Chapter 1
Mechanisms of Cardiac Arrhythmias

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Electrophysiological Basis of the Arrhythmias

Cardiac myocytes are specialized cells responsible for both mechanical contraction and conduction of electrical impulses. 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 (AP) are propagated through cardiac myocytes, which are excitable, referring to their ability to respond to a stimulus with a regenerative AP [2]. Propagation of the cardiac impulse is enabled by gap junctions. Gap junctions are membrane structures composed of multiple intercellular ion channels that facilitate chemical and electrical communication between cells. Cardiac AP are

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regionally distinct due to each myocyte type expressing different numbers and types of ion channels [3].

Usually, the sinoatrial node is the primary pacemaker of the heart, with a resting membrane potential of approximately-60 mV. I_f ("funny") current plays an important 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).

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 activation, 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 (Na^+ in muscle cells). It is classified as either

Table 1.1 Mechanisms of cardiac arrhythmias

Disorders of impulse formation	Disorders of impulse conduction
• Automaticity – Altered normal automaticity – Abnormal automaticity • Triggered activity – Delayed afterdepolarization (DAD) – Early afterdepolarization (EAD)	• Reentry – Anatomic reentry – Functional reentry

absolute or relative, depending on whether it is completely unexcitable or needs a greater stimulus than normal.

The mechanisms responsible for cardiac arrhythmias may be divided into disorders of impulse formation, disorders of impulse conduction or a combination of both (Table 1.1).

Disorders of Impulse Formation

Normal Automaticity

As previously described, some specialized heart cells (sinoatrial nodal cells, the atrioventricular (AV) node, the His-Purkinje system, some cells in both atria) [5], possess the property of 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 subsidiary pacemaker cells fire at slower rates. The firing rate is determined by the interaction of three factors:

– The maximum diastolic potential,
– The threshold potential at which the AP is initiated,
– The rate or slope of phase 4 depolarization.

A change in any of these may alter the rate of impulse initiation [6, 7].

Pacemaker activity is controlled by the autonomic system and can be modulated by a lot of factors, including metabolic alterations or pharmacologic substances.

Parasympathetic activity reduces the rate of the pacemaker cells by releasing acetylcholine (Ach) and hyperpolarizing the cells by increasing conductance of the K^+ channels. It may also decrease $I_{Ca\text{-}L}$ and If 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 usually 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 (this phenomenon is called "post-vagal tachycardia") [8].

Conversely, sympathetic activity increases the sinus rate. Catecholamines increase the permeability of $I_{Ca\text{-}L}$, increasing the inward Ca^{2+} current. Sympathetic activity also results in enhancement of the If current [9], thereby increasing the slope of phase 4 repolarization.

Metabolic disorders 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 [8].

In degenerative diseases that affect the cardiac conduction system, suppression of the sinus automaticity cells can be seen, resulting in sinus bradycardia or even sinus arrest. A subsidiary pacemaker may manifest as a result of suppression of sinus automaticity.

An essential property of normal automaticity, so characteristic that constitutes a "trademark" is the phenomenon called "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 rate called the "warm-up" period. The degree of suppression and the recovery time are

proportional to the rate and duration of the applied stimulation [8, 9].

This mechanism plays an important role in maintaining sinus rhythm because the sinus node continuously inhibits the activity of subsidiary pacemaker cells [6]. In patients with external pacemakers, the intrinsic rhythm may also be suppressed by this mechanism [10].

The absence of overdrive suppression may indicate that the arrhythmia mechanism is different of 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 during exercise, fever, and thyrotoxicosis; inappropriate sinus tachycardia and AV junctional rhythms.

Abnomal Automaticity: I_{CaL}

Atrial and ventricular myocardial cells, which in the healthy heart do not show 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 K^+ conductance.

The intrinsic rate of an automatic abnormal focus depends on the membrane potential; the less negative the membrane potential, the faster the automatic rate [6]. Abnormal automaticity is thought to play a role in cases of elevated extracellular K^+, low intracellular pH, and elevated catecholamines.

An important distinction between enhanced normal and abnormal induced automaticity is that the latter is less sensitive to overdrive suppression [11]. Under these circumstances, an ectopic automatic focus displays characteristics of other arrhythmia mechanisms [12]. Clinical examples: some atrial tachycardias, premature beats, accelerated idioventricular rhythm, some ventricular tachycardia (VT), particularly in

the acute phase of myocardial infarction, associated with ischemia and reperfusion.

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) [13]. 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, two 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.

DADs

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 [14].

As the cycle length decreases, the amplitude and rate of the DADs increases, and therefore DADs are expected to initiate arrhythmias when the heart rate increases (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 during an ongoing arrhythmia, 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 the overdrive suppression seen with automatic rhythms [6].

Toxic concentration of digitalis was the first observed cause of DAD [15]. This occurs secondary to the inhibition of the Na/K pump, which promotes the release of Ca^{2+} from the sarcoplasmic reticulum. Clinically, bidirectional fascicular tachycardia due to digitalis toxicity is an example of TA [16].

Catecholamines can cause DADs by causing intracellular Ca^{2+} overload via an increase in $I_{Ca\text{-}L}$ and the Na^{+}-Ca^{2+} exchange current. Ischemia-induced DADs are thought to be mediated by the accumulation of lysophosphoglycerides in the ischemic tissue [17], 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 [18] (Fig. 1.1).

An important 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.

Adenosine can be used as a test for the diagnosis of DADs. Adenosine reduces the Ca^{2+} inward current by inhibiting effects on adenylate cyclase and cyclic adenosine monophosphate.

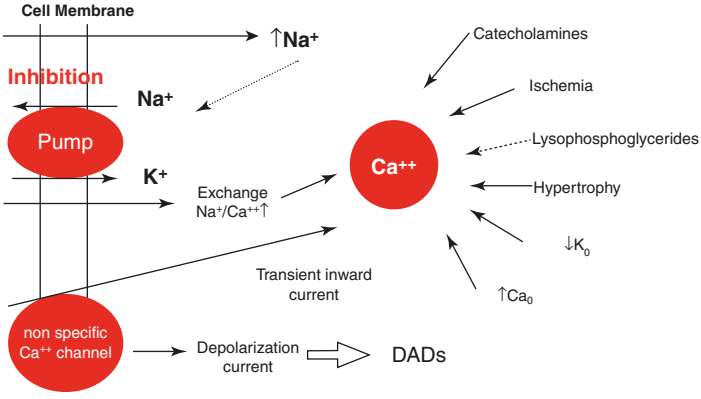

FIGURE 1.1 Mechanisms responsible for DAD (modified from Jalife et al.) [8]

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 suggests catecholamine-induced DADs as the underlying mechanism [19].

Clinical examples: some atrial tachycardias, digitalis toxicity-induced tachycardia, accelerated ventricular rhythms during ischemia, some forms of repetitive monomorphic VT, reperfusion-induced arrhythmias, ventricular outflow tract VT, exercise-induced VT (e.g. catecholaminergic polymorphic VT).

EADs

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 $I_{Ca\text{-}L}$ current [20], while phase 3 EADs may be the result of electronic current across repolarization or the result of low I_{K1} [21].

The plateau of the AP is a period of high membrane resistance [3] and little current flow. Therefore, small changes in either repolarizing or depolarizing currents can have profound effects on the AP duration and profile. A wide variety of agents and conditions can result in a decreased outward current or increased inward current and therefore establish the conditions necessary for EADs (Table 1.2.).

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 1.2.) can predispose to the formation of EADs, particularly when associated with $\downarrow K^+$ and/or bradycardia, additional factors that result in prolongation of the AP [8]. Several drugs have been associated with QT prolongation and *torsades de pointes* ([22],

Table 1.2 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 IC antiarrhythmic drugs (flecainide, encainide, indecainide)
– Class III antiarrhythmic drugs (amiodarone, sotalol, bretylium)
– Phenothiazines
– Tricyclic and tetracyclic antidepressants
– Erythromycin
– Antihistamines
– Cesium
– Amiloride
– Barium

www.qtdrugs.org]. Catecholamines may enhance EADs by an increase in 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 [8]. Experimental studies have shown that magnesium can eliminate TA of these EAD and can provide an effective treatment of certain cases of drug induced *torsades de pointes* [23].

An EAD-mediated TA appears to be the underlying cause of arrhythmias that develop in the setting of long QT syndrome (LQTS). The true mechanism of these arrhythmias is still debated, but it is accepted that an enhanced dispersion of repolarization seen in the syndrome can create a proarrhythmic substrate [24]. There is growing interest in the effects of genetic mutations in repolarizing membrane currents in relation to the congenital LQTS associated with polymorphic ventricular tachycardia like *torsades de pointes*, and repolarization in general [22]. These tachycardias probably begin by EAD and TA, although a reentrant mechanism may also be involved in its genesis [25]. Patients with LQTS have a greater dispersion of refractoriness which could favor the presence of unidirectional block and the development of a reentrant mechanism. Several genetic mutations responsible for alterations in the flow of K^+ and Na^+ have been identified (Table 1.3) [26, 27].

EAD 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* [28]. Clinical examples: *torsades de pointes*, that is the characteristic polymorphic VT seen in patients with LQTS.

Disorders of Impulse Conduction

Block

Conduction delay and block occurs when the propagating impulse fails to conduct. Several factors 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 con-

Table 1.3 LQTS genes (modificado de Schwartz PJ et al.) [26]

	Gene	Locus	Protein	Current (functional effect)	Frecuency (%)
LQT1	KCQ1	11p.15.5	Iks (α subunity)	↓Iks	40–55%
LQT2	KCNH2	7q35-q36	Ikr (α subunity)	↓Ikr	30–45%
LQT3	SCN5A	3p21-p24	Na channel (α subunity)	↑INa	5–10%
LQT4	ANK2	4q25-q27	Arqkirin B	↓Ncx1, Na/k, ATPasa INsP3	<1%
LQT5	KCNE1	21q22.1	Iks (β subunity)	↓Iks	<1%
LQT6	KCNE2	21q22.1	Ik (β subunity)	↓Ikr	<1%
LQT7	KCNE2	17q23	Ik1 (α subunity)	↓Ik1	<1%
LQT8	CACNA1C	12p13.3	CaV1.2	↓ICa	<1%
LQT9	CAV3	3p25	Caveolin 3	↓INa	<1%
LQT10	SCN4B	11q23.3	Na (β4 subunity)	↓INa	<1%
LQT11	mAKAP	7q21-q22	A-kinase anchorin	↓IKs	<1%

(continued)

Table 1.3 (continued)

	Gene	Locus	Protein	Current (functional effect)	Frecuency (%)
LQT12	SNTA1	20q11.2	Shyntophin α1	↓INa	<1%
LQT13	KCNJ5	11q24	Kir 3.4	↓IK	<1%

LQT long-QT syndrome, *KCNQ1* potassium voltage-gated channel, *KCNH2* potassium voltage-gated channel, subfamily H, memeber 2, *SCN5A* sodium voltage-gated channel, type V, α subunity, *ANKB* ankyrin B, *KCNE1* potassium voltage-dependent channel, subfamily ISK, member 1, *KCNE2* potassium voltage-dependent channel, subfamily ISK, member 2, *KCNJ2* potassium internal rectifier channel, subfamily J, member 2, *CACNA1C* calcium voltage-dependent channel type L, 1C subunity, *CAV3* caveolin 3, *SCN4B* sodium voltage-gated channel, type IV, à subunity, *mAKAP9* A-kinase anchor protein 9, *SNTA1* syntrophina 1, *KCNJ5* potassium channel, inwardly rectifying, subfamily J, member 5.
Functional effect: (↓) loss-of-function or (↑) gain-of-function at the cellular in vitro level.

ducted [14]. Gap junction coupling plays a crucial role for the velocity and safety of impulse propagation [29].

Usually, impulses are blocked at high rates as a result of incomplete recovery from 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 block of a premature beat, Ashman's phenomenon during atrial fibrillation (AF), and acceleration-dependent aberration.

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

Many factors can alter 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 [13].

Table 1.4 Types of reentry

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

Reentry has been divided in 2 main groups (Table 1.4.):

– Anatomical or classic reentry, where the circuit is determined by anatomical structures
– 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 [30]. 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 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 site with 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.

Macroreentry/Anatomical

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 two pathways (Fig. 1.2a). When a premature impulse encounters the obstacle, it will block in one pathway (unidirectional block) and travel down the other pathway propagating until the point of block, thus initiating a reentrant circuit (Fig. 1.2b).

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 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. The excitable gap refers to the excitable myocardium that exists between the head of the reentrant wavefront and the tail of the preceding wavefront (Fig. 1.3) [30]. This gap allows the reentrant wavefront to continue propagation around the circuit. The presence of an excitable gap also makes it possible for an external wavefront to enter the reentrant circuit. This can be performed 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 (common flutter and many of the atypical flutters), 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].

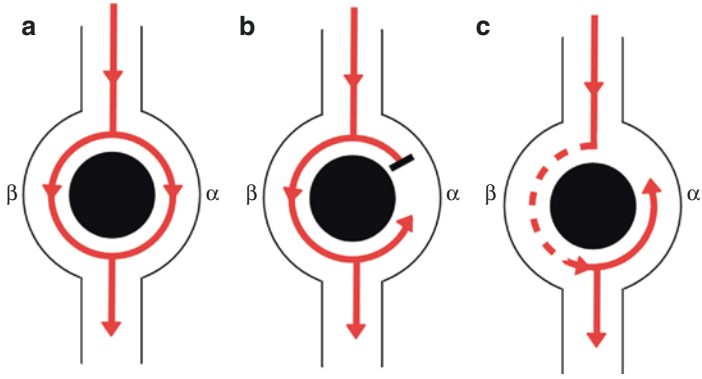

FIGURE 1.2 Schematic representation of classic reentry mechanism: (**a**) An anatomical obstacle (central cicle) causes bifurcation of wavefront (upper arrow) in two pathways (β and α). For both pathways the wavefront propagates downward if the heart rate is slow despite a zone with prolonged refractory period. (**b**) when a premature impulse reaches the structure shown in (**a**), the wavefront is blocked in the pathway with long refractory period and it progresses through the other route. The impulse accesses the blocked route in the opposite direction (retrograde), which could be blocked when accessing α occurs again. (**c**) An area of slow conduction is added to the panel (**b**) (dashed line in β pathway). Now the impulse accesses retrogradely through α pathway that is recovered from the refractory period causing impulse reentry

The 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*
  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 [31]. Leading circle was defined as "the smallest possible pathway in which the impulse can continue to circulate" [32].

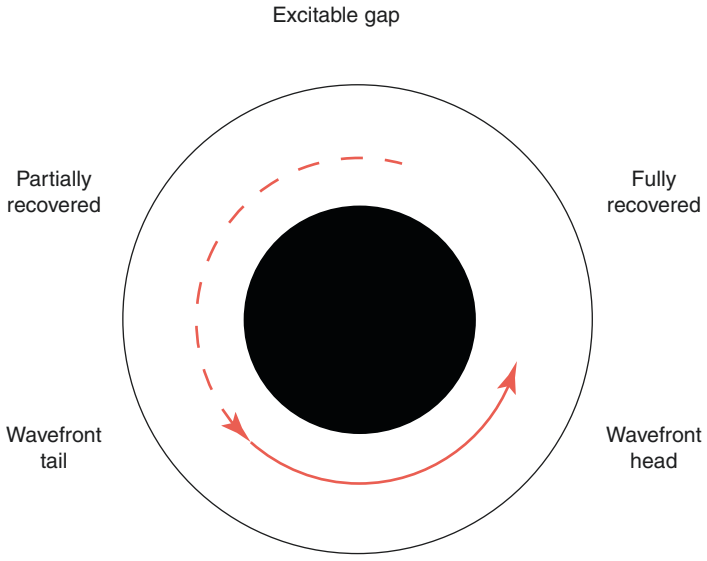

FIGURE 1.3 Schematic representation of an excitable gap

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 [33] 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 [30]. Clinical examples: anisotropic reentry in atrial and ventricular muscle, which may be responsible in the setting of VT originating in surviving myocardial infarction [34].

- *Figure of eight reentry*
  This type of reentry consists of two concomitant wavefronts circulating in opposite directions (clockwise and counterclockwise) around two 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 or atrial flutter in patients with prior atriotomy.
- *Reflection*
  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 [35].
- *Spiral wave activity (rotor)*
  Spiral waves occur in a wide variety of excitable media [36]. They represent a two-dimensional form of rotating wave propagation, which may also occur in three dimensions "scroll waves". Initially the term "rotor" described the rotating source and "spiral wave" defined the shape of the emerging wave [6]. Other terms for this phenomenon could be found 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 (Fig. 1.4). This curvature also limits the spiral propagation velocity, resulting in slow conduction and block [31]. 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.

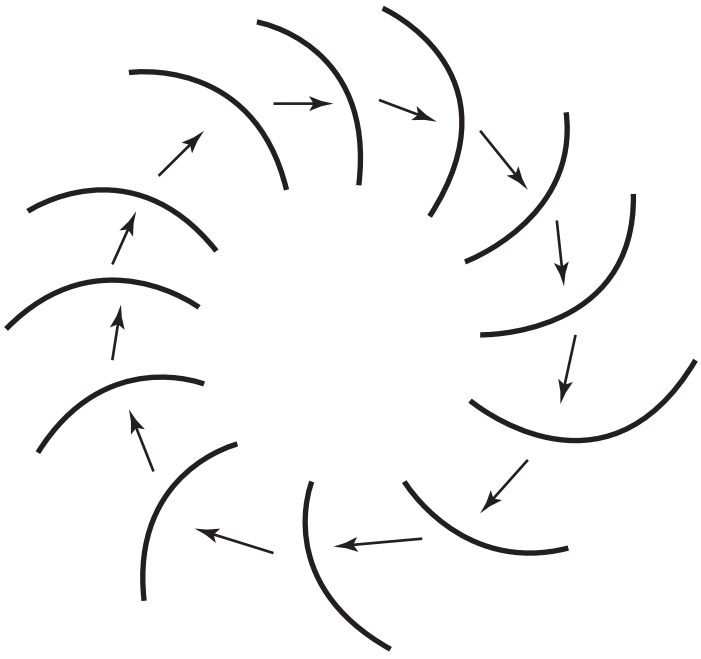

FIGURE 1.4 Schematic representation of a rotor

Relationship to Clinical Arrhythmias

Bradyarrhythmias

Bradyarrhythmias can be explained by two mechanisms:

– Failure of impulse generation. Failure of impulse generation is the failure of pacemaker cells to generate appropriate electrical impulses. In degenerative processes is frecuently seen this form of bradyarrhythmia. 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.

– 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.

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 [37] and is caused by enhanced normal automaticity.

Focal Atrial Tachycardia

– Atrial tachycardias may be due to automaticity, TA, or reentrant mechanisms, but most of them correspond to automaticity or reentry mechanisms. They can be distinguished by their behavior in relation to various maneuvers.

Atrial Flutter

– Atrial flutter may further be categorized into common (typical) and atypical atrial flutter.
  • Common Atrial Flutter: The wavefront in common 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.
  • 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).

Atrial Fibrillation

- AF is the most common sustained arrhythmia. Even though its underlying mechanism is still debated, 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 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.

Atrioventricular Nodal Reentrant Tachycardia

- This common paroxysmal supraventricular tachycardia is caused by a classic reentrant mechanism. The presence within the AV node of two 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 path-

way can have time to recover, thus setting the stage for a reentrant circuit, translating into AV nodal tachycardia when perpetuated.
– An "uncommon" 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 most 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 atrioventricular reentrant tachycardia occurs less frequently, and can be precipitated by conditions that impair antegrade conduction over the AV node with rapid conduction preserved over the AV node in a retrograde direction.
– In patients with the Wolff-Parkinson-White (WPW) syndrome 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 WPW 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 have 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 [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. Reentry is the most frequent mechanism causing VT in patients with ischemic cardiomyopathy [45].

Monomorphic Ventricular Tachycardia

– In the absence of structural heart disease, most VTs are thought to correspond to TA or an automatic mechanism. However, most monomorphic VT occur 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 postinfarction 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 abnormal automaticity or triggered mechanisms.
- Reentry is also the principal mechanism in VT due to arrhythmogenic right ventricular cardiomyopathy. In this condition, a reentrant circuit is formed around the characteristic fibrofatty tissue that has replaced areas of the right ventricle. A similar mechanism of VT can occur 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.
- Idiopathic VT. Idiopathic VT is found in structurally normal hearts and can be divided into two main groups:
  - Outflow tract tachycardia. Outflow tract tachycardias represent the most frequent idiopathic VTs. Although the pathogenesis is not fully understood, their behavior suggest that many of them are due to TA as a result of delayed 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.

Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

- The initiation and maintenance of these tachyarrhythmias remain unknown; however, previous work supports a similar mechanism as that 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:
  - LQTS: 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 produce a phase 2 reentrant arrhythmia [35].
  - 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 calsequestrin) 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.

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