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The Role of Sodium Channel Current in Modulating Transmural Dispersion of Repolarization and Arrhythmogenesis

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Abstract

Role of Late Na Current in Arrhythmogenesis. Ventricular myocardium in larger mammals is composed of three distinct cell types: epicardial, M, and endocardial cells. Epicardial and M cell, but not endocardial cell, action potentials have a prominent I_{to}-mediated notch. M cells are distinguished from the other cell types in that they display a smaller I_{Ks}, but a larger late I_{Na} and $I_{Na\text{-}Ca}$-. These ionic differences may account for the longer action potential duration (APD) and steeper APD-rate relationship of the M cell. The difference in the time course of repolarization of phase 1 and phase 3 contributes to the inscription of the electrocardiographic J wave and T wave, respectively. These repolarization gradients are modulated by electrotonic interactions, $[K^+]_o$, and agents or mutations that alter net repolarizing current. An increase in late I_{Na}, as occurring under a variety of pathophysiological states or in response to certain toxins, leads to a preferential prolongation of the M cell action potential, thus prolonging the QT interval and increasing transmural dispersion of repolarization (TDR), which underlies the development of torsade de pointes (TdP) arrhythmias. Agents that reduce late I_{Na} are effective in reducing TDR and suppressing TdP. A reduction in peak I_{Na} or an increase in net repolarizing current in the early phases of the action potential can lead to a preferential abbreviation of the action potential of epicardium in the right ventricle, and thus the development of a large TDR, phase 2 reentry, and polymorphic ventricular tachycardia associated with the Brugada syndrome.

Keywords

cardiac heterogeneity; M cell; electrocardiogram; long QT syndrome; Brugada syndrome

Electrical Heterogeneity

Heterogeneity of repolarization within the ventricular myocardium was recognized by Einthoven at the turn of the 20th century, and by the great men of science who followed him. Transmural differences in repolarization were largely delineated over the past decade and a half. Today, three distinct myocardial cell types are recognized: epicardial, M, and endocardial cells. Differences in the electrophysiologic characteristics and pharmacologic profiles of these three myocardial cell types have been described in the dog, guinea pig, rabbit, and human ventricles.[1]

The three predominant cell types differ with respect to the currents that contribute to the early repolarization phase or phase 1. The action potentials of epicardial and M cells have a prominent transient outward current (I_{to})-mediated phase 1 that is absent in endocardial cells (see Antzelevitch and Dumaine[1] for references). The early repolarization phase gives the

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epicardial action potential a notched appearance. In the canine heart, I_{to} and the action potential notch are much larger in the right than in the left ventricular (LV) epicardium[2] and M cells.[3]

The hallmark of the M cell is the ability of its action potential to prolong more than that of epicardium or endocardium with slowing of rate. In the early 1990s, the M cells became the focus of intense investigation after their identification and characterization in the deep structures of the canine ventricle.[4-6] M cell distribution in the ventricular wall has been investigated in great detail in the canine LV. M cells with the longest action potential duration (APD) are typically found in the deep subepicardium to midmyocardium in the lateral wall, deep subendocardium to midmyocardium in the anterior wall, and throughout the wall in the region of the outflow tracts. M cells are also present in the deep layers of papillary muscles, trabeculae, and interventricular septum.[7] In some species, like the rabbit, cells with M cell characteristics occupy the entire endocardium of the adult ventricle, although cells with the longer APD can be identified in the deep subendocardium at seven weeks of age.

Tissue slices isolated from the M region display an APD at 90% repolarization (APD_{90}) that is more than 100 ms longer than tissues isolated from the epicardium or endocardium at basic cycle lengths of 2,000 ms or greater. In the intact ventricular wall, this disparity in APD_{90} is less pronounced due to electrotonic coupling of cells. The transmural increase in APD is relatively gradual, except between the epicardium and subepicardium where there is often a sharp increase in APD. This has been shown to be due to an increase in tissue resistivity in this region,[8] which may be related to the sharp transition in cell orientation in this region as well as to reduced expression of connexin 43,[9,10] which is principally responsible for intracellular communication in the ventricular myocardium. In addition, fibrofatty infiltration tends to localize in the deep subepicardial region, accentuating the electrical insulating properties of this region of the wall. Thus, both the degree of electrotonic coupling and intrinsic APDs play a key role in the expression of electrical heterogeneity in the ventricular myocardium.

The longer APD of the M cell as compared to that of epicardial and endocardial cells has been shown to be due to a number of ionic differences, such as a smaller I_{Ks} and a larger late I_{Na}[11,12] and sodium-calcium exchange current ($I_{Na\text{-}Ca}$).[13] The net result is a decrease in repolarizing current (i.e., decreased net repolarizing current or “reserve”) during phases 2 and 3 of the M cell action potential. These ionic differences sensitize the M cells to a variety of pharmacological agents. Agents that block I_{Kr}, I_{Ks}, or increase I_{Ca} or late I_{Na} generally produce much greater APD prolongation of M than of epicardial or endocardial cells.

Electrical Heterogeneity Contributes to Inscription of J Wave and T Wave of ECG

Transmural differences among the three predominant myocardial cell types in early and later repolarization generate voltage gradients that contribute to the inscription of the J wave and T wave of the ECG. The transmural gradient resulting from the presence of an I_{to}-mediated notch in epicardium but not endocardium gives rise to the J wave, or Osborne wave.[14] In the canine heart, voltage gradients developing as a result of the different time course of repolarization of phases 2 and 3 in the three cell types have been shown to give rise to opposing voltage gradients on either side of the M region, which inscribe the T wave (Fig. 1).[15] In the case of an upright T wave, the epicardial response is the earliest to repolarize and the M cell action potential is the latest. When studied in wedge preparations isolated from the LV of the canine heart, full repolarization of the epicardial action potential coincides with the peak of the T wave, and repolarization of the M cells is coincident with the end of the T wave. The duration of the M cell action potential determines the QT interval and the duration of the epicardial action potential determines the QT_{peak} interval. These observations in the perfused wedge preparation suggest that the T_{peak}-T_{end} interval may provide an index of the magnitude of the transmural

dispersion of repolarization (TDR) in the *in vivo* heart, and thus, be useful as an estimate of how TDR may be changing.[5,15]

Enhanced TDR and Arrhythmogenesis

Long QT Syndrome

The long QT syndrome (LQTS) is characterized by the appearance of long QT intervals in the ECG, an atypical polymorphic ventricular tachycardia (VT) known as torsade de pointes (TdP), and an increased risk for sudden cardiac death.[16-18] Congenital LQTS is classified into eight genotypes distinguished by mutations in at least seven different ion channel genes and a structural anchoring protein located on chromosomes 3, 4, 6, 7, 11, 17, and 21.[19-25] Acquired LQTS refers to a syndrome similar to the congenital form, but caused by exposure to drugs that prolong the duration of the ventricular action potential,[26] or QT prolongation secondary to bradycardia or an electrolyte imbalance. In recent years, this syndrome has been extended to encompass the reduced repolarization reserve (i.e., decrease in net repolarizing current) attending remodeling of the ventricular myocardium that accompanies dilated and hypertrophic cardiomyopathies.[27-31]

Accentuation of spatial dispersion, secondary to an increase of transmural and trans-septal dispersion of repolarization, and the development of early afterdepolarization (EAD)-induced triggered activity underlie the substrate and trigger for the development of TdP arrhythmias observed under LQTS conditions.[1,32] Models of the LQT1, LQT2, and LQT3 forms of the LQTS have been developed using the canine arterially perfused LV wedge preparation.[33-36]

Increased late I_{Na} gives rise to the LQT3 form of the congenital LQTS. Experimentally this can be mimicked using ATX-II or anthopleurin-A.[37-43] These toxins produce a preferential prolongation of the action potential of the M cell, and have the greatest potential to prolong TDR in association with a prolongation of the QT interval, leading to the development of TdP (Fig. 2).

An increase in late I_{Na} due to slowing or incomplete inactivation of I_{Na} is associated with congenital diseases (e.g., LQT3 syndrome) owing to mutations of the cardiac sodium channel gene SCN5A. Enhancement of late I_{Na} is also observed, and is associated with arrhythmogenesis and LV dysfunction in a variety of pathophysiological states, including heart failure,[30,44] following hypoxia[45] after exposure to free oxygen radicals,[46] amphiphiles such as lysophophatidylcholine[43] and palmitoyl-L-canitine,[47] and in post-ischemia remodeled myocytes.[48]

Whereas an increase in late I_{Na} is highly arrhythmogenic, its reduction is associated with potent antiarrhythmic activity.[34,35,42,49->51] Because of the greater magnitude of late I_{Na} in M cells, sodium channel blockers such as mexiletine have a greater effect to abbreviate APD in M cells than in other ventricular cell types (Fig. 3).[34,35] The result is a reduction in TDR. These actions of mexiletine have proven to be effective in suppressing TdP in experimental models of LQT1, LQT2, and LQT3.[34,35]

While relatively pure late I_{Na} blockers, such as TTX and lidocaine, abbreviate the ventricular action potential and the QT interval, agents that block potassium channels in addition to late I_{Na} are capable of prolonging QT while abbreviating TDR. Pentobarbital is an example of such an agent.[52] Pentobarbital inhibits I_{Kr}, I_{Ks}, and late I_{Na}.[53] This multichannel inhibition leads to a greater prolongation of APD in epicardial and endocardial cells than in M cells, causing a significant reduction in TDR (Fig. 4). Despite its actions to prolong QT, pentobarbital does not induce TdP[52] and is effective in suppressing D-sotalol-induced TdP.[54]

Ranolazine, a novel anti-anginal agent, is a potent late I_{Na} blocking action that is capable of producing a modest prolongation of the QT interval[51] blocks I_{Kr} (IC_{50} 12 μM), late I_{Na}, late I_{Ca}, peak I_{Ca}, I_{Na-Ca} (IC_{50} 5.9, = 50, 296, and 91 μM, respectively), and I_{Ks} (17%=at 30 μM). In LV tissue and wedge preparations, ranolazine produces a concentration-dependent prolongation of APD in epicardium, but abbreviation of APD of M cells, leading to either no change or a reduction in TDR.[51,55] The result is a modest prolongation of the QT interval. Prolongation of APD and QT by ranolazine is fundamentally different from that of other drugs that block I_{Kr} and induce TdP in that APD prolongation is rate-independent (i.e., does not display reverse rate-dependent prolongation of APD), and is not associated with EADs, triggered activity, increased spatial dispersion of repolarization, or polymorphic VT. TdP arrhythmias are not observed in response to the drug. Indeed, ranolazine has been found to possess significant antiarrhythmic activity, acting to suppress the arrhythmogenic effects of other QT-prolonging drugs that mimic LQT3 and LQT2 (Fig. 5). In three similar experiments, ranolazine (10-30 μM) completely suppressed PVBs and VTs induced by ATX-II (6 nM; n = 3, LQT3). Ranolazine (10 μM) decreased spontaneous and pause-triggered activity caused by E-4031 (60 nM; LQT2) from a control of 42±6 beats/min to 12±8 beats/min (n = 6, $P < 0.05$).

These results highlight the fact that I_{Kr} block, even if relatively potent, does not in and of itself predict the arrhythmogenic potential of pharmacological agents. Ranolazine's potent late I_{Na} block underlies its action to reduce TDR, eliminate EADs, and suppress TdP.[42,43,56,57]

Brugada Syndrome

Arrhythmogenesis in the Brugada syndrome is also due to amplification of TDR, but in this case secondary to preferential abbreviation of the right ventricular (RV) epicardial action potential. The arrhythmogenic substrate responsible for the development of extrasystoles and polymorphic VT in the Brugada syndrome is believed to be secondary to amplification of heterogeneities intrinsic to the early phases (phase 1-mediated notch) of the action potential of cells residing in different layers of the RV wall of the heart. Rebalancing of currents active at the end of phase 1 is thought to underlie the accentuation of the action potential notch in RV epicardium, which is responsible for the augmented J wave and ST segment elevation associated with the Brugada syndrome (see Antzelevitch[58] for references). The presence of a transient outward current (I_{to})-mediated spike and dome morphology, or notch, in ventricular epicardium, but not endocardium, creates a transmural voltage gradient responsible for the inscription of the electrocardiographic J wave.[14,59] The ST segment is normally isoelectric due to the absence of transmural voltage gradients at the level of the action potential plateau. Accentuation of the RV action potential notch under pathophysiologic conditions leads to an increase of transmural voltage gradients, and thereby to an accentuation of the J wave or to J point elevation. If the epicardial action potential continues to repolarize before that of endocardium, the T wave remains positive, giving rise to a saddleback configuration of the ST segment elevation. Further accentuation of the notch is accompanied by a prolongation of the epicardial action potential, causing it to repolarize after the endocardium, hence leading to inversion of the T wave. The down-sloping ST segment elevation, or accentuated J wave, observed in experimental wedge models often appears as an R′, suggesting that the appearance of a right bundle branch block morphology in Brugada patients may be due in large part to early repolarization of RV epicardium, rather than major delays in impulse conduction in the right bundle.[60] Despite the appearance of a typical Brugada sign, accentuation of the RV epicardial AP notch alone does not give rise to an arrhythmogenic substrate. The arrhythmogenic substrate may develop with a further shift in the balance of current, leading to loss of the action potential dome at some epicardial sites but not others. A marked TDR develops as a consequence, creating a vulnerable window, which when captured by a premature extrasystole can trigger a reentrant arrhythmia. Because loss of the action potential dome in epicardium is generally heterogeneous, epicardial dispersion of repolarization develops as

well. Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local re-excitation via phase 2 reentry, leading to the development of a closely coupled extrasystole capable of capturing the vulnerable window across the ventricular wall, thus triggering a circus movement reentry in the form of VT/VF.[61,62] Support for these hypotheses derives from experiments involving the arterially perfused RV wedge preparation[61] and from recent studies in which MAP electrodes were positioned on the epicardial and endocardial surfaces of the RVOT in patients with the Brugada syndrome.[63,64]

A shift in the balance of current at the end of phase 1, leading to loss of the epicardial action potential dome and amplification of TDR, can occur as a result of a reduction in rapidly activating I_{Na} or as a result of a speeding up of inactivation of I_{Na},[65,66] both leading to loss of function. It stands to reason that an agent that slows inactivation of I_{Na} may exert an antiarrhythmic effect in the setting of Brugada syndrome. Such a therapeutic potential has been demonstrated for dimethyl lithospermate B, a derivative of Danshen, in the arterially perfused RV wedge model of the Brugada syndrome.[67]

Conclusion

Amplification of transmural heterogeneities of repolarization in ventricular myocardium can predispose to the development of potentially lethal reentrant arrhythmias (alternative: enhanced late I_{Na}). Augmentation of late I_{Na} can amplify TDR by causing a preferential prolongation of the M cell action potential, whereas a reduction in peak (early) I_{Na} can contribute to a preferential abbreviation of the epicardial action potential. These alterations contribute to the electrophysiological phenotype of the long QT and Brugada syndromes, respectively. Agents that either reduce late I_{Na} or augment I_{Na} during the action potential notch can exert antiarrhythmic actions in these syndromes.

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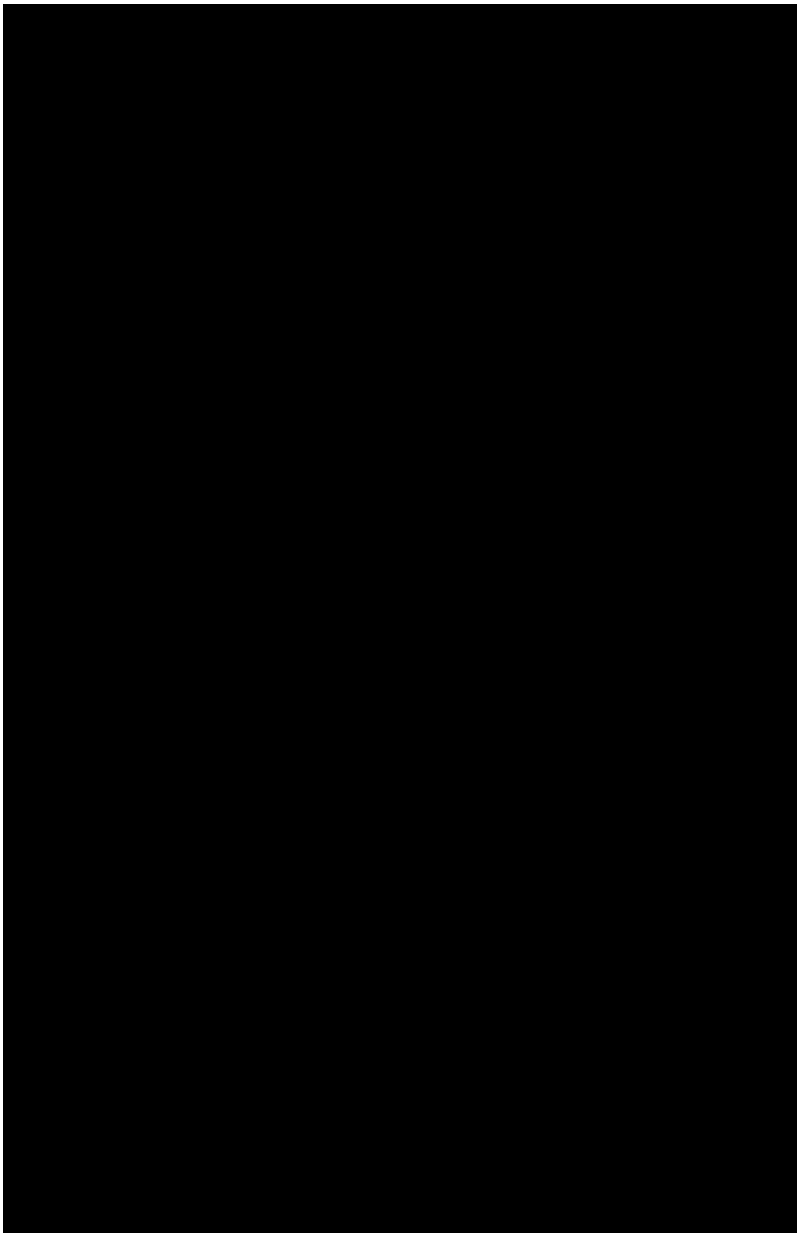

Figure 1.

Voltage gradients on either side of the M region are responsible for inscription of the electrocardiographic T wave. **Top:** Action potentials simultaneously recorded from endocardial, epicardial, and M region sites of an arterially perfused canine left ventricular wedge preparation. **Middle:** ECG recorded across the wedge. **Bottom:** Computed voltage differences between the epicardium and M region action potentials ($\Delta V_{M\text{-}Epi}$) and between the M region and endocardium responses ($\Delta V_{Endo\text{-}M}$). The center trace, the average of the two opposing voltage gradients, closely resembles the ECG. (Modified from Yan and Antzelevitch,[15] with permission.)

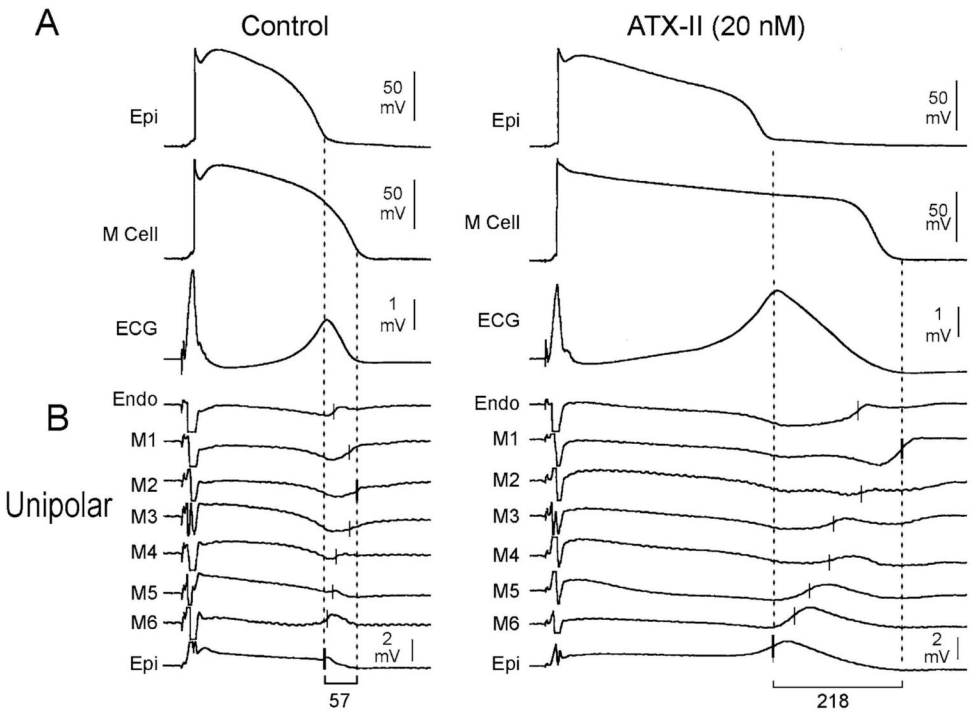

Figure 2.

ATX-II-induced augmentation of late I_{Na} amplifies transmural dispersion of repolarization in the coronary-perfused wedge preparation. Each panel shows: A: Transmembrane action potentials recorded from M (M2) and epicardial sites of a canine left ventricular wedge preparation together with a transmural ECG recorded across the bath (BCL of 2,000 ms) in the absence (left) and the presence (right) of ATX-II (20 nmol/L); B: Eight intramural unipolar electrograms recorded approximately 1.2 mm apart from endocardial (Endo), M (6 sites; M1-M6), and epicardial (Epi) regions (120-μm silver electrodes insulated except at the tip) inserted midway into the wedge preparation. Dashed vertical lines in the unipolar electrograms denote the maximum time of the first derivative (Vmax) of the T wave (local repolarization time). (Modified from Antzelevitch et al.,[68] with permission.)

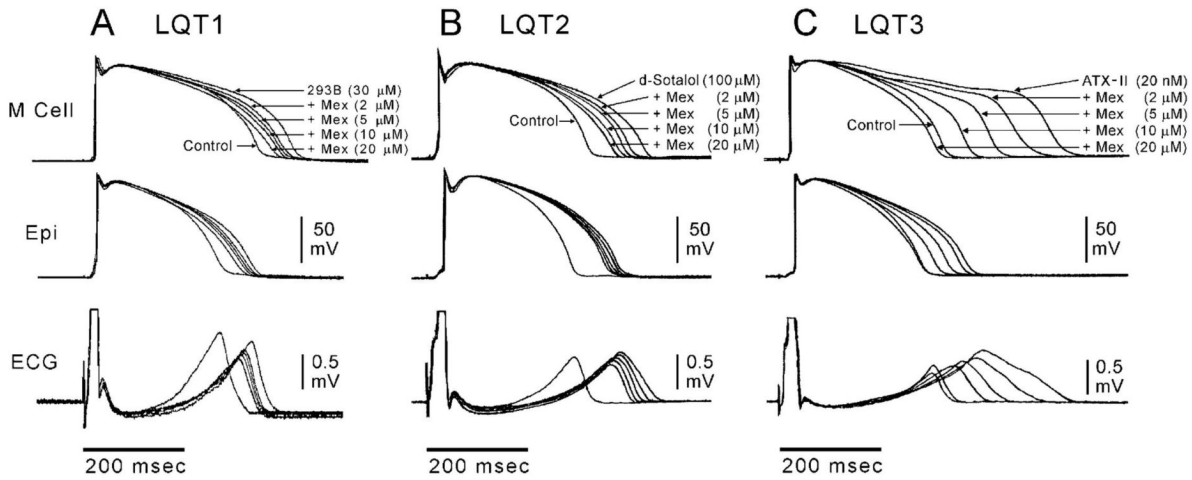

Figure 3.

Block of late I_{Na} with mexiletine reduces TDR in experimental models of the long QT syndrome. Each panel shows transmembrane action potentials recorded from M and epicardial (Epi) sites in canine left ventricular wedge preparations together with a transmural ECG recorded across the bath (BCL of 2,000 ms). Traces are recorded in the presence of the I_{Ks} blocker, chromanol 293B (LQT1), I_{Kr} blocker D-sotalol (LQT2), and late I_{Na} agonist, ATX-II (LQT3), plus increasing concentrations of mexiletine. Mexiletine produced a greater abbreviation of the M cell vs epicardial action potential at every concentration, resulting in a reduction in transmural dispersion of repolarization in all three LQTS models. (Modified from Shimizu and Antzelevitch,[34,35] with permission.)

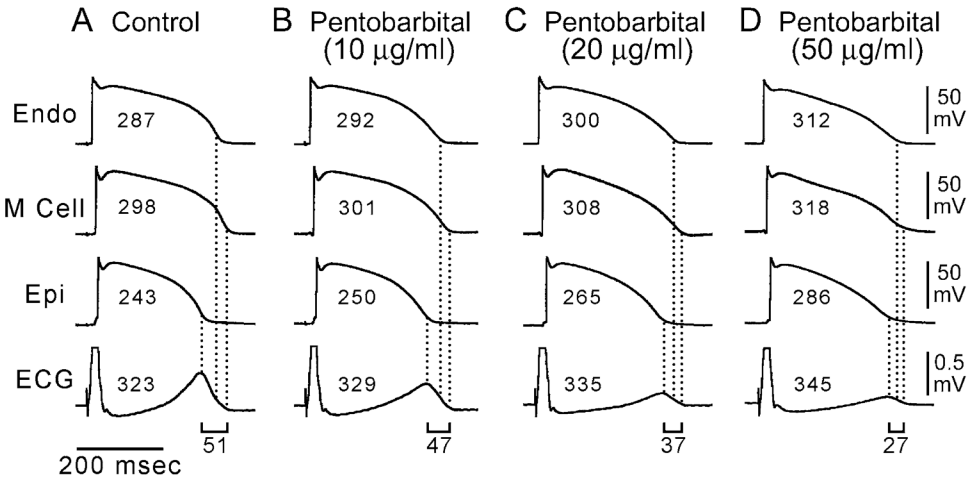

Figure 4.

Pentobarbital-induced QT prolongation but reduction in transmural dispersion of repolarization. Each panel shows transmembrane action potentials recorded from endocardial (Endo), M, and epicardial (Epi) cells in a canine left ventricular wedge preparation together with a transmural ECG recorded across the bath (BCL of 2,000 ms). Numbers in the action potentials denote APD_{90} values. Numbers above the ECGs denote the QT intervals. (Modified from Shimizu et al.,[52] with permission.)

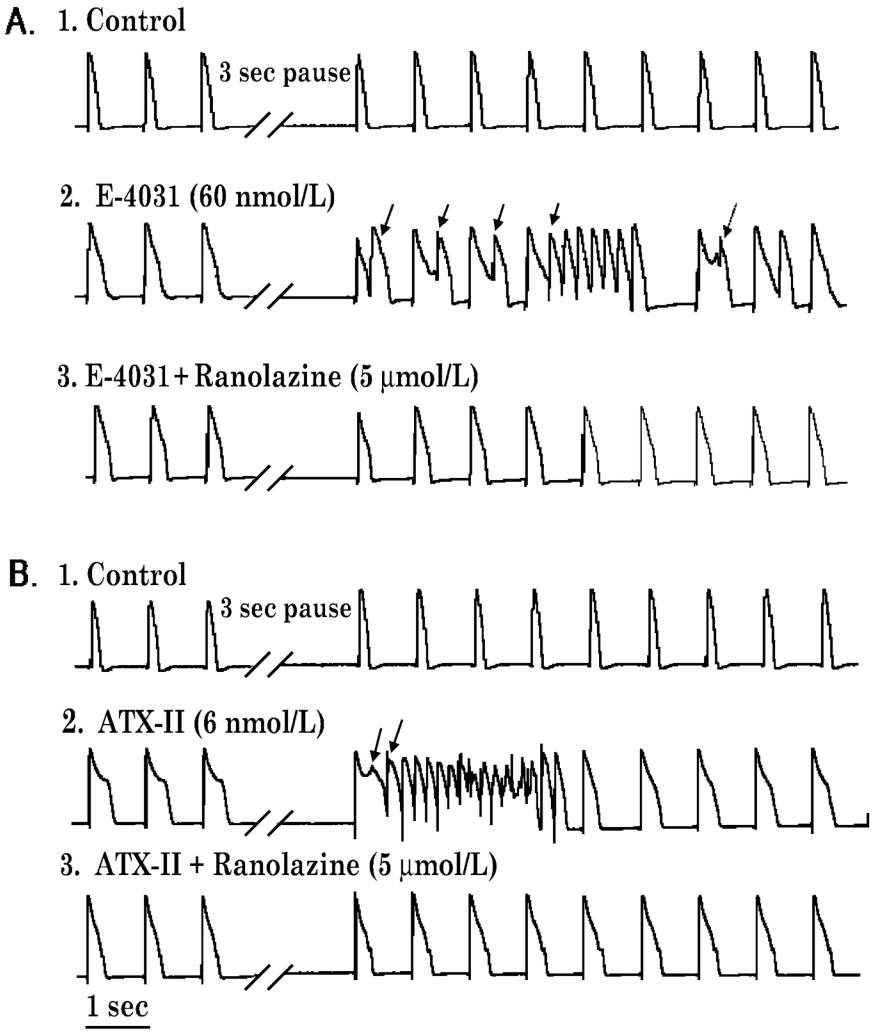

Figure 5.

Inhibition by ranolazine of pause-triggered early afterdepolarizations (EADs) and ventricular tachycardias (VTs) in the presence of either E-4031 (panel A) or ATX-9II (panel B) in a female rabbit isolated perfused heart paced at 1 Hz. Records 1-3 in each panel were obtained serially from the same heart; panels A and B represent different hearts. Representative monophasic action potentials (MAPs) were recorded before and after a three-second pause during (A1 and B1) control conditions (no drug) and during perfusion with (A2) E-4031 (60 nmol/L) alone, (A3) E-4031 (60 nmol/L) plus ranolazine (5 μmol/L), (B2) ATX-II (6 nmol/L) alone, or (B3) ATX-II (6 nmol/L) plus ranolazine (30 μmol/L). Arrows indicate EADs, EAD-triggered premature ventricular beats, and VTs ranolazine suppressed EADs and VTs induced in the presence of E-4031 (panel A3), and ATX-II (panel B3). Similar results were obtained from five and two additional hearts treated with either E-4031 or ATX-II, respectively (see text).