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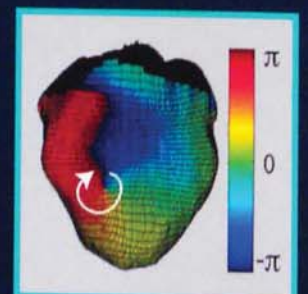
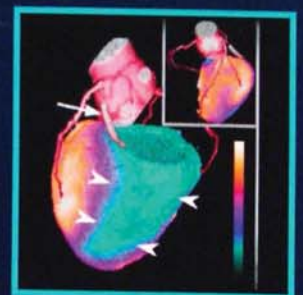
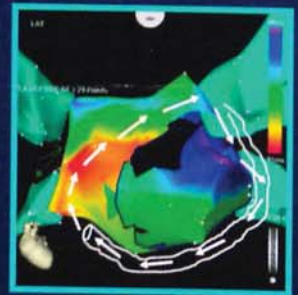
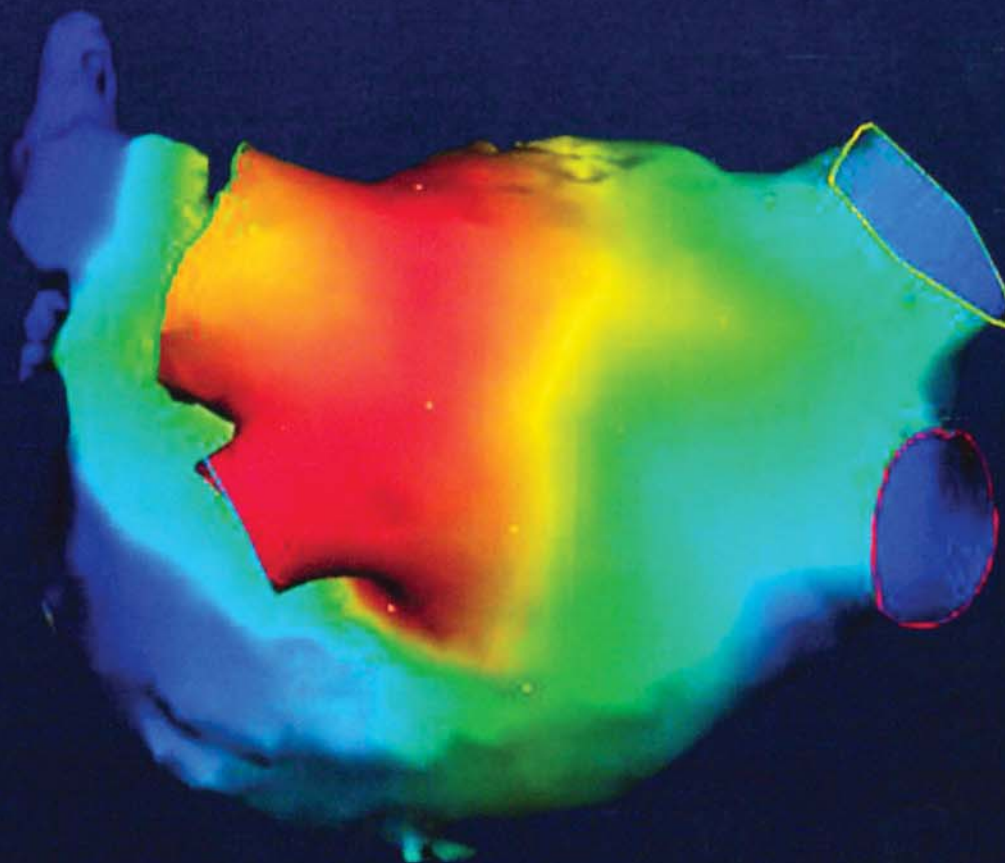
CARDIAC MAPPING

Edited by

Mohammad Shenasa, Gerhard Hindricks,
Martin Borggrefe, Günter Breithardt
and Mark E. Josephson

Foreword by

Douglas P. Zipes



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Cardiac Mapping

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Cardiac Mapping

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FOURTH EDITION

FOREWORD BY DOUGLAS P. ZIPES

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Multiple Mechanisms Causing Ventricular Tachycardia

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Summary

Ventricular tachycardia (VT) can be caused by any of the mechanisms responsible for arrhythmogenesis. That different mechanisms can cause the same arrhythmia has important implications concerning therapy since some therapeutic interventions can terminate some of electrophysiological mechanisms and not others. Therefore, a mechanistic approach to therapy is sometimes useful.

Classification of arrhythmogenic mechanisms

The recording of transmembrane potentials from heart cells *in vitro* has led the way to the discovery of arrhythmogenic mechanisms. There are two primary mechanisms, abnormal impulse generation and abnormal conduction. "Impulse generation" indicates an electrical impulse arising in a single or group of closely coupled cells through spontaneous depolarization of the membrane to initiate an action potential. Automaticity under this heading, infers a specific mechanism for this depolarization based on pacemaker membrane currents. Triggered activity, also under this heading, is dependent on depolarizing after potentials. The second primary mechanism, abnormal conduction causes reentrant excitation.

Automaticity

Automaticity is subdivided into normal and abnormal. Arrhythmias caused by normal automaticity originate in cells that have normal intrinsic pacemaker properties

although some abnormal event may be needed for pacemaker activity to be expressed. Abnormal automaticity occurs in cells that do not have the normal property of automaticity but express automaticity when membrane properties are altered by disease.

Normal automaticity

Basic electrophysiology

Normal automaticity occurs in the sinus node, as well as in subsidiary or latent pacemakers. The cause of normal automaticity is a spontaneous decline in the transmembrane potential during diastole, referred to as the pacemaker potential or spontaneous diastolic depolarization, (Figure 13.1a, arrow), until it reaches threshold potential for activating inward depolarizing current that causes the cell to generate an action potential as compared to non pacemaker cells where diastolic membrane potential is at a constant negative value (Figure 13.1b, arrow). There are a number of membrane currents that contribute to the pacemaker potential of the sinus node [1], some flowing inward (inward currents) from the extracellular space into the cell carrying positive charges that depolarize the cell membrane. Other membrane currents consist of positive charges moving outward from inside the cell to the extracellular space (outward currents), tending to move membrane potential in a negative direction. The pacemaker current is a summation of all these currents and is a net inward current [1].

In addition to the sinus node, myocytes with the property of normal automaticity occur in the right and left atria, possibly the pulmonary veins, the atrioventricular (AV) junction, and the His-Purkinje system [1,2]. There is a hierarchy of intrinsic rates of these latent pacemakers with atrial pacemakers having faster rates than AV nodal pacemakers,

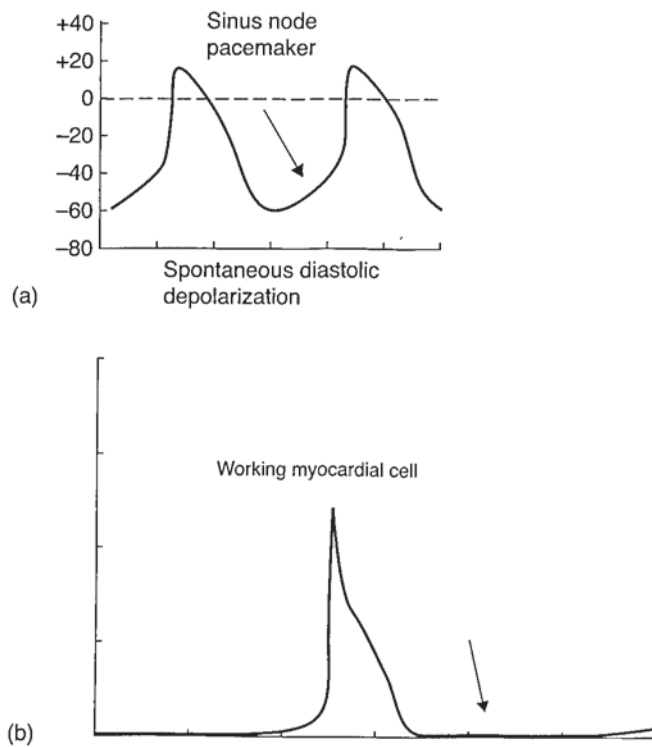


Figure 13.1 Comparison of transmembrane action potentials in a normally automatic sinus node cell (a) with spontaneous diastolic depolarization (arrow) and a working atrial myocardial cell (b) without a pacemaker potential (arrow).

which have faster rates than His bundle pacemakers, which have faster rates than Purkinje pacemakers in the distal ventricular conducting system (rate is determined by the time required for the pacemaker potential to decrease from its maximum diastolic level to the threshold potential). Because the sinus node has the fastest intrinsic rate, the latent pacemakers are excited by propagated impulses from the sinus node before they have sufficient time to depolarize spontaneously to threshold potential. In addition spontaneous diastolic depolarization of latent pacemakers is inhibited by being repeatedly depolarized by the impulses from the sinus node, a phenomenon called overdrive suppression [2]. This repeated depolarization during sinus rhythm increases Na^+ entering the latent pacemaker cell which in turn stimulates the electrogenic Na^+/K^+ which generates outward pump current, I_p . The enhanced I_p decreases net inward current during the pacemaker potential suppressing spontaneous diastolic depolarization and hyperpolarizing the membrane potential. Overdrive suppression can be demonstrated by suddenly stopping the sinus node such as by vagal activation. There ensues a period of quiescence caused by the continued generation of I_p inhibiting pacemaking that lasts until intracellular Na^+ concentration, and hence I_p , becomes small enough to allow the pacemaker potential to depolarize spontaneously to threshold.

The quiescent period is followed by resumption of spontaneous activity at a slow rate that gradually speeds up to the intrinsic rate as intracellular Na^+ concentration progressively decreases and I_p is reduced. Overdrive suppression is intensified by increasing the amount of Na^+ entering the latent pacemaker cell such as during sinus tachycardia.

A shift in the site of impulse initiation from the sinus node to one of the regions where latent pacemakers with normal automaticity are located results in arrhythmias caused by normal automaticity. For ventricular tachycardia to occur, pacemaker rate in the Purkinje or other ventricular ectopic sites must increase above that of the sinus node and atrial latent pacemakers. The most important cause is sympathetic activation when it enhances the rate of spontaneous diastolic depolarization in latent ventricular pacemakers more than in the sinus node.

Clinical electrophysiology

Fascicular ventricular tachycardia

Enhanced automaticity in Purkinje cells of the fascicles of the ventricular conducting system can cause ventricular tachycardia although it is not common [3]. Fascicular tachycardia is associated with intraventricular conduction delay or bundle branch block pattern on the electrocardiogram (ECG). A His bundle electrogram has an HV interval that is shorter than for conducted sinus beats since the His bundle is activated retrogradely from the focus. Automaticity fascicular tachycardia may occur spontaneously or during exercise where adrenergic stimulation causes automaticity.

Exercise induced ventricular tachycardia

Automatic exercise induced VT can be distinguished from triggered activity (delayed afterdepolarization [DAD]) induced VT by several characteristics: (i) Automatic VT cannot be started or stopped by electrical stimulation (Figure 13.2a,b) although it is predicted to be transiently overdrive suppressed by electrical stimulation. It is started by beta adrenergic stimulation (Figure 13.2c). DAD dependent triggered activity can be started and terminated by overdrive stimulation (see next section). (ii) The onset of automatic VT has variable coupling intervals to the prior QRS whereas the onset of DAD VT has coupling intervals inversely related to the prior sinus cycle length. (iii) Automatic VT is transiently slowed by adenosine but not terminated. Adenosine terminates DAD dependent triggered activity. (iv) Automatic VT is not terminated by L-type Ca^{2+} channel blocking drugs that stop VT caused by DADs.

Automatic tachycardias often originate endocardially at the entrance to the outflow tract on the interventricular septal surface. The electrophysiology of this region has not been defined but RVOT myocytes may be related embryologically to the Purkinje system.

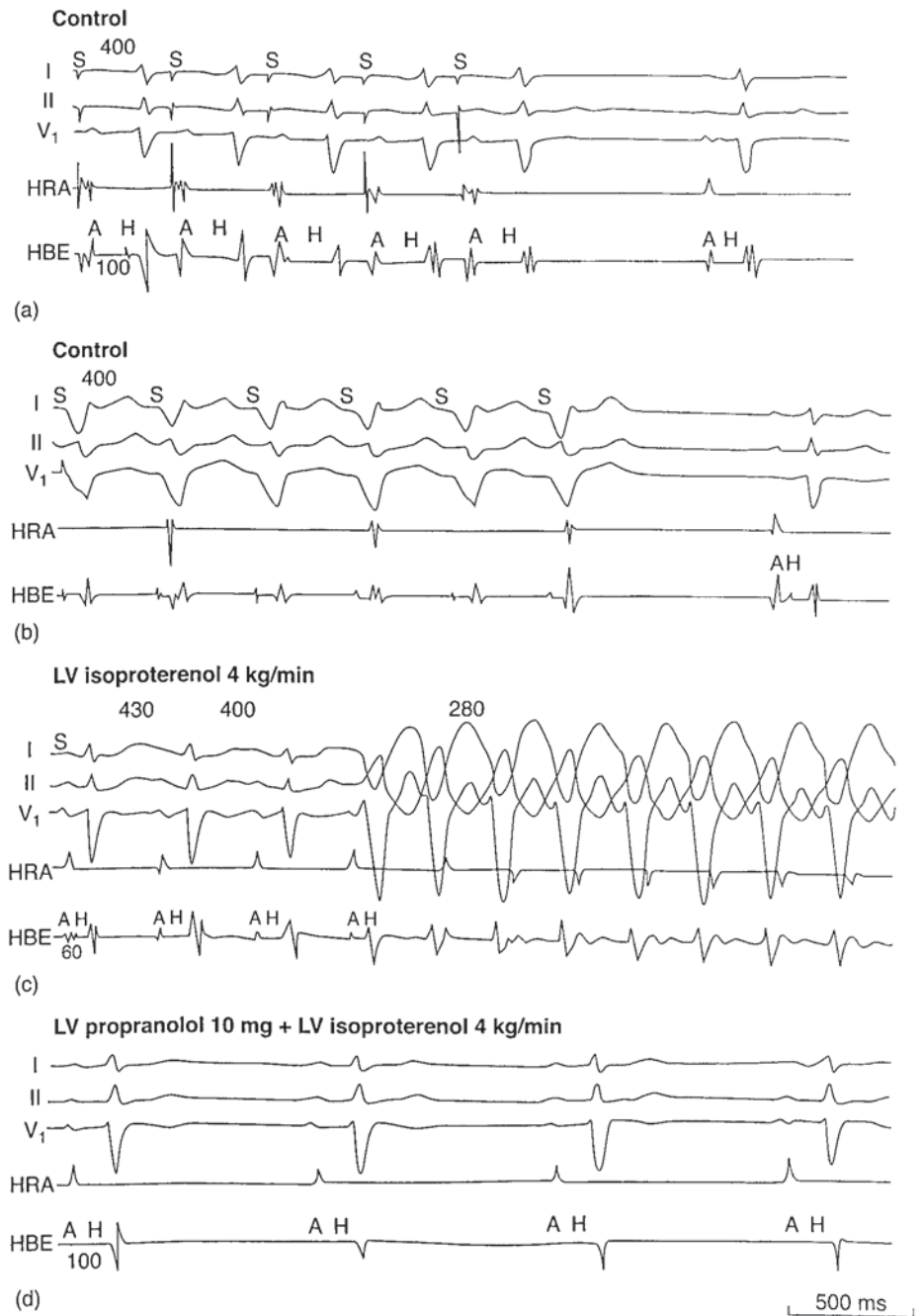


Figure 13.2 Verapamil insensitive exercise induced ventricular tachycardia (VT). VT cannot be elicited by atrial (a) or ventricular (b) stimulation at a cycle length of 400 ms, but is provokable with intravenous infusion of isoproterenol (c) that decreases cycle length to 400 ms. After β -adrenergic blockade with intravenous propranolol (0.2 mg/kg), infusion of isoproterenol does not provoke the arrhythmia. (From Sung R, et al. *J Clin Invest* 1988;81:688, with permission.)

Abnormal automaticity

Basic electrophysiology

Working atrial and ventricular myocardial cells do not normally initiate spontaneous impulses. When their resting potentials are reduced sufficiently (range between -70 and -30 mV from -80 to -90 mV), spontaneous diastolic depolarization may occur and cause impulse initiation and arrhythmias. The rate is directly related to the amount of membrane depolarization (Figure 13.3). Such depolariza-

tion may occur in a pathological environment [2]. Likewise, cells in the Purkinje system that are normally automatic at high levels of membrane potential also show abnormal automaticity when the membrane potential is reduced.

The pacemaker mechanism at reduced membrane potentials is not the same as the normal mechanism [1,2]. Depolarization of the membrane potential also inactivates Na^+ channels leading to action potential upstrokes caused by inward current carried by a combination of any remaining Na^+ current and the L-type Ca^{2+} current [4].

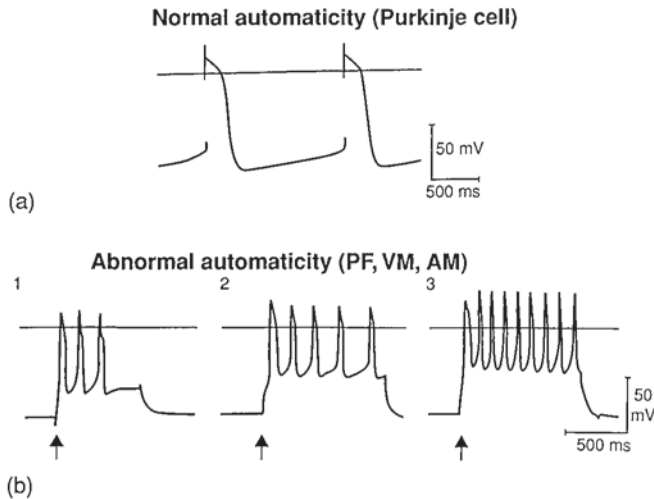


Figure 13.3 Normal automaticity in a Purkinje cell (a) and abnormal automaticity caused by depolarization of the membrane potential with an intracellular current pulse (arrow) (b). Abnormal automatic rate is directly related to the amount of depolarization (b, 1, 2, 3). (From Wit AL, Friedman PL. *Arch Intern Med* 1975;135:459, with permission.)

While normal I_f pacemaker channels occur in ventricular muscle, they are expressed at lower levels than in normal latent pacemaker cells, and are not functional at membrane potentials near the resting potential. In pathological conditions leading to hypertrophy, there may be an increase in the expression of I_f channel mRNA and protein [5] leading to an increase in an I_f pacemaker current that may cause arrhythmias in heart failure and hypertrophic diseases.

At reduced levels of membrane potential less Na^+ enters the cell through partially inactivated Na^+ channels during overdrive resulting in decreased stimulation of I_p . It would therefore be expected that arrhythmias caused by abnormal automaticity at a low level of membrane potential would not be started or stopped by overdrive nor would they exhibit overdrive suppression.

Clinical electrophysiology

Accelerated idioventricular rhythm (AIVR) that occurs 3–24 hours after myocardial infarction, is likely caused by abnormal automaticity in Purkinje fibers surviving on the endocardial surface of the infarct with partially depolarized membrane potentials (Figure 13.4) [2]. It has a rate of 50–120 beats/min intermediate between idioventricular escape rhythms (30–40/min) and VT (>100/min). The ECG features of AIVR are consistent with an arrhythmia caused by abnormal automaticity. The pacemaker is not overdrive suppressed since it appears immediately upon sinus slowing whereas a pacemaker with normal automaticity requires a longer period of sinus slowing that decreases overdrive suppression. During tachycardia fusion beats may occur. Tachycardia is terminated when sinus cycle length shortens enough to capture the abnormal focus. AIVR is terminated

by verapamil because of the involvement of the L-type Ca^{2+} in abnormal automaticity (Figure 13.4b & c) [2,4].

Triggered activity

Triggered activity describes impulse initiation dependent on afterdepolarizations [6,7], which are oscillations in membrane potential that follow the upstroke of an action potential. There are two kinds of afterdepolarizations. One occurs early during repolarization (early afterdepolarizations [EADs]), and the other is delayed until repolarization is complete or nearly complete (delayed afterdepolarizations [DADs]).

DADs and triggered activity

Basic electrophysiology

A DAD is an oscillation in membrane potential which occurs after repolarization (arrow in Figure 13.5d). A triggered impulse is initiated when a DAD depolarizes the membrane potential to the threshold potential for activation of the inward current responsible for the upstroke of the action potential (arrow in Figure 13.5e). A triggered action potential is also followed by a DAD that may or may not reach threshold. When it does reach threshold a “train” of additional triggered action potentials occur each arising from the DAD caused by the previous action potential (Figure 13.5e).

DADs occur when Ca^{2+} in the myoplasm and sarcoplasmic reticulum (SR) increases above normal levels (“calcium overload”). Abnormalities in the sequestration and release of Ca^{2+} by the SR also may contribute to their occurrence. When intracellular Ca^{2+} is elevated, Ca^{2+} in the SR may rise during repolarization to a critical level at which a secondary spontaneous release of Ca^{2+} occurs after the action potential and relaxation of contraction (calcium sparks), generating a transient inward (TI) current (the DAD) [2,6,7]. The TI current may flow through a non-selective channel or may be caused by electrogenic exchange of Ca^{2+} for Na^+ . The increased intracellular Ca^{2+} that causes DADs may result from digitalis inhibition of the Na^+-K^+ pump, catecholamine enhanced L-type Ca^{2+} current [2,6,7] or other effects of pathology that increase calcium loading (e.g. heart failure, hypertrophy) [2,6,7].

The amplitude of DADs is dependent on the cycle length at which action potentials are occurring; triggered activity can be induced by a critical decrease in the drive cycle (Figure 13.5e). A premature impulse also increases the amplitude of the DAD that follows the premature cycle. Decreasing the drive cycle length or premature stimulation also tends to decrease the coupling interval of DADs to the action potential upstroke. As a result there is a direct relationship between the drive cycle length or premature coupling interval at which triggered impulses are initiated, and the

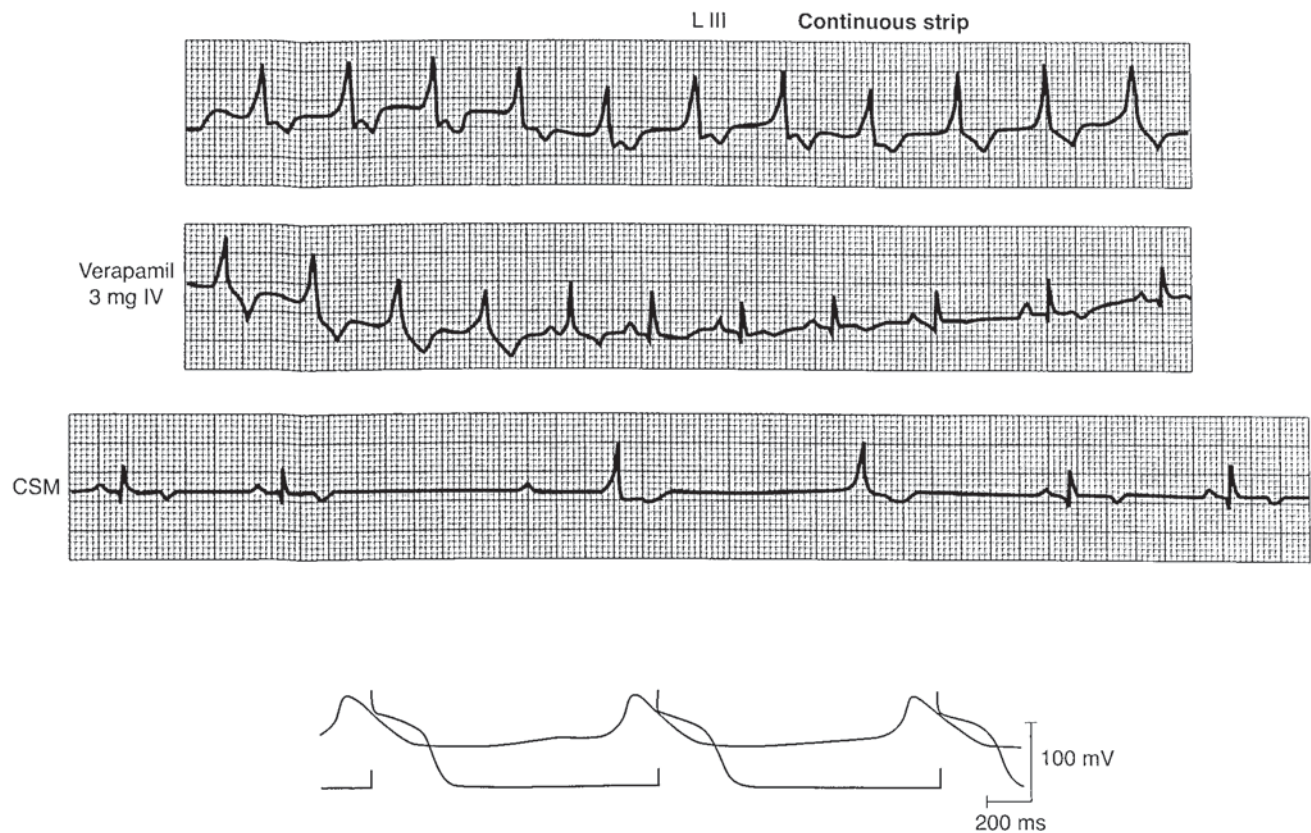


Figure 13.4 Accelerated idioventricular rhythm in a patient with a myocardial infarct (top 3 electrocardiogram [ECG] traces). The top trace shows the ECG prior to administration of verapamil (middle trace which restores sinus rhythm). The third trace shows that the abnormal impulse initiation that caused tachycardia is not present when sinus rate is slowed by carotid sinus massage (CSM). Below are shown action potentials

recorded from an abnormally automatic Purkinje cell surviving in a 24-hour-old canine infarct causing accelerated idioventricular rhythm (AIVR) (top trace) and a normal Purkinje fiber adjacent to the infarct (bottom trace). (ECGs from Sclerovsky S, et al. *Am J Cardiol* 1983;52:43, with permission.)

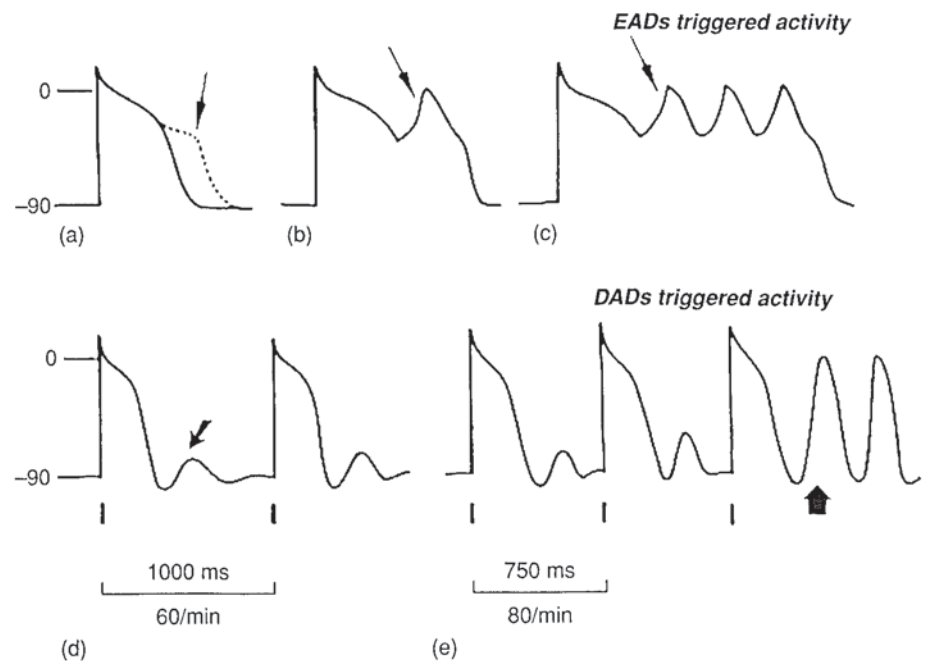


Figure 13.5 (a) Early afterdepolarization (EAD) (arrow) leading to a single (b) or multiple triggered impulses (c) (arrows). (d) Delayed afterdepolarization (DAD) (arrow) leading to triggered activity (e, arrow) when stimulus cycle length is decreased from 1000 to 750 ms.

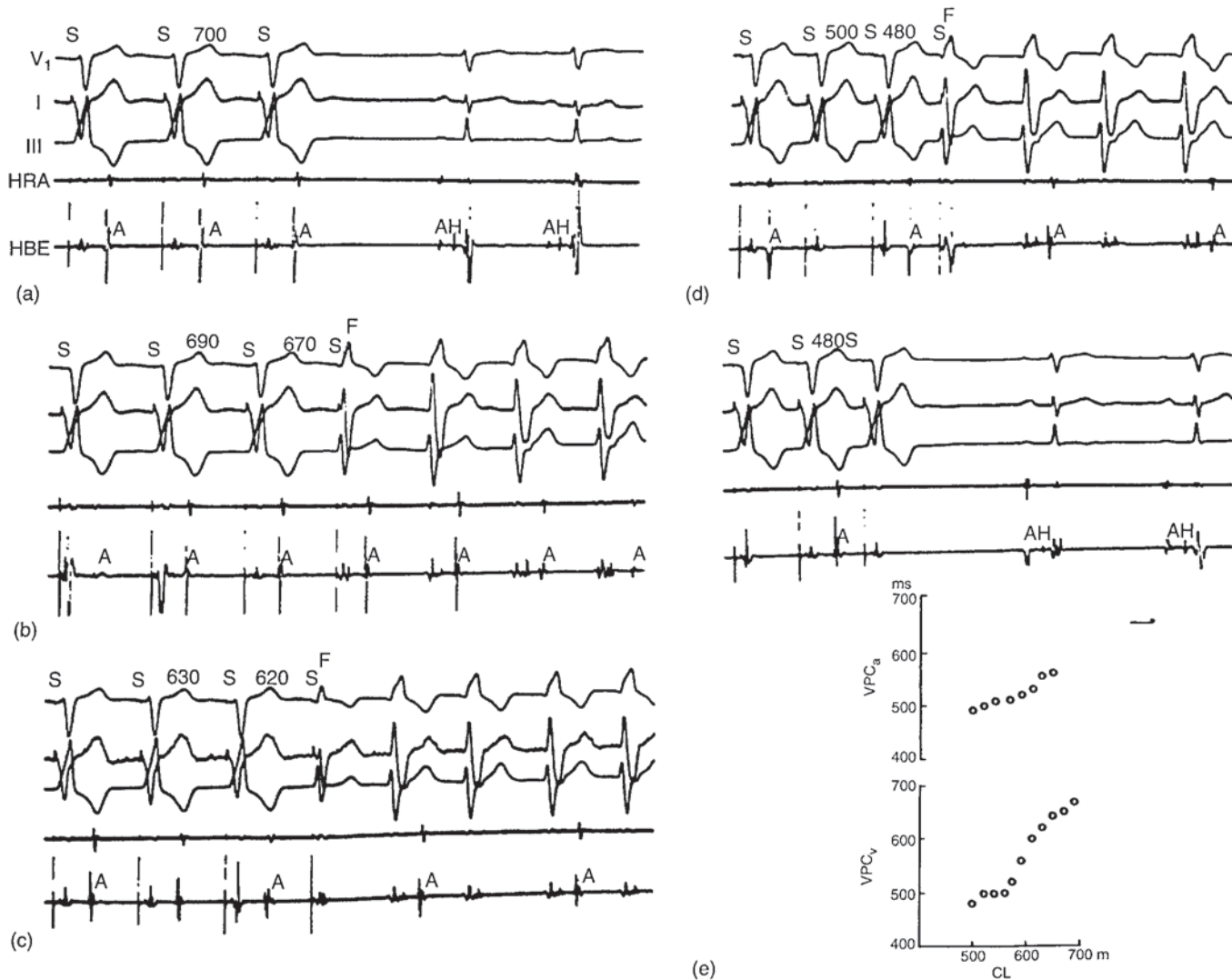


Figure 13.6 Induction of delayed afterdepolarization (DAD) dependent ventricular tachycardia (VT) by ventricular pacing. (a) Pacing at a cycle length (S-S) of 700 ms initiates no VT. (b-d) Pacing at cycle lengths of 690, 630 and 500 ms, respectively, initiates VT. (e) Pacing at a cycle length of 480 ms initiates no VT. Note that the interval between the first beat of VT and its preceding ventricular paced beat gradually shortens pacing rate progressively increases. This direct relationship is plotted in the graph in the lower right corner. (Reproduced from Sung R, et al. *J Clin Invest* 1983;72:350, with permission.)

coupling interval between the first triggered impulse and the last stimulated impulse. This is one of the ways that triggered activity can sometimes be distinguished from reentrant activity induced by a decrease in the drive cycle length or premature impulse which shows the opposite (inverse) relationship (Figure 13.6) [3]. Increased rate or premature stimulation increases intracellular Ca^{2+} , thereby increasing the current that causes DADs. Intracellular Na^+ may also rise at rapid rates increasing intracellular Ca^{2+} through $\text{Na}^+-\text{Ca}^{2+}$ exchange [2,6,7].

Triggered activity can be stopped by overdrive stimulation because of enhanced activity of the electrogenic sodium pump. Premature stimuli may also terminate triggered rhythms although termination is less frequent than by overdrive [7]. Effects of premature stimuli that fail to termi-

nate resemble the effects of premature impulses on abnormal automaticity [7]. Sometimes the triggered rhythm may be accelerated transiently.

Clinical VT caused by DADs

The most common VT due to DAD triggered activity is one form of exercise induced idiopathic VT. VT results from catecholamine stimulation of adenylyl cyclase formation that enhances intracellular Ca^{2+} . VT often arises in the right (RVOT) and left ventricular outflow tract (LVOT). Triggered VTs also arise around the mitral annulus [3]. Interventions which decrease catecholamine increased cyclic AMP can stop VT such as parasympathetic activation (carotid sinus pressure or Valsalva maneuver), and adenosine. Calcium channel blockers prevent or stop tachycardia by reducing influx

of Ca^{2+} , sodium channel blockers may stop tachycardias by reducing the transient inward current [3,7].

The arrhythmia characteristics are consistent with a DAD mechanism and not with reentry [3]. Atrial or ventricular pacing at a critical rate initiates VT. Isoproterenol infusion may be required (Figure 13.6). VT is more difficult to initiate with programmed premature ventricular stimulation. The coupling interval between the last stimulated impulse and the first tachycardia impulse is sometimes directly related to the pacing cycle length (shorter cycle length with more rapid pacing) although the coupling interval can also remain constant.

A polymorphic VT dependent on DADs also results from a mutation of the ryanodine receptor of the SR that results in leakage of calcium into the myoplasm [8].

Early afterdepolarizations and triggered activity

Basic electrophysiology

Early afterdepolarizations (EADs) occur when repolarization of an action potential does not follow the normal smooth trajectory but suddenly shifts in a depolarizing direction (Figure 13.5a, dashed line, arrow). An EAD occurs when the current voltage relationship is altered to cause outward current during repolarization to approach or attain 0, at least transiently. Such a shift can be caused by a decrease in outward current or increase in inward current (Figure 13.5b, arrow). EADs generated at membrane voltages negative to I_{CaL} activation are likely caused by Ca^{2+} -activated inward current (I_{NCX}) resulting from the secondary "spontaneous" Ca^{2+} release from the SR [6,9,10].

Triggered activity is initiated when the depolarization reaches threshold to activate an inward current causing an action potential upstroke. It may consist of only a second upstroke or it may be more sustained (Figure 13.5b & c). When it persists, the mechanism for the perpetuation is uncertain. It may involve the same membrane currents that cause either abnormal automaticity or delayed afterdepolarizations [6]. Triggered action potentials occurring during the plateau and early during phase 3 when most fast Na^+ channels are inactivated, have upstrokes caused by the inward L-type calcium current (I_{CaL}). At higher membrane potentials during late phase 3, where there is partial reactivation of the fast Na^+ channels, action potentials caused by I_{Na^+} predominate. Current flowing through both L-type calcium channels and partially reactivated fast Na^+ channels occur over intermediate ranges of membrane potential.

EADs occur under conditions that delay repolarization (prolong action potential duration) by increasing inward current or decreasing outward current. They occur more readily in Purkinje fibers than in ventricular or atrial muscle although it has been proposed that M cells in the ventricle may be prone to develop EADs. Antiarrhythmic drugs

that prolong the duration of the action potential of Purkinje fibers (e.g. class III drugs such as sotalol and dofetilide or class IA drugs such as quinidine) can cause early EADs and triggered activity by inhibiting the I_{Kr} component of the repolarizing K^+ current, I_{K} [11]. Hypoxia, the combination of hypoxia and acidosis, with or without catecholamine, as well as stretch can induce EADs in Purkinje fibers [2,6].

Mutations in genes controlling ion channel formation, translocation and function can cause action potential prolongation, EADs and triggered activity. K^+ channel mutations cause some of the long QT syndromes (LQT_1 and LQT_2) by decreasing outward current. Mutations that cause an increase in inward Na^+ or Ca^{2+} current during repolarization also prolong action potential duration to cause EADs and triggered activity (LQT_3 ; Timothy syndrome) [12,13].

Because prolongation of action potential duration favors the occurrence of EADs and triggered activity, interventions that shorten action potential duration prevent them. Therefore, overdrive or premature stimulation, both of which accelerate repolarization do not initiate EAD triggered activity but might prevent its occurrence.

EADs and triggered activity can occur in the absence of action potential prolongation in atrial muscle at the antrum of the pulmonary veins and the pulmonary vein myocardial sleeve where action potential duration is short. Under conditions when acetylcholine (vagal activation) maintains a short action potential duration, catecholamines can increase I_{CaL} , maintaining an elevated $[\text{Ca}^{2+}]_i$ after repolarization is completed and membrane potential is negative to the equilibrium potential of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger. This in turn activates inward I_{NCX} that causes EADs [14].

Clinical arrhythmias caused by EADs

EAD triggered activity causes a polymorphic VT called torsades des pointes. Many causes of torsades have in common that they prolong QT interval on the ECG. Since action potentials are prolonged at slow heart rates, torsades sometimes occurs in patients with complete heart block and a slow idioventricular rhythm. Long pauses, particularly those associated with short-long-short cycle length sequences related to premature ventricular depolarizations, can also prolong action potential duration and lead to VT that might be due to EADs [3]. Such pauses can also prolong refractoriness heterogeneously facilitating the occurrence of reentry which may be involved in initiation of polymorphic VT-VF [3].

Torsades des pointes is also associated with QT interval prolongation caused by genetic changes in channel function. Triggers for torsades differ among the three major genotypes of LQTS [15,16]. In the LQT_1 variant (I_{Kr} loss of function), exercise is a trigger for greater than 60% of tachyarrhythmias, while barely 3% are triggered while at rest. In the LQT_2 variant, many events occur due to emotional stress or while at rest, while exercise is a trigger in only 13%. In LQT_3 ,

the majority of events occur during sleep or at rest. Abnormalities of the autonomic nervous system have also been proposed to be responsible for LQT₂. Stellectomy or beta-receptor blocking drugs has sometimes prevented arrhythmias in these patients [3].

Polymorphic VT, resembling torsades de pointes, is also a feature of toxicity of some drugs that prolong action potential duration. Some patients are more prone to this effect owing to a mutation in a K⁺ channel subunit that controls I_{Kr} function. Arrhythmias may occur at drug levels that are not much elevated above normal [11,12]

Polymorphic VT-VF associated with acquired or congenital LQTS cannot be reproducibly initiated by overdrive or premature stimulation because both patterns of stimulation decrease action potential duration which decreases EAD amplitude [3]. It has been proposed that patterns of stimulation with short cycles followed by long cycles might sometimes cause EAD dependent tachycardia but this is usually not successful. Pacing can prevent the occurrence of bradycardic-dependent arrhythmias associated with long QT intervals [3]. Torsades associated with chronic A-V block or sinus bradycardia can be prevented by ventricular pacing or dual-chamber pacing. Occasionally, long-term suppression by pacing has been shown in patients with acquired bradycardia abnormalities or polymorphic VT associated with congenital long QT [3]. Whether overdrive or premature stimulation can terminate on going triggered activity has not been studied. However, based on the cellular electrophysiology, it is unlikely that the arrhythmias can be terminated by this approach.

Reentrant excitation

Basic electrophysiology

Abnormal impulse conduction causes reentrant excitation. For reentry to occur, a region of block must be present, at least transiently which is necessary to launch propagation of the impulse in one direction and to prevent excitation of the return pathway that the impulse eventually uses to reenter the region it is to reexcite. Transient block can occur after rapid repetitive activation or after premature excitation during electrophysiological study. Reentry also may occur when there is permanent unidirectional block.

In addition, for reentry to occur, the impulse conducting through the reentrant pathway (circuit) must find excitable tissue. This requires that conduction time around the circuit be longer than the effective refractory period of the cardiac fibers that comprise it; the wavelength of the reentrant impulse which is the product of the conduction velocity and the effective refractory period, must be shorter than the length of the reentrant pathway. If it is not, conduction would block in the circuit. Conduction velocity and refractory period may vary from site to site in a reentrant circuit, causing changes in the wavelength in different locations.

However, the average wavelength must still be less than the path length. Slowed conduction and/or short refractory periods permits reentry to occur and are often a consequence of pathology (see below). Programmed stimulation during ongoing reentry can terminate it by pre excitation of myocardium in the reentrant circuit.

The reentrant circuit can have an anatomical structure with a central obstacle that prevents the impulse from taking a "short-cut" that would stop reentry. It may also be functional, its existence, size and shape determined by its electrophysiological properties. The central inexcitable region of a functional circuit can be the result of refractoriness of cells in the center such as in the leading circle model or the inability of the curved reentrant wavefront to excite such as in the spiral wave model. The size and location of an anatomically defined reentrant circuit remains fixed ("ordered reentry") while the size and location of functional circuits may change (random reentry). Random reentry is probably most often associated with atrial or ventricular fibrillation, whereas ordered reentry can cause most other types of arrhythmias.

Arrhythmogenic substrate in structural heart disease

Reentry causes VT in both ischemic (coronary artery disease, dilated cardiomyopathy) and non ischemic cardiomyopathies (dilated and hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy). There are common structural alterations that form an arrhythmogenic substrate with the necessary properties of slowed conduction and conduction block.

A low conduction velocity and block can be a consequence of alterations of active membrane properties (ion channels) or alterations in passive properties governing the flow of current between cells [17]. Here, we focus on how structural alterations lead to reentrant ventricular tachycardia.

Connectivity of cardiac myocytes

During conduction of the impulse, axial current flows from one myocardial cell to another through gap junctions in the intercalated disks [18]. An increased resistance to axial current flow caused by pathological structural alterations decreases the magnitude and spread of current along a myocardial bundle which can decrease conduction velocity and cause conduction block.

Gap junctions are specialized regions of close interaction between the sarcolemmata of neighboring myocytes in which clusters of transmembrane channels bridge the paired plasma membranes [19]. Because gap-junctional membrane is several orders of magnitude more permeable than non-junctional plasma membrane, it provides low resistance pathways for current flow between cells that is important for propagation. The primary proteins that form the channels of the gap junctions are called connexins. Connexin43

(Cx43) is the primary connexin isoform found in the ventricles [20,21].

Gap junctions are mainly at the ends of the myocytes in the intercalated disks rather than along their sides but the overlapping nature of the junctions effectively connects myocytes in the transverse as well as the longitudinal direction [22]. Ventricular myocardium is better coupled in the direction of the long axis of its cells and bundles than in the direction transverse to the long axis. This is reflected in a lower axial resistivity in the longitudinal direction than in the transverse direction [23]. Therefore conduction through ventricular myocardium is more rapid in the longitudinal direction owing to the lower resistivity than in the transverse, a property termed anisotropic conduction [24]. This property can be altered by fibrosis and remodeling of gap junctions.

Fibrosis occurs in both ischemic and non-ischemic cardiomyopathies. The pattern and extent of fibrosis may range from patchy in some forms of heart failure to extensive fibrotic scars in myocardial infarction. Fibrosis affects conduction, by several mechanisms. It may increase the extracellular resistivity of myocyte bundles [18]. Fibrosis can also distort size and shape of myocardial bundles trapped in scar tissue. In ischemic cardiomyopathy, fibrosis that is replacing necrotic regions, often extends into non ischemic bordering regions. The number of cell-to-cell contacts may be reduced with side-to-side connections selectively affected [25,26]. In healing infarct border zones, increased interstitial collagen disrupts the long transversely oriented gap junctions in interpendiculate segments of the disks enhancing anisotropy by increasing the axial resistivity transverse to the long fiber axis [26]. Plicate segment gap junctions, embedded entirely within the adhesive components of intercalated disks and concentrated at the ends of myocytes, undergo fewer changes. Thus the normal property of uniform anisotropy is converted to non-uniform anisotropy; tight electrical coupling between cells in the longitudinal direction, but recurrent areas in the transverse direction in which side-to-side electrical coupling of adjacent groups of parallel fibers is absent [25,26]. There is no evidence that fibroblasts make electrical connections with myocytes in the *in situ* ventricles.

When there is a large scar such as in hearts with myocardial infarcts, "peninsulas" and bridges of intact myocytes, can project into or completely across areas of fibrosis (called "channels" by clinical electrophysiologists). Myocytes in these bridges sometimes link with normal myocytes on the lateral border of the infarct [27]. This likely results in impedance mismatch where small bundles constricted by fibrotic scar tissue make connections with larger bundles not affected as much by the fibrosis. Axial current flow from small bundles may not be sufficient to rapidly depolarize larger bundles, resulting in slow conduction or block. Apparent slow conduction may also result from circuitous propa-

gation through myocardial bundles trapped in scar tissue. Conduction velocity within the individual fiber bundles may not be slowed but the complex patterns of activation around fibrous tissue barriers may slow activation of the arrhythmogenic substrate (Figure 13.7). Some of these effects of fibrosis involve the disruption of gap junction connections [28]. These effects of fibrosis on conduction is often detectable by low amplitude, long duration, fractionated electrograms with delayed activation, the basis for substrate mapping for ablation of ventricular tachycardia.

Gap junction remodeling

The turnover of connexins that form gap junction channels, is a highly dynamic process with a half-life in the order of three hours for Cx43 [29]. Disease processes may influence the conductance properties of gap junctions by affecting connexin turnover, influencing gap junctional size, number and distribution. The primary changes in the arrhythmogenic substrate in structural heart disease are a decrease in Cx43 quantity and occurrence of increased amounts of Cx43 on lateral sarcolemma where it is not normally present (lateralization). The molecular mechanisms include unhooking of Cx43 from anchoring proteins in the intercalated disks which allows it to move into lateral membranes from which it is sequestered intracellularly and destroyed. Cx43 on lateral membranes represents protein that has not formed functional gap junctions [30]. Alterations in phosphorylated state of the connexin molecule also affects targeting and docking of Cx43 at normal disk locations, reducing channel function [31].

Reentrant ventricular tachycardia in structural heart disease

Ischemic cardiomyopathy

Healed myocardial infarction is a frequent clinical setting for the development of reentrant sustained VT. Endocardial and epicardial border zones along with fiber bundles trapped in the scar form reentrant circuits. Both functional and anatomical reentrant pathways have been documented by mapping and unique electrograms features (low amplitude, fractionation, delayed activation). Tachycardias can be started and stopped by electrical stimulation [3].

Dilated cardiomyopathy

A common feature of dilated cardiomyopathy (DCM) irrespective of the underlying cause is ventricular arrhythmias and sudden death [32]. Although bundle branch reentrant VT is one mechanism, tachycardia caused by reentry in scarred, fibrotic regions also occurs [33,34]. Typical electrograms characteristic of structurally remodeled arrhythmogenic substrate (low amplitude, long duration, fractionated,

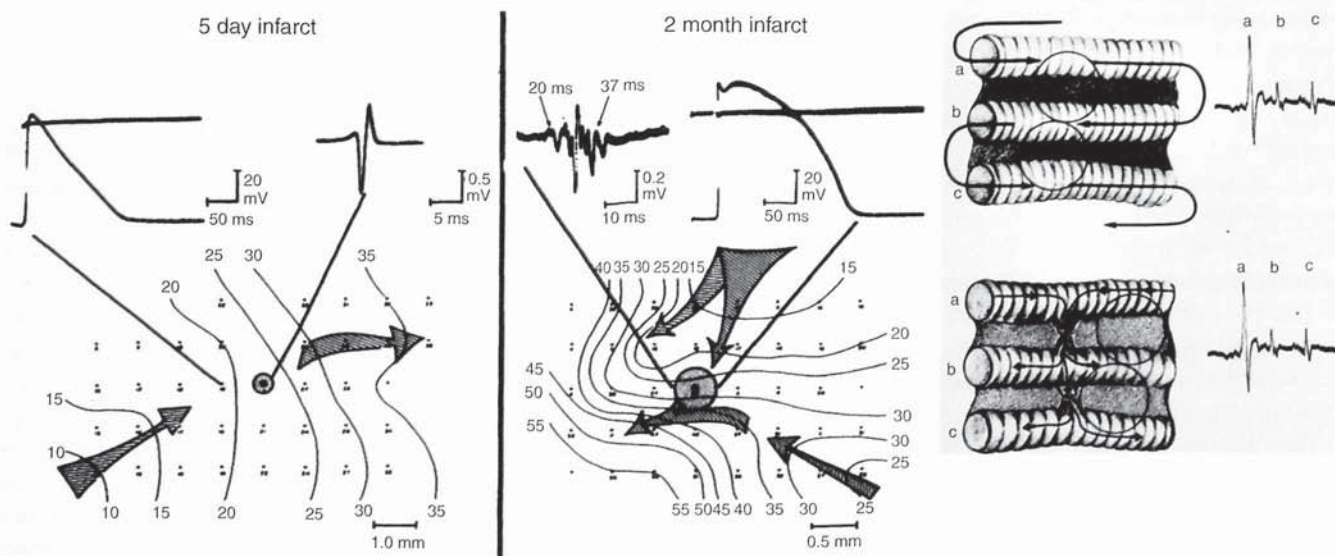


Figure 13.7 Myocardial fiber bundles (arrows) trapped in the scar of a healed canine infarct (E is epicardial surface). Action potentials and isochronal maps from a 2-week and 2-month-old infarct with extracellular electrograms at the top of each panel. Fractionated electrograms occur in healed infarct border zone associated with normal action potentials. Two models showing propagation patterns in myocardial bundles trapped in scar tissue that might give rise to fractionated electrograms (From Gardner PI, et al. *Circulation* 1985;72:596, with permission).

long delays) occur on both endocardial and epicardial surfaces of the ventricles. The isthmus of reentrant circuits in the arrhythmogenic substrate have been identified and ablated [34].

Arrhythmogenic right ventricular cardiomyopathies

The most frequently encountered form of arrhythmogenic right ventricular cardiomyopathy is arrhythmogenic right ventricular dysplasia (ARVD) [35]. Polymorphic and monomorphic ventricular tachycardias that can sometimes be initiated and terminated by programmed stimulation are characteristic of this syndrome.

The arrhythmogenic substrate has the features described above, e.g. fibrosis, gap junction remodeling, but also unique characteristics; genetic abnormalities in the desmosomal proteins plakoglobin or plakophilin which are involved in the transmission of mechanical forces among myocytes, and the transcriptional switch from myogenesis to adipogene-

sis through suppression of the Wnt pathway. The epicardial and intra mural layers of right ventricular myocardium can be replaced by fat and fibrosis. Fibrosis generally borders or embeds surviving fibers [35].

Hypertrophic cardiomyopathy

Ventricular tachyarrhythmias are a prominent feature and likely related to SCD that occurs in a subgroup of patients [36]. They probably emanate from an arrhythmogenic substrate created by the disorganized left ventricular myocardial architecture, which features ischemia induced myocyte necrosis and repair by replacement fibrosis and scarring that can lead to impedance mismatch and non-uniform anisotropy.

Heart failure

A majority of sudden deaths in heart failure are from ventricular tachyarrhythmias [37,38]. These arrhythmias can result from DAD induced triggered activity and reentrant

excitation. The remodeled arrhythmogenic substrate has all of the components discussed above necessary for reentry including fibrosis and remodeling of gap junctions.

Conclusion

Ventricular tachycardia can be caused by any of the mechanisms responsible for arrhythmogenesis. These mechanisms include abnormal impulse generation and abnormal impulse conduction. Abnormal impulse generation includes automaticity, normal and abnormal, and triggered activity, caused by DADs and early afterdepolarizations. Each mechanism has specific characteristics that can be used to identify the mechanism of VT in the clinical electrophysiological laboratory. These mechanisms and example arrhythmias caused by each of them are described in this chapter.

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