Mechanisms of Cardiac Arrhythmias

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A B S T R A C T

Cardiac arrhythmias are prevalent among humans across all age ranges and may occur in the setting of underlying heart disease as well as in structurally normal hearts. While arrhythmias are widely varied in their clinical presentations, they possess shared electrophysiologic properties at the cellular level. The 3 main mechanisms responsible for cardiac arrhythmias are automaticity, triggered activity, and reentry. Although identifying the specific mechanism may at times be challenging for the clinician and require invasive electrophysiologic study, differentiating and understanding the underlying mechanism may be critical to the development of an appropriate diagnosis and treatment strategy.

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Mecanismos de las arritmias cardiacas

R E S U M E N

En la especie humana, las arritmias cardiacas son muy prevalentes en todos los grupos de edad y pueden darse tanto en el contexto de una cardiopatía subyacente como en corazones estructuralmente normales. Aunque las formas de presentación clínica de las arritmias son muy diversas, en las células comparten propiedades electrofisiológicas comunes. Los 3 mecanismos principales de las arritmias cardiacas son las alteraciones en el automatismo, la actividad desencadenada y la reentrada. Aunque la identificación del mecanismo específico a veces pueda resultar difícil para el clínico y requerir un estudio electrofisiológico invasivo, diferenciar y comprender el mecanismo subyacente puede ser crucial para desarrollar una correcta estrategia diagnóstica y terapéutica.

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INTRODUCTION

Understanding the mechanisms of arrhythmias is helpful to the appropriate management and treatment of all arrhythmia types. Since the mechanisms that lead to clinical arrhythmias are frequently due to abnormalities beyond the tissue level, it is also essential to understand what occurs at the cellular level.

NORMAL CARDIAC CELLULAR ELECTROPHYSIOLOGY

Cardiac myocytes are highly specialized cells responsible for both conduction of electrical impulses and mechanical contraction. Some myocytes demonstrate automaticity, defined by the capability of cardiac cells to undergo spontaneous diastolic depolarization and to initiate an electrical impulse in the absence of external electrical stimulation.[1]

Spontaneously originated action potentials (APs) are propagated through cardiac myocytes, which are excitable, referring to their ability to respond to a stimulus with a regenerative AP.[2] Successful propagation of the cardiac impulse is enabled by gap junctions, specialized membrane structures composed of multiple intercellular ion channels that facilitate electrical and chemical communication between cells. Cardiac APs are regionally distinct (Fig. 1) due to each cell type expressing different numbers and types of ion channels.[3]

Under normal conditions, the sinoatrial node is the primary pacemaker of the heart, with a resting membrane potential of approximately -60 mV. Prior research has demonstrated that the I_f ("funny") current plays a major role in the initiation of diastolic depolarization.[4] The aggregate activity of various currents results in a net inward flow of sodium (Na^+) and thus an increase in the membrane potential. When it reaches -40 mV, calcium (Ca^{2+}) currents (T-type $I_{Ca,T-}$ and L-type $I_{Ca,L}$) are activated, and serve as the predominant ion carriers during the AP upstroke of pacemaker cells[4] (Ca^{2+}-dependent). Subsequently, outward potassium (K^+) currents are activated and Ca^{2+} currents are inactivated. The membrane potential decreases due to the outward flow of K^+, the major repolarizing ion of the heart. Upon reaching the resting membrane potential, the cycle is ready to repeat itself.

The resting membrane potential of muscle cells is -90 mV. Inflow of positive charge (Ca^{2+} and Na^+) through the gap junction increases the voltage towards threshold (approximately -65 mV)[3] initiating an AP. At this point, Na^+ channels are triggered to open, resulting in a large but transient inward Na^+ current (phase 0). The Na+ current is quickly inactivated, followed by a subsequent outward K^+ current and thereby initiating repolarization (phase 1).

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The $I_{Ca,L}$ plays an important role during the AP plateau (phase 2), opposing the K^+ current. The $I_{Ca,L}$ is the main route for Ca^{2+} influx and triggers Ca^{2+} release from the sarcoplasmic reticulum, initiating contraction of the myocyte. Activation of delayed rectifier K^+ channels and inactivation of Ca^{2+} channels leads to termination of the plateau and initiates late repolarization (phase 3). Finally, outward K^+ channels mediate the final repolarization (phase 4).

Following contraction, the cardiac myocytes must enter a relaxation or refractory phase during which they cannot be depolarized. The refractory period is defined by the time interval following excitation during which the cell remains unexcitable. This is due to the lack of availability of depolarizing current (which is Na^+ in muscle cells). It is classified as either absolute or relative (Fig. 2), depending on whether it is completely unexcitable or needs a greater stimulus than normal.

PRINCIPAL MECHANISMS OF CARDIAC ARRHYTHMIAS

The mechanisms responsible for cardiac arrhythmias may be divided into disorders of impulse formation, disorders of impulse conduction or a combination of both (Table 1).

Disorders of Impulse Formation

Automaticity

Altered Normal Automaticity

As described previously, some specialized heart cells, such as sinoatrial nodal cells, the atrioventricular (AV) node, and the His-Purkinje system, as well as some cells in both atria,[5] possess the property of pacemaker activity or automaticity. Suppression or enhancement of this activity may lead to clinical arrhythmias.

Under normal conditions, the sinoatrial nodal cells have the fastest rate of firing and the so-called "subsidiary" pacemaker cells fire at slower rates, so the normal hierarchy is maintained. The firing rate is determined by the interaction of 3 factors: the maximum diastolic potential, the threshold potential at which the AP is initiated, and the rate or slope of phase 4 depolarization.
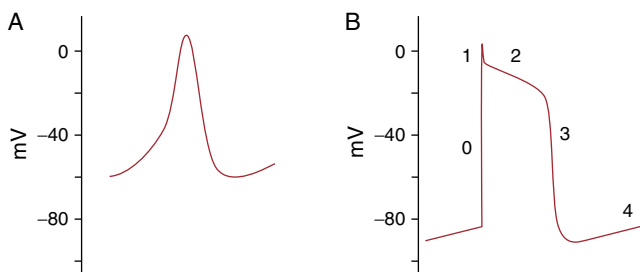

Figure 1. The cardiac action potential. A: sinus node action potential. B: muscle cell action potential.
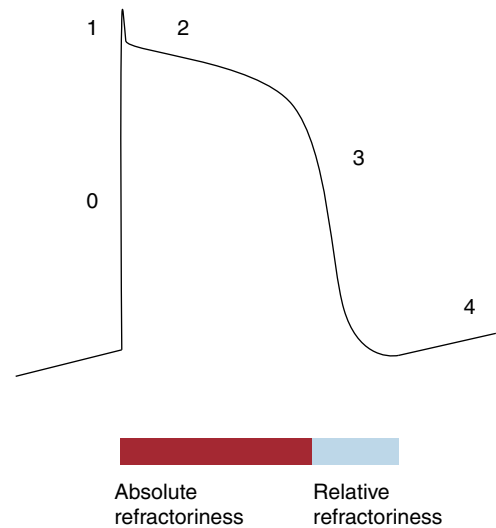

Figure 2. Refractory periods, showing the absolute and relative refractory periods during the action potential.

Table 1
Mechanisms of Cardiac Arrhythmias

Disorders of impulse formation	Disorders of impulse conduction
Automaticity	*Reentry*
Altered normal automaticity	Anatomic reentry
Abnormal automaticity	Functional reentry
Triggered activity	
Delayed afterdepolarization	
Early afterdepolarization	

A change in any of these (Fig. 3) may alter the rate of impulse initiation.[6]

Pacemaker activity is controlled by the autonomic nervous system and can be modulated by a variety of systemic factors, including metabolic abnormalities and endogenous or pharmacologic substances.

Parasympathetic activity reduces the discharge rate of the pacemaker cells (Fig. 4) by releasing acetylcholine (Ach) and hyperpolarizing the cells by increasing conductance of the K^+ channels. It may also decrease I_{Ca-L} and I_f activity, which further slows the rate.

The suppressive effect of Ach is frequently used in practice for both diagnostic and therapeutic purposes. Tachycardias resulting from enhanced normal automaticity are expected to respond to vagal maneuvers (promoting Ach release) with a transient decrease in frequency, and a progressive return towards baseline after transiently accelerating to a faster rate upon cessation of the maneuver (a phenomenon known as "post-vagal tachycardia").[7]

Conversely, sympathetic activity increases the sinus rate. Catecholamines increase the permeability of I_{ca-L}, increasing the inward Ca^{2+} current. Sympathetic activity also results in enhancement of the I_f current,[8] thereby increasing the slope of phase 4 repolarization.

Metabolic abnormalities such as hypoxia and hypokalemia can lead to enhanced normal automatic activity as a result of Na/K pump inhibition, thereby reducing the background repolarizing current and enhancing phase 4 diastolic repolarization.[7]

In degenerative conditions that affect the cardiac conduction system, suppression of the sinus pacemaker cells can be seen,
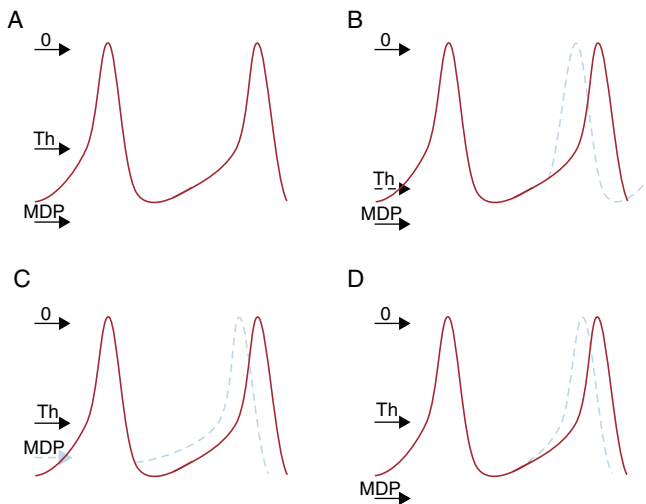
Figure 3. Mechanisms of enhanced automaticity. A: normal. B: increased threshold voltage. C: decreased membrane diastolic potential. D: increased slope phase 4 depolarization. MDP, membrane diastolic potential; Th, threshold.

resulting in sinus bradycardia or even sinus arrest. A subsidiary pacemaker may manifest as a result of suppression of sinus automaticity.

The hallmark of normal automaticity is "overdrive suppression." Overdriving a latent pacemaker cell faster than its intrinsic rate decreases the slope of phase 4, mediated mostly by enhanced activity of the Na/K exchange pump. When overdrive stimulation has ended, there is a gradual return to the intrinsic firing rate called the "warm-up" period (Fig. 5). The degree of suppression and the recovery time are proportional to the rate and duration of the applied stimulation.[7,8]
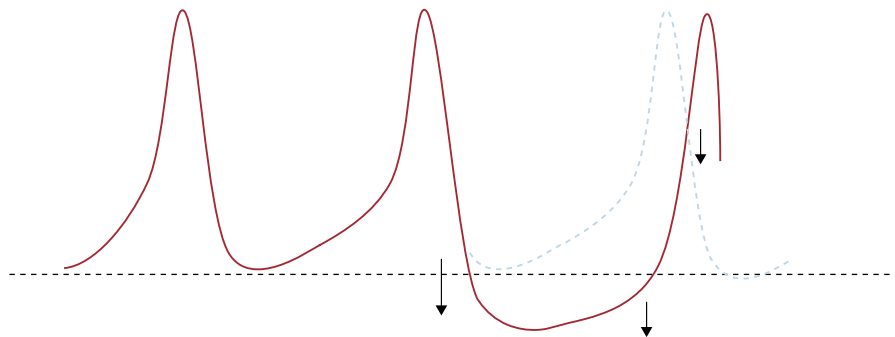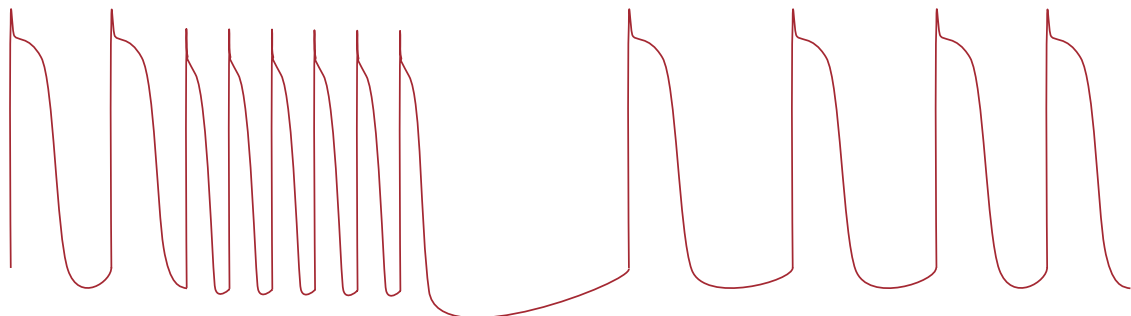
This mechanism plays an important role in maintaining sinus rhythm, continuously inhibiting the activity of subsidiary pacemaker cells.[6] In patients with external pacemakers, the intrinsic rhythm is also suppressed by this mechanism.[9]

The absence of overdrive suppression may indicate that the arrhythmia is the result of a mechanism other than enhanced normal automaticity. However, the reverse is not always true because enhanced normal automatic activity may not respond to overdrive pacing or faster intrinsic rates due to entrance block.[3]

Clinical examples: sinus tachycardia associated with exercise, fever, and thyrotoxicosis; atrial and ventricular accelerated rhythms; inappropriate sinus tachycardia and AV junctional rhythms.

Abnormal Automaticity

Atrial and ventricular nonpacemaker myocardial cells, which in the normal heart typically do not exhibit spontaneous activity, may exhibit automaticity properties. This can happen under conditions that drive the maximum diastolic potential towards the threshold potential, which is explained by the interplay of numerous currents that together result in a net inward depolarizing current associated with a decrease in potassium conductance.

The intrinsic rate of an automatic abnormal focus depends on the membrane potential; the more positive the membrane potential, the faster the automatic rate.[6] Abnormal automaticity is thought to play a role in cases of elevated extracellular potassium, low intracellular pH, and catecholamine excess.

An important distinction between enhanced normal and abnormal induced automaticity is that the latter is less sensitive to overdrive suppression,[10] although there are situations where it may be observed. Under these circumstances, an ectopic automatic focus displays characteristics of other arrhythmia mechanisms.[11]

Clinical examples: premature beats, atrial tachycardia, accelerated idioventricular rhythm, ventricular tachycardia (VT), particularly in the acute phase, associated with ischemia and reperfusion.

Figure 4. Parasympathetic effects on the action potential (reduction of the heart rate).

Figure 5. Overdrive suppression in a Purkinje fiber and postsupression warm-up period.

Triggered Activity

Triggered activity (TA) is defined by impulse initiation caused by afterdepolarizations (membrane potential oscillations that occur during or immediately following a preceding AP).[12] Afterdepolarizations occur only in the presence of a previous AP (the trigger), and when they reach the threshold potential, a new AP is generated. This may be the source of a new triggered response, leading to self-sustaining TA.

Based on their temporal relationship, 2 types of afterpolarizations are described: early afterdepolarizations (EADs) occur during phase 2 or 3 of the AP, and delayed afterdepolarizations (DADs) occur after completion of the repolarization phase (Fig. 6).

Delayed Afterdepolarization-Induced Triggered Activity

A DAD is an oscillation in membrane voltage that occurs after completion of repolarization of the AP (during phase 4). These oscillations are caused by a variety of conditions that raise the diastolic intracellular Ca^{2+} concentration, which cause Ca^{2+} mediated oscillations that can trigger a new AP if they reach the stimulation threshold.[13]

As the cycle length decreases, the amplitude and rate of the DADs increases, and therefore is expected to initiate arrhythmias triggered when DADs increase the heart rate (either spontaneously or during pacing). In fact, the amplitude and number of triggered responses are direct functions of both the rate and duration of overdrive pacing (easier to induce with continued stimulation). When overdrive pacing is performed, the TA can slow until it stops, or when it is not rapid enough to terminate the triggered rhythm it can cause overdrive acceleration, in contrast to overdrive suppression seen with automatic rhythms.[6]

Toxic concentration of digitalis was the first observed cause of DAD.[14] This occurs via inhibition of the Na/K pump, which promotes the release of Ca^{2+} from the sarcoplasmic reticulum. Clinically, digoxin toxic bidirectional fascicular tachycardia is felt to be an example of TA.[15]

Catecholamines can cause DADs by causing intracellular Ca^{2+} overload via an increase in I_{Ca-L} and the Na^+-Ca^{2+} exchange current, among other mechanisms. Ischemia-induced DADs are thought to be mediated by the accumulation of lysophosphoglycerides in the ischemic tissue,[16] with subsequent elevation in Na^+ and Ca^{2+}. Abnormal sarcoplasmic reticulum function (e.g. mutations in ryanodine receptor) can also lead to intracellular Ca^{2+} overload, facilitating clinical arrhythmias, such as catecholaminergic polymorphic VT.[17]

A critical factor for the development of DADs is the duration of the AP. Longer APs are associated with more Ca^{2+} overload and facilitate DADs. Therefore, drugs that prolong AP (eg, Class IA antiarrhythmic agents) can occasionally increase DAD amplitude.

Triggered arrhythmias induced by DADs may be terminated by single stimuli; therefore, other electrophysologic features are needed to distinguish them from the reentrant tachycardias. The rate dependency of the coupling interval may be useful, because in most cases of DAD-induced arrhythmias the shorter the cycle of stimulation, the shorter the coupling interval to the induced arrhythmia. This is in contrast to the inverse relationship seen in reentrant arrhythmias, where the shorter the coupling intervals of the initiating stimuli, the longer the coupling interval of the first arrhythmia beat.[3] Since this is not always the case, other electrophysiologic properties must be taken into account.

Adenosine has been used as a test for the diagnosis of DADs. Adenosine reduces the Ca^{2+} inward current indirectly by inhibiting effects on adenylate cyclase and cyclic adenosine monophosphate. Thus, it may abolish DADs induced by catecholamines, but does not alter DADs induced by Na^+/K^+ pump inhibition. The interruption of VT by adenosine points toward catecholamine-induced DADs as the underlying mechanism.[18]

Clinical examples: atrial tachycardia, digitalis toxicity-induced tachycardia, accelerated ventricular rhythms in the setting of acute myocardial infarction, some forms of repetitive monomorphic VT, reperfusion-induced arrhythmias, right ventricular outflow tract VT, exercise-induced VT (e.g. catecholaminergic polymorphic VT).

Early Afterdepolarization-Induced Triggered Activity

The EADs are oscillatory potentials that occur during the AP plateau (phase 2 EADs) or during the late repolarization (phase 3 EADs). Both types may appear during similar experimental conditions, but they differ morphologically as well as in the underlying ionic mechanism. Phase 2 EADs appear to be related to I_{ca-L} current,[19] while phase 3 EADs may be the result of electronic current across repolarization or the result of low I_{K1}.[20]

The plateau of the AP is a period of high membrane resistance[3] and little current flow. Consequently, small changes in either repolarizing or depolarizing currents can have profound effects on the AP duration and profile. As a wide variety of agents and conditions can result in a decreased outward current or increased inward current (so shifting the normal outward current), they can establish the conditions necessary for EADs (Table 2).

A fundamental condition underlying the development of EADs is AP prolongation, which manifests on the surface electrocardiogram (ECG) as QT prolongation. Some antiarrhythmic agents, principally class IA and III drugs, may become proarrhythmic because of their therapeutic effect of prolonging the AP. Many other drugs (Table 2) can predispose to the formation of EADs, particularly when associated with hypokalemia and/or bradycardia, additional factors that result in prolongation of the AP.[7] Catecholamines may enhance EADs by augmenting Ca^{2+} current, however the resultant increase in heart rate along with the increase in K^+ current effectively reduces the APD and thus abolishes EADs.[7]

An EAD-mediated TA appears to be the underlying cause of arrhythmias that develop in the setting of long QT syndrome. While the true mechanism of these arrhythmias is still debated, it is accepted that enhanced repolarization dispersion seen in the
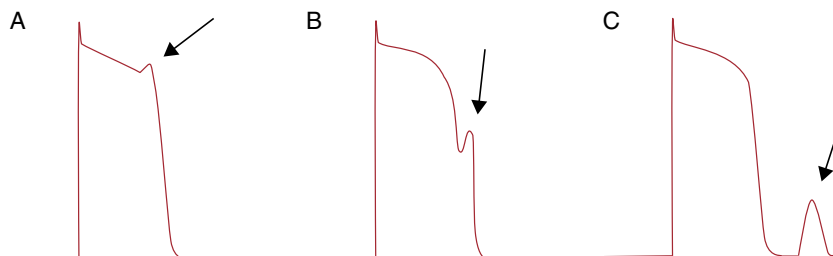

Figure 6. Representation of triggered activity. A: phase 2 early afterdepolarization. B: phase 3 early afterdepolarization. C: delayed afterdepolarization.

Table 2
Agents and Manipulations That May Lead to Early Afterdepolarizations

• Slow rate (bradycardia, complete heart block, etc.)
• Mechanical stretch
• Hypokalemia
• Hypoxia
• Acidosis
• Low extracellular K$^+$ concentration
• Low extracellular Ca^{2+} concentration
• Low extracellular magnesium (Mg^{2+}) concentration
• Class IA antiarrhythmic drugs (quinidine, disopyramide, procainamide)
• Class IB antiarrhythmic drugs (flecainide, encainide, indecainide)
• Class III antiarrhythmic drugs (amiodarone, sotalol, bretylium)
• Phenothiazines
• Tricyclic and tetracyclic antidepressants
• Erythromycin
• Antihistamines
• Cesium
• Amiloride
• Barium

syndrome can create a proarrhythmic substrate.[21] In such an electrophysiologic milieu an EAD can initiate the tachycardia.

Early afterdepolarization-triggered arrhythmias are rate dependent, and in general the EAD amplitude increases at a slow rate. Therefore, this type of TA is not expected to follow premature stimulation (which is associated with an acceleration of repolarization that decreases the EAD amplitude), with the exception of a long compensatory pause following a premature stimulus, which can be even more important than bradycardia in initiating *torsades de pointes*.[22]
Clinical examples: torsades de pointes ("twisting of the tips"), the characteristic polymorphic VT seen in patients with long QT syndrome.

Disorders of Impulse Conduction

Block

Conduction delay and block occurs when the propagating impulse fails to conduct. Various factors involving both active and passive membrane properties determine the conduction velocity of an impulse and whether conduction is successful, such as the stimulating efficacy of the impulse and the excitability of the tissue into which the impulse is conducted.[13] Gap junction coupling plays a crucial role for the velocity and safety of impulse propagation.[23]

Most commonly, impulses are blocked at high rates as a result of incomplete recovery of refractoriness. When an impulse arrives at tissue that is still refractory, it will not be conducted or the impulse will be conducted with aberration. This is the typical mechanism that explains several phenomena, such as block or functional bundle brunch conduction of a premature beat, Ashmańs phenomenon during atrial fibrillation (AF), and acceleration-dependent aberration.

Bradycardia or deceleration-dependent block is suggested to be caused by the reduction excitability at long diastolic intervals with subsequent reduction in the AP amplitude.

Many factors can alter the conduction, including rate, autonomic tone, drugs (eg, calcium channel blockers, beta blockers, digitalis, adenosine/adenosine triphosphate), or degenerative processes (by altering the physiology of the tissue and the capacity to conduct impulses).

Reentry

During normal electrical activity, the cardiac cycle begins in the sinoatrial node and continues to propagate until the entire heart is activated. This impulse dies out when all fibers have been depolarized and are completely refractory. However, if a group of isolated fibers is not activated during the initial wave of depolarization, they can recover excitability in time to be depolarized before the impulse dies out. They may then serve as a link to reexcite areas that were previously depolarized but have already recovered from the initial depolarization.[6] Such a process is commonly denoted as reentry, reentrant excitation, circus movement, reciprocal or echo beats, or reciprocating tachycardia (RT), referring to a repetitive propagation of the wave of activation, returning to its site of origin to reactivate that site.[12]

Reentry has been divided in 2 main groups (Table 3): anatomical or classic reentry, where the circuit is determined by anatomical structures, and functional reentry, which in turn includes different mechanisms. It is characterized by a lack of anatomic boundaries. Both forms can coexist in the same setting and share biophysical mechanisms.[24] Reentry is the most common arrhythmia mechanism seen in clinical arrhythmias, both in classical or variant forms.

Prerequisites for reentry include:

- A substrate: the presence of joined myocardial tissue with different electrophysiological properties, conduction, and refractoriness.
- An area of block (anatomical, functional, or both): an area of inexcitable tissue around which the wavefront can circulate.
- A unidirectional conduction block.
- A path of slowed conduction that allows sufficient delay in the conduction of the circulating wavefront to enable the recovery of the refractory tissue proximal to the site of unidirectional block.
- A critical tissue mass to sustain the circulating reentrant wavefronts.
- An initiating trigger.

Types of Reentry

Anatomical Reentry/Classic Reentry

The classic reentry mechanism is based on an inexcitable anatomical obstacle surrounded by a circular pathway in which the wavefront can "reenter", creating fixed and stable reentrant circuits. The anatomic obstacle determines the presence of 2 pathways (Fig. 7). When the wavefront encounters the obstacle, it will travel down one pathway (unidirectional block), propagating until the point of block, thus initiating a reentrant circuit.

Initiation and maintenance of reentry will depend on the conduction velocity and refractory period of each pathway, which determines the wavelength (wavelength=conduction velocity × refractory period). For reentry to occur, the wavelength must be shorter than the length of the pathway. Conditions that decrease conduction velocity or shorten the refractory period will allow

Table 3
Types of Reentry

Anatomic reentry
Functional reentry
Leading circle
Anisotropic reentry
Figure of 8 reentry
Reflection
Spiral wave (rotor) reentry

the creation of smaller circuits, facilitating the initiation and maintenance of reentry.

The *excitable gap* is a key concept essential to understanding the mechanism of reentry (Fig. 8). The excitable gap refers to the excitable myocardium that exists between the head of the reentrant wavefront and the tail of the preceding wavefront.[24] This gap allows the reentrant wavefront to continue propagation around the circuit. The presence of an excitable gap also makes it possible to enter in the reentrant circuit using external pacing and explains the phenomena of resetting, entrainment, and termination of the tachycardia with electrical stimulation.

Clinical examples: AV reentrant tachycardia associated with a bypass tract, AV nodal reentrant tachycardia, atrial flutter, bundle branch reentry VT, post-infarction VT.

Functional Reentry

In functional reentry, the circuit is not determined by anatomic obstacles; it is defined by dynamic heterogeneities in the electrophysiologic properties of the involving tissue.[2]

The location and size of functional reentrant circuits can vary, but they are usually small and unstable.

As previously stated, functionally determined reentrant circuits can occur due to different mechanisms:

- Leading circle reentry (Fig. 9). In 1976, Allesie et al. described a reentrant mechanism in the absence of an anatomical boundary. They postulated that the impulse circulates around a central core that is maintained in a refractory state because it is constantly bombarded by impulses and travels through partially refractory tissue.[25] Leading circle was defined as "the smallest possible pathway in which the impulse can continue to circulate."[26]
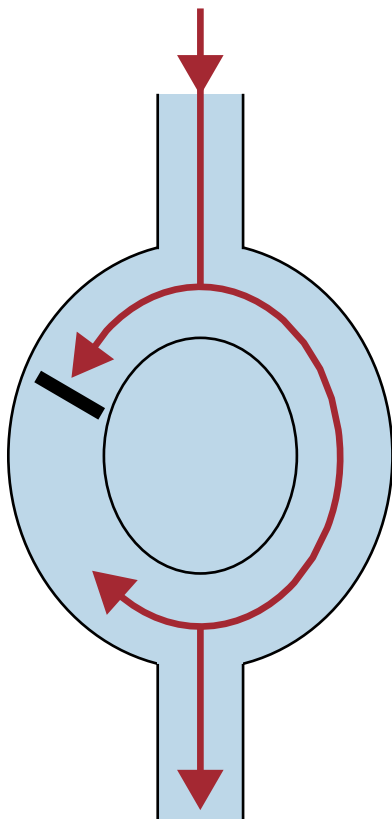

Figure 7. Anatomic reentry: the central obstacle creates 2 paths; when the impulse arrives, unidirectional block occurs and slow conduction through the other path allows reentry.
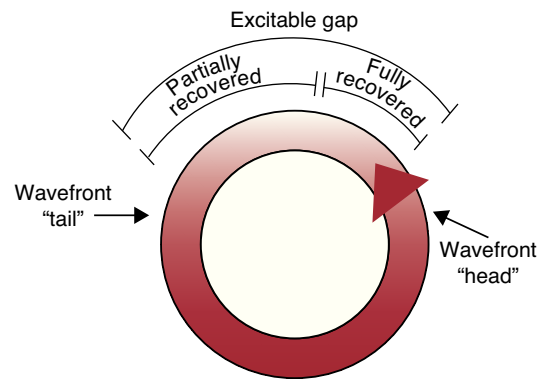

Figure 8. Schematic representation of an excitable gap.

This type of reentry is less susceptible to resetting, entrainment, and termination by pacing maneuvers because there is not a fully excitable gap.

- Anisotropic reentry. Anisotropic conduction relates to directionally dependent conduction velocity in cardiac muscle[27] and depends on the structure and organization of myocytes within cardiac tissue. These include the orientation of fibers and nonuniform distribution of gap junctions, with a larger number of channels poised to propagate the impulse longitudinally rather than transversely.[4] The heterogeneity in conduction velocities and repolarization properties of the anisotropic tissue can result in blocked impulses and slowed conduction that allows reentry even in small anatomical circuits.[24]
Clinical examples: anisotropic reentry in atrial and ventricular muscle, which may be responsible in the setting of VT originating in surviving myocardial infarction.[28]
- Figure of eight reentry. This type of reentry consists of 2 concomitant wavefronts circulating in opposite directions (clockwise and counterclockwise) around 2 functional or fixed arcs of block that merge into a central common pathway.
Clinical example: this type of reentry may be seen in the setting of infarction-related VT.
- Reflection (Fig. 10). Reflection is a unique subclass of reentry that occurs in a linear segment of tissue, where the impulse travels in both directions over the same pathway in the presence of severely impaired conduction.[29]
- Spiral wave (rotor) activity (Fig. 11). Spiral waves occur in a wide variety of excitable media.[30] They represent a 2-dimensional form of rotating wave propagation, which may also occur in 3 dimensions. When spiral wave activity occurs in 3 dimensions this phenomenon is called "scroll waves." Initially the term "rotor" described the rotating source and "spiral wave" defined the shape of the emerging wave.[6] One may encounter other terms for this phenomenon in the literature, such as "vortices" or "reverberators." Spiral wave activation is organized around a core, which remains unstimulated because of the pronounced curvature of the spiral. This curvature also limits the spiral propagation velocity, resulting in slow conduction and block.[25] In contrast to the leading circle model, there is a fully excitable gap. The tip of the wave moves along a complex trajectory and can radiate waves into the surrounding medium (known as "break-up" of a mother wave). Spirals may have completely different dynamics and can circulate with different patterns, change one to another, become stationary or continuously drift or migrate.[6] These characteristics result in both monomorphic and polymorphic patterns.
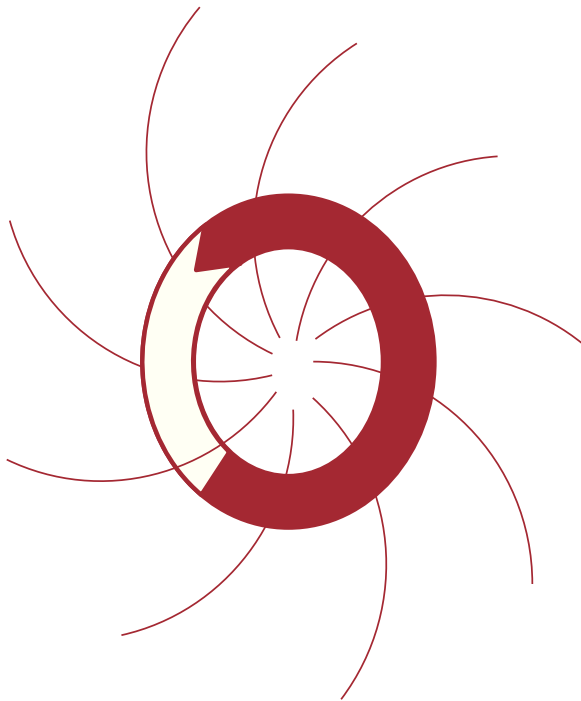*Clinical examples:* atrial and ventricular fibrillation, polymorphic VT.

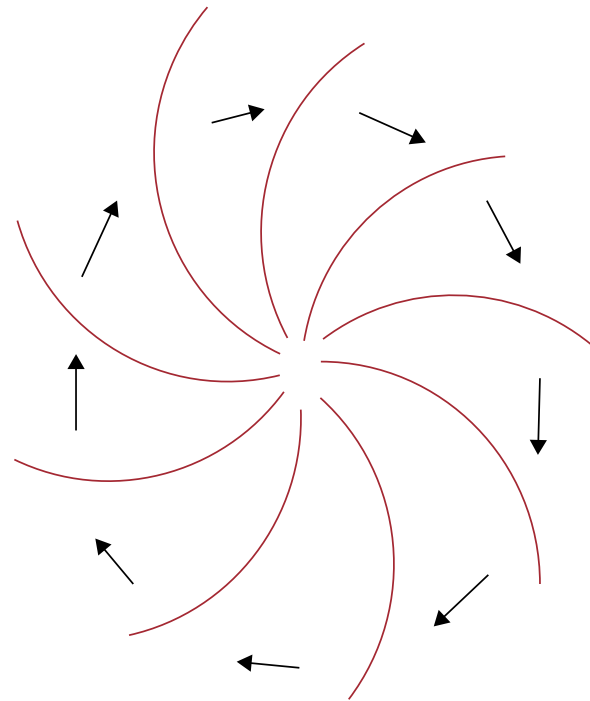**Figure 9.** Schematic representation of a leading circle.

Figure 11. Schematic representation of a spiral wave.

Resetting and Entrainment of Reentrant Arrhythmias

Resetting

Resetting is the act of advancing a tachycardia impulse by timed premature electrical stimuli. The first tachycardia complex in return should have the same morphological feature and cycle length as before the extrastimulus, and the pause to this first tachycardia complex should be "reset" and therefore less than twice the tachycardia cycle length.[6]

To reset a tachycardia the stimulated wavefront must reach the tachycardia circuit from the pacing site (the closer the pacing the less prematurity is need) and enter the excitable gap. Once it has entered the circuit, it will propagate in both directions, colliding in the retrograde direction with the previous tachycardia impulse (antidromically) while in the anterograde direction it will propagate and occur earlier than expected in time.[31] After that, the tachycardia will continue unchanged.

The degree of advancement depends on the prematurity of the extrastimulus and its conduction within the circuit (ie, the stimulus will propagate slower if the gap is only partially excitable).

If the stimulus enters the circuit during the relative refractory period, it can block in the anterograde direction (because it is absolutely refractory) and collide antidromically with the previous beat, thus terminating the tachycardia.[32]

Entrainment

Entrainment is the continuous resetting of a tachycardia circuit (Fig. 12). During overdrive pacing all myocardial tissue will maintain the pacing rate, with resumption of the intrinsic
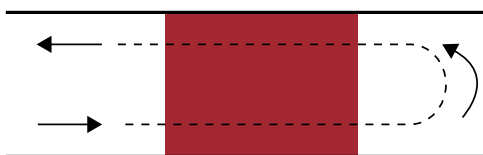

Figure 10. Schematic representation of reflection mechanism.

morphology and rate upon either abrupt cessation of pacing or slowing of the pacing rate below the intrinsic rate.[33]

Fusion

A fused beat possesses intermediate morphology between a fully stimulated complex and the tachycardia complex. It can be observed on the surface ECG (if a significant amount of myocardium is depolarized[34]) or intracardiac recordings. For fusion to occur, the tachycardia wavefront must exit the circuit and collide with the pacing stimulus before depolarization of the surrounding myocardium (Fig. 13). This requires a circuit with distinct entry and exit sites supporting a reentrant mechanism. Resetting and entrainment with fusion are specific to reentrant arrhythmias, but since they are sometimes challenging to identify, failure to detect them does not invalidate reentry as the arrhythmia mechanism.

FEATURES OF ARRHYTHMIA MECHANISMS

We now present an approach to the differential diagnosis of arrhythmia mechanisms. Table 4 is a schematic diagram of useful maneuvers (explained above) for distinguishing between the different arrhythmia mechanisms.

It is important to note that sometimes it may be very difficult to identify the mechanism responsible for the arrhythmia, and even more challenging if we take into account that an arrhythmia can be initiated by one mechanism but perpetuated by others (e.g. AF).

As shown in Table 4, automatic arrhythmias cannot be reproducibly initiated or terminated by programmed electric stimulation. They can be reset, and rapid pacing can result in overdrive suppression or produce no effect. The initiation may be facilitated by isoproterenol, in which the arrhythmia will typically start with a warm-up period with the first tachycardia beat being identical to the next one. Adenosine can slow but usually does not terminate the tachycardia.

Although TA can be initiated with pacing, initiation frequently requires isoproterenol. Arrhythmias due to TA can be reset and usually pacing can terminate a TA tachycardia. The first beat is
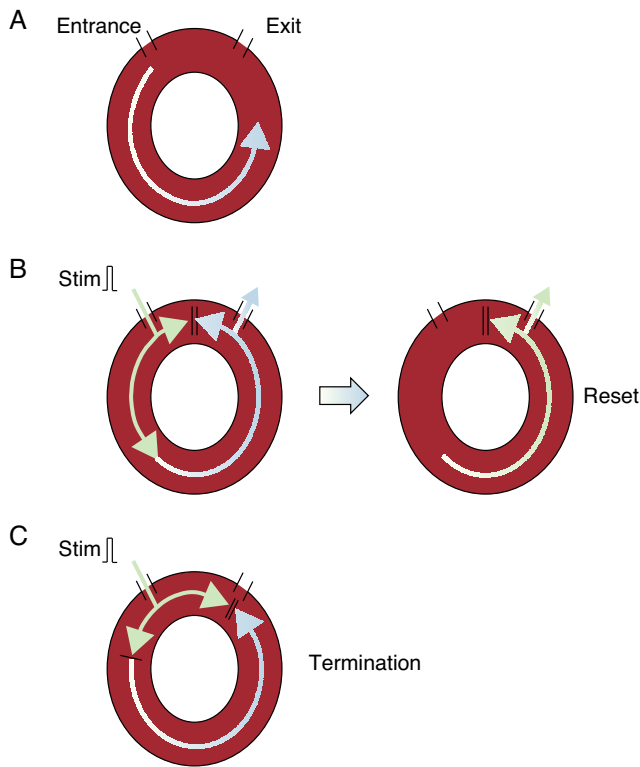
Figure 12. A: reentrant circuit. B: a timed premature stimulus can enter the circuit, collide in a retrograde fashion with the previous impulse while in the anterograde direction exiting earlier than expected. C: termination occurs if the stimulus enters during the relative refractory period (anterograde block and retrograde collision). Stim, stimulus.
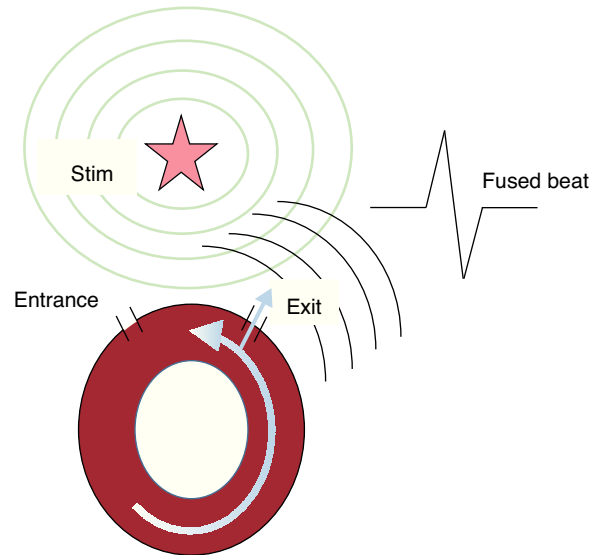

Figure 13. Schematic representation of a fused beat. Stim, stimulus.

consistent with prior myocardial infarction suggest the substrate for reentry; *b)* a long QT interval raises suspicion for afterdepolarizations; *c)* a "delta wave" makes reentry over an accessory pathway a plausible mechanism, and *d)* epsilon waves or Brugada pattern ECGs suggest reentrant mechanisms.

RELATIONSHIP TO CLINICAL ARRHYTHMIAS

In the following section, we will comment on the mechanisms that sustain the most frequent arrhythmias seen in practice.

Bradyarrhythmias

Bradyarrhythmias can be explained by 2 mechanisms (Fig. 14).

- Failure of impulse generation. Failure of impulse generation is the failure of pacemaker cells to generate appropriate electrical impulses. This form of bradyarrhythmia is commonly seen in the context of degenerative processes. Although any automatic normal foci can be affected, their failure may only be seen when the superior pacemaker cell function is depressed. Thus, the failure of the sinus node will cause major or minor pauses, depending on the function of the subsidiary pacemaker cells.

usually the extrastimulus or premature beat, and therefore different from the subsequent one. These arrhythmias terminate in response to adenosine.

Reentrant tachycardias respond to pacing and demonstrate the hallmark features of resetting and entrainment with fusion. Adenosine can terminate a reentrant tachycardia involving the AV node, but will not affect sodium-dependent cells in the atria and ventricles.

Furthermore, other noninvasive tools such as surface ECG should always be considered. The surface ECG may not confirm a particular mechanism, but it can provide important clues.[35] The sinus rhythm ECG may reveal disease processes known to be associated with specific types of arrhythmias: *a)* Q waves

Table 4

Maneuvers for Distinguishing Between the Different Arrhythmia Mechanisms

	Automaticity	Triggered activity	Reentry
Initiation by PES	No	Yes (continuous stimulation)	Yes
Termination by PES	No	Some times	Yes
First interval at initiating	Long, warm-up	Short (same as or shorter than rest)	Long (longer than subsequent)
Morphology of first beat	Identical to subsequent	Different from subsequent	Different from subsequent
Adenosine	Transient slowing or no response	Termination	No response or AV block
Catecholamines	Increase	Increase (DAD)	Increase/decrease
Response to PES during tachycardia	Reset or compensatory pause	Reset or termination	Reset or termination
Reset with fusion	No	No	Yes
Response to continuous stimulation during tachycardia	Overdrive suppression if enhanced normal automaticity	Acceleration or termination	Entrainment or termination
Entrainment with fusion	No	No	Yes

AV, atrioventricular; DAD, delayed afterdepolarization; PES, programmed electric stimulation.

- Failure of impulse propagation. The failure of impulse propagation is the failure of electrical impulses generated by pacemaker cells to conduct normally through the conduction system. This mechanism implies an abnormality of conduction velocity and/or refractoriness in the conducting system, causing heart block at various levels.

Tachyarrhythmias

Sinus Tachycardia

- Physiologic sinus tachycardia represents an enhancement of the sinus node in response to physiologic stress, and is characterized by an increased slope of phase 4 depolarization in sinus node cells.
- Inappropriate sinus tachycardia refers to a condition in which the sinus rate is increased continuously or out of proportion to the degree of physiologic stress[36] and is caused by enhanced normal automaticity. An automatic tachycardia originating in the region of the sinus node and sinoatrial reentrant circuit must be ruled out.

Focal Atrial Tachycardia

Atrial tachycardias may be due to automaticity, TA, or reentrant mechanisms, but most of them correspond to automaticity or reentering mechanisms. They can be distinguished by their behavior in relation to various maneuvers. Although fusion may be more difficult to determine because of the P wave, intracardiac recordings can help identify this phenomenon.

Recently lidocaine-sensitive atrial tachycardia has been described, suggesting a less common underlying mechanism.[37]

Atrial Flutter

Atrial flutter may further be categorized into typical and atypical atrial flutter.

Typical Atrial Flutter

The wavefront in typical flutter circulates in the right atrium around the tricuspid valve annulus in a counterclockwise or clockwise direction. Typical atrial flutter is the most common example of a macroreentrant circuit, where anatomical and functional barriers create the substrate.

Atypical Atrial Flutter

In this type of flutter, the obstacle is usually related to previously performed procedures that create large anatomic barriers (atriotomy scar, suture line, or radiofrequency ablation) or facilitate a zone of slow conduction such that reentry may occur (eg, left atrial flutter related to previous AF ablation). In contrast to the typical form, atypical atrial flutter occasionally exhibits features of a focal mechanism and overlaps with atrial tachycardias.

Atrial Fibrillation

AF is the most common sustained arrhythmia. Even though its underlying mechanism is still debated among electrophysiologists, AF likely represents a complex interaction between drivers responsible for initiation and the anatomic atrial substrate required for perpetuation of the arrhythmia.[38]

The drivers are located predominantly in the pulmonary veins and can represent variable forms of focal abnormal automaticity or TA within the vein or microreentrant circuits around the vein orifices with strong autonomic potentiation.[39] Not only do they
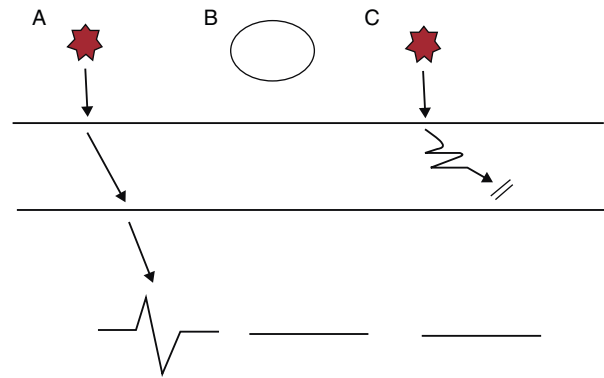

Figure 14. A: normal conduction. B: suppressed automaticity. C: conduction block.

contribute to the initiation of AF, but they also participate in the maintenance of the arrhythmia.[40] Other nonpulmonary triggering foci have also been described, such as the coronary sinus, superior vena cava,[41] or ligament of Marshall.[42]

Maintenance of the arrhythmia lies in a combination of electrophysiological and structural factors, which create the substrate to perpetuate AF. Different mechanisms have been postulated, including multiple wavelets of reentry or a mother rotor circuit, as well as high frequency activity in the atria.[42] Moreover, structural and electrical remodeling of the atria over time contributes to the arrhythmogenic substrate.

Junctional Premature Complexes

Junctional premature complexes are very uncommon. They are likely attributed to enhanced normal automaticity.

Atrioventricular Nodal Reentrant Tachycardia

This common paroxysmal supraventricular tachycardia is caused by a classic reentrant mechanism. The presence within the AV node of 2 pathways with distinct electrophysiological properties makes this arrhythmia possible.

Under normal conditions, a sinus impulse will travel through both pathways. In response to a premature stimulation, the stimulus can block in the fast pathway due to a longer refractory period and travel through the slow pathway. If conduction is slow enough, the blocked fast pathway can have time to recover, thus setting the stage for a reentrant circuit, translating into AV nodal tachycardia when perpetuated (Fig. 15).

An atypical form of AV nodal tachycardia can occur when activation of the circuit proceeds in the reverse direction.

Atrioventricular Junctional Tachycardia

Atrioventricular junctional tachycardias typically occur in the setting of increased adrenergic tone or drug effect in patients with sinus node dysfunction who have undergone a previous procedure or digitalis toxicity. They can be related to enhanced normal automaticity, abnormal automaticity or TA.[43]

Atrioventricular Reentrant Tachycardia Mediated by an Accessory Pathway

The typical accessory pathway has rapid conduction and a longer refractory period in comparison to the AV node, which creates the substrate for reentry. The circuit that involves an

accessory pathway is usually a large macroreentrant circuit consisting of the native conduction system, the accessory pathway, and the intervening atrial and ventricular tissue. In the orthodromic type, the more common arrhythmia related to accessory pathways, the AV node serves as the anterograde pathway and the accessory pathway as the retrograde pathway. Antidromic tachycardia occurs when activation proceeds in the reverse direction (antegrade over the accessory pathway and retrograde over the AV node), thus creating a wide QRS complex. Antidromic AVRT occurs less frequently, and can be precipitated by conditions that slow antegrade conduction over the AV node with rapid conduction preserved over the AV node in a retrograde direction.

In patients with Wolff Parkinson White and AF, rapid conduction over the accessory pathway with ventricular preexcitation may occur. Preexcitation may lead during AF to ventricular fibrillation and cardiac arrest. The prevalence of AF in patients with Wolff Parkinson White syndrome is unusually high in the absence of organic heart disease. While the precise mechanism remains unclear, the presence of the accessory pathway itself and retrograde activation of the atria during orthodromic supraventricular tachycardia has been postulated to play an important role in the initiation of AF.[44]

Accelerated Idioventricular Rhythm

Accelerated idioventricular rhythm is thought to be due to abnormal automaticity related to the acute phase of myocardial infarction, as well as cocaine intoxication, acute myocarditis, digoxin intoxication, and postoperative cardiac surgery conditions.[45]

Ventricular Tachycardia

This arrhythmia has a wealth of different characteristics and behaviors. The predominant mechanisms underlying most VTs are abnormal automaticity, TA, and reentry. The latter is the most frequent mechanism causing VT.[45]

Monomorphic Ventricular Tachycardia

In the absence of structural heart disease, most VTs are thought to correspond to TA or an automatic mechanism[35] (distinguished by previously explained maneuvers). However, most monomorphic VT occurs in the presence of structural heart disease, with the predominant mechanism being reentry. The majority of patients within this group demonstrate VT in relation to ischemic cardiomyopathy. The post-infarction process results in a scar associated with surviving islands of cardiac myocytes. This can result in slow and discontinuous conduction and/or block in conduction through the viable tissue, likely attributable to disruption in gap junction distribution and function and poor cell-to-cell coupling.[46] These changes create the ideal electrophysiologic and anatomic substrate for developing reentrant arrhythmias (slow conduction and unidirectional block).

The second most common cause of VTs due to reentry is nonischemic cardiomyopathy. In such patients the reentrant circuit frequently involves a region of a scar near the valvular orifices or in the subepicardium. Occasionally, VTs in this setting appear to be mediated by an autonomic or triggered mechanism.[35]

Reentry is also the principal mechanism in VT due to arrhythmogenic right ventricular dysplasia/cardiomyopathy. In this condition, a reentrant circuit is formed around the characteristic fibro-fatty tissue that has replaced the right ventricle. A similar mechanism of VT occurs in the setting of hypertrophic cardiomyopathy (especially in the presence of an apical aneurysm), valvular heart disease, surgically repaired congenital heart diseases (large resections are needed, creating large anatomical barriers), infiltrative cardiomyopathy (eg, cardiac sarcoidosis) and neuromuscular disorders.

Characteristics of some specific monomorphic VTs:

- Bundle branch reentrant VT. In presence of underlying His-Purkinje disease (often seen in idiopathic nonischemic and valvular cardiomyopathy) a large macroreentrant circuit can be created involving the His-Purkinje network. Slow conduction through a diseased His-Purkinje network allows the initiation of the reentrant circuit,[32] in which the right bundle typically serves as the anterograde limb (explaining the left bundle morphology of the tachycardia) and the left fascicle as the retrograde limb. Frequently the circuit can be reversed by stimulating in the left ventricle to create a right bundle branch block VT pattern.
- Idiopathic VT. Idiopathic VT is found in structurally normal hearts and can be divided into 2 main groups:

  - Outflow tract tachycardia. Outflow tract tachycardias represent the most frequent idiopathic VTs. Although the pathogenesis is not fully understood, their behavior suggests that many of them are due to TA as a result of afterdepolarizations.
  - Fascicular ventricular tachycardia. Fascicular VT lies in the left ventricular His-Purkinje system and although the mechanism is accepted to be a macroreentry circuit involving calcium-dependent slow response fibers of the ventricular Purkinje network,[47] typically terminated by verapamil, some automatic forms of the tachycardia have also been described.
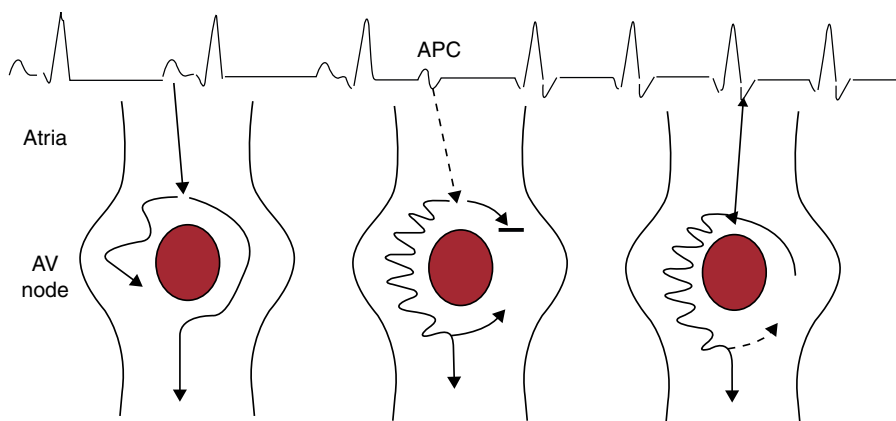

Figure 15. Initiation of atrioventricular nodal tachycardia with an atrium premature complex, which is blocked in the fast pathway and travels through the slow pathway to establish reentry. APC, atrium premature complex; AV, atrioventricular.

Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

The initiation and maintenance of these tachyarrhythmias remain unknown; however, previous work supports a similar mechanism as suspected in AF. The initiating trigger could be mediated by TA, automaticity, or a reentrant mechanism, while maintenance may be due to different forms of functional reentries, including rotors, migrating scroll waves, or intramural or Purkinje network reentry. Elucidation of the underlying mechanism is still in its experimental phase. It is also possible that VF may be the final common endpoint of a heterogeneous group of electrical disturbances and it may not be possible to identify a single mechanism that adequately accounts for all of them.[48]

Genetically determined abnormalities predisposing to polymorphic VT:

- Long QT syndrome. Both congenital and acquired (especially via certain drugs[49]) conditions lead to a long QT interval due to lengthening of the AP plateau phase. The onset of the arrhythmia occurs due to EADs potentiated by intracellular calcium accumulation from a prolonged AP plateau.[38]
- Brugada syndrome. Genetic mutations resulting in diminished inward sodium current in the epicardium of the right ventricular outflow tract cause this syndrome. Because of the ionic alteration, the outward potassium current is unopposed at some epicardial sites, which gives rise to epicardial dispersion of repolarization that creates a vulnerable window during which a premature impulse can develop phase 2 reentrant arrhythmia.[29]
- Short QT syndrome. Genetic abnormalities that cause this syndrome lead to decreased repolarization time and decrease myocyte refractoriness, thus promoting reentrant arrhythmias.[50]
- Catecholaminergic polymorphic VT. Catecholaminergic polymorphic VT is due to genetic disorders of channels and proteins (ryanodine and calquestrin) that regulate intracellular calcium.[17] The defects cause an accumulation of intracellular calcium, which can facilitate the TA mediated by DADs. Precipitants include exercise or emotional stress as a result of increasing intracellular calcium concentration.

CONFLICTS OF INTEREST

None declared.

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