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Mechanisms for cardiac arrhythmias

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Summary. Possible cellular electrophysiological mechanisms for arrhythmias have been investigated through studies of isolated cardiac tissues. Records through extracellular and intracellular electrodes indicate that arrhythmias may result from either focal or non-focal mechanisms. Focal mechanisms include abnormal impulse initiation (normal or abnormal automaticity,), triggering from either early or delayed afterdepolarizations and reflection, whereas the non-focal mechanisms are various forms of reentry due to circus movement. It is reasonable to assume that these mechanisms also occur in vivo. Although it is safe to identify macro-re-entry as the cause of some atrial and ventricular arrhythmias, for the most part direct proof of mechanism usually is lacking for the focal arrhythmias. If 'on line' activation sequence mapping techniques can be developed to quickly and specifically locate arrhythmogenic foci in the in situ heart, it may be possible to use unipolar extracellular recording techniques to identify the exact cellular electrophysiological mechanisms operating within them.
Key words. Cardiac arrhythmias; reentry; triggering; automaticity; transmembrane action potentials; early afterdepolarizations; delayed afterdepolarizing actions.

Mechanisms for cardiac arrhythmias

A consideration of the mechanisms for cardiac arrhythmias must deal with two different types of questions. First, it is necessary to identify the abnormalities of cellular electrical function or structure that can induce arrhythmic activity. These abnormalities may be induced by either pathological processes or by experimental interventions. Second, it then is necessary to determine which of these possible mechanisms are actually responsible for specific arrhythmias in the in situ heart. The problem in this case is to be able to make a certain and explicit identification of the cellular electrophysiological mechanism that is involved in the genesis of the rhythm disturbance. It is possible that the response of many arrhythmias to therapeutic interventions depends on the mechanism causing the arrhythmia. Even though the evidence for this presumed dependence is not strong, the assumption deserves continuing tests as improved drug design can provide agents with more restricted and specific activities. Furthermore, increasing our understanding of the mechanisms responsible for particular arrhythmias is important, because this knowledge should ultimately lead to improved drug therapy of cardiac disease and reduced morbidity and mortality.

Possible mechanisms

It is well established that certain normal cardiac cells have the property of automaticity. These cells include the pacemaker cells of the sinus node, as well as subsidiary specialized atrial fibers [26], the NH region of the atrioventricular junction[24], and the His bundle and Purkinje fiber ramifications in the ventricle[14]. It is reasonable to assume that, just as the activity of the sinus node pacemakers gives rise to normal or abnormal sinus rhythm, spontaneous impulse initiation in the subsidiary pacemakers can give rise to abnormal atrial or ventricular rhythms. Such abnormal rhythms might be manifest either as premature depolarizations or sustained rhythms that compete with or supercede the sinus rhythm. During sinus rhythm, the propagation of the cardiac impulse is an orderly process. The speed and direction of the impulse spread is controlled by the electrical properties and spatial distribution of the cardiac fibers. As a result of this and the long duration of the refractoriness of cardiac cells, when a sinus impulse has activated the tissues excited last in the normal activation sequence, all of the adjacent tissues are refractory and propagation ceases. However, this need not be the case. A localized unidirectional failure of conduction,

Table 1. General classes of arrhythmogenic mechanisms

A. Abnormal impulse generation
B. Abnormal impulse conduction
C. Simultaneous abnormalities of impulse generation and conduction

associated with either sufficiently slow impulse propagation or a suitable abbreviation of refractoriness, might permit the impulse to turn back upon itself, reenter tissues it previously had excited and generate either an ectopic beat or a sustained ectopic rhythm.

In terms of these general considerations, cardiac arrhythmias might result from either abnormal impulse generation or abnormal conduction. Moreover, since abnormal impulse generation and conduction might coexist, some arrhythmias might result from the simultaneous operation of both mechanisms (table 1).

Arrhythmias that are caused by abnormal impulse generation can be regarded as resulting from focal mechanisms. That is, these arrhythmias originate in a single fiber or a small group of well-coupled fibers (the 'focus'), and ectopic impulses spread radially from this focus when the pacemaker cell undergoes spontaneous depolarization. Arrhythmias that occur as a result of abnormal impulse conduction may be focal or non-focal. For instance, a ventricular hemiblock might be regarded as occurring as a result of a focal mechanism, whereas macroreentrant arrhythmias (e.g., those of the Wolff-Parkinson-White syndrome) must be regarded as resulting from a non-focal mechanism.

We will first consider arrhythmias resulting from abnormal impulse generation.

Automatic rhythms

Normal automaticity

Most cardiac cells do not normally become automatic. Isolated preparations of normal working myocardial tissue from either the atria or ventricles usually are quiescent. These myocardial cells have maximum diastolic potentials of -80 to -100 mV, and only fire action potentials when they are stimulated. After cessation of stimulation, these preparations typically show diastolic hyperpolarization or stable resting potentials. That is, they do not show 'normal automaticity'. However, as mentioned above, specialized atrial fibers and ventricular Purkinje fibers do become automatic in the absence of stimulation. After cessation of overdrive, these normally automatic fibers will show slow depolarization from maximum diastolic potential, which typically is ≥ -85 mV. This diastolic depolarization carries the transmembrane potential to the threshold voltage (typically between -80 and -70 mV) for the fast sodium current. At that point, a regenerative response occurs, there is a sudden influx of sodium ions through the fast channels, and the upstroke of an action potential occurs. This constitutes the beginning of an automatic or 'escape' beat. In the continued absence of external stimulation, these automatic beats will occur repeatedly, and the interval between them will gradually decrease (typically over 1–3 min) until a minimal cycle length occurs. In peripheral canine Purkinje fibers, this minimal cycle length is typically 2–4 s. This minimal cycle length is shorter in specialized atrial and junctional conduction tissue.

It is quite reasonable to presume that enhanced pacemaker activity in normal specialized atrial and ventricular tissues can produce automatic cardiac arrhythmias. Such a mechanism could well produce many non-paroxysmal junctional tachycardias. However, the existence of normal automaticity in some specialized cardiac cells is clearly unable to explain the full spectrum and nature of arrhythmias noted in the clinical population. Moreover, many of the properties of normally automatic cardiac cells suggest that normal automaticity probably is not the cause of a significant fraction of the arrhythmias attributed to abnormal impulse generation. With the exception of the sinus pacemakers, normally automatic cells usually do not generate very rapid rhythms and typically their automaticity is largely suppressed by the more rapid sinus pacemaker.

In summary, even though (a) ectopic normal automatic pacemakers may be protected from overdrive suppression by a suitable area of unidirectional conduction block, as is postulated for parasystolic rhythms, and (b) rates of normal automatic firing may be increased by the action of norepinephrine or circulating hormones, or by currents between the automatic focus and adjacent partially depolarized areas, other characteristics of many arrhythmias caused by abnormal impulse generation suggest that mechanisms other than normal automaticity must be operative.

Abnormal automaticity

An additional mechanism that may be responsible for cardiac arrhythmias caused by abnormal impulse generation is what we have termed abnormal automaticity[25]. This is the spontaneous impulse initiation that can occur in any type of cardiac fiber if, because of a decrease in background potassium conductance, or an increase in inward current, the resting transmembrane potential is reduced to -60 mV or less (fig. 1). Under these conditions, slow diastolic depolarization seems not to result from the pacemaker current, i_f [which is thought to operate in normal Purkinje fibers[13]], but rather from time- and voltage-dependent changes in potassium and calcium currents[23, 32] engendered at 'plateau potential'. Unlike normal automatic impulses, rhythms caused by abnormal automaticity are not perturbed by single permature impulses. Also, in contrast to the marked overdrive suppression that occurs in normal Purkinje fiber pacemakers, abnormally automatic foci are not greatly affected by rapid stimulation[10]. These abnormal foci may show very slight overdrive suppression or very slight overdrive enhancement of impulse initiation, but generally the 'escape' cycle length to the first spontaneous impulse immediately after cessation of overdrive, as well as that of the succeeding automatic impulse, is not significantly different than that of the spontaneous beats occurring before the start of stimulation. In contrast to the results with abnormally automatic pacemakers, we have also found that significant overdrive suppression can occur if the maximum diastolic potential of the pacemaker fibers is even slightly positive to -60 mV. We have suggested that the absence of significant overdrive suppression in the abnormally automatic cells may reflect the fact that the sodium channels are largely inactivated by the low maximum diastolic potential[49]. Rapidly repeating impulses may therefore cause only a small increase in $[Na^+]_i$ and provide a minimum stimulus to the sodium pump.

The presence of abnormal automaticity thus largely eliminates the need to postulate protection of an ectopic automatic focus by unidirectional conduction block. Also, unlike normal automaticity, which is a property of specialized conduction tissue with fixed anatomical distribution, abnormal automaticity can occur in any type of cell in any location in the heart. Once again, however, the rate of impulses generated by abnormal automaticity tends to be rather low, even when firing is enhanced by the action of catecholamines[42].

Triggered rhythms

Enhanced automaticity is not the only type of ectopic impulse initiation that may lead to tachycardias. Impulses from depolarizing afterpotentials represent a second class of cellular mechanisms that may cause either atrial or ventricular arrhythmias (fig. 2). Impulses from these afterpotentials (or afterdepolarizations) are by definition triggered by a prior

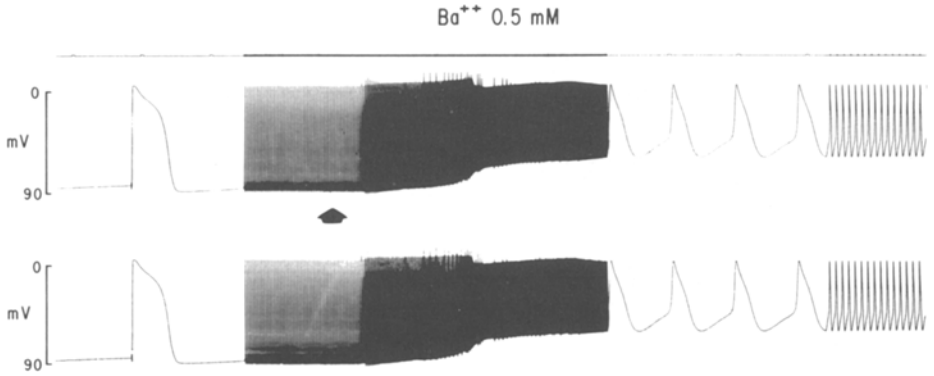


Figure 1. Transmembrane potentials recorded from two sites in a bundle of canine Purkinje fibers; records are obtained with a pen recorder that does not reproduce rapid transients. Control records, at the left, are obtained at fast and slow paper speed during regular stimulation in control Tyrode's solution. At the arrow the superfusate is changed to one containing Ba^{2+}, 0.5 mM. Note the decrease in MDP and development of abnormal automaticity with similar transmembrane action potentials at both sites. (Reprinted from Hoffman and Dangman[25], 1985, with permission)

impulse and thus are not automatic[17]. Afterdepolarizations can be divided into two main classes: Early afterdepolarizations are positive-going afterpotentials that occur during phases 2 or 3 of a primary action potential, and occur most frequently in Purkinje fiber preparations with longer action potential durations. Delayed afterdepolarizations are positive going afterpotentials that occur during phase 4. Few studies have addressed the biophysical mechanisms responsible for early afterdepolarizations, but they probably are caused by ionic currents quite similar to those that underlie abnormal automaticity. The mechanism for delayed afterdepolarizations has been studied more extensively[17, 31, 47].

Early afterdepolarizations

Early afterdepolarizations have two general forms. In one repolarization is interrupted and transmembrane potential sits at a level somewhat more positive than the normal resting potential. A new impulse or a series of impulses may arise in this incompletely repolarized fiber. This is the pattern of activity seen when a toxin, such as aconitine, is used to prevent inactivation of some fast channels[48]. In the other pattern, one that typically is observed if outward currents are attenuated, repolarization is interrupted by a series of depolarizations that closely resemble those that occur during abnormal automaticity. However, the rhythms that are caused by early afterdepolarizations tend to be intermittent. That is, after a primary (sinus) beat, generation of a sequence of triggered (ectopic) impulses occurs when the fibers fail to repolarize. The salvoe of ectopic beats is terminated when full repolarization occurs. Then, after subsequent primary impulses, the afterdepolarizations and resulting arrhythmia may reappear.

Early afterdepolarizations become more prominent when action potential duration is prolonged. Thus triggered arrhythmias from early afterdepolarizations are more likely to occur during bradycardia; rapid pacing usually will suppress these afterdepolarizations completely[44]. This might be the result of an increase in repolarizing delayed rectifier current, increased pump current, or both.

Delayed afterdepolarizations

Delayed afterdepolarizations typically occur in Purkinje fibers when the cells become overloaded with calcium as during poisoning with digitalis[31]. In other cardiac tissues, such as those of the canine coronary sinus[53] delayed afterdepolarizations also may occur in apparently normal cells. The mechanism postulated for delayed afterdepolarizations is the following. It is thought that calcium overload causes a cyclic release and reuptake of calcium by the sarcoplasmic reticulum. This results in cyclic changes in intracellular calcium activity, and this in turn, engenders a transient inward depolarizing current. Whether the current flows in calcium-activated channels or results from sodium-for-calcium exchange is not yet certain[40].

The characteristics of delayed afterdepolarizations and the triggered activity arising from them depend, at least in part on the tissue in which they are being induced and on the means used to induce them. Nevertheless, some characteristics seem reasonably typical of all delayed afterdepolarizations. The amplitude and the coupling interval of delayed afterdepolarizations varies with the rate of the train of beats that is used to induce them. In ouabain-treated Purkinje fibers the amplitude of the first afterdepolarization usually increases as the cycle length of the stimulation used to

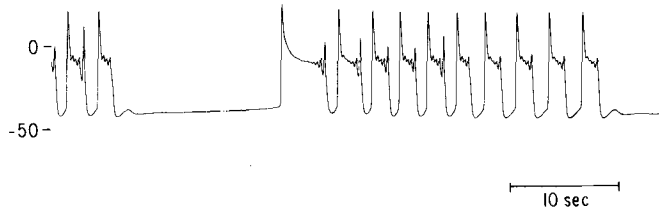


Figure 2. Early and delayed afterdepolarizations induced by superfusing a Purkinje fiber with Tyrode's solution containing cesium, 20 mM. The preparation is driven for the first three cycles and stimulation discontinued; the stimulus then is reinstituted for 10 cycles and discontinued again. Early afterdepolarizations (EAD) occur during phase 2 of the driven action potentials; delayed afterdepolarizations (DAD) occur after full repolarization and are seen clearly after the last driven beat in each sequence. Vertical calibration, voltage (mV); horizontal, time (s). (Reprinted from Hoffman and Rosen, Circ. Res. *49* (1981) 69–83, with permission)

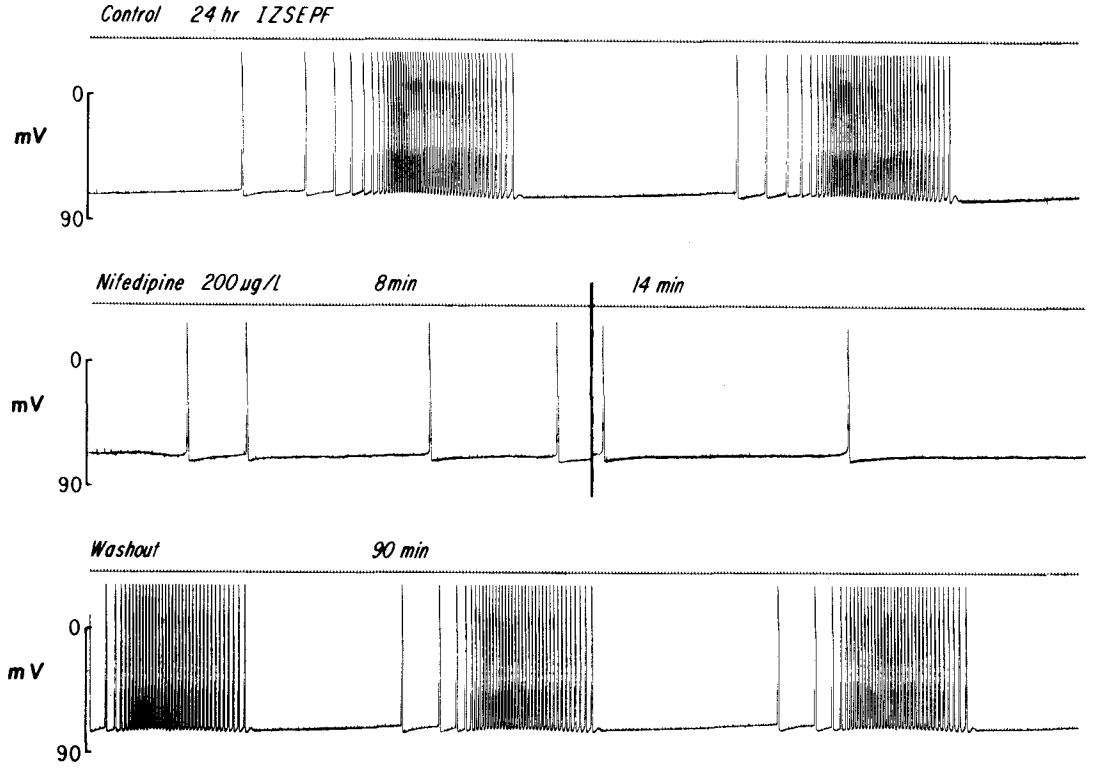


Figure 3. Effects of nifedipine on bursts of action potentials occurring in a preparation of subendocardial Purkinje fibers of a 24-h infarct zone. Upper panel, control recordings; middle panel, the effects of the drug; lower panel, washout of the drug. Within 8 min after start of nifedipine, 200 µg/l, bursts of action potentials were abolished, and final spontaneous action potentials were recorded at 14 min. No subsequent spontaneous action potentials occurred for an additional 16 min while drug superfusion continued. Note voltage calibrations at left, 1 s time marks above each panel. For further discussion, see text. (Reprinted from Dangman and Hoffman, Am. J. Cardiol. *46* (1980) 1059–1067, with permission)

induce it is decreased to about 300 ms[9]. Therefore, the likelihood that an afterdepolarization will initiate a triggered action potential is increased by a more rapid rate or by a premature impulse. Once an afterdepolarization attains threshold and initiates an action potential, that premature action potential will be followed by a larger than usual afterdepolarization and it in turn probably also will attain threshold and thus initiate a self-sustaining rhythm.

The effects of overdrive on rhythms triggered by delayed afterdepolarizations are complex. In canine subendocardial Purkinje fibers from 24-h infarct zones, for instance, triggered activity occurs frequently in preparations with cells with maximum diastolic potentials of −70 to 80 mV. In this triggered activity, overdrive suppression can occur[10, 12, 16]. In some instances, this leads to spontaneous waxing and waning of the triggered rhythm (fig. 3).

In summary, arrhythmias caused by abnormal impulse generation might be either automatic or triggered: the automatic rhythms could be caused by either normal or abnormal automaticity and the triggered rhythms by either early or delayed afterdepolarizations.

Abnormal conduction

Arrhythmias resulting from abnormalities of conduction include those caused by simple conduction block. Sinoatrial block and atrioventricular block are examples of this mechanism. These need no further consideration. Each abnormality would cause an ectopic, normally automatic rhythm. In addition, abnormalities of impulse propagation can result in reentrant arrhythmias.

Circus movement

The concept of circus movement is well established: as shown by Mines[37], if an impulse once can be induced to propagate in only one direction in a ring of excitable cardiac tissue that impulse will continue to circulate and reexcite the tissues in front of it. There have been many studies on the conditions necessary for reentry due to circus movement to occur in the heart. In general, it was thought that reentrant excitation of this sort required an area of unidirectional block in a sequestered path and a marked local abbreviation of refractoriness[54]; the shortened refractory period was needed because, with a normal refractory period, normal rapid conduction of the cardiac impulse would necessitate quite a long path. Studies on reentrant excitation occurring in a path that included the atrioventricular node[29] demonstrated that if the impulse propagated slowly enough the path need not be long. Subsequently, it was shown that if because of partial depolarization, a slow response replaced the normal fast response in Purkinje fibers, circus movement might occur in quite short loops of Purkinje tissues[8, 55]. In the normal a-v node, and in the partially depolarized Purkinje fiber, the unidirectional block needed to initiate circus movement was readily demonstrated. Other studies showed that the difference in duration of action potentials of terminal Purkinje fibers and adjacent ventricular muscle[38] was sufficient to block propagation into the Purkinje fibers of early premature impulses arising in ventricle and that this type of block could lead to a reentrant impulse that propagated retrogradely in one bundle branch and antegradely in the other[35]. In summary, initiation of reentrant excitation due to circus movement often but not always depends on slow conduction in some part of the circus

path but always requires unidirectional block of the initiating impulse.

In Mines' demonstration of circus movement the impulse circulated around a hole in the cardiac tissue and most subsequent studies assumed that the reentering impulse must circulate around an anatomical barrier or a permanently inexcitable area. Allessie[1] then showed in studies on isolated atrial tissue that a propagating impulse can create the inexcitable barrier around which it circulates; he termed this type of reentry 'leading circle' reentry. In this model the initiating impulse is diverted around an area that still is refractory; electrotonic current from the propagating impulse keeps the refractory area partially depolarized and inexcitable so that the impulse can continue to circulate around it.

The characteristics of reentrant excitation due to circus movement depend to some extent on the anatomical and electrophysiological conditions present in the circus path, but some patterns of behavior are reasonable common. Reentrant excitation frequently is initiated by a premature impulse or by rapidly repeating impulses presumably because such impulses are more likely to undergo unidirectional block. Reentrant excitation due to circus movement also can be terminated by a properly timed premature impulse or by rapidly repeating impulses. In this case there may be differences in the response of leading circle reentry and circus movement around an inexcitable barrier. In the former case the leading edge of the circulating impulse propagates in partially refractory tissue, in theory at the end of the effective refractory period. Thus, these is no interval during which a premature impulse can enter the circuit and block propagation of the reentering impulse. In contrast, when the impulse circulates around a sufficiently large inexcitable barrier, tissue in advance of the wave-front may have largely or fully recovered from prior excitation. In this case, premature impulses can readily penetrate the circuit during the so-called excitable gap and reset or terminate the reentry. In addition, during classical circus movement it usually is possible to entrain the rhythm by pacing at a rate slightly faster than the intrinsic rate[41]. The paced impulses enter the circus path and propagate in both directions: the wavefront travelling in a retrograde direction blocks but that travelling in the antegrade direction propagates successfully at the imposed shorter cycle length.

A model of reentrant rhythm causing atrial flutter and due to circus movement in the ring of tissue around the tricuspid orifice shows all these characteristics[18]. The model is of interest because the path for circus movement is made up of normal atrial muscle in which the fibers generate fast response action potentials with uniform characteristics. The reentrant impulse propagates at reasonably high velocity – 0.75 to 0.85 m/s – in either direction around the tricuspid ring. Thus slow conduction and an area of persistent unidirectional block are not needed to sustain circus movement. All that is necessary is a suitably bounded, closed path of sufficient length. In the model described, one boundary is provided by the tricuspid orifice and the other by a Y-shaped lesion in the right atrium (fig. 4).

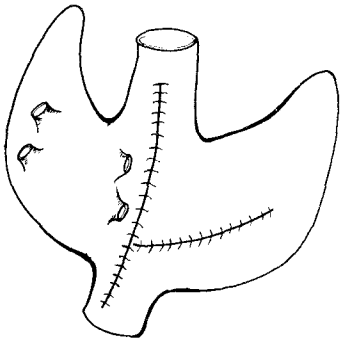


Figure 4. Schematic representation of the posterolateral view of the canine right atrium showing superior and inferior venae cavae, right and left appendages and sites of entry of pulmonary veins into left atrium. The incision used is indicated by the crosshatched lines extending from superior to inferior cavae and toward the right atrial appendage parallel to the a–v groove.

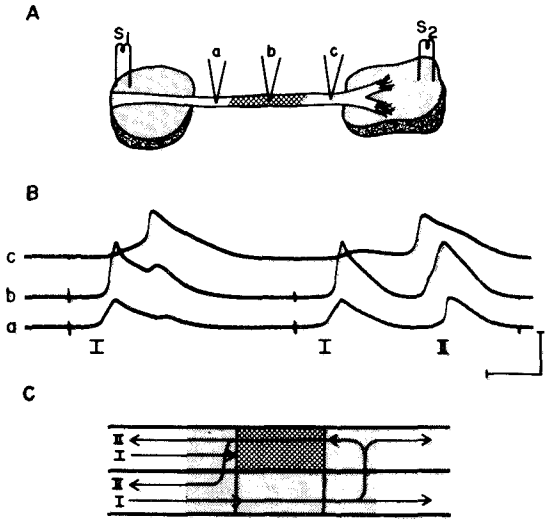


Figure 5. Reentry (reflection) in a linear bundle of canine Purkinje fibers. *A* Diagram of preparation showing location of stimulating electrodes (S_1 and S_2) and recording electrodes (a, b, c). The center segment, depressed by high K_o, is indicated by crosshatched area. The bundle is stimulated at S_1 only. *B* The first group of action potentials show conduction of an impulse originating at S_1 without reentry; conduction from a to c, through the depressed area, required 100 ms. In the second group of action potentials I shows conduction of another impulse from S_1 with a marked increase in the conduction delay between recording sites b and c to 250 ms. A reentrant impulse (II) returning in the opposite direction is shown at recording sites b and a. *C* Diagrammatic representation of a possible pathway of impulse propagation during reentry in two parallel fibers. Severely depressed area indicated by crosshatches, moderately depressed area by stipples. Impulse I is completely blocked in the upper fiber at an area of unidirectional block but traverses the moderately depressed area in the lower fiber, then reenters the upper fiber to travel in the reverse direction as impulse II. Calibrations: vertical, 100 mV for traces a and c and 50 mV for trace b; horizontal 250 ms. (Reprinted from Cranefield, Wit and Hoffman, 1973, with permission)

Reflection

In addition to circus movement as a cause of reentrant excitation it has been shown that reentry can result from reflection of the impulse from an inexcitable segment[3,7]. Reflection occurs when, distal to the inexcitable segment, the electrotonic depolarization caused by the blocked impulse causes a markedly delayed action potential. The electrotonic spread of current due to this delayed action potential then reexcites the tissues proximal to the site of block (fig. 5). The characteristics of reflected impulses and their modulation by changes in rate and rhythm have been described in considerable detail for isolated Purkinje fiber bundles[3]. The important variables are any interval-dependence of transmission across the inexcitable segment, the interval-dependence of action potential duration and the presence or absence of phase 4 depolarization on either side of the blocking segment.

Table 2 summarizes the general mechanisms for arrhythmias resulting from abnormal conduction: those of particular interest are: circus movement around an inexcitable barrier,

Table 2. Electrophysiological mechanisms for arrhythmias

Abnormal impulse generation
A. Automatic rhythms
1. Normal automaticity
2. Abnormal automaticity
B. Triggered rhythms
1. Early afterdepolarizations
2. Delayed afterdepolarizations
Abnormal impulse conduction
A. Conduction block
B. Unidirectional conduction block and reentry
1. Circus movement
2. Reflection

leading circle type reentry and reentrant excitation due to reflection. Fibrillation is assumed to result from what is called random reentry. In this case, perhaps due to multiple local differences in refractoriness, the propagating impulse fractionates and a number of areas of leading circle reentry are established[2].

Actual mechanisms

Some of the possible mechanisms for arrhythmias listed in table 2 undoubtedly can and do cause arrhythmias of the in situ heart. A clear example of reentrant excitation due to circus movement is provided by the heart with an anomalous connection between the atria and ventricles. The path for circus movement thus includes the atria, the a–v node and His Purkinje system, the ventricles and the accessory pathway. The a–v node provides a site for slow conduction and the accessory pathway often is a site of unidirectional conduction. An impulse can spread from the atria to the ventricles over the normal pathways and reenter the atria over the accessory pathway establishing a reentrant tachycardia; in some instances propagation is in the reverse direction. Surgical interruption of the accessory path prevents reinitiation of the arrhythmia. Maps of excitation sequence during tachycardias induced in canine hearts with a ventricular infarction have provided satisfactory evidence of circus movement around part of the damaged epicardium[15, 19, 52] and similar although less satisfactory evidence is available for human hearts[27, 36, 50]. In canine hearts with infarcts caused by ligation of the left anterior descending coronary artery, the initiating impulse, usually premature, blocks at one border of the tissues damaged by ischemia but propagates around the margins of the damaged area. At some point, it enters the abnormal region and spreads in a retrograde direction. Usually this retrograde spread is quite slow and thus, by the time the impulse arrives at the site of block, distal tissues have recovered excitability. The impulse thus can reenter the normal ventricular myocardium and repeat the circulation. As mentioned above, reentry due to circus movement is the cause of persistent inducible atrial flutter in dogs with a suitable right atrial lesion[18]. Reentrant excitation of the leading circle type has been demonstrated in the isolated canine heart rendered susceptible to atrial flutter by acetylcholine by mapping the sequence of excitation at many sites[2]. Leading circle reentry also is the most likely mechanism for persistent atrial flutter in dogs with right atrial enlargement due to tricuspid insufficiency and pulmonary artery constriction[5]. Evidence for the operation of the other mechanisms in causing arrhythmias of the in situ animal heart or the diseased human heart is much less adequate. Reentry due to circus movement is not too difficult to demonstrate in experimental animals since in many cases the sequence of activation can be mapped through the use of multiple electrodes and because the arrhythmia usually responds in a predictable manner to induced perturbations of rate and rhythm. Maps of excitation sequence in the human heart can be obtained during cardiac surgery and some support reentry as the arrhythmogenic mechanism. Responses of arrhythmias to premature stimulation and overdrive have indicated that some arrhythmias such as one type of atrial tachycardia[4], one type of atrial flutter[51] and certain inducible ventricular tachycardias[30] are caused by reentry of the classical type. Leading circle reentry is more or less excluded because during leading circle reentry there is little or no excitable gap in the circuit and the rhythm thus is relatively immune to the effects of induced impulses. In summary, there is good evidence that reentrant excitation due to circus movement is the cause of a variety of clinically important arrhythmias.

For the other postulated mechanisms (table 2) the evidence is less satisfactory. Some indication of the mechanism for an arrhythmia can be obtained by classifying the typical responses of automatic and triggered rhythms to induced changes in rate and rhythm; this has led to the probable identification of delayed afterdepolarizations as the cause of some accelerated a–v junctional rhythms[46] and abnormal automaticity as the mechanisms for ventricular tachycardias seen soon after infarction[33]. A comparison of the characteristics associated with a clinical arrhythmia with the characteristics of an arrhythmia created in vitro can provide suggestive evidence for the mechanism operating in the patient. For example, there is evidence indicating that the 'torsades de pointes' often seen in hypokalemic patients taking quinidine is caused by early afterdepolarizations[44, 45] and, indeed, this mechanism probably is operative for other antiarrhythmic drugs that cause use-dependent block of fast channels, significant attenuation of the repolarizing potassium current i_x and a torsades-like arrhythmia.

A somewhat more powerful method is to characterize the response of arrhythmogenic mechanisms both to induced changes in rate and rhythm and to selected antiarrhythmic drugs. This method has been employed only to a limited extent but its effectiveness has been demonstrated in one animal model[28]. In dogs the His bundle was interrupted by local injection of formalin. Early after the creation of the lesion, the dogs showed a rapid ventricular rhythm; later this was replaced by a slower ventricular rhythm. During both types of arrhythmias the dogs were tested with overdrive, lidocaine and ethmozin. The former drug readily suppresses normal but not abnormal automaticity, whereas, the latter exhibits opposite effects[11].

The early arrhythmia did not show overdrive suppression and was slowed by ethmozin but not by lidocaine. The later arrhythmia showed overdrive suppression and was slowed by lidocaine but not by ethmozin. These results strongly indicate that the early arrhythmia was caused by abnormal automaticity and the subsequent rhythm by the normal automatic mechanism.

These techniques to identify mechanisms for arrhythmias of the in situ heart often are not totally satisfactory because there is considerable overlap among the various postulated arrhythmogenic mechanisms both in responses to induced changes in rate and rhythm and to many antiarrhythmic drugs. What is needed to prove the mechanism for automatic or triggered rhythms of the in situ heart is the ability to record an electrical signal characteristic of the arrhythmogenic mechanism and to show this signal is present during the arrhythmia and absent when the arrhythmia has been terminated by drugs or other interventions. This approach would place identification of automatic and triggered rhythms on a par with the reentrant rhythms for which circus movement can be directly demonstrated by mapping activation sequence.

Some years ago we began to explore the possibility of doing this by characterizing the extracellular potential changes associated with impulse generation in the sinus node[6, 20] (fig. 6)

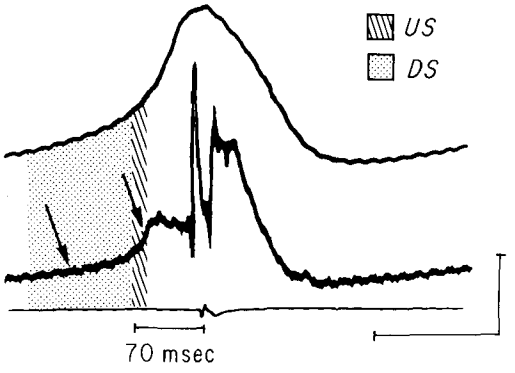
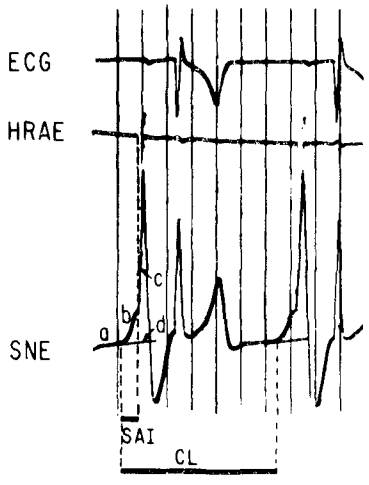


Figure 6. *A* Transmembrane potential (top trace) and a unipolar extracellular electrogram (middle trace) from the primary pacemaking area recorded simultaneously with a bipolar atrial electrogram (bottom trace). Diastolic slope (DS) and upstroke slope (US) are indicated by arrows. DS is within the stippled area and US is within the area indicated by diagnoal lines. Horizontal bar is 150 ms and vertical bar corresponds to 35 mV for the transmembrane record and 25 μV for the unipolar electrogram. High frequency components of the electrogram have been retouched for clarity. (Reprinted from Cramer et al.[6], 1977, with permission) *B* A record from a conscious dog showing, from top to bottom, inverted Z lead of the ECG, a high right atrial electrogram (HRAE), and sinus electrograms (SNE) recorded using AC amplifiers. Each sinus electrogram shows a slow negative-going diastolic slope (a) and a slow negative-going upstroke slope (b) followed by rapid primary negativity (c). The sinoatrial interval (SAI) is measured from the point of departure of the upstroke slope from the line of trajectory of the diastolic slope (d) to the beginning of the primary negativity or the high right atrial electrogram. The cycle length (CL) of an automatic group is the interval between two consecutive points of departure of the upstroke slope from the trajectory of the diastolic slope. Voltage calibration is for sinus electrograms. (Reprinted from Cramer et al.[6], 1977, with permission)



and subsequently, showing that an extracellular waveform characteristic of automatic firing could be recorded from the in situ canine heart[20] and, through catheter electrodes, from the human heart[22, 43]. Others have used this method to study sinus node activity in humans[39] and some studies have been conducted on ectopic automatic rhythms[22]. We also showed that both early and delayed afterdepolarizations gave rise to characteristic electrogram deflections[25] that might be used, in conjunction with other evidence, to identify these mechanisms in the in situ heart. As is the case for automatic rhythms, a limited number of recordings of early and delayed afterdepolarizations from in situ hearts have been obtained[34, 55], but the method has not yet been subjected to suitable tests and so it is not possible to assess its utility or precision.

In summary, studies of isolated cardiac tissues have provided many insights into the possible cellular mechanisms of cardiac arrhythmias. However, much work remains in order to be able to clearly demonstrate that specific mechanisms cause particular rhythms in the in situ heart.

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Conduction of the impulse in the ischemic myocardium – implications for malignant ventricular arrhythmias

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Summary. Ventricular arrhythmias occurring consequent to regional disturbances of myocardial perfusion are the most frequent cause of sudden cardiac death. They are related to marked changes of impulse propagation in the ischemic region, which consist of circulating excitation with re-entry. Mapping of the impulse during ventricular tachycardias and ventricular fibrillation shows that the circus movements change their shape and localization from beat to beat. Zones of tissue which block the impulse during one beat may conduct the impulse at a fast rate during the next beat. The main cause underlying this behavior is the depression of the ischemic action potential. This depression is caused by the partial inactivation and the