Historical Perspectives

The derangements of cardiac rhythm that result from occlusion of coronary arteries caught the attention of the earliest experimenters in the field. By the time of the studies of Porter in 1894, it was known that "fibrillar contractions" often were the end result of coronary occlusion and that irregularities of cardiac rhythm commonly preceded terminal ventricular fibrillation. Porter remarked that the pioneer investigator, Erichsen, in 1842, saw a "slight tremulous motion" after cessation of the regular heart beat following coronary occlusion. To Porter, disturbance of the cardiac rhythm was the salient feature of coronary occlusion. Thomas Lewis, in 1909, demonstrated the relationship of paroxysmal ventricular tachycardia to coronary occlusion in experimental animals; Robinson and Hermann, in 1921, established this relationship in man. Clinicians observed a multitude of arrhythmias resulting from ischemia and infarction but the fascination of experimenters with ischemic rhythm disorders waned. During the first half of the 20th century, the attention of researchers was focused more on the effects of ischemia and infarction on the configuration of the ventricular complexes, the QRS and T waves, than on rhythm.

There were two notable exceptions to this trend. Wiggers and associates noted that a region of ischemia facilitated the induction of ventricular fibrillation by strong stimuli applied during the T wave. Ischemia lowered the "fibrillation threshold", i.e., the current requirement, and broadened the "vulnerable period," i.e., the time interval for the induction of fibrillation.

Harris and associates were distinctive in their attempts to determine the mechanisms for disorders of rhythm by directly recording from ischemic tissues in dogs with occluded coronary arteries. They concluded that ectopic beats are generated near the borders of infarct by automatic foci induced by potassium released from ischemic cells. They discounted the importance of the interior of the ischemic zone in the generation of arrhythmias because electrograms recorded from the interior did not precede or even accompany each beat. In fact, the interior cells often did not respond with every normal beat; there was conduction block within the ischemic zone. Also they discounted reentry because they were not able to record continuous activation, i.e., activation potentials detected throughout the interval between two beats, during ectopic tachycardia. They made an observation which has greatly influenced later research, that is, that ectopic ventricular rhythms after coronary occlusion occur in two phases separated by a "quiescent" period of sinus rhythm. The first or early phase occupies the first half-hour after occlusion and frequently climaxes in ventricular fibrillation. The second, or delayed, phase begins 4-8 hours after occlusion and lasts for 2-4 days. In this delayed phase, there often are impressive multifocal ventricular tachyarrhythmias, but ventricular fibrillation rarely ensues. Harris et al. speculated that the electrophysiological mechanisms operating during the two phases might be different, a speculation which later evidence has supported.

In the past 10 years, the pace of research into ischemic disorders of rhythms has quickened; there are now partial descriptions of the electrophysiological alterations of specialized conducting tissues and of working myocardium during the different phases of ectopic rhythm disorders. In addition, there are data relevant to atrioventricular (AV) conduction disorders due to ischemia of the specialized conducting system. The description which follows is the result mostly of observations made after coronary occlusion in dogs because in this brief, and necessarily selective, review we have chosen to emphasize studies which included direct assessment of the electrophysiological function of ischemic tissues. All recognize that the experimental model may differ from the clinical condition. For various reasons, including the presence of multiple lesions and more variable collateral blood flow, the clinical pathophysiology undoubtedly is more variable and complex than the experimental. Also, many studies have used anesthetized open-chest animals in which the heart rate and level of sympathetic stimulation are high. There is a need to extend such observations to unanesthetized animals and to man.
Genesis of Ectopic Ventricular Beats

Evolution of Abnormalities of Specialized Conducting Cells

There is some disagreement concerning the involvement of specialized conducting cells during the early phase of ventricular arrhythmias. Lazzara et al. noted diminution of the amplitude of subendocardial Purkinje fiber electrograms within a few minutes of occlusion of the anterior descending coronary artery in the dog. On the other hand, Cox and co-workers recorded from ischemic regions and reported that Purkinje fiber electrograms were not altered during the first 8-12 hours after coronary occlusion. In the report of Cox et al., a smaller branch of the left coronary artery was ligated. Arrhythmias were not documented, and the subendocardial myocardial electrograms in the figure shown were not severely affected. It is possible that the preservation of Purkinje spikes reflected sites which were only mildly ischemic. On the other hand, Lazzara et al. used plunge wire electrodes in their studies. The possibility of artifact related to dislodgment of the wires was discussed by them; it cannot be discounted. The findings of Cox et al. are more in accord with earlier observations indicating that specialized conducting cells are relatively resistant to hypoxia and to global ischemia. However, in preparations excised 20 minutes after coronary occlusion and superfused, Purkinje cells in the ischemic region were partially depolarized and generated action potentials with diminished amplitudes, upstroke velocities, and durations. Automaticity was not enhanced and conduction was not severely impaired in the ischemic cells. In that report, the transmembrane potentials of acutely ischemic Purkinje cells resembled those of cells exposed to modest elevation of extracellular potassium. However, isolation techniques have significant limitations for the study of rapidly reversible ischemic effects. The issue is not resolved, but whether Purkinje cells are affected early or not, there is no compelling evidence that they play an important part in the generation of arrhythmias in the early phase; i.e., marked conduction delay, abnormally enhanced automaticity, and anomalous automaticity have not been observed in studies reported so far.

On the other hand, the distinctive electrophysiological alterations of the specialized conducting cells during the delayed phase of arrhythmias, which have been described similarly by several groups of investigators, are probably critical in the genesis of ectopic beats. Scherlag and co-workers showed that the ectopic beats of the delayed phase usually are electrograms of Purkinje fibers in the infarcted region. Friedman et al. and Lazzara et al. found that Purkinje cells in infarcts isolated in vitro are partially depolarized and excessively automatic. The amplitudes and upstroke velocities of action potentials are reduced and their durations are strikingly prolonged due mainly to a prolongation of phase 3 of repolarization. This abnormality, plus the disparity in durations of action potentials within normal and infarcted regions and the heterogeneity of involvement of the infarcted region, constitute conditions conducive to reentry if cells are excited during phase 3. Self-terminating runs of fibrillation can be induced with ease in small preparations containing a part of the Purkinje network of the infarct. The abnormal Purkinje cells undergo a remarkable transition in vitro. The low resting potentials and enhanced automaticity are restored toward normal during superfusion even in oxygen-poor, glucose-free solutions. Friedman et al. observed some tendency to recovery during superfusion but placed less emphasis on this finding than did Lazzara et al. However, the former group did not collect data during the first hour after isolation. In the studies of Lazzara et al., the enhanced automaticity recovered toward normal more slowly than the resting potential, and the prolonged duration of the action potential altered little during 12 hours of superfusion. The recovery in vitro inspired a revival of the speculation that Purkinje cells may be affected by a toxic factor(s) present in vitro, perhaps a product of necrosis of myocardial cells. The abnormal Purkinje fibers appear to generate many of the ectopic beats of the delayed phase both by automatic and reentrant mechanisms.

Several days after coronary occlusion, about the end of the delayed phase of arrhythmias, Purkinje fibers in the infarcted region recover toward normal. It has been known for some time that there are surviving Purkinje strands in chronic infarctions. Recent recordings of transmembrane potentials indicate that surviving cells are relatively normal in the late stage of healing. It is not known whether these recovered cells comprise the entire original population of Purkinje fibers or whether some have died. There is some disagreement as to how "normal" these surviving fibers are. Some investigators concluded that most of the cells are normal but a relatively small number may be slightly depolarized and generate abnormal action potentials. On the basis of statistical comparisons of mean values of transmembrane potentials in infarcted and normal regions, another group of investigators has inferred that most of the fibers in the infarcted region are slightly abnormal. At this time, this does not appear to be a crucial issue in relation to arrhythmias, since severe impairment of conduction, abnormal automaticity, or arrhythmias have not been described in this late stage. The temporal sequence of observed changes in transmembrane potentials in specialized conducting cells following coronary occlusion is depicted in Figure 1.

Evolution of Abnormalities in Ventricular Myocardial Cells

The electrophysiological properties of ventricular myocardial cells are quite sensitive to ischemia. Within minutes after coronary occlusion in dogs, there is lessening of the durations of action potentials and the amplitudes of resting potentials recorded in vivo. Impairment of conduction may become severe in the first half-hour after occlusion. There appears to be a strong relationship between delay in activation of ischemic myocardium and the appearance of ectopic beats. Boineau and Cox, having observed fractionated electrograms, i.e., abnormally long, low amplitude, and polyphasic potentials, suggested that activation in myocardium is irregular...
because the effects of ischemia are not uniform. They showed that ectopic beats appeared when the duration of the fractionated electrogram extended beyond the T wave of the ECG. Their recordings and those of Waldo and Kaisen answered the requirement of Harris and Rojas that continuous activation be observed before reentry could be considered as a mechanism for the generation of ectopic beats. Their report does not provide information concerning the localization of the conduction delays. Scherlag and coworkers compared the electrograms of subendocardial, subepicardial, and intramural layers. They inferred that the greatest delays occur in the superficial subepicardial layers and that reentry occurs there. The marked delays of subepicardial electrograms could reflect slow conduction in deeper intramural layers as well as in the subepicardial layers themselves. The coincidence of the occurrence of ectopic beats and marked conduction delay in ischemic myocardium (which outlasts the refractory period of normal myocardium) is strongly suggestive but not proof of reentry. The inferences relating to the localization of the delays and the existence of reentry require verification by detailed mapping of activation in the ischemic region. This information is not available now.

Disappearance of the ectopic beats of the early phase coincides with improvement in the epicardial electrograms. About one-half hour after occlusion, there is an increase in amplitude of epicardial electrograms and improvement in conduction. In view of the many kinds of evidence indicating that subendocardial layers are more affected during ischemia than subepicardial layers, the rapid and severe deterioration of the electrophysiological properties of subepicardial cells is curious and unexplained. Also unexplained is the partial improvement in subepicardial cells which marks the termination of the first phase.

The subepicardial localization of marked conduction delay applies to infarction of the free wall. Septal infarction following occlusion of the anterior septal coronary artery presents a similar temporal sequence of rhythm disturbances, but no subepicardial layers are involved. In these cases, the conduction delays appear to occur in the myocardium near the crest of the septum and are detectable by catheter electrodes positioned in the vicinity of the His bundle. Such recordings have indicated that activation in ischemic ventricular myocardium may assume a Wenckebach pattern in sequential beats. As activation of ischemic myocardium progressively delays in the Wenckebach sequence, ectopic beats may occur when the delay exceeds the refractory period of surrounding normal myocardium.

In summary, available data suggest that the early phase of arrhythmias is the result of reentry from markedly delayed activation of those ischemic myocardial regions which are the most distant along the normal conduction pathways. In the case of free wall infarction, the subepicardial layers are implicated; in the case of upper septal infarction, the crest of the septum is involved.

The arrhythmias of the early phase are intimately rate-related. It has been known since early in the century that vagal induced cardiac slowing could avert or abort ectopic ventricular rhythms conversely, ectopic ventricular rhythms can be induced by cardiac pacing. It has been claimed, on the basis of measurement of fibrillation thresholds, that vagal stimulation has an antiarrhythmic effect over and above that produced by cardiac slowing. The electrophysiological relevance of the measurement of fibrillation thresholds is uncertain, but one study indicated that survival was improved by vagal stimulation with heart rate constant. This point aside, it is clear that simply slowing the heart is potently antiarrhythmic during the early phase. Concomitant with the disappearance of ectopic beats, cardiac slowing lessens the delay of epicardial electrograms. It is reasonable to infer that some of the salutary effect of cardiac slowing is due to oxygen sparing and consequent mitigation of ischemia. In addition, another factor probably is operative. It has been shown that ischemia affects refractoriness of Purkinje or myocardial cells in such a way that recovery of the ability of the cell to generate an upstroke with amplitude and velocity equivalent to that of the basic response is delayed beyond the completion of repolarization. This time-dependent recovery of responsiveness has been observed in lesser degree in normal myocardial cells in vitro and attributed to delay in "reactivation" of the rapid sodium channel. In cells with normal resting potentials, the time required for full reactivation of the rapid sodium channel may be on the order of 50-100 msec after the completion of repolarization, but if cells are potassium-depolarized, intervals on the order of 200 msec or more may be required. Time-dependent recovery also termed "postrepolarization refractoriness" may be quite prolonged by ischemia and may have an anomalous relationship to heart rate; that is, the duration of postrepolarization refractoriness may increase as heart rate increases. Some of the features of postrepolarization refractoriness are illustrated in Figure 2.
higher rates, or with premature beats, there may be more slowing and disintegration of conduction within the ischemic region because of this mechanism.

Recently, it has been demonstrated clinically and experimentally that, after ischemia, the "vulnerable period" may extend beyond the T wave into diastole. Also, it has been shown that premature beats produce greater fractionation and delay of electrograms in the ischemic region even if they occur after the T wave. Yet, most reports indicate that the duration of action potentials of myocardial cells shortens or changes little during ischemia. In one study, very prolonged action potentials were found in deeper layers of ischemic papillary muscle exposed by transection of the muscle in vitro. There was no indication by the authors of the frequency of this finding. These observations indicate that the extension of the vulnerable period beyond the T wave is related to postrepolarization refractoriness or prolonged action potentials in ischemic myocardium.

The relationship of ectopic beats to heart rate may not be a simple direct one in the open-chest dog, as it is in the closed-chest dog. There is evidence that the incidence of ectopic beats may be minimal at heart rates between 100 and 150 in open-chest dogs and may increase at slower rates as well as faster rates. The mechanism for an increase in ectopic beats at slow heart rates during the early phase of arrhythmias in the open-chest dogs is unclear. The factor of increased "dispersion of refractoriness" at slow heart rates has been mentioned. Dispersion of refractoriness can be a factor in reentry only if refractoriness is impinged upon and conduction is thereby retarded and disorganized. To explain ectopic beats coupled to sinus beats on this basis, refractoriness in the ischemic myocardium must outlast the sinus cycle. Indeed, the original observations of Harris and Rojas of intermittent block deep within the ischemic zone during sinus rhythm indicate that the refractory period at some sites might exceed the duration of the sinus cycle.

The question of refractoriness in the ischemic zone and its relationship to heart rate is rather complex. Some consideration of this question is appropriate here since the spatial distribution of variations of refractoriness and the influence of changes in rate and rhythm on this distribution are probably critical determinants of the pattern of activation of the ischemic region which, in turn, determines reentry. Refractoriness can be defined on the basis of the threshold for excitation by applied stimuli at varying coupling intervals. Traditionally, this definition has been most commonly applied experimentally. On the other hand, refractoriness also may be defined in terms of the character of the responses themselves, i.e., the recorded electrograms or action potentials generated during natural propagation at varying coupling intervals, as illustrated in Figure 2. These two aspects of "refractoriness" do not necessarily reflect identical electrophysiological mechanisms. Studies have indicated that the absolute refractory period assessed by the application of external stimuli tends to shorten in early and mild ischemia but to lengthen in later or more severe ischemia. The significance of refractoriness assessed by external stimuli in relationship to natural excitation and conduction is not fully clarified. In terms of the character of the responses during natural propagation, there are indications that there are opposing effects of ischemia on refractoriness. The tendency of the duration of the action potential to shorten with ischemia might result sometimes in a shortened refractory period if the refractory period corresponds closely in time to the duration of the action potential. On the other hand, the superimposition of postrepolarization refractoriness might result in refractory periods longer than normal despite shortening of the action potential. Indications are present that the latter process is more prominent in more severely affected cells. The co-existence of these two processes may further increase dispersion of refractoriness in ischemic regions.

The influences of heart rate on refractoriness may be disparate. Action potential duration may vary inversely with heart rate, whereas, under certain conditions, the duration of postrepolarization refractoriness may vary directly with heart rate. Information is far from adequate with respect to the patterns of response and activation in

Figure 2. Certain characteristics of postrepolarization refractoriness in ischemic cells. Driven action potentials are shown to the far left of each trace at different driving cycle lengths (CL). The responses to premature stimulation are shown to the right of the driven action potentials in the top and bottom traces but not in the middle trace. The resting potentials are unchanged, but the responses are dependent on the driving cycle length (basic heart rate) and on the coupling interval of premature stimulation. Decreasing the driving cycle length (increasing heart rate) may result in intermittent block, often with a Wenckebach sequence, as in the middle trace which shows four consecutive driven beats superimposed. The action potentials diminish progressively in sequence reaching a nadir of amplitude at the fourth or blocked beat; then the sequence repeats. Another type of response to decreased cycle length is uniform depression of each driven response, illustrated in the lower trace. Compare the driven action potentials of the bottom trace with the driven action potentials of the top trace, representing the longer cycle length. This consistent depression of driven responses might result in continuous block as opposed to the intermittent block shown in the middle trace. Depression of responses is reflected as loss of amplitude plus slowing and irregularity of the upstroke. The ability of the cell to respond to premature stimulation is more impaired at faster rather than at slower rates. Compare the coupling intervals and action potentials of the premature responses in the top and bottom traces. Voltage calibration in millivolts is shown to the left of the traces. The horizontal bar at the bottom left represents 100 msec.
ischemic regions as heart rate varies or extrastimuli are introduced. Available but insufficient evidence suggests that conduction improves in the infarcted zone with lowering of the heart rate. This observation suggests that the dominant effect of slowing of the heart is a decrease in the duration of postrepolarization refractoriness. If this were so, it would be difficult to attribute bradycardia-dependent ectopic beats to an increase in dispersion of refractoriness. However, it is conceivable that bradycardia-induced improvement in conduction in reentrant pathways in the ischemic zone paradoxically could result in more ectopic beats. If there were continuous or intermittent block in a reentrant pathway at the higher rates, the cardiac slowing might lessen the degree of block in the pathway and produce more successfully conducted reentrant impulses.

It also is possible that the increase in ectopic beats at slow heart rates is not due to reentry but to enhanced automaticity of Purkinje fibers in the ischemic zone. If the rate of diastolic depolarization of Purkinje fibers is increased, ectopic beats could be generated by automatic firing. However, available information indicates that the rate of diastolic depolarization in Purkinje fibers and resultant automatic firing are not enhanced during the early phase of arrhythmias. There is little information on the direct electrophysiological effects of autonomic mediators and various types of antiarrhythmic agents on ischemic tissues during the early phase of arrhythmias.

The early phase of arrhythmias is antagonized by various measures which have in common a reduction of adrenergic stimulation and, consequently, a reduction of heart rate. However, the effectiveness of standard antiarrhythmic drugs during the early phase is controversial. There is little information on the direct electrophysiological effects of autonomic mediators and various types of antiarrhythmic agents on ischemic tissues during the early phase of arrhythmias.

One day after coronary occlusion, during the delayed phase of arrhythmias, the subendocardial layers of myocardial cells within the infarcted region are electrophysiologically dead. At the endocardium, demarcation between normal and infarcted regions is fairly sharp. Within a millimeter, there is a transition from normal myocardial cells to a region devoid of myocardial electrical activity—a region where only abnormal Purkinje cells survive. However, over the epicardial surface, diminutive, slowed, and fragmented myocardial electrograms can be recorded. The myocardial cells near the epicardial surface of the ischemic region are alive but electrophysiologically abnormal. Activation of the subepicardial myocardium is delayed, but usually not as severely as in the early phase of arrhythmias. In this delayed phase, the greatest number of ectopic ventricular beats appear to originate near the endocardium but a smaller number are preceded by epicardial electrograms. In short, there is a broad canopy of ectopic ventricular beats that overlie the dead subendocardial layers of the infarct. These cells remain in precarious balance for days or weeks and may generate some of the ectopic beats that are visible in the delayed phase.

When the overt arrhythmias of the delayed phase subside on the 3rd or 4th day after occlusion, ectopic beats can be induced readily by changes in heart rate or rhythm, including the introduction of pauses or premature beats. These ectopic beats are preceded by marked delay and fractionation of the epicardial electrograms of the prior beat. With suitable recording techniques, continuous activity in epicardial electrograms nearly always can be demonstrated between an ectopic beat and its preceding beat. The strong dependence of the delay and fractionation of electrograms on rate and rhythm implicates abnormal, spatially heterogeneous refractoriness as a crucial factor in retardation and disorganization of the activation wavefronts. During this late period, there is no enhanced automaticity as assessed by induced atrial arrest or heart block. Subendocardial myocardial layers in the infarcted region, for the most part, are dead. These observations suggest that the late arrhythmia originates in damaged subepicardial layers of myocardium in this canine model. This period of latent propensity for arrhythmias lasts for about 10 days. After this time, ectopic beats and delay and fractionation of epicardial electrograms cannot be induced readily.

There have been no attempts to chart on anatomic maps the ultimate fate of the jeopardized subepicardial cells. The epicardial surface of chronic infarctions is usually of lesser extent than the endocardial surface. The epicardial surface often is streaked with apparently viable myocardium. This indicates that some of the cells of the subepicardial layers survive but others die. The electrophysiological state of the surviving cells has not been clarified, but presumably there is some return toward normality. Electrograms recorded from the subepicardial layers of chronic infarcts are frequently reduced in amplitude, polyphasic, and somewhat delayed. However, these characteristics could result simply from intermingling of scar tissue within subepicardial layers, resulting in circuitous pathways and irregular wavefronts even though the cells are electromyographically normal. There is no evidence of a significant incidence of spontaneous arrhythmias after healing of an infarct when the remainder of the coronary vessels are normal. However, systematic studies with long-term electrocardiographic monitoring are not available for the dog model. The temporal sequence of changes in transmembrane potentials in subendocardial myocardial cells with free wall infarction are shown in Figure 3.

**Atrioventricular Conduction Disorders**

Anatomic data have been interpreted to indicate that the source of blood for the AV node is largely distinct from the source for the His bundle and proximal bundle branches both in dogs and in man. Oclusion proximal to the AV nodal artery, the branch of the posterior descending coronary artery which supplies the AV node, produces neither immediate nor invariable impairment of conduction through the AV node. There may be delay in conduction. Less often there is intermittent conduction block with a Wenckebach pattern. In a sequence of beats in which there is progressive prolongation of conduction in successive beats culminating in complete block of conduction of one beat. Rarely, there is high grade block. Normal conduction usually is restored within hours or days. These observations might be interpreted to indicate that the AV node is comparatively insensitive to ischemia. However, when the entire dog...
heart was made ischemic, block of conduction in the AV node rapidly ensued. Also, when both the AV nodal artery and the anterior septal coronary artery are occluded, the AV node is rapidly and severely affected. These observations suggest that the inconsistent effect of occlusion proximal to the AV nodal artery on AV nodal conduction is due to blood flow from other sources, probably branches of the anterior descending coronary artery. The effects of ischemia on pacemaker function in the AV node are unclear but, in the event of high grade block, adequate junctional pacemakers usually supervene and prevent clinical catastrophe. Perhaps because the inability to record directly AV nodal potentials in vivo has deterred investigators, there is a dearth of studies in which the effects of ischemia on the electrophysiological functions of the AV node have been assessed.

The electrophysiological effects of ischemia of the proximal His-Purkinje system have been explored somewhat more thoroughly in studies on dogs. When there is occlusion of the anterior septal coronary artery, the branch of the left coronary artery which supplies the His bundle and proximal bundle branches in dogs, ectopic ventricular beats occur in the same temporal pattern that follows occlusion of other vessels. However, conduction in the specialized conducting system is not impaired for several hours. Deterioration of conduction can be hastened by rapid pacing. The conduction disorder is manifested first as intra-His conduction delay with fractionation of the His bundle electrogram, i.e., “split” His potentials. Then there is intermittent conduction block which always assumes a Wenckebach pattern. However, sometimes the Wenckebach pattern involves increments in conduction time of only a few milliseconds with each beat, so that the pattern at relatively slow recording speed appears to satisfy the criteria for the clinical classification of Mobitz II block, i.e., intermittent complete conduction block of single beats with constant conduction time in the intervening beats. The presence of apparent Mobitz II block—"millisecond Wenckebach"—is a herald of paroxysmal continuous block, which is always directly rate-related in experimental ischemia. In this experimental model, obvious Wenckebach periodicity does not appear to transform readily into paroxysmal block. Thus, clinical observations that Mobitz II patterns are more ominous than Wenckebach patterns have some basis in the experimental setting, although all sequences of intermittent block have a Wenckebach pattern on close scrutiny. The abnormalities may also involve the proximal bundle branches and result in bundle branch delay and block.

Like distal Purkinje fibers, proximal conducting cells are depolarized by ischemia. However, the sequence and character of cellular electrophysiological changes are not the same for the proximal conducting cells as for the distal cells. In contrast to the distal fibers, enhanced automaticity and strikingly prolonged action potentials have not been observed in the proximal conducting system. The depolarized fibers have action potentials of decreased duration but prolonged refractoriness lasting after repolarization. Action potential upstroke velocities are slower and amplitudes are lower as a consequence of both partial depolarization and encroachment on postrepolarization refractoriness at normal heart rates.

Certain features of the responses of the more severely depolarized cells, e.g., resting potentials more positive than —60 mV and action potentials with very slow upstrokes, raise the question whether the action potentials result from inward current flow through the “slow channel.” However, this speculation has not yet been verified by more direct experimental tests, such as the use of specific blockers of the fast and slow channels.

The consequences of repetitive encroachment on postrepolarization refractoriness at constant heart rates differ somewhat depending on conditions not yet entirely understood. One pattern of response is a beat-by-beat progressive delay and diminution of the upstroke often associated with a "foot potential" of increasing duration culminating in a diminished, brief, nonconducted response (Figure 2, middle trace). One possible mechanism for this pattern might be a beat-by-beat progressive prolongation of the duration of postrepolarization refractoriness until the blocked beat. At the site of block, the blocked impulse should appear as an abbreviated action potential which transmits downstream as an electrotonic, i.e., attenuated and passive, change in membrane potential. The abbreviated action potential (active response) and the electrotonic (passive) response would be expected to leave in their wake shortened or no refractoriness. This would permit an improved response in the beat following the nonpropagated one which therefore would propagate. The difference between Wenckebach and Mobitz II patterns reflects a difference in the cumulative extent of the beat-to-beat deterioration of the upstrokes of the beats before the blocked beat. It is not at present obvious why there is less tendency to paroxysmal continuous block when the pattern shows marked progressive delay of the upstrokes.
before the nonpropagated beat (Wenckebach). In paroxysmal continuous block, encroachment on postrepolarization refractoriness may result in such poor active responses of cells just proximal to the site of block that each response fails to excite cells at the site of block. The nonpropagated responses at the site of block would not be followed by improved responses which propagate (as in the example above) because there is not enough excitation current generated from the low amplitude action potentials of the cells just upstream. It is likely that the gradation and the anatomic extent of the functional abnormalities in the zone of block as well as other factors determine whether the pattern of conduction is Wenckebach, Mobitz II, or continuous block.

Although automaticity of proximal cells has not been shown to be obviously enhanced, it is abnormal. Beat-to-beat shifts in the level of threshold potential have been recorded. Also, at times, the membrane potential may depolarize spontaneously to a level which is equivalent to the threshold potential of previous beats, but an action potential is not generated and the potential drifts back toward more negative values. The threshold potential generally is moved to more positive levels in depolarized fibers. The resulting spontaneous upstrokes are slow and diminished in amplitude and the propagation of automatic beats may be uncertain.

The late cellular changes have not been described, but presumably, healing restores function toward normal. Clinical and experimental observations indicate that atrioventricular and intraventricular conduction usually return toward normal as assessed by the electrocardiogram.

Biochemical Correlates of Abnormal Electrophysiological Function

The linkages between the electrophysiological changes and the biochemical changes caused by ischemia are poorly identified. Ischemia depresses the energy-dependent membrane sodium, potassium pumping system which should lead to loss of intracellular potassium and gain in sodium. These alterations in intracellular electrolytes during ischemia have been documented for a long time. The leak of intracellular potassium can be detected as a rise in coronary venous potassium concentration within minutes of the onset of ischemia. However, depression of the pumping system, the Na⁺, K⁺, -ATPase, cannot be demonstrated until 7 days after the onset of ischemia. Of course, there could be depression of activity of the pump in vivo which would not be manifested under optimal conditions in vitro. The findings of MacDonald and co-workers in hypoxic myocardial cells may have relevance to this point. They interpreted their studies as indicating that the energy for the Na⁺,K⁺ pump may come from ATP generated by glycolysis. If so, pump activity may be relatively preserved by anaerobic glycolysis early in ischemia. Also their data suggest that if glycolysis is maintained or enhanced, electrogenic sodium pumping may sustain the membrane potential near normal despite considerable loss of the transmembrane gradient for potassium. To what extent this factor may operate in ischemic regions is unknown.

Whatever the mechanisms involved in the early loss of potassium from myocardial cells, the consequent elevation of extracellular potassium concentration in the vicinity of the sarcolemma should result in partial depolarization of the cells. If this were the only factor, the electrophysiological behavior of ischemic cells should simulate that of cells exposed to high concentrations of extracellular potassium. In the first phase of arrhythmias, certain observations are compatible with this simple hypothesis. The first phase arrhythmias can be mimicked by intravenous injections of potassium. The early changes in excitability and refractoriness in the ischemic zone also can be duplicated by injection of potassium. The characteristics of transmembrane potentials resemble those resulting from an elevation of the extracellular concentration of potassium: diminished resting potentials, slow rates of diastolic depolarization in Purkinje fibers, and abbreviated action potentials. However, there is a possibility that the shortened duration of the action potential plateau in ischemia is not simply an effect of elevated extracellular potassium. Abnormality of the plateau of the action potential is an early and sensitive sign of hypoxia, substrate depletion, and various types of metabolic inhibition as well as ischemia. It now appears that both the level and duration of the plateau of Purkinje and myocardial cells depend strongly on the slow inward current. Evidence has been offered that the rapid loss of the plateau in ischemia is due to a rapid decline in the slow inward current which, in turn, is related to a decrease in cyclic AMP and ATP in the cell.

The recent study of Downar et al. further discredits the thesis that the electrophysiological abnormalities and arrhythmias of the early phase are the outcome simply of elevation of extracellular potassium. Cardiac cells superfused in vitro by coronary venous blood draining an ischemic region develop abnormal electrophysiological properties. These abnormalities were not duplicated if the cells were superfused with coronary venous blood from a normal region even if the concentrations of potassium, lactate, oxygen, and H⁺ were equaled with those of the blood from the ischemic region. They concluded that unidentified factor(s) contribute to electrophysiological abnormalities of the early phase.

In the later stage of ischemia, Purkinje fibers show changes which are opposite to the effects of elevation of extracellular potassium. One day after occlusion, Purkinje fibers in the ischemic region show long-lasting rather than abbreviated action potentials, and the rate of diastolic depolarization is high rather than low. The long-lasting action potentials bring to mind the effects observed in cardiac cells superfused with acidic solutions.

Recently, the excitatory current and upstroke of the action potential have attracted interest in relation to the generation of arrhythmias. It has been suggested that ventricular ectopic beats may be generated in markedly depolarized cells operating at levels of membrane potential where the rapid sodium channel is inactivated. Studies of voltage-clamped cardiac cells indicate that a slow current of calcium, or possibly calcium and sodium ions, can be activated at membrane potentials more positive than −55 mV. Experimental conditions can be
contrived so that propagated action potentials may be generated by this slow current. Because these action potentials have slow upstrokes and propagate very slowly with a low safety factor, they are prone to block and to reenter. On the other hand, it is not as easy to induce reentry in the normal specialized conducting system when action potential upstrokes are generated by the rapid sodium current, even if this current is at its lowest levels, that is, at membrane potentials around -60 mV. Consequently, it has been hypothesized that reentrant ectopic ventricular beats in vivo may be predominantly or exclusively a consequence of “slow channel” action potentials. More specifically, it has been postulated that in ischemic regions, high concentrations of extracellular potassium may depolarize cells to the extent that the rapid sodium channel is inactivated and high concentrations of catecholamines may stimulate the slow channel, resulting in “slow responses,” i.e., action potentials dependent on slow current. Such a milieu of high potassium and high catecholamines in vitro is indeed conducive to slow response, and propitious for reentry.

The harmony of these speculations and observations is perturbed by certain considerations. We pointed out earlier that distrust of the rapid channel as a generator of reentrant impulses was a major impetus for the hypothetical implication of the slow channel in reentrant arrhythmias. This distrust was, in part, an outgrowth of past preoccupation with Purkinje cells as experimental objects in vitro. Purkinje cells are specialized for rapid conduction with a high safety factor, that is, a large reserve of generated electrical energy during propagation. They may not be the most appropriate model for the study of reentrant arrhythmias in ischemia. There is increasing evidence that ventricular myocardium may be a common source of reentry in ischemia. Ventricular myocardium, which normally has slower conduction and presumably a lower safety factor than Purkinje fibers, may be more susceptible to reentrant activation under conditions that result in depression, but not complete inactivation, of the rapid sodium channel. Comparatively little study has been directed toward conduction in ventricular myocardium which is depressed but retains activity of the rapid sodium channel.

The postulation of a high potassium, high catecholamine environment in ischemic regions is only partially supported by data. Total catecholamines decline in the ischemic region after coronary occlusion to a very low level on the day after occlusion, at a time when rhythm disorders are still prominent. The concentration of free catecholamines is not known. During the early phase of arrhythmias, the postulate has some plausibility, since it is likely that catecholamines are released from nerve terminals in the ischemic region at this time. The effect of slow channel-blocking agents on conduction in ischemic regions and on arrhythmias of the early phase should be of some interest.

The hypothesis of action potentials generated by slow inward current in ischemia is somewhat undermined by the observation that current flow through the slow channel appears to be much more intimately dependent on energy than is current flow through the fast channel. Both hypoxia and ischemia inhibit slow responses which arise in an environment of high potassium and high catecholamines. Apart from its intrinsic interest, the question of the source of the activating current responsible for reentrant conduction in ischemia has important implications in relation to selection of antiarrhythmic agents, because the rapid and slow channels have different sensitivities to inhibition or stimulation by various agents.

Summary

Electrophysiological studies of coronary occlusion in the dog indicate that early (first half-hour) ventricular arrhythmias are due to severe impairment of conduction in ischemic myocardium, especially the subepicardial layers, producing reentry. The subsidence of the early arrhythmias is marked by unexplained improvement in conduction in subepicardial layers of ischemic myocardium. Although Purkinje cells in the ischemic region may be affected early by ischemia, evidence does not implicate them in the generation of ectopic beats until the delayed phase (1–4 days after occlusion) of arrhythmia. During this period, Purkinje cells manifest enhanced automaticity (enhanced diastolic depolarization), impaired conduction, and heterogeneously prolonged refractoriness (prolonged action potentials). These abnormalities probably produce both automatic and reentrant ectopic beats from the Purkinje network in the ischemic region. During this period, the visible region of infarction has no surviving myocardial cells in subendocardial layers. However, surviving subepicardial layers show abnormalities of conduction and refractoriness which may contribute to the generation of reentrant ectopic beats. The abatement of overt arrhythmias by the 3rd or 4th day after occlusion correlates with recovery toward normal of the abnormal Purkinje cells. There is a period of latent propensity for arrhythmias lasting up to 2 weeks after occlusion and apparently related to continued abnormalities of conduction and refractoriness in jeopardized subepicardial layers.

Atrioventricular conduction disorders may occur from ischemia of the AV node or proximal conduction system. These may be severe, but usually they are transient. In the ventricular conducting system, the most severe effects of ischemia are most proximal. The salient features of ischemic cells are partial depolarization, upstrokes of reduced amplitude and velocity, and prolongation of postrepolarization refractoriness. The latter change results in marked rate dependence of the conduction disorder. The characteristic pattern of intermittent conduction failure is the Wenckebach sequence. Wenckebach sequences with very slight increments of conduction delay in successive beats may appear to represent Mobitz II sequence at standard electrocardiographic recording speeds. Continuous block is most likely to occur after apparent Mobitz II sequences.

The biochemical basis for the electrophysiological alterations caused by ischemia are complex and poorly understood and involve both the effects of deprivation of oxygen and nutrients in arterial blood and the effects of accumulated metabolites and products of anaerobic metabolism and necrosis. The partial depolarization of cardiac cells produced by ischemia probably derives, at least in part,
from loss of intracellular potassium and accumulation of the lost potassium in the extracellular space. Loss of potassium probably is related, at least in later stages, to depression of the activity of Na+/K+ ATPase due to depletion of intracellular ATP. Partial depolarization leads to partial inactivation of the rapid channel, slow and diminished upstrokes of action potentials, and finally slow and irregular conduction. There is also a speculation that the rapid channel may be inactivated completely in severely depolarized cells, but very slow upstrokes may be generated via the slow channel stimulated by high concentrations of free catecholamines in the ischemic region. The marked sensitivity of the plateau of the action potential of myocardial cells to ischemia has been attributed to the accumulation of potassium in extracellular space and/or to the decrease in intracellular cyclic AMP with consequent reduction in inward current. The prolongation of the action potentials of peripheral fibers is similar to the change in vitro during exposure to acidic solutions. The biochemical basis for the prolongation of postrepolarization refractoriness, i.e., the delay in reactivation (restoration time) of the rapid channel, is unknown. A clear and complete explication of the effects of ischemia on ion movements and transport across cell membranes will not be possible until there is better understanding of the biochemical processes influencing ion movements in normal cells.

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