

REVIEW ARTICLE

Clinical Relevance of Cardiac Arrhythmias Generated by Afterdepolarizations

Role of M Cells in the Generation of U Waves, Triggered Activity and Torsade de Pointes

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Recent findings point to an important heterogeneity in the electrical behavior of cells spanning the ventricular wall as well as important differences in the response of the various cell types to cardioactive drugs and pathophysiologic states. These observations have permitted a fine tuning and, in some cases, a reevaluation of basic concepts of arrhythmia mechanisms. This brief

review examines the implications of some of these new findings within the scope of what is already known about early and delayed afterdepolarizations and triggered activity and discusses the possible relevance of these mechanisms to clinical arrhythmias.

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Despite important advances in cardiology in recent years, cardiac arrhythmias remain an important cause of mortality and morbidity. Pharmacologic control of cardiac arrhythmias is largely empiric, and the criteria that can be applied to the differential diagnosis of arrhythmia mechanisms are few and far between. Differential diagnosis of cardiac arrhythmias requires an understanding of basic mechanisms and establishment of mechanism-specific electrophysiologic criteria. Both in turn depend on our knowledge of the electrophysiology of the cells and tissues of the heart and the extent to which heterogeneity or specialization exists. Until recently, most investigations of the electrophysiology and pharmacology of the ventricles focused on two main cardiac cell types: ventricular myocardium and Purkinje fibers (or conducting tissues). Recent studies have provided evidence for the existence of at least four electrophysiologically and functionally distinct cardiac cell types in the ventricle (for review see Antzelevitch et al. [1]). These findings point to an important heterogeneity in the electrical behavior of cells spanning the ventricular wall as well as important differences in the response of the various cell types to cardioactive drugs and pathophysiologic states. These recent observations have permitted a fine tuning and, in some cases, a reevaluation of

basic concepts of arrhythmia mechanisms. Our aim in this brief review is to examine the implications of some of these new findings within the scope of what is already known about early and delayed afterdepolarizations and triggered activity and to discuss the possible relevance of these mechanisms to clinical arrhythmias.

The number of excellent studies that form the foundation of our present-day understanding of this field are far too numerous to mention individually. We apologize in advance to those authors whose specific contributions could not be cited because of space limitations.

Basic Concepts

Definition of Afterdepolarizations

In cardiac cells, oscillations of membrane potential that attend or follow the action potential and depend on preceding transmembrane activity for their manifestation are referred to as afterdepolarizations (2). They are generally divided into two subclasses: early and delayed afterdepolarizations. Early afterdepolarizations interrupt or retard repolarization during phase 2 or 3, or both, of the cardiac action potential, whereas delayed afterdepolarizations arise after full repolarization. When early and delayed afterdepolarizations are sufficiently large to depolarize the cell membrane to its threshold potential, they induce spontaneous action potentials referred to as triggered responses (3). These triggered events are believed to be responsible for extrasystoles and tachyarrhythmias that develop under a variety of conditions (4,5).

Early afterdepolarization-induced triggered activity has been observed in vitro in response to a wide variety of drugs,

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Table 1. Experimental Interventions Associated With Early Afterdepolarizations*

Slow stimulation rates	Cesium
Stretch	Barium
Hypothermia	Sotalol
Hypoxia	Clofilium
Acidosis	Bretylum
Low potassium	Amiloride
Low calcium	Aconitine
Quinidine	Veratridine
Disopyramide	Batrachotoxin
Procainamide	Anthopleurin-A
N-acetyl procainamide	ATX-II
Catecholamines	Erythromycin
Bay K 8644	Ketanserin

*Modified from ref 43.

including antiarrhythmic agents like quinidine and procainamide (6,7). This type of activity is usually most prominent at slow stimulation rates and low levels of extracellular potassium. Delayed afterdepolarization-induced triggered activity, in contrast, is most prominent at fast stimulation rates and is usually induced by drugs or conditions that increase intracellular levels of calcium (8-11).

Early Afterdepolarizations and Triggered Activity

Early afterdepolarizations and early afterdepolarization-induced triggered activity have been observed *in vitro* in isolated cardiac tissues under a variety of conditions, including injury (12,13), changes in the ionic environment, hypoxia, acidosis (14,15), high concentrations of catecholamines (16), pharmacologic agents (17-20) and antiarrhythmic drugs (6,7,21,22). Ventricular hypertrophy is also known to predispose to early afterdepolarizations (23,24). Table 1 lists the different experimental conditions known to prolong repolarization and generate early afterdepolarizations in Purkinje fibers.

Figure 1 illustrates two types of early afterdepolarizations generally encountered. Figure 1A shows an example of an early afterdepolarization arising from the plateau of an action potential recorded from a canine Purkinje fiber exposed to quinidine. Oscillatory events of this type, appearing at potentials positive to -30 mV, have been referred to as phase 2 early afterdepolarizations. Those occurring at more negative potentials are generally termed phase 3 early afterdepolarizations (Fig. 1B). Phase 2 and phase 3 early afterdepolarizations sometimes appear in the same preparation. The right panels show that triggered responses develop when the preparations are paced at slower rates (7).

Frequency dependence of triggered activity. The incidence of early afterdepolarization-induced triggered activity is a sensitive function of the stimulation rate. Early afterdepolarizations and early afterdepolarization-induced triggered activity are most prominent at slow stimulation rates

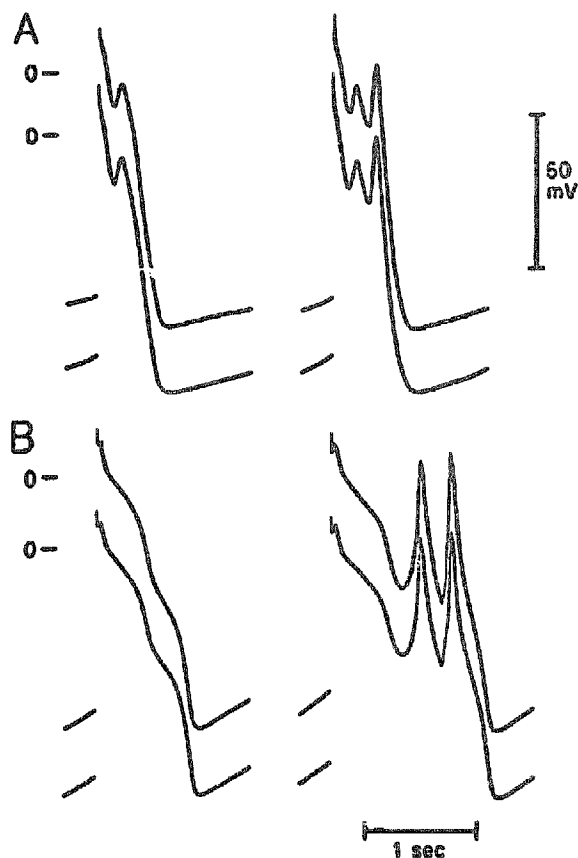


Figure 1. Two types of quinidine-induced early afterdepolarizations and triggered activity. Each panel shows two traces representing intracellular activity recorded from opposite ends of three different Purkinje preparations. Left, Responses displaying only early afterdepolarizations. Right, responses manifesting triggered activity. A, Early afterdepolarization and triggered activity occurring at the plateau level only (phase 2). B, Early afterdepolarization and triggered activity occurring during phase 3 only. Reprinted, with permission, from Davidenko et al. (7).

and can be totally suppressed at rapid stimulation rates (6,7). The rate dependence of triggered activity arising from phase 3 of the action potential is illustrated in Figure 2. Triggered beats develop as the rate of stimulation is slowed, giving rise to patterns of quadrigeminy and then bigeminy. When the preparation is allowed to beat spontaneously, multiple triggered responses are observed (panel D). Triggered activity arising from early afterdepolarizations occurring during phase 2 of the action potential are also rate dependent but over a range of frequencies characterized by shorter basic cycle lengths (7).

Effect of extracellular potassium and magnesium on early afterdepolarizations and triggered activity. Both types of early afterdepolarization-induced triggered activity (phases 2 and 3) are sensitive to changes in extracellular concentrations of potassium and magnesium. Reduced levels of these electrolytes facilitate the manifestation of triggered activity, whereas elevated levels suppress the activity.

Magnesium has been shown to suppress early afterdepo-

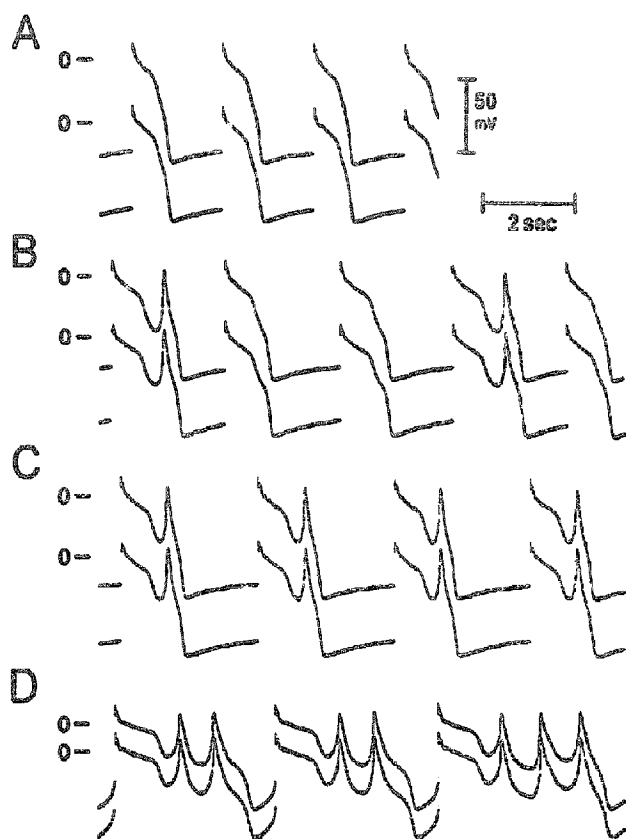


Figure 2. Frequency dependence of quinidine-induced triggered activity (phase 3). Each panel depicts transmembrane activity recorded from opposite ends of a Purkinje preparation exposed to 0.5 $\mu\text{g/ml}$ of quinidine for 120 min. Reprinted, with permission, from Davidenko et al. (7).

larizations and triggered activity induced by cesium, quinidine, and 4-aminopyridine (7,25,26). Davidenko et al. (7) reported that a slight increase in extracellular magnesium from 0.5 to 1.0 mmol/liter could either totally suppress or decrease the incidence of triggered activity in Purkinje fibers pretreated with quinidine. Changes in extracellular magnesium were shown to produce different effects on the two types of early afterdepolarizations. Increases in magnesium to concentrations as high as 5 mmol/liter produced little change in the manifestation of phase 3 early afterdepolarizations but completely abolished phase 2 early afterdepolarizations.

Origin and propagation of early afterdepolarization-induced triggered activity. *Early afterdepolarizations originating in Purkinje fibers.* Early afterdepolarizations are more readily induced in conducting tissues (Purkinje fibers) than in isolated myocardial tissues. An example of the differential sensitivity of the two tissues is illustrated in Figure 3, recorded by El-Sherif et al. (19) from a Purkinje muscle preparation exposed to anthopleurin-A. The drug caused marked lengthening of the plateau, early afterdepolarizations and triggered activity in the Purkinje fiber but not in the attached muscle. The early afterdepolarization-

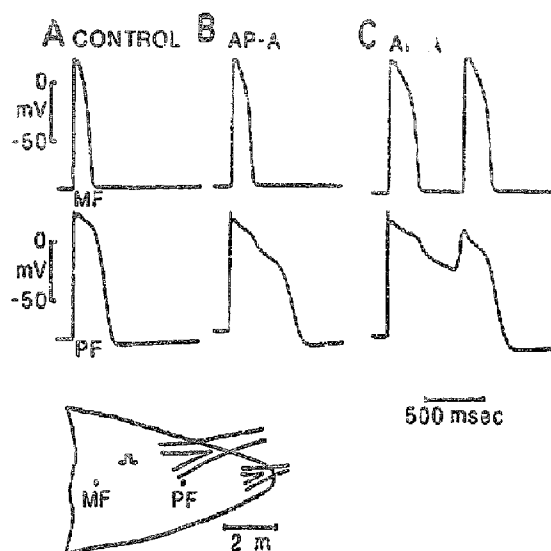


Figure 3. Simultaneous recordings of action potentials from a Purkinje fiber (PF) and a muscle fiber (MF) in a canine papillary muscle preparation exposed to anthopleurin-A (AP-A, 50 $\mu\text{g/liter}$). The preparation was paced at a constant cycle length of 3 s. A, Control recording. B, 24 min after exposure to AP-A, the Purkinje fiber action potential duration increased from a control value of 330 to 580 ms, whereas the muscle fiber action potential duration increased from a control value of 180 to 190 ms. C, Early afterdepolarization gives rise to a triggered response in PF that conducts to MF. Reprinted, with permission, from El-Sherif (43).

induced triggered response is seen to conduct from the Purkinje fiber to the attached papillary muscle.

Early afterdepolarizations originating in ventricular muscle: the role of M cells. Studies examining early and delayed afterdepolarization induction in vivo and in vitro have yielded conflicting results. Monophasic action potential recordings obtained in vivo have been used to suggest that early afterdepolarization-induced triggered activity could arise from ventricular myocardium (19,24,26,27). However, when syncytial myocardial preparations are studied in vitro, such activity is generally not observed. Early afterdepolarizations are rarely observed in myocardial tissues isolated from the ventricular surface (28-30), and early afterdepolarization-induced triggered activity has never been reported in syncytial epicardial or endocardial preparations.

Although afterdepolarization-induced triggered activity is generally not observed in isolated cardiac tissues studied in vitro, early and delayed afterdepolarizations and, in some cases, triggered activity have been reported in myocytes enzymatically dissociated from ventricular myocardium (16,31). One possible explanation for this apparent disparity is that afterdepolarizations and triggered activity may be limited to or more readily induced in a discrete population of ventricular myocardial cells.

Recent studies (32) have described the existence of a unique subpopulation of cells in the deep subepicardial to midmyocardial regions of the canine ventricle. These cells, termed M cells, exhibit electrophysiologic characteristics

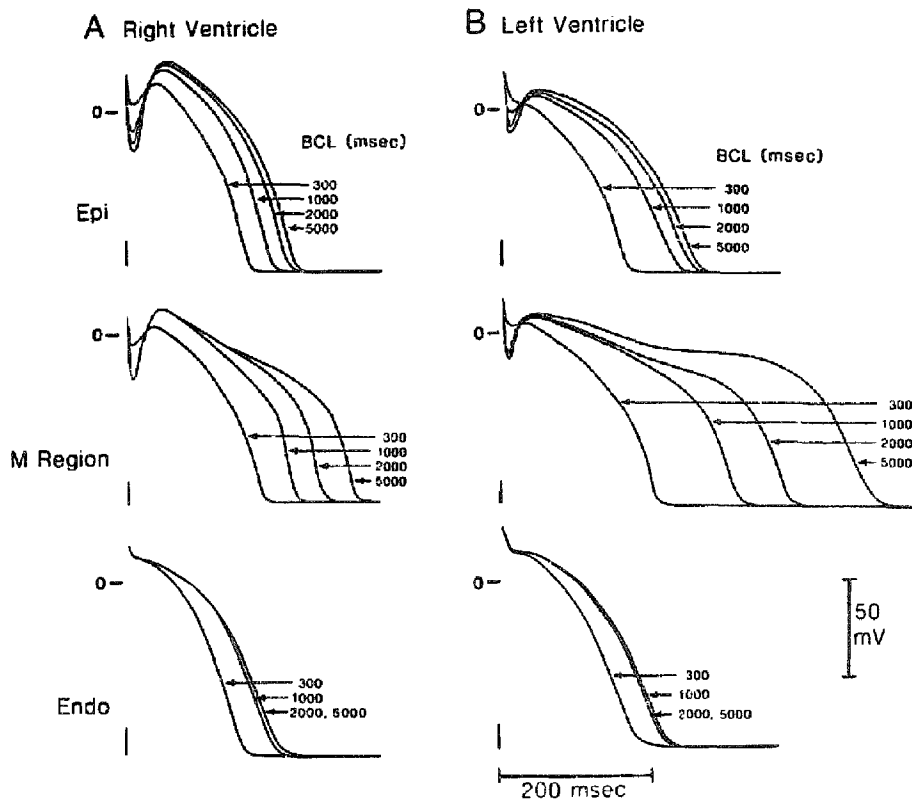


Figure 4. Rate dependence of canine ventricular epicardial (Epi), M region and endocardial (Endo) action potentials, right versus left ventricle. Shown is transmembrane activity from epicardial, endocardial and M cell preparations recorded at basic cycle lengths (BCL) of 300, 1,000, 2,000 and 5,000 ms. Modified, with permission, from Sicouri and Antzelevitch (32).

intermediate between those of muscle and conducting (Purkinje) tissues. The hallmark of the M cell action potential is its ability to prolong dramatically with slowing of the stimulation rate (Fig. 4). The rate dependence of the action potential duration of cells in the M cell region is more accentuated than that of epicardium or endocardium but more akin to that of Purkinje fibers. Phase 4 depolarization, however, is never observed in M cells, not even in the presence of catecholamines and low extracellular potassium. Purkinje fibers are not observed histologically in this region of the canine ventricle (33,34). Evidence for the existence of M cells in the human heart was recently provided in a preliminary report by Drouin et al. (35), and *in vivo* evidence for the existence of M cells in the canine heart was provided in a preliminary report by Hariman et al. (36).

Tissues isolated from the M cell region of the canine ventricle can also be distinguished from epicardium and endocardium by their ability to develop early and delayed afterdepolarization activity. Agents that produce early afterdepolarization-induced triggered activity in Purkinje fibers, including 4-aminopyridine, quinidine, cesium, amiloride, erythromycin and Bay K 8644, have been shown to induce early afterdepolarizations and triggered activity in M cells but not in endocardium or epicardium (Fig. 5, Table 2) (1,37,38).

These results suggest that in canine ventricular myocardium, early afterdepolarizations and triggered activity may be limited to or much more readily induced in a select population of cells. M cells are thought to comprise at least

40% of the left ventricular free wall (39), and they have recently been identified in the deep subendocardial tissues of endocardial structures formed by invagination of the free wall (papillary muscles, trabeculae and septum). Preliminary data suggest that M cells in these endocardial structures also display afterdepolarizations and triggered activity in response to agents that induce this activity in the deep subepicardial M cells.

Ionic mechanisms. The mechanisms underlying early afterdepolarizations and triggered activity are still poorly understood. The manifestation of an early afterdepolarization is usually associated with a critical prolongation of the repolarization phase due to a reduction in net outward current. A reduction in repolarizing current can result from an increase in one or more inward currents or a decrease in one or more outward currents, or both. The majority of pharmacologic interventions associated with early afterdepolarizations can be grouped as acting predominantly through one of three different mechanisms: 1) a decrease in the availability of potassium currents that contribute to repolarization (I_K , delayed rectifier and I_{K1} , inward rectifier currents) (class IA antiarrhythmic drugs [e.g., quinidine, procainamide], class III antiarrhythmic drugs [e.g., sotalol, bretylium, clofilium], cesium and 4-aminopyridine [>1 mmol/liter]); 2) an increase in the availability of transsarcolemmal calcium current (Bay K 8644 [20,38,40-42], elevated extracellular calcium [30] and catecholamines [16]); and 3) a delay in sodium current inactivation (aconitine, veratridine, batrachotoxin and sea anemone toxins [e.g., anthopleurin-A and ATX-II] [19,43]).

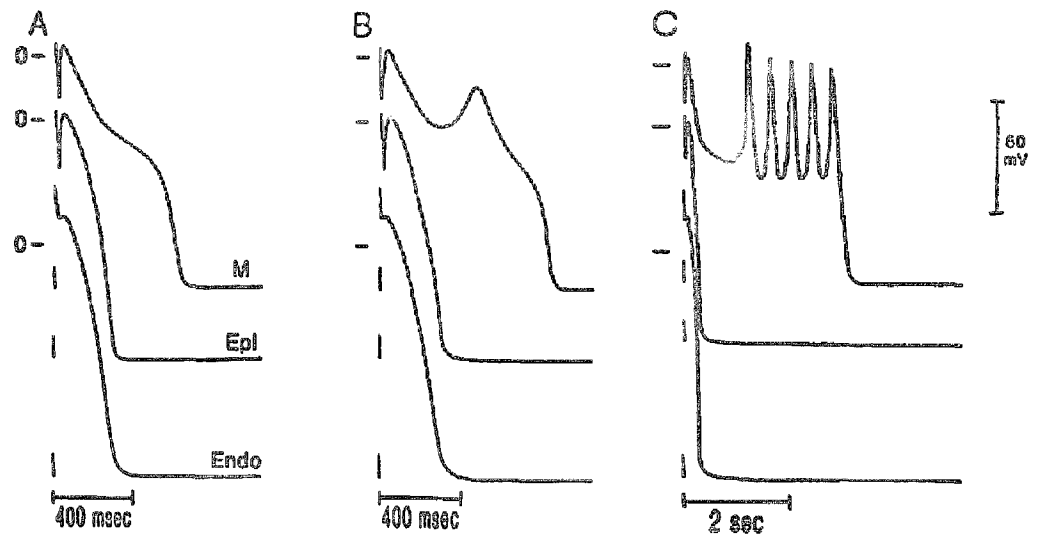


Figure 5. Quinidine-induced early afterdepolarization and triggered activity. Each panel depicts transmembrane activity recorded from isolated epicardial (Epi), M cell and endocardial (Endo) tissues after 60 min of exposure to quinidine (1 $\mu\text{g/ml}$). Basic cycle lengths 3.500 s (A), 5.000 s (B) and 20 s (C). Extracellular potassium = 2 mmol/liter. Early afterdepolarizations are observed in the M cell preparation but not in epicardium or endocardium. Reprinted, with permission, from Sicouri and Antzelevitch (37).

Early afterdepolarizations produced by any of these mechanisms can be antagonized by drugs that activate potassium channels, such as phorbol esters, and potassium channel openers, such as pinacidil (44-48), or by agents that block slowly inactivating or "window" sodium current (e.g., TTX, class IB or IC antiarrhythmic drugs). Early afterdepolarization activity induced by calcium agonists, elevated extracellular calcium and catecholamines can also be antagonized by calcium channel or beta-adrenergic blocking agents, or both.

In some cases, but not all, relatively large concentrations of drugs are required to induce early afterdepolarizations and triggered activity. The class IA antiarrhythmic drugs represent an exception to this rule. Quinidine produces greater prolongation of action potential duration and more readily induces early afterdepolarizations at low concentrations than at high levels of drug. This is because at slow rates, low levels of the drug cause a much greater inhibition of outward potassium currents than of the inward sodium current. Higher concentrations of quinidine lead to greater inhibition of the sodium current, which serves to counter the action potential prolongation effected by quinidine-induced block of outward currents.

Early afterdepolarizations are more readily induced at

slow rates and low extracellular potassium for a number of reasons, including the following: 1) Less electrogenic outward (repolarizing) current is generated by the sodium-potassium pump at slow rates; 2) more complete decay of the delayed rectifier current at slower rates decreases the repolarizing influence of this current; 3) some potassium channel blocking agents show reverse-use dependent block, resulting in greater block of outward repolarizing current at slower rates; 4) a reduction in extracellular potassium is also known to diminish the sodium potassium pump and inward rectifier currents (49). The net effect of these changes is to further decrease the contribution of outward current to the repolarization process, thus facilitating early afterdepolarization and triggered activity induction.

The recent demonstration of a smaller intrinsic contribution of the delayed rectifier current to repolarization in M cells (50) may also explain why early afterdepolarizations and triggered activity are readily induced in M cell preparations but not in epicardial or endocardial preparations.

Early afterdepolarizations and triggered activity as a cause of arrhythmia. Identification of early afterdepolarization and triggered activity mechanisms in vivo has been in large part based on the electrocardiographic (ECG) characteristics of the arrhythmia, on monophasic action potential recordings from the epicardial or endocardial surfaces of the ventricles, as well as on the response of the arrhythmia to pacing, drugs or changes in electrolyte levels (e.g., potassium, magnesium).

Table 2. Early Afterdepolarization-Induced Triggered Activity

	Epicardium	Endocardium	M Cells
Quinidine (3.3 $\mu\text{mol/liter}$)	-	-	+
4-aminopyridine (2.5-5 mmol/liter)	-	-	+
Amiloride (1-10 $\mu\text{mol/liter}$)	-	-	+
Clofilium (1 $\mu\text{mol/liter}$)	-	-	+
Bay K 8644 (1 $\mu\text{mol/liter}$)	-	-	+
Cesium (5-10 mmol/liter)	-	-	+
D,L-sotalol (100 $\mu\text{mol/liter}$)	-	-	+
Erythromycin (10-100 $\mu\text{g/ml}$)	-	-	+

- = triggered activity never observed; + = triggered activity readily induced.

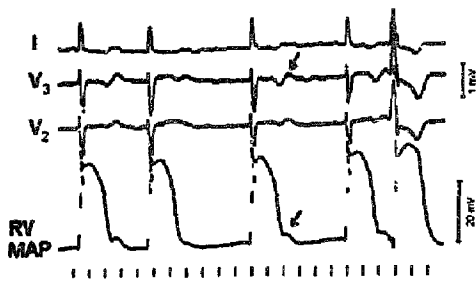


Figure 6. Simultaneous recording of surface electrocardiographic leads I, V₂ and V₃ and a monophasic action potential (MAP) from the endocardial surface of the posterior and paraseptal region of the right ventricle (RV) in a patient with quinidine-induced long QTU syndrome and torsade de pointes. The monophasic action potential shows a distinct hump on phase 3 repolarization (arrow) characteristic of an early afterdepolarization. The peak of the early afterdepolarization is synchronous with the peak of the U wave, and the amplitude of both waves (arrows) varies significantly with the length of the preceding RR interval. Ventricular ectopic beats occur only after RR intervals >1,000 ms and seem to arise close to the peak of the U wave. Electrocardiographic leads are recorded at twice standard amplitude. Reprinted, with permission, from El-Sherif (43).

Monophasic action potential recording in humans. Reports of monophasic action potential recordings in patients with congenital or acquired long QTU syndrome (51–54) have shown deflections on late phase 2 or 3 resembling early afterdepolarizations. Figure 6 shows monophasic action potential recordings from the right ventricle of a patient presenting with quinidine-induced long QTU syndrome (51). The apparent early afterdepolarization on phase 3 of the monophasic action potential is synchronous with registration of the U wave in the surface ECG, and good correlation is apparent between the amplitude of the U wave and the apparent early afterdepolarization. A strong correlation was also present between the cardiac cycle length and the U wave amplitude, with larger amplitude U waves observed at slower rates. Ventricular ectopic beats occurred only after long cycles, usually arising close to the peak of the U wave. Rapid ventricular pacing suppressed the ectopic rhythm as well as the appearance of both the U wave and the apparent early afterdepolarization. These and similar studies have implicated the early afterdepolarization as the basis for the accentuated U waves in acquired long QT syndrome.

Shimuzu et al. (53) used monophasic action potential recordings to examine the influence of isoproterenol administration in patients with congenital long QTU syndrome and in a control group of patients. Monophasic action potential duration measured at 90% repolarization was significantly longer in the long QT syndrome group than in the control group (275 ± 36 vs. 231 ± 22 ms [mean \pm SD]). Isoproterenol was found to increase monophasic action potential duration in the long QT syndrome group (275 ± 36 to 304 ± 50 ms) but abbreviated this value in the control group. Isoproterenol also induced apparent early afterdepolarizations at some recording sites in four of the six patients with

long QT syndrome but not in the control group patients. Early afterdepolarization-like activity was associated with an increased amplitude of the late component of the TU complex, and the corrected QT interval was prolonged by isoproterenol from 543 ± 53 to 600 ± 30 ms. Neither ectopic beats nor ventricular tachyarrhythmias were recorded after isoproterenol administration, although a significant increase in dispersion of repolarization was noted.

Qualitatively similar results were reported by Zhou et al. (54) in a case report of a patient with familial long QT syndrome. Epinephrine infusion promoted early afterdepolarization-like activity in endocardial monophasic action potential recordings that was associated with TU changes but no arrhythmic activity. Ectopic beats and ventricular tachycardia could be provoked by pauses after rapid ventricular pacing and could be suppressed by propranolol and verapamil.

These and similar reports suggest that patients with idiopathic long QT syndrome have primary repolarization abnormalities that are exaggerated by adrenergic agonists. They also suggest a role for early afterdepolarizations in arrhythmogenesis in these patients, although the specific mechanism is far from clear.

In vivo experimental animal models of early afterdepolarization-induced arrhythmia. Several experimental models of drug-induced polymorphic ventricular tachycardia have been described. Three in vivo models in the dog have been shown to display bradycardia-dependent QTU prolongation and polymorphic ventricular tachyarrhythmias that resemble torsade de pointes. The three agents utilized were cesium (17,27,55,56), the sea anemone polypeptide anthopleurin-A (19,43) and the calcium agonist Bay K 8644 (24). In all three models, monophasic action potential recordings obtained using endocardial contact electrodes demonstrated early afterdepolarization-like deflections. In the cesium chloride model, Levine et al. (27) recorded epicardial monophasic action potentials displaying deflections resembling early afterdepolarizations and triggered activity that were associated with the induction of ventricular polymorphic tachycardias. In the anthopleurin-A model, El-Sherif et al. (19) similarly observed bradycardia-dependent early afterdepolarization-like deflections in endocardial and epicardial monophasic action potentials that corresponded to the appearance of prominent U waves in the surface ECG. Ventricular premature depolarizations arising from the U or TU complex were shown to initiate polymorphic ventricular tachyarrhythmias that terminated spontaneously or degenerated into ventricular fibrillation. The development of TU alternans in the surface ECG was also shown to coincide with the occurrence of 2:1 alternation of early afterdepolarization in endocardial monophasic action potentials. These observations were used to suggest that under certain conditions, a prominent U wave in the long QTU syndrome may represent early afterdepolarizations generated in the Purkinje network or in ventricular muscle, or both.

Such interpretation must be approached with some cau-

tion. The presumption is that the early afterdepolarization-like deflections in monophasic action potential recordings are representative of true early afterdepolarizations that develop in the underlying tissues. Several arguments can be leveled against this hypothesis. First is the observation that early afterdepolarizations are generally not observed in the syncytial preparations with which the monophasic action potential electrodes make contact when these tissues are isolated and exposed to the same drug. Second is the observation that M cells in the deep subepicardium or deep layers of endocardial structures (including the septum), or both, show a much greater action potential prolongation in response to these agents than do the surface tissues. Because monophasic action potential electrodes record activity far beyond the surface layer of cells, it is possible that the prolonged action potentials in the deep layers could manifest as an early afterdepolarization-like deflection in the monophasic action potential recording (Fig. 7). In support of this conclusion is the observation that the early afterdepolarization-like deflections recorded using monophasic action potential electrodes show behavior uncharacteristic of a true early afterdepolarization (continuous shift in the position of the early afterdepolarization along phase 3 of the action potential and its appearance at very negative potentials close to the resting membrane potential) but more in line with electrotonic manifestations at the surface of events occurring in deeper structures. This activity would be associated with the appearance of prominent U waves and long QTU intervals in the surface ECG because prolongation of M cell action potentials is thought to underlie these ECG manifestations (57) (Fig. 7 to 9).

Basis for the ECG U wave. The origin of the U wave has long been a matter of controversy and debate (58). Einthoven (59), who first described this ECG deflection in 1903, hypothesized that the U wave represents late repolarization of certain regions of myocardium (60). Because ventricular myocardium isolated from various regions on the surface of the heart did not exhibit action potential activity consistent with the timing and rate dependence of the U wave, the emerging theories focused predominantly on the Purkinje system (61-64), early or delayed afterdepolarizations (65,66) and "mechanoelectrical feedback" mechanisms (67,68).

Hoffman and Cranefield (61) were the first to suggest that the U wave might be caused by repolarization of the Purkinje network on the basis of the observation that action potentials of free-running Purkinje fibers are considerably longer than those of ventricular myocardium and approximately coincide with the appearance of the U wave. Although experimental (63) and clinical (64) support for the hypothesis have been advanced, it has been difficult to reconcile the small mass of the Purkinje network with the amount of current that is necessary to produce a discernible voltage deflection in the standard ECG (69). The weakness of the Purkinje hypothesis is even more apparent when it is applied to

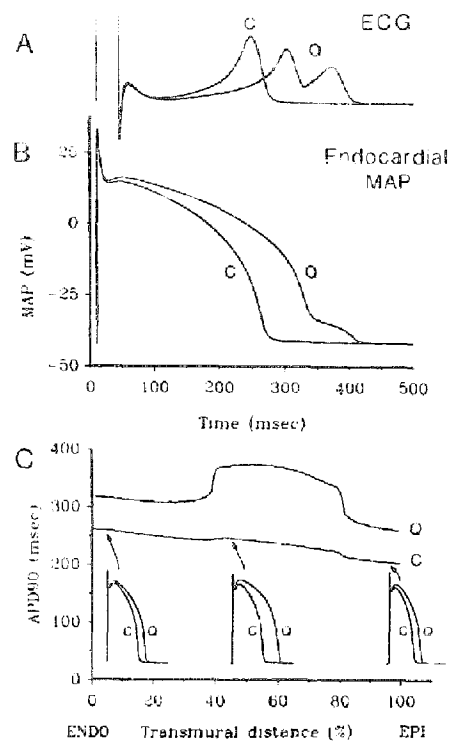


Figure 7. Computer simulation of a transmural electrocardiogram (ECG) and endocardial monophasic action potential (MAP) showing that preferential prolongation of the M cell action potential in response to quinidine and bradycardia can result in the development of a U wave in the ECG and an "apparent" early afterdepolarization in the monophasic action potential recording. Propagated electrical activity was simulated in a 1 × 1-cm surface representing a transmural slice of the left ventricular wall. The M cell region, containing cells with intrinsically longer action potentials, starts 4 mm from the endocardial surface and is 4 mm wide. A, ECG. B, Endocardial monophasic action potential signal calculated as a product of the "electrode field" and instantaneous voltage distribution. C, Distribution of action potential duration measured at 90% repolarization (APD 90) across the wall. Inset shows select action potentials at discrete sites in the endocardial (ENDO), M cell and epicardial (EPI) regions. The two superimposed traces simulate the control (C) situation and the response to quinidine and bradycardia (Q). The greater response of cells in the M region results in the development of a U wave in the ECG and an early afterdepolarization-like deflection in the monophasic action potential recording in the absence of early afterdepolarization activity anywhere in the preparation. (Nesterenko VV, Antzelevitch C, unpublished observation.)

explain the "giant" positive or negative U waves recorded in certain pathologic conditions (70).

Evidence in support of the last two hypotheses is also less than compelling. Because afterdepolarizations do not normally occur in ventricular myocardium, they cannot easily account for the U wave that appears under normal conditions (>40% of adults) (71). As discussed earlier, much of the data in support of the afterdepolarization hypothesis derive from monophasic action potential recordings (72). Early monophasic injury potential traces presented by Lepeschkin (66) displayed "humps" resembling early and

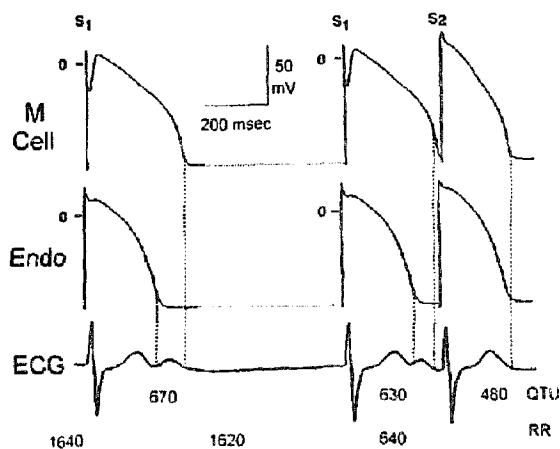


Figure 8. M cell as the basis for the U wave. Combined clinical electrocardiographic (ECG) trace with transmembrane recordings from canine ventricular tissues to demonstrate concordance between rate-dependent changes in the duration of the M cell action potential and in the manifestation of the U wave. Upper traces, Action potentials recorded from the endocardial (Endo) and M cell region of a transmural strip of canine left ventricular free wall. The first two responses are basic beats elicited at a basic cycle length (S_1 - S_2) of 2,000 ms. The third response was evoked by a stimulus introduced at an S_1 - S_2 interval of 300 ms. Lower trace (electrocardiographic [ECG] trace from an 85-year old man presenting with syncope) shows marked bradycardia due to sinoatrial block and a long QTU interval. A prominent U wave is apparent after the long RR intervals (1,640 and 1,620 ms) but not after the much shorter RR of 640 ms. ECG trace courtesy of Drouin E, and coworkers.

delayed afterdepolarizations. However, simultaneous transmembrane recordings obtained using microelectrodes failed to show similar deflections (62). This apparent paradox could be explained by the fact that monophasic action potential deflections recorded at the ventricular surface may represent the activity of M cells in the deeper structures of the myocardium. Figure 7 presents a simulation of a transmural ECG and endocardial monophasic action potential showing that preferential prolongation of the M cell action potential in response to quinidine and bradycardia can result in the development of a prominent U wave in the ECG and an "apparent" early afterdepolarization in the monophasic action potential recording, both a reflection of prolonged action potential durations in the deep structures of the myocardium.

These observations suggest that M cells in the midmyocardium of the free wall and deep layers of endocardial structures (including the septum) could contribute prominently to the manifestation of U waves and long QTU intervals. Figures 8 and 9 provide further evidence in support of this hypothesis, illustrating concordance between the rate dependence of the U wave (clinical traces) and that of the M cell action potential (canine ventricular tissues). The greater prolongation of the M cell response after deceleration is consistent with the pause-dependent accentuation of the U wave. Although the time base for the human ECG and canine action potential traces are understandably different,

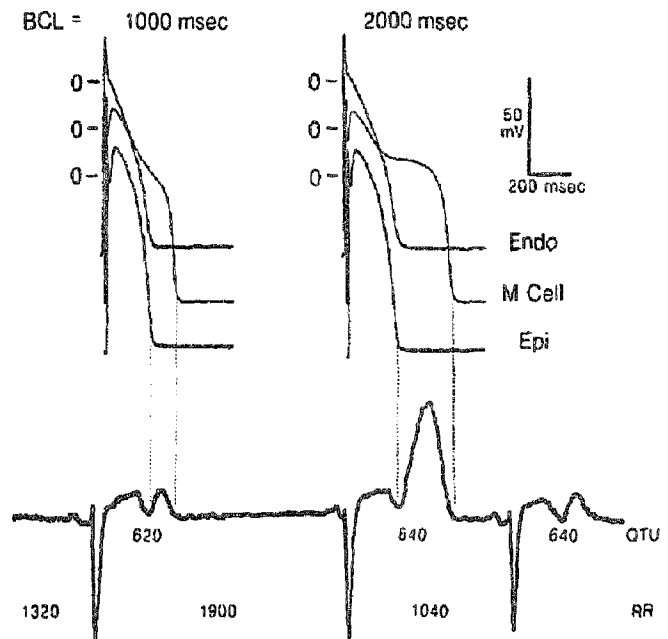


Figure 9. M cells and the "giant" U wave. Upper trace, Transmembrane activity recorded simultaneously from endocardial (Endo), deep subepicardial (M cell) and epicardial (Epi) tissues obtained by successive dermatome shavings made parallel to the epicardial surface (canine left ventricular free wall). The M cell action potential, free of the electrotonic influence of epicardium and endocardium, shows a dramatic prolongation of the action potential as the basic cycle length (BCL) is increased from 1,000 to 2,000 ms. Lower trace, Holter recording (equivalent to a lead V_1 or V_2) from a patient taking amiodarone who died of torsade de pointes that degenerated into ventricular fibrillation shortly after this trace was recorded. The trace shows dramatic rate-dependent changes in the QTU interval, with a "giant U wave" apparent after a pause of 1,900 ms. The rate-dependent changes in the action potential duration of the M cell correlate well with the manifestation of the U wave in the electrocardiogram. QTU and RR interval measurements are in ms. Clinical trace courtesy of Acunzo R, Rosenbaum MB.

the temporal relations shown point to repolarization of endocardium (and epicardium) as the likely determinants of the QT interval and repolarization of the M cells as the determinants of the QTU interval.

Thus, the appearance of prominent electrocardiographic U waves may be observed in the absence of true early afterdepolarization activity anywhere in the heart. The development of true early afterdepolarizations or triggered responses in M cells and Purkinje fibers, or both, could, however, further accentuate the manifestation of both U waves and monophasic action potential deflections recorded at the surfaces of the ventricles (Fig. 10).

Characteristics of arrhythmias associated with early afterdepolarizations. Acquired long QT syndrome and torsade de pointes. Drug-induced ventricular tachyarrhythmias, in particular the polymorphic ventricular tachycardia known as torsade de pointes, are frequently associated with hypokalemia, hypomagnesemia, plasma levels of drug within the therapeutic range and prolongation of the QTU interval

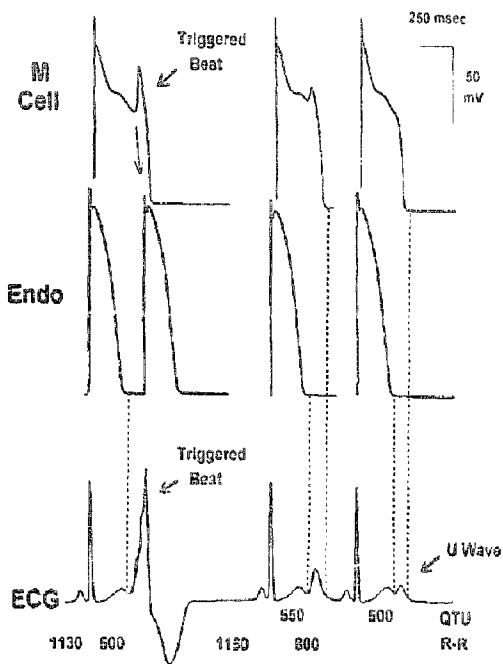


Figure 10. Early afterdepolarization-induced triggered activity in M cells as the basis for extrasystolic activity arising from the U wave. Upper trace, Transmembrane activity recorded from an endocardial cell (Endo) and deep subepicardial M cell (3 mm from the epicardial border) in a transmural preparation isolated from the canine left ventricular free wall. Early afterdepolarization and triggered activity were induced by superfusing the preparation with 4-aminopyridine (3 mmol/liter) (potassium = 2 mmol/liter). At a basic cycle length of 5 s (left), an early afterdepolarization-induced triggered response develops in the M cell region and is observed to propagate to the endocardium, causing "extrasystolic" activation of the preparation. At a basic cycle length of 3 s (middle), a prominent early afterdepolarization is observed in the M cell but not at the endocardial site. At a basic cycle length of 2 s (right), the early afterdepolarization is less obvious, but the M cell response remains considerably longer than that of endocardium. Lower trace, Electrocardiographic (ECG) tracing (lead II) obtained during a Valsalva maneuver in an 18-year-old man with frequent episodes of ventricular bigeminy and prolonged repolarization due to a marked U wave. The pause-dependent changes in the appearance of the U wave and attendant development of extrasystolic activity in the clinical trace appear to correlate well with the rate dependence of early afterdepolarization development and action potential prolongation in the M cell. QTU and RR measurements are in ms. The ECG trace reprinted, with permission, from Brugada and Wellens (163).

(73-76). In addition, the initiation of torsade de pointes is usually preceded by a premature response displaying a long coupling interval to the beat of sinus origin. This cycle is usually preceded by a slow heart rate or a long pause (5) during which prominent diastolic U waves appear in the ECG (71) (Fig. 11). The clinical syndrome of acquired long QTU syndrome and torsade de pointes, also commonly referred to as "pause-dependent long QT syndrome," occurs in association with numerous pharmacologic agents, electrolyte abnormalities and bradycardic states (Tables 3 and 4). Most pharmacologic agents capable of prolonging the QTU interval appear to be capable of causing torsade de

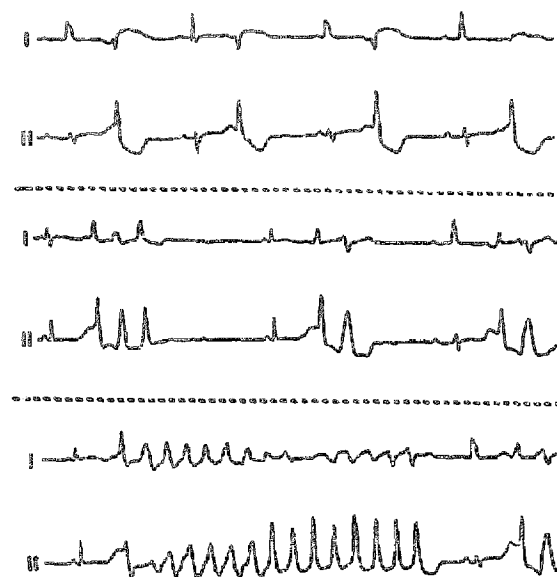


Figure 11. Classical aspect of torsade de pointes. Upper trace, A bigeminal rhythm with long-short intervals. The premature beats interrupt the greatly prolonged repolarization phase of the preceding beat whatever its origin and morphology: wide QRS escape beats or narrow QRS sinus beats due to varying degrees of atrioventricular (AV) block. Middle trace confirms the presence of AV block, and longer pauses are responsible for the repetitive activity that follows initial long-coupled extrasystoles. Lower trace, Repetitive responses form a typical torsade de pointes. Reprinted, with permission, from Coumel (5).

pointes. A combination of predisposing factors is not uncommon in clinical practice. Genetic variability in the hepatic P_{450} metabolic pathway may predispose some patients to torsade de pointes because many agents that cause long QTU syndrome are metabolized via this route. For example, $P_{450IIIA}$, the most common isoform of the P_{450} family of drug-oxidizing enzymes, shows highly variable expression. This isoform is responsible for the metabolism of agents like terfenadine, astemizole and disopyramide. Low activity of this enzyme or its inhibition by agents such as erythromycin and ketoconazole can lead to high plasma levels of terfenadine, astemizole or disopyramide capable of inducing long QTU syndrome and torsade de pointes (77).

The most notable examples of torsade de pointes occur in patients taking quinidine who also develop hypokalemia from potassium-wasting diuretic agents and have a slow cardiac rhythm or long pauses, or both (e.g., complete atrioventricular [AV] block, during atrial fibrillation or postextrasystolic compensatory pauses). Quinidine-induced syncope or torsade de pointes has been reported to occur in 1.5% to 8.5% of patients receiving the drug orally, with a mortality rate as high as 12%. In the majority of patients, the plasma concentration of the drug is within or below the accepted therapeutic range. It should be noted that the range of QT intervals in patients who receive quinidine without developing torsade de pointes overlaps with the range of those who develop the arrhythmia (71). It has been sug-

Table 3. Long QTU Syndromes and Torsade de Pointes*

Acquired (pause dependent)
Drug or toxin induced (see Table 4)
Electrolyte abnormalities
Hypokalemia
Hypomagnesemia
Hypocalcemia
Altered nutritional states
Liquid protein diet
Starvation
Severe bradyarrhythmias
Atrioventricular block
Sinus node dysfunction
Miscellaneous
Mitral valve prolapse
Intracranial disease
Hypothyroidism
Coxsackie B3 myocarditis
Congenital or idiopathic (adrenergic dependent)
Jervel-Lange-Nielson syndrome
Autosomal recessive inheritance
Neural deafness
Romano-Ward syndrome
Autosomal dominant inheritance
Normal hearing
Sporadic
Nonfamilial
Normal hearing

*Modified from References 79, 164 and 165.

gested that quinidine-induced torsade de pointes as well as other ventricular tachycardias associated with long QT intervals (17,78,79) may be precipitated by triggered responses arising from early afterdepolarizations that develop in Purkinje fibers (6,7) or in myocardial cells (M cells) (1,38). The occurrence of prominent U waves at slow rates could be explained by quinidine-induced marked prolongation of the action potential of cells in the M cell region (37) (Fig. 7).

Thus, the conditions that predispose to torsade de pointes in the clinic (hypokalemia, slow heart rates, long QT intervals, U waves) are similar to the conditions under which quinidine and other drugs induce triggered activity and marked prolongation of the action potential in isolated Purkinje fibers and ventricular cells (M cells). Moreover, alterations that protect against torsade de pointes in the clinic (magnesium, potassium, pacing) prevent or diminish drug-induced triggered activity and action potential duration prolongation in vitro. These agents and agencies are thought to act by suppressing early afterdepolarization-induced triggered activity that is responsible for the initiation of episodes of torsade de pointes (7,80-82).

Possible mechanisms of torsade de pointes. The role of early afterdepolarizations and triggered activity in the genesis and maintenance of torsade de pointes is far from clear. Some have suggested that torsade de pointes may at times be due to triggered activity originating at two independent foci (83). The available data suggest that conditions that give rise to early afterdepolarizations and triggered activity (drugs

Table 4. Drugs and Toxins Associated With Torsade de Pointes*

Antiarrhythmic agents
Class IA
Quinidine
Procainamide
Disopyramide
Class III
N-acetylprocainamide
Amiodarone
Sotalol
Vasodilators
Prenylamine
Bepridil
Psychotropic agents
Phenothiazines
Tricyclic and tetracyclic antidepressant agents
Miscellaneous drugs
Corticosteroids (e.g., prednisone)
Diuretic agents (e.g., furosemide)
Antimicrobial agents (e.g., erythromycin, trimethoprim-sulfamethoxazole)
Antihistamines (e.g., terfenadine, astemizole)
Antifungal agents (e.g., ketoconazole, itraconazole)
Hormones (e.g., vasopressin)
Serotonin antagonists (e.g., ketanserin)
Toxins
Anthopleurin-A
Organophosphate insecticides
Liquid protein diets
Some Chinese herbs

*Modified from References 79, 164 and 165.

with class III actions, slow stimulation rates, low extracellular potassium) also produce a marked dispersion of repolarization and refractoriness between the conduction system and the myocardium because of a much greater lengthening of the action potential duration of Purkinje fibers (84) as well as a dispersion of repolarization and refractoriness between cells of the M region and the rest of the myocardium. This heterogeneity provides an ideal substrate for reentry. Thus, bradycardia or hypokalemia, or both, attending the use of action potential duration-prolonging drugs may facilitate the development of triggered activity as well as set the stage for a variety of reentrant arrhythmias. Indeed, several studies have suggested circus movement reentry as a mechanism for torsade de pointes (1,85-88).

A spiral wave of reentrant excitation migrating along the epicardial surface is one mechanism suggested to explain the twisting of points of the ECG R wave that characterizes torsade de pointes (86). This proposal is independent of the factors known to predispose to torsade de pointes. An alternative mechanism, more consistent with the conditions that usually attend torsade de pointes, may involve the unique characteristics and pharmacologic responsiveness of the M cell. The greater prolongation of the M cell action potential in response to agents and conditions that predispose to torsade de pointes could create a column of functional refractoriness in the midmyocardial layers of the ventricular wall. A premature beat, in the form of a triggered

or automatic response, would propagate along the edges of the column, reentering the M cell region only after expiration of refractoriness in this region. Retrograde conduction of the wave would be limited to the M cell region because the bordering regions are now refractory. As functional refractoriness of the borders dissipates, the excitation wave would exit and once again travel anterogradely, circumscribing the M cell region. Repetition of this type of circus movement with progressively shifting sites of reentry could yield the electrical migration characteristics seen with torsade de pointes.

Relevance of QT dispersion. To what extent QT dispersion (i.e., variation of the QT interval among the leads of the surface ECG) may provide an index of transmural heterogeneity of repolarization across the ventricular walls is not clear. Recent studies have demonstrated the effects of class III agents in decreasing QT dispersion (89). However, these results must be approached with some caution. Reported measurements of QT dispersion often do not properly account for changes in the U wave. If M cells are among the primary targets of class III agents, and M cell action potential prolongation is best reflected by changes in the QTU interval, then disregard of the U wave will yield QT dispersion measurements that do not accurately reflect transmural heterogeneity. A QTU/QT dispersion ratio may provide a more meaningful index of heterogeneity within the heart.

Congenital long QT syndrome. The clinical syndrome of long QTU syndrome and torsade de pointes can also be congenital or idiopathic (Table 3). The congenital long QTU syndrome differs from the acquired type with respect to cycle-length dependence and sympathetic nervous system involvement. The onset of torsade de pointes in the congenital long QTU syndrome need not be bradycardia dependent, as is frequently the case in the acquired type.

Three groups of patients with congenital disorders characterized by abnormally delayed ventricular repolarization constitute the idiopathic long QT syndrome. The Jervell-Lange-Nielsen syndrome is transmitted as an autosomal recessive pattern and includes congenital neural deafness. The Romano-Ward syndrome shows autosomal dominant transmission. These patients have normal hearing, as do those with the nonfamilial sporadic form (71,90,91). Through linkage analysis performed in a family with a form of long QT syndrome, Keating et al. (92) recently identified a DNA marker near the Harvey *ras-1* locus, located on the short arm of chromosome 11, linked to the long QT syndrome, confirming the genetic basis of the syndrome. The recent cooperative study of families with long QT syndrome suggests that the *ras* oncogene may not be a marker in all patients with long QT syndrome (93). The genetic basis of the disease, however, is clear from its presentation in familial pedigrees.

The syndrome includes several distinct features: long QT interval with abnormal T or TU waves; T wave alternans; a lower than normal heart rate, especially in children; sinus pauses; ventricular tachycardia, torsade de pointes in par-

ticular, usually precipitated by physical or emotional stress, causing syncope and sudden death (71,90,91). Patients with congenital long QTU syndrome characteristically develop torsade de pointes during periods of increased adrenergic activity. Reports by Coumel (5) indicate that torsade de pointes is more commonly triggered by adrenergic stimulation of neural origin (i.e., emotion) than stimulation of humoral origin (i.e., exercise).

Hypotheses invoked to explain long QT syndrome fall into two categories: 1) abnormalities of sympathetic innervation (94,95) or 2) intrinsic abnormalities of the myocardial cell, or both (90,95-98). The first of these proposes a sympathetic imbalance between right and left cardiac sympathetic innervation as the basis for long QT syndrome and attendant malignant arrhythmias. This hypothesis can explain the beneficial effects of left-sided cardiac sympathetic denervation in some patients (99) and perhaps some of the sinus nodal abnormalities. However, the concept of sympathetic imbalance as the basis for long QT syndrome and its arrhythmic complications has been challenged in other studies (55,91,100-102). A number of studies suggest that the left stellate ganglion normally exerts a qualitatively greater adrenergic influence on the ventricles because of greater innervation and more abundant release of catecholamines (91). This quantitative difference, rather than a pathophysiologic imbalance, may underlie the greater arrhythmogenic potential of left versus right stellate ganglion stimulation.

In many cases in which left stellectomy or therapy with beta-adrenergic blockers is protective against ventricular arrhythmias, the QT interval shortens a bit but remains prolonged (99). Thus, it has been suggested that QT prolongation may be an abnormality that, although not arrhythmogenic in its own right, may predispose to malignant arrhythmias when presented with a trigger in the form of elevated sympathetic activity (97).

In some cases, left stellate ganglion interruption reduces the incidence of arrhythmia and sudden death in patients in whom treatment with beta-adrenergic blockers is unsuccessful (99). This observation suggests that in some patients with long QT syndrome, arrhythmogenicity is triggered by alpha-adrenergic stimulation. Indeed, several studies (103-105) have shown an effect of alpha-adrenergic stimulation on arrhythmia prevalence in experimental models of long QT syndrome.

Some investigators have invoked the adrenergic dependence of the congenital or idiopathic long QTU syndrome to suggest an electrophysiologic mechanism different from that of acquired long QTU syndrome. Others (5,43,71) point to the similarities of the acquired and congenital syndromes to suggest a common underlying mechanism but with a greater adrenergic influence in the case of the congenital long QTU syndrome.

This brings us to the second hypothesis commonly used to explain long QT syndrome, that of an intrinsic abnormality in cellular function of the cardiac myocyte. This hypothesis presumes that the repolarization abnormalities are due

to defects in the cardiac tissue, perhaps an altered configuration of ionic channels giving rise to a decrease in outward repolarizing (i.e., potassium) current or an increase in inward depolarizing (i.e., calcium) current. As previously discussed, blockade of potassium current as well as augmentation of calcium current can prolong the action potentials of conducting and myocardial fibers. The most dramatic effects are observed in Purkinje fibers and M cell preparations, where action potential duration prolongation is often accompanied by the development of early afterdepolarizations and early afterdepolarization-induced triggered activity (7,16,19,20,26,36,38,40,84,106,107).

This intrinsic defect in cellular function might be induced by abnormalities in sympathetic innervation of the heart or modulated by the activity of the sympathetic system, or both. Recent evidence points to a role for innervation in the expression of ion channels. Ogawa et al. (108) have presented evidence suggesting a role for innervation in the regulation of calcium channels. They showed that coculture of neonatal rat ventricular myocytes with sympathetic ganglia increased the number of dihydropyridine binding sites and the density of L-type calcium channels. Malfatto et al. (97,109) used nerve growth factor antibodies to delay sympathetic nerve growth in neonatal rats and demonstrated a relatively prolonged QT interval in these animals that was due to the failure of the QT interval to abbreviate with age as it usually does in the rat. This finding suggests the possibility that defective or absent sympathetic innervation may alter potassium channel expression. This hypothesis is supported by the recent demonstration of altered repolarizing current expression in ventricular myocytes isolated from the hearts of dogs chronically treated with beta-blockers (Antzelevitch C, et al., unpublished observation).

The role of early afterdepolarizations and triggered activity in the genesis and maintenance of torsade de pointes is unclear in the congenital long QT syndrome as it is in the acquired form. Although beta-adrenergic stimulation is a clear facilitator of early afterdepolarization-induced triggered activity, low level alpha- and beta-adrenergic stimulation can produce significant prolongation of action potential duration without inducing early afterdepolarizations and triggered activity (16). In the setting of cellular electrophysiologic abnormalities, these effects of the sympathetic system could be exaggerated. Regional differences in the response to sympathetic stimulation would give rise to a marked dispersion of repolarization and refractoriness within the myocardium, setting the stage for reentry. In the congenital form of long QT syndrome, as in the acquired form, malignant arrhythmias such as torsade de pointes are probably due to a reentrant mechanism but could be precipitated or triggered by an early afterdepolarization-induced triggered response arising from Purkinje fibers or M cells. QT dispersion has been found to be greater in patients with congenital long QT syndrome but unaffected by beta-blockade in these same patients (110). The clinical relevance of these findings is not clear, especially because these

studies, as most studies of QT dispersion, neglected the U wave and thus may have neglected the principal marker for repolarization of the deep layers of the myocardium.

Delayed Afterdepolarizations and Delayed Afterdepolarization-Induced Triggered Activity

Delayed afterdepolarizations are oscillations of transmembrane activity that occur after full repolarization of the action potential and depend on a previous activation of the cell for their manifestation. Delayed afterdepolarizations that achieve threshold give rise to spontaneous responses known as triggered activity (3).

Causes and origin of delayed afterdepolarization-induced triggered activity. In isolated tissues, delayed afterdepolarizations and delayed afterdepolarization-induced triggered activity are generally observed under conditions that lead to large increases in intracellular calcium or calcium overload of the cell. Classical examples are delayed afterdepolarizations and triggered activity caused by cardiac glycosides (digitalis) in Purkinje fibers (8-11) or by catecholamines in atrial (111), ventricular (112), mitral valve (113) and coronary sinus (114) tissues. This activity is also manifest in hypertrophied ventricular myocardium (115) and in Purkinje fibers surviving myocardial infarction (116).

Digitalis-induced delayed afterdepolarizations and triggered activity have been well characterized in isolated Purkinje fibers (3) but are generally not seen in syncytial myocardial preparations of most species; the ferret and guinea pig are exceptions (30). However, delayed afterdepolarizations are frequently observed in myocytes enzymatically dissociated from ventricular myocardium (31,44,117). Sicouri and Antzelevitch (37,38) recently showed that exposure of canine ventricular myocardium to digitalis, high extracellular calcium or Bay K 8644, a calcium agonist, cause delayed afterdepolarizations and triggered activity in tissues isolated from the M region but not in epicardial or endocardial tissues (Fig. 12). In the subendocardium, digitalis-induced delayed afterdepolarizations and triggered activity were shown to occur in subendocardial Purkinje fibers but not in the immediately adjacent myocardium. These studies indicate that delayed afterdepolarizations and delayed afterdepolarization-induced triggered activity may be limited to or more readily induced in M cells in ventricular myocardium (1,37,38). These findings may also provide an explanation for the apparent discrepancy in the results of experiments performed in syncytial versus myocyte preparations. Further studies are needed to assess whether the induction of delayed afterdepolarizations and triggered activity in enzymatically dissociated ventricular myocytes is related to the origin of these cells within the ventricular wall or to other factors, such as a less limited extracellular space for the isolated myocytes or to calcium loading of the cells during the isolation procedure, or both.

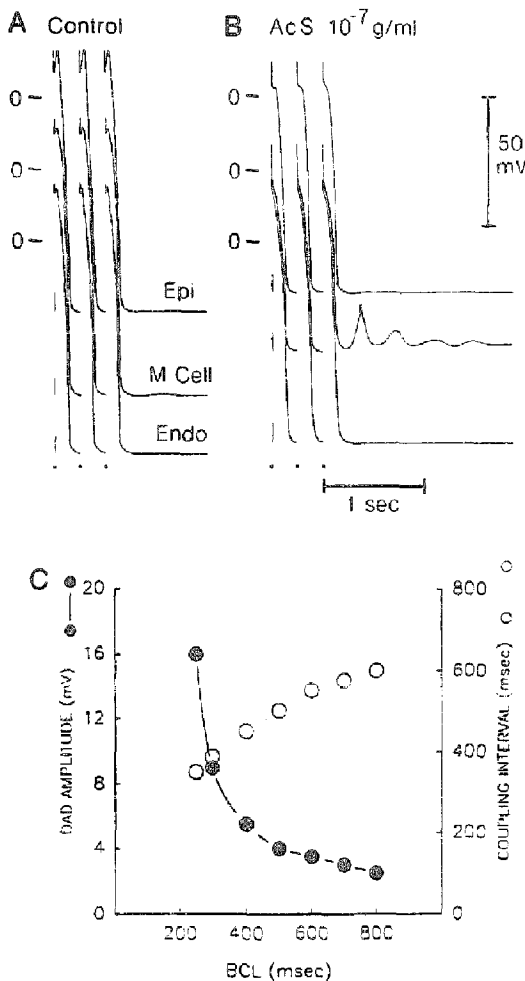


Figure 12. Rate dependence of coupling intervals and amplitudes of digitalis-induced delayed afterdepolarizations in the M cell. Each panel shows transmembrane activity recorded from epicardial (Epi), endocardial (Endo) and M cell preparations. Shown are the last two beats of a train of 10 basic responses elicited at a basic cycle length of 250 ms. Each train was followed by a 3-s pause. **A**, Control. **B**, Acetylstrophanthidin (AcS) (10^{-7} g/ml, 90 min). Acetylstrophanthidin induced prominent delayed afterdepolarizations in the M cell but not in epicardium or endocardium. **C**, Coupling intervals and amplitudes of acetylstrophanthidin-induced delayed afterdepolarizations (DAD) are plotted as a function of the basic cycle length (BCL) of the train of 10 beats. The coupling interval was measured as the interval from the upstroke of the last beat of the train to the peak of the delayed afterdepolarizations. Reprinted, with permission, from Sicouri and Antzelevitch (38).

Characteristics of digitalis-induced delayed afterdepolarizations. The characteristic behavior of the delayed afterdepolarization is such that as the stimulating rate increases, the amplitude of the delayed afterdepolarization increases, and its coupling interval to the action potential decreases (8,9,37,38,118). Figure 12C shows an example of the rate dependence of delayed afterdepolarization activity in an M cell preparation exposed to toxic levels of digitalis. These rate-dependent changes in the amplitude and the coupling interval of the delayed afterdepolarizations in M cells are similar to those of the second but not the first delayed

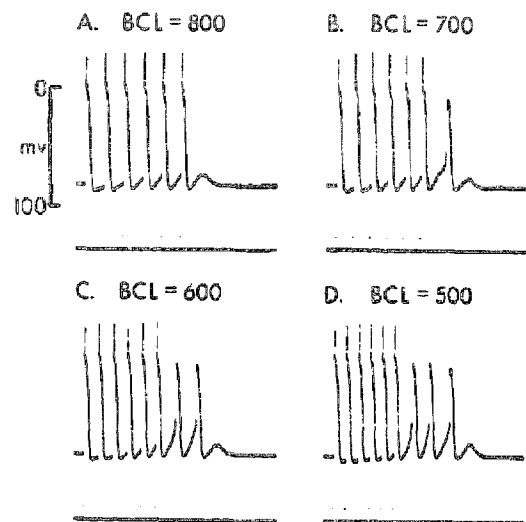


Figure 13. Rate dependence of delayed afterdepolarization-induced triggered activity in a canine Purkinje fiber exposed to toxic levels of digitalis. Bottom trace is stimulus marker. BCL = basic cycle length. Reprinted, with permission, from Ferrier et al. (8).

afterdepolarization observed in digitalis-treated Purkinje fibers (8-11). In Purkinje fibers, the amplitude of the first delayed afterdepolarization usually increases, with acceleration up to a basic cycle length of 600 ms and then decreases. However, the amplitude of the second delayed afterdepolarization increases progressively as the basic cycle length decreases. The result of this behavior is that at the faster rates, delayed afterdepolarizations may attain threshold and give rise to ectopic responses or triggered activity (Fig. 13).

Another important variable capable of modifying the manifestation of delayed afterdepolarization-induced triggered activity is the resting membrane potential. Ferrier and Wasserstrom (28,119) suggested that the absence of delayed afterdepolarizations and triggered activity in canine ventricular myocardium (endocardium) may, in part, be due to the resistance of this tissue to depolarization when exposed to toxic levels of acetylstrophanthidin. This conclusion was based on the appearance of delayed afterdepolarizations in canine ventricular papillary muscle preparations exposed to acetylstrophanthidin and depolarized by injection of bias current. Marked depolarization after exposure to digitalis appears to be a characteristic common to both M cells and Purkinje fibers.

Ionic mechanisms underlying delayed afterdepolarizations. Delayed afterdepolarizations and accompanying aftercontractions are thought to be caused by oscillatory release of calcium from the sarcoplasmic reticulum under calcium overload conditions. The afterdepolarization is believed to be induced by a transient inward current that is generated by either a nonselective cationic current or the activation of an electrogenic sodium-calcium exchanger (120,121). Both are secondary to the release of calcium from the overloaded sarcoplasmic reticulum. Considerable controversy exists

concerning the specific membrane currents involved in the generation of the transient inward current.

Pharmacology of delayed afterdepolarizations and delayed afterdepolarization-induced triggered activity. Any intervention capable of altering intracellular calcium, either by modifying transsarcolemmal calcium current or by inhibiting sarcoplasmic reticulum storage or release of calcium could affect the manifestation of the delayed afterdepolarization. Alternatively, any intervention capable of directly inhibiting or enhancing the transient inward current may influence delayed afterdepolarization and triggered activity. Cardiac glycosides are believed to induce delayed afterdepolarizations and triggered activity through their action to inhibit the sodium-potassium pump. Pump inhibition increases intracellular sodium, thus reducing the activity of the sodium-calcium exchanger, which leads to an increase in intracellular calcium.

Catecholamines, through their actions to stimulate adrenergic receptors, can directly induce delayed afterdepolarization and triggered activity (112,114,122,123) or augment digitalis- or ischemia-induced delayed afterdepolarizations (124,125) by enhancing calcium entry into the cell as well as calcium release from intracellular stores. Calcium channel blockers, such as verapamil, D600, nifedipine and manganese, have been shown to be effective in suppressing the transient inward current, delayed afterdepolarizations, aftercontractions and triggered activity (118,120,121,126-129). Decreasing intracellular calcium has similar effects. Sodium channel blocking agents, such as TTX, lidocaine, ethmozin, aprindine, procainamide, quinidine, mexiletine and amiodarone, are also effective in suppressing delayed afterdepolarization and triggered activity (121,130-137). Sodium channel blockers are believed to act by decreasing intracellular sodium, which causes a decrease in intracellular calcium and thus a decrease in the transient inward current. Sodium channel blockers have been shown not to suppress delayed afterdepolarizations in human atrial fibers (138). In the coronary sinus, quinidine not only fails to suppress delayed afterdepolarizations but causes them to grow larger and to trigger activity because of its actions to prolong the action potential (139).

Pharmacologic agents that affect the release and uptake of calcium by the sarcoplasmic reticulum, including caffeine and ryanodine, also influence the manifestation of delayed afterdepolarizations and triggered activity. Low concentrations of caffeine facilitate calcium release from the sarcoplasmic reticulum and thus contribute to augmentation of delayed afterdepolarization and triggered activity. High concentrations of caffeine prevent calcium uptake by the sarcoplasmic reticulum and thus abolish the transient inward current, delayed afterdepolarizations, aftercontractions and triggered activity (140-147). Ryanodine produces similar suppression by blocking release of calcium from the sarcoplasmic reticulum (148). Doxorubicin, an anthracycline antibiotic, has been shown to be effective in suppressing digitalis-induced delayed afterdepolarizations, possibly

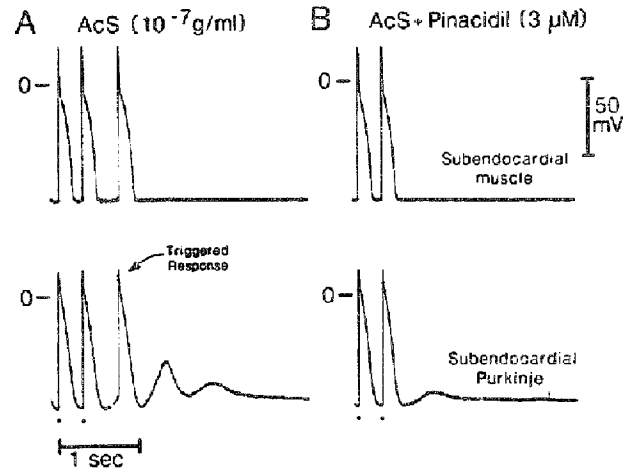


Figure 14. Effects of pinacidil on digitalis-induced delayed afterdepolarizations and triggered activity in endocardial tissue isolated from the free wall of the canine left ventricle. The preparation was obtained by an oblique dermatome shaving extending from the endocardial surface to a depth of 1.5 mm in the deep subendocardium. Dots denote stimulated beats. Each panel shows transmembrane activity recorded simultaneously from a subendocardial Purkinje cell (lower trace) and an adjacent myocardial cell (upper trace) in the deep subendocardium. Shown are the last two beats of a train of 10 basic responses elicited at a basic cycle length of 300 ms. Each train was followed by a 3-s pause. **A**, Recorded after exposure to acetylcholine (AcS) (10^{-7} g/ml, 120 min). A triggered response arising in the Purkinje cell is seen to propagate to muscle. The triggered beat is followed by two prominent delayed afterdepolarizations. **B**, Pinacidil ($3 \mu\text{mol/liter}$) in the continued presence of digitalis readily suppressed the triggered response and greatly decreased the amplitude of the delayed afterdepolarizations.

through inhibition of the sodium-calcium exchange mechanism (149,150). Potassium channel activators, like pinacidil, can also suppress delayed afterdepolarization and triggered activity by activating adenosine triphosphate-regulated potassium current (Fig. 14) (44). Finally, flunarizine has been shown to suppress delayed afterdepolarization and triggered activity (151), in part through inhibition of both L- and T-type calcium current (152).

Delayed afterdepolarization-induced triggered activity as a cause of arrhythmia. Although numerous studies performed in isolated tissues and cells suggest an important role for delayed afterdepolarization-induced triggered activity in the genesis of cardiac arrhythmias, especially bigeminal rhythms and tachyarrhythmias observed in the setting of digitalis toxicity (11), only indirect evidence of delayed afterdepolarization-induced triggered activity is available in vivo. Definitive in vivo recordings of delayed afterdepolarizations are not available. Thus, even when triggered activity appears to be the most likely mechanism, it is often impossible to completely rule out other mechanisms (e.g., reentry, enhanced automaticity).

Several behavioral characteristics suggest the involvement of delayed afterdepolarization-induced triggered activity in cardiac arrhythmias (11,151,153,154): 1) Ectopic beats occur more readily at faster heart rates. 2) The coupling

interval of the premature beat shows a consistent relation to the preceding heart rate such that the coupling interval of the extrasystole progressively shortens as heart rate increases. 3) Arrhythmias caused by delayed afterdepolarization-induced triggered activity are difficult to initiate but relatively easy to terminate and are more likely to accelerate over a number of beats once a tachycardia is initiated. 4) The response to programmed electrical stimulation can be a useful tool in differentiating between reentry and delayed afterdepolarization-induced triggered activity as the mechanism based on the mode of initiation, postpacing interval and mode of termination of the tachycardia. Triggered rhythms are more easily induced with rapid pacing than with extrastimuli. The coupling interval of the first ectopic beat of a triggered rhythm should show a direct relation to the pacing cycle length, and the tachycardia is more likely to be accelerated by overdrive stimulation (151). 5) Response to drugs: Although sodium and calcium blockers as well as adrenergic blockers would be expected to suppress delayed afterdepolarization-induced triggered activity, these agents lack mechanism specificity. Flunarizine has been shown to be specific in suppressing digitalis-induced triggered activity without effect on other mechanisms of arrhythmia, such as reentry and automaticity (151,155).

Delayed afterdepolarization-induced triggered activity and clinical arrhythmias. *Idioventricular rhythms: digitalis and myocardial infarction.* The ECG characteristics of accelerated AV junctional escape rhythms are consistent with those indicative of a triggered mechanism (11). These arrhythmias occur predominantly as a result of digitalis toxicity or in a setting of myocardial infarction. A direct relation is usually found between the escape beats and the previous sinus cycle, and the first escape beat generally occurs late in diastole.

Idiopathic ventricular tachyarrhythmias. These arrhythmias, presenting in patients without structural heart disease (156,157), are often ascribed to focal mechanisms of subepicardial or midmyocardial origin. In such patients, as well as in neural stimulation-induced tachycardia models in dogs, the origin of the ventricular tachycardia is often localized to a distinct region, usually the right ventricular outflow tract (158,159). Neither pacemaker nor triggered activity has been recorded from syncytial myocardial ventricular preparations (canine or human) in response to adrenergic agonists or most other agents known to induce or facilitate this type of activity. An explanation for the focal mechanism of arrhythmogenesis could be the presence of delayed afterdepolarization-induced triggered activity in M cells in the deep layers of the ventricle. The greater sensitivity of M cells to catecholamines was recently demonstrated (1). Norepinephrine induced delayed afterdepolarizations and triggered activity in M cell preparations at concentrations that produced little if any effect in epicardial and endocardial tissues.

Other possible "delayed afterdepolarization-mediated" arrhythmias. These arrhythmias include exercise-induced adenosine-sensitive ventricular tachycardia, as described by Lerman et al. (160), and supraventricular tachycardias, including arrhythmias originating in the coronary sinus (161).

Conclusions

Substantial evidence has been advanced implicating afterdepolarizations and triggered activity in experimental and clinical arrhythmias. However, much of the clinical evidence is indirect and based on extrapolation of data obtained with experimental pacing protocols and agents used to produce early and delayed afterdepolarizations in isolated tissues. Intracellular recordings showing early or delayed afterdepolarizations or afterdepolarization-induced triggered activity in vivo are not available, and the interpretation of monophasic action potential recordings is at times equivocal. Delayed afterdepolarizations have not been observed in vivo with monophasic action potential electrodes, and monophasic action potential deflections resembling early afterdepolarizations have been called into question in view of the fact that exaggerated M cell prolongation within the ventricular wall is thought to be able to generate apparent early afterdepolarizations in surface monophasic action potential recordings. The conditions that predispose to early afterdepolarizations also exaggerate electrical heterogeneity within ventricular myocardium. The dispersion of repolarization that results not only provides the substrate for recording of electrotonic deflections resembling early afterdepolarizations but also the substrate for reentry. Indeed both early and delayed afterdepolarizations can contribute importantly to dispersion of repolarization and excitability and thus may predispose to a variety of reentrant arrhythmias. Because of this overlap, it is often difficult to establish the mechanism of "triggered rhythms" with total confidence. Although triggered activity appears at times to be the most likely mechanism, other possibilities are often difficult to rule out. Preliminary reports of monophasic action potential recordings of discrete drug-induced early and delayed afterdepolarizations from the M cell region of canine and guinea pig ventricles in vivo provide some hope for a more definitive assessment of mechanisms in the future (36,162). We think it fair to conclude that more precise delineation of these complex electrophysiologic mechanisms is required before we can ascribe a more definitive role for afterdepolarizations and triggered activity in clinical arrhythmias.

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