under fluoroscopic guidance. The position was regarded as satisfactory when the threshold of stimulation was below 1.0 v with a duration of the stimulus of 2.0 msec. Short periods (three seconds) of stimulation at frequencies of six to nine cycles per second (50 to 60 periods at each frequency in each animal) were delivered with an electronic stimulator (Nihon-Kohden MSE-3) through an isolation unit. The stimulation voltage was 4 to 6 v. Lead 2 of the ECG and the aortic pressure were continuously monitored and recorded on a multichannel photographic recorder (Electronics for Medicine DR-7).

Determination of Ventricular Automaticity

Ventricular automaticity was evaluated by the length of the ventricular escape interval and the rate of the idioventricular rhythm during sustained vagal stimulation. Silver electrodes were placed on the distal cut ends of both vagus nerves. The ECG and the aortic pressure were monitored and recorded. The nerves were stimulated for one minute with pulses of 2 to 6 v (2.0 msec and 30 cps).

Sequence of Changes after Major Ligation

The animals in this part of the study were divided into six groups, each containing three dogs. In group 1, vagal stimulation and rapid endocardial stimulation (as described previously) were performed prior to ligation and at five-minute intervals up to eight hours after the coronary ligation. Anesthesia was maintained by periodic intravenous administration of pentobarbital. Coronary ligation in this group was performed in one stage, in order to delineate exactly the onset of injury. To assess the effects of the prolonged anesthesia with pentobarbital, three comparable animals were anesthetized, and the same investigative procedures were performed, except for the actual coronary arterial ligation. There were no changes in automaticity and no vulnerability to ventricular arrhythmias in the period of eight hours.

In groups 2 through 6, the same studies were performed at one, two, three, five, and seven days, respectively, following the coronary arterial ligation. Upon completion of the studies, the animals were killed, their hearts were examined, and the size of the infarction was determined.

Effect of Size of Injury

The same sequence of studies (as described previously) was repeated in 18 dogs who underwent minor coronary ligation. They were again divided into six groups that were studied immediately after ligation and one, two, three, five, and seven days thereafter. Again, animals from each group were killed upon completion of the studies, and the size of the infarct was determined.

Results

Size of Infarction

The myocardial infarction produced by the major ligation was always transmural, its diameter was above 4.0 cm, and the location was anteroseptal. The infarction following minor ligation was always smaller, and it never reached a diameter larger than 1.5 cm. The location varied from small intramural to subendocardial but was never transmural.

Arrhythmias Immediately after Ligation

The bursts of spontaneous ventricular arrhythmias frequently seen 2 to 20 minutes after ligation of the major vessel were never observed in the animals with minor ligations.

Arrhythmias 12 to 24 Hours after Ligation

All of the animals with major ligations developed classic, multiform, almost continuous ventricular tachyarrhythmia. Four animals with minor ligation displayed no arrhythmias at this stage. In three of these four animals, the infarct was less than 0.5 cm in diameter and intramural. In the rest (11 out of 15), a slower and more uniform ectopic mechanism was present. The size of infarction following minor ligation was between 0.5 and 1.5 cm in diameter.

Changes in Stimulation-Induced Arrhythmias

Vulnerability for short or sustained tachycardia developed extremely early after the major ligation and persisted in all groups studied. In all animals, whether in sinus rhythm or during the spontaneous, multiform, and mostly irregular ventricular tachycardia (which developed six to eight hours after ligation and persisted for 48 to 72 hours), short or sustained ventricular tachycardia could readily be produced following short periods of rapid ventricular stimulation (Fig 1). No dogs were examined later than seven days following the major coronary ligation. The characteristics of the vulnerability for arrhythmias were at any stage similar to those described earlier.11 Single or repetitive ventricular stimulation could readily stop the ventricular tachycardia at any time. No such vulnerability to rapid
stimulation was ever observed in animals with minor ligation, which behaved in this respect like normal controls. Repetitive ventricular premature beats (two successive beats) and short or sustained ventricular tachycardia were never observed at any stage after the minor ligation (Fig 2). Even when spontaneous idioventricular tachycardia was present at rest, no rapid and regular ventricular tachycardia could be observed; and upon cessation of the hundreds of periods of stimulation, the mechanism immediately returned to control.

Changes in Automaticity

Shortening of the escape interval and acceleration of the idioventricular rate were first observed only 30 to 45 minutes after ligation and gradually developed fully over a period of hours (Fig 3). This gradual increase in ventricular automaticity resulted in a continuous ventricular tachycardia which controlled the ventricle for 48 to 72 hours. The ventricular automaticity reached its maximal level within the first 24 hours and declined gradually thereafter as the escape interval lengthened and the idioventricular rate became slower. Seven days following ligation, the level of ventricular automaticity seemed to be almost back to normal. There was a clear difference in the severity of augmented ventricular automaticity between the groups with major and with minor ligation (Fig 3). At any one stage following the ligation procedure, the escape interval was longer and the rate of the idioventricular rhythm was slower and more uniform than in the group with large infarcts.

Discussion

The capability of the ventricular pacemaker cells to depolarize spontaneously may become manifest upon slowing or suppression of higher pacemakers. Since vagal endings are sparse in the ventricles and since pacemaker cells below the atrioventricular junction are relatively resistant to the electrophysiologic actions of acetylcholine, vagal stimulation is an acceptable method to study the characteristics of the activity of the ventricular pacemaker in vivo. The production of acute myocardial infarction altered significantly both the length of the escape interval (preautomatic phase) and the rate of the escape rhythm. In the literature, only few data are available on the characteristics of the acute changes in ventricular automaticity dur-

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These data suggest delay in the development of the early phase following the myocardial injury. Recent studies by El-Sherif et al. have demonstrated the existence of electrical activity throughout the cardiac cycle several days after the coronary ligation, thus demonstrating actual reentrant pathways.

In contrast to the persistent and reproducible production of ventricular tachycardia in the groups with major ligation, not a single ventricular tachycardia was ever provoked by the hundreds of periods of stimulation in any animal with a minor coronary ligation. Also, no infarction was ever larger than 1.5 cm in diameter. Furthermore, the minor infarctions were never transmural and were all located in the subendocardial or intramural areas. Located at these regions, the infarction did not become a "complete" obstacle and could not produce long enough pathways for a sustained ventricular tachycardia to occur. By measuring only the threshold for ventricular fibrillation in dogs, Bloor et al. could demonstrate a good correlation between the reduction in the threshold for ventricular fibrillation and the size of the infarction.

The clear relationship between the size of the infarction and vulnerability to arrhythmias becomes, according to the previously mentioned considerations, a strong indirect support to the theory of circus movement as the basis for the phenomenon of vulnerability. Direct demonstration of circus movement in the intact animal is extremely difficult and
has not been fully accomplished as yet. Sustained reentrant activity was demonstrated in preparations of tissue,\(^7\) where under certain conditions the reentrant pathways could be reduced to 12 mm. Many other studies have demonstrated delayed conduction in the areas of acute ischemia a few minutes after coronary ligation and actually satisfied almost all criteria for reentry as the basis for the arrhythmias occurring immediately after ligation.\(^4\)\(^7\)

Therefore, the situation in the intact heart can be summarized as follows: the acute ischemic process produces immediate changes which result in the appearance of ventricular premature beats due to delayed activation within the infarcted area, causing reentry. The existence of a major area of ischemia in the form of a major myocardial infarction therefore provides ideal conditions for further disorganization and deterioration of the ventricular premature beat to ventricular fibrillation. This is followed by a quiescent period during which reentrant arrhythmias can still be elicited by rapid stimulation. At a later stage the marked enhancement in automaticity of the surviving Purkinje’s fibers results in a continuous idioventricular tachycardia. The size of the infarct does not affect the occurrence of automaticity but does affect the rate of discharge. This, in itself, may result in more reentrant ventricular premature beats, ventricular tachycardia, and ventricular fibrillation as the major infarction becomes an obstacle of sufficient size to sustain a circus movement around or within itself.

**Clinical Consideration**

Manifestations of increased ventricular automaticity are not uncommon in patients with acute myocardial infarction. In fact, such manifestations may occur in up to 20 to 30 percent of the cases. The basic benign character of “idioventricular rhythms” is well known.\(^8\) The main danger to the life of the patient with acute myocardial infarction is from the reentrant phenomena. One of the main features of the present study was the clear dependence of the potentially dangerous reentrant arrhythmias on the size of the injury in acute myocardial infarction. Our study strongly supports the recent clinical observation describing a clear correlation between the incidence of ventricular ectopic beats and the size of the infarction as determined by hourly measurements of the serum level of creatine phosphokinase.\(^9\)

Superficially, our report contradicts a well-known fact, namely, that in many cases of sudden death, no acute lesion is found in the myocardium; however, there is no contradiction, as most of the sudden deaths due to coronary arterial disease occur in the first few hours following the acute event, when regular histologic examination cannot detect the injury. Furthermore, when special staining techniques were used, in which ischemia of 20 to 30 minutes was clearly detected, a major ischemic area was demonstrated in 80 percent of the so-called sudden deaths with no acute myocardial ischemia.\(^10\) While a significant portion of the patients who developed primary instantaneous ventricular fibrillation and were resuscitated did not develop an acute myocardial infarction, most of them had severe coronary arterial disease and may have sustained a transient ischemic episode large enough to provide for potentially lethal reentry.\(^11\)

**References**

2. Wit AL, Bigger JT: Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. Circulation 52 (suppl 3):96-115, 1975

Organ Transplantation: A Comprehensive Overview
The Department of Surgery and Office of Continuing Education, Louisiana State University School of Medicine, will present the course on Organ Transplantation at the Hilton Hotel, New Orleans, August 3-5. For information, contact: Office of Continuing Education, LSU School of Medicine, 1542 Tulane Avenue, New Orleans, Louisiana 70112.

Third International Conference on Lung Sounds
The Third International Conference on Lung Sounds will be held at Tulane University School of Medicine, New Orleans, September 21-22, under sponsorship of the International Lung Sounds Association. The Committee on Nomenclature will meet the morning of September 23. For information concerning the conference, contact Dr. Raymond L. H. Murphy, Jr., Lemuel Shattuck Hospital, 170 Morton Street, Jamaica Plain, Massachusetts 02130.