Cellular Basis for Arrhythmogenesis in an Experimental Model of the SQT1 Form of the Short QT Syndrome

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Abstract

Background—Short QT syndrome (SQT) is a primary electrical disease associated with a high risk of sudden cardiac death. A gain-of-function in I_{Kr}, due to a mutation in *KCNH2*, underlies SQT1.

Objective—To examine the cellular basis for arrhythmogenesis in an experimental model of SQT1 created using PD-118057, a novel I_{Kr} agonist.

Methods—Transmembrane action potentials were simultaneously recorded from epicardial, M and endocardial regions of arterially-perfused canine left ventricular (LV) wedge preparations, together with a pseudo-ECG.

Results—PD-118057 (10 µmol/L) abbreviated QT interval from 267±4 to 232±4 ms and increased transmural dispersion of repolarization (TDR) from 33.7±2.0 to 49.1±3.1 ms ($p<0.001$). T wave amplitude increased from 18.0±1.4 to 23.1±1.7% of R wave amplitude ($p=0.027$). Reversing the direction of activation of the LV wall (epicardial pacing) resulted in an increase in QT interval from 269±5 to 282±5 ms and increase in TDR from 34.1±2.0 to 57.6±3.3 ms ($p<0.001$) under baseline conditions. PD-118057 abbreviated the QT interval from 282±5 to 258±5 ms and produced a proportional decrease in effective refractory period (ERP). TDR increased from 57.6±3.3 to 77.6 ±4.3 ms ($p<0.001$). Polymorphic ventricular tachycardia (pVT) was induced in 10 out of 20 preparations with a single S2 applied to epicardium. Quinidine (10 µmol/L) increased the ERP and QT interval, did not significantly alter TDR, and prevented induction of pVT in 5/5 preparations.

Conclusion—Our results suggest that a combination of ERP abbreviation and TDR amplification underlie the development of pVT in SQT1 and that quinidine prevents pVT principally by prolonging ERP.

Keywords

arrhythmias; electrophysiology; antiarrhythmia drugs; inherited syndromes; sudden cardiac death; pharmacology

INTRODUCTION

Short QT syndrome (SQTS) is a recently recognized, inherited, primary electrical cardiac syndrome characterized by abnormally short QTc interval (<360 ms) and an increased

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Potential Conflicts of Interest: None

propensity for development of atrial and ventricular tachyarrhythmias, including sudden cardiac arrest.[1–5] It is a genetically heterogeneous disease and thus far mutations of 5 different genes encoding cardiac ion channels have been identified in familial or sporadic cases. Gain-of-function mutations in *KCNH2*[6], *KCNQ1*[7] and *KCNJ2*[8] genes encoding for the rapidly and slowly activating potassium channel currents (I_{Kr} and I_{Ks}) and the inward rectifier potassium channel current (I_{K1}) give rise to the SQT1, SQT2 and SQT3 forms of SQTS. Our group recently described loss-of-function mutations in *CACNA1c* and *CACNB2b* genes encoding the α1 and β subunits of cardiac L-type calcium channels. This clinical phenotype, characterized by a new clinical entity consisting of a combined Brugada-like ST segment elevation and short QT intervals, has been designated SQT4 and SQT5.[9]

The ECG in SQTS is characterized by shorter than normal QT intervals (QTc<360 ms), short or absent ST segment, and in some cases, tall peaked T waves and augmented T_{peak}-T_{end} intervals. The rate dependence of QT interval or QT/RR interval relationship has been reported to be less steep than normal.[4, 5, 10] Electrophysiological testing in patients with SQTS shows marked abbreviation of atrial and ventricular refractory period. Polymorphic ventricular tachycardia (pVT) is readily inducible in a large fraction of affected individuals.[3, 10]

Due to the unavailability of I_{Kr}, I_{Ks} or I_{K1} agonists, the only previously developed models of short QT syndrome were ones in which the activator of the ATP-sensitive potassium current (I_{K-ATP}), pinacidil, was used to augment outward current in canine left ventricular wedge preparations[11] or Langendorff-perfused rabbit hearts.[12] The present study involves the development and characterization of a specific model of SQT1 made possible by the recent availability of a selective I_{Kr} agonist, PD-118057.[13] Available data indicate that PD-118057 binds to the I_{Kr} channel directly and increases its open channel probability without affecting the voltage-dependence and kinetics of gating parameters.

The SQT1 variant of SQTS is due to an N588K mutation in *KCNH2*, the gene that encodes the α subunit of the I_{Kr} channel. The mutation abolishes rectification of I_{Kr} current at positive voltages within the voltage range of the action potential, leading to a marked gain of function. We used the novel I_{Kr} agonist PD-118057 to mimic this gain-of-function and thus to examine the cellular basis for the electrocardiographic and arrhythmogenic manifestations of this model of SQT1. Our study also probes the mechanism underlying the antiarrhythmic effects of quinidine under SQT1 conditions.

METHODS

All experiments were performed in conformance with the guidelines of the Institutional Animal Care Committee. The left ventricular wedge was prepared as previously described.[11, 14] Transmembrane action potentials were recorded from epicardial (Epi), subendocardial (M) and endocardial (Endo) regions of the wedge with the use of floating microelectrodes. A transmural pseudo-ECG was recorded using 2 AgCl half cells placed approximately 1 cm from the epicardial (+) and endocardial (−) surfaces of the preparation and along the same axis as the transmembrane recordings. QT interval was defined as the time interval between QRS onset and the point at which the line of maximal downslope of T wave crossed the isoelectric line. T_{peak}-T_{end} interval was defined as the time interval between peak of the T wave and the point at which the line of maximal downslope of T wave crossed the isoelectric line. TDR was defined as the difference between the longest and the shortest repolarization times (activation time plus action potential duration (APD) measured at 90% repolarization (APD_{90})) of transmembrane action potentials recorded across the wall (typically M cell minus epicardial cell repolarization time).

The basic stimulus (S_1) was delivered to endocardium at a BCL of 2000 ms. A premature stimulus (S_2) was delivered to the epicardium at progressively briefer S_1–S_2 intervals until the refractory period was reached in an attempt to induce pVT. A similar protocol was repeated after switching the basic stimulus (S_1) to epicardium as reversal of direction of activation of the left ventricle has been shown to amplify TDR and facilitate induction of pVT.[15] The effective refractory period (ERP) was defined as the longest S_1–S_2 interval at which S_2 failed to capture. Ventricular tachycardia (VT) inducibility was examined under each condition (control, PD-118057, + Quinidine).

Drugs

PD-118057, a kind gift of Pfizer Pharmaceuticals, was prepared as a 10mmol/L stock in 100% Dimethyl Sulfoxide (DMSO) and added to Tyrode's solution to final concentration of 10 µmol/ L. Quinidine was prepared as a 20mmol/L stock in Millipore water and added to Tyrode's solution to achieve a final concentration of 10 µmol/L.

Statistical analysis

Statistical analysis was performed using a paired t-test or repeated measures analysis of variance (ANOVA) followed by Tukey's test, as appropriate. All data are reported as mean ±SEM.

RESULTS

Effect of PD-118057 on QT interval, TDR, T_{peak}-T_{end} and APD_{90} (Endo Stimulation)

Figure 1 illustrates the effect of the I_{Kr} agonist PD-118057 to abbreviate the QT interval and amplify transmural dispersion of repolarization (TDR). Shown are action potentials simultaneously recorded from epicardial and M cells of a canine left ventricular wedge preparation, together with a pseudo-ECG. Figure 2 summarizes the effects of PD-118057 on APD_{90} as recorded in 24 wedge preparations. PD-118057 abbreviated the APD_{90} of epicardial and M cells leading to abbreviation of QT interval. QT interval abbreviated from 267.2±4.0 to 232.3±4.1 ms (n=20, $p<0.001$)(Fig. 3A). Preferential abbreviation of the epicardial action potential led to an increase of TDR from 33.7±2 to 49.1±3.1 and T_{peak}-T_{end} from 37.7±1.2 to 52.6±2.7 (n=20, $p<0.001$, Figure 3A). The amplitude of the T wave increased from 18.0±1.4 to 23.1±1.7% of the R wave (n=20, $p<0.05$).

Effect of reversal of direction of activation of the left ventricular wall (Epi Stimulation)

Figure 4 illustrates the effect of reversing the direction of activation of the left ventricular wall. When basic stimulation (S_1) was shifted from endocardium to epicardium, the epicardial cells activated earlier and repolarized earlier, whereas the M cells activated later and repolarized later. As a consequence, the QT interval prolonged from was 291 to 311 ms and TDR increased from 32 to 64 ms. Addition of PD-118057 (10 µmol/L) abbreviated the QT interval from 311 to 255 ms and increased TDR from 64 to 85 ms.

Composite data from 16 similar experiments are summarized in Table 1 and Figure 3B. Reversing the direction of activation across the ventricular wall by shifting basic stimulation (S_1) from endocardium to epicardium caused an increase of the QT interval from 269.2±4.8 to 282.2±5.1, TDR from 34.1±2.0 to 57.7±3.3 and T_{peak}-T_{end} from 37.3±1.4 to 63.1±2.3 under baseline conditions (BCL=2000, n=16, $p<0.001$). Addition of PD-118057(10µmol/L) abbreviated the QT interval from 282.2±5.1 to 258.1±5.4 and increased TDR and T_{peak}-T_{end} from 57.7±3.3 to 77.6±4.3 and 63.1±2.3 to 86.1± 2.6, respectively (BCL=2000 ms, n=16, $p<0.001$). PD-118057 reduced ventricular ERP from 203.1±4.7 to 156.3±4.2 (BCL=2000 ms, n=16, $p<0.001$).

I_{Kr}-agonist-induced arrhythmogenesis

With basic stimulation (S_1) applied either to epicardium or endocardium, a premature stimulus (S_2) was delivered to epicardium at progressively briefer S_1–S_2 intervals in an attempt to induce pVT. When S_1 was applied to endocardium, programmed electrical stimulation failed to induce pVT in all 20 preparations, under control conditions and following PD-118057. With basic stimuli applied to epicardium, pVT could not be elicited under baseline conditions but was successfully induced in 10 out of 20 preparations following PD-118057 (Table 1).

Figure 5 illustrates an example of pVT induced with both S_1 and S_2 applied to epicardium in the presence but not absence of PD-118057. ERP abbreviated from 220 to 160 ms following exposure to PD-118057.

Effect of Quinidine

The effect of quinidine was evaluated in 5 preparations in which pVT could be induced and in 2 preparation in which pVT was not induced after PD-118057. Addition of quinidine(10µmol/L) to the coronary perfusate containing PD-118057 prolonged the QT interval from 266.9±9.9 to 319.3±9.7 (n=7, $p<0.001$), but TDR remained largely unchanged (89±6.4 vs. 83.4±5.8, n=7) (Figure 6, Table 1). Quinidine prolonged the ERP from 154.2±4.2 to 214.2±9.7 (n=7, $p<0.001$, Figure 6, Table 1). Programmed electrical stimulation failed to induce pVT in all 5 preparations in which pVT was elicited prior to quinidine (Figure 5, Table 1).

DISCUSSION

To our knowledge this is the first experimental model of short QT syndrome in which the affected ion channel current is one previously shown to underlie a congenital form of the syndrome. The model recapitulates the electrocardiographic and arrhythmic manifestations of SQT1 and provides an understanding of the cellular basis for these changes utilizing the coronary-perfused LV wedge preparation. This preparation has been successfully used to reproduce the electrocardiographic and arrhythmic manifestations of long-QT syndrome, Brugada syndrome and catecholaminergic VT.[16] A gain-of-function mutation in *KCNH2*, the gene that encodes the α-subunit of the I_{Kr} channel, has been shown to underlie SQT1[6] and we used PD-118057, a novel I_{Kr} agonist, to mimic this gain of function. PD-118057 at a concentration of 10 µmol/L has been shown to increase peak tail current of I_{Kr} by 111.1 % in human embryonic kidney cells and abbreviate QT interval by 25% in the isolated rabbit ventricle.[13]

Our principle findings are that: 1) PD-118057(10 µmol/L) abbreviates APD, QT interval, ERP and increases T_{peak}-T_{end} interval and TDR; 2) Preferential abbreviation of epicardial APD is responsible for the increase in TDR and T_{peak}-T_{end} interval; 3) Reversal of the direction of activation of the left ventricular wall by pacing from the epicardium instead of the endocardium increases TDR and exaggerates the effects of the I_{Kr} agonist to increase TDR, thus facilitating the induction of pVT; 4) Quinidine (10 µmol/L) prevents the induction of pVT by reversing the effect of PD-118057 on QT interval and ERP, but not on TDR. These results suggest that a gain of function of I_{Kr} predisposes to pVT via an abbreviation of ERP as well as an augmentation of TDR.

PD-118057 is thought to increase I_{Kr} by increasing open channel probability.[13] The drug showed no major effect on I_{Na}, I_{Ca-L}, I_{K1}, or I_{Ks}.[13] The increase in net repolarizing current during phases 2 and 3 abbreviates action potential duration and hence QT interval. PD-118057 induces preferential abbreviation of epicardial APD as compared to M cell and endocardial APD, leading to increase in T_{peak}-T_{end} interval and TDR. The ionic basis of preferential abbreviation of epicardial cell action potential is not clear but may be related to the fact that

epicardium has the strongest repolarizing forces under baseline conditions. Interestingly, in rabbit left ventricular wedge preparations, Zhou at el [13] demonstrated preferential abbreviation of the endocardial APD in response to PD-118057.

Previous studies conjectured that a gain of function in I_{Kr} would have little effect on the Purkinje action potential because little I_{Kr} is expected to activate at the relatively negative plateau potentials encountered in action potentials recorded from isolated Purkinje myocytes. [17] Our results clearly indicate that a gain of function of I_{Kr} produces an abbreviation of the Purkinje fiber action potential comparable to that observed in the ventricular myocardium.

Our data indicate that PD-118057 abbreviates ERP and increases TDR in the ventricular myocardium. The critical role of TDR as substrate for functional re-entry has been demonstrated in experimental models of long-QT syndrome, Brugada syndrome as well as in the short QT syndrome. [16] Whereas increased TDR facilitates unidirectional block and the initiation of reentry, the abbreviated ERP reduces the wavelength (product of ERP and conduction velocity) and thus facilitates maintenance of reentry. When basic stimuli are applied to the endocardium, the increase in TDR was insufficient to permit induction of pVT. Shifting basic stimulation to epicardium increased TDR to 57.7±3.3 ms (71% increase) under baseline conditions and to 77.6±4.3 ms in the presence of the I_{Kr} agonist. The arrhythmogenic substrate created under these conditions permitted induction of pVT in 50% (10 out of 20) of preparations. The arrhythmogenic effect of reversing the direction of activation of the LV wall by pacing from epicardium instead of endocardium, has been demonstrated previously under a variety of conditions. [14, 16, 18, 19]

Quinidine (10 µmol/L) completely reversed the effect of PD-118057 on QT interval and ERP. In the presence of quinidine, the increase in TDR persisted but pVT could no longer be induced. Quinidine is known to block sodium channel current (I_{Na}), I_{Kr}, I_{Ks}, I_{K1}, I_{K-ATP} and the transient outward current (I_{to}). Through its action on K currents, it prolongs APD and ERP, thus reversing the effect of PD-118057 and leading to an increase in wavelength. Maintenance of reentrant wavefront requires that the wavelength be less than pathlength. Our data suggest that an increase in wavelength is a plausible explanation for the antiarrhythmic effect of quinidine in our model of SQT1. The inability of quinidine to alter TDR likely stems from the fact that quinidine, in the absence of PD-118057, causes an increase in TDR. [20]

Our results are consistent with a previously reported model of SQTS in which QT abbreviation was achieved by activation of I_{K-ATP} using pinacidil. In left ventricular wedge preparation, pinacidil caused preferential abbreviation of M cell and endocardial APD leading to increase in TDR along with abbreviation of ERP and QT interval and inversion of the T wave. [11] The threshold of TDR that permitted induction of pVT was 50 ms, significantly lower than in the present model.

Milberg et al. [12] reported another experimental model of SQTS induced by pinacidil using a Langendorff-perfused rabbit heart. With simultaneous recording of eight monophasic action potentials (MAP), they demonstrated that pinacidil causes a concentration-dependent decrease in MAP and ERP and an increase in total and interventricular dispersion of repolarization, thereby increasing ventricular vulnerability to pVT. The effects of pinacidil were completely reversed by quinidine, but not sotalol or flecainide. In contrast to the present model, quinidine reversed the effect of pinacidil to increase dispersion of repolarization.

Clinical Implications

The present model is mechanistically similar but phenotypically different from the pinacidil models of SQTS in that it more closely mimics the gain-of-function mutation in *KCNH2*. [11, 12] The ECG phenotype created by PD-118057 closely resembles the ECG observed in patients

with SQT1. Along with abbreviation of QT interval, the model recapitulates the decrease in length of the ST segment, the increase in T_{peak}-T_{end} interval and increase in amplitude of the T wave observed clinically. Data recorded from telemetry and implantable cardioverter defibrillators (ICDs) in patient with SQTS suggest that closely coupled premature ventricular complexes initiate episodes of pVT.[21–23] Electrophysiological studies in these patients show marked abbreviation of ventricular ERP and programmed electrical stimulation inducibility of pVT in 61% of patients using two or three premature stimuli.[3, 10] Consistent with these clinical findings, our experimental model displays reduced ventricular ERP and induction of pVT with closely coupled extrasystoles. Quinidine has been proposed as drug of choice for SQT1 as an adjunct to ICD. Treatment with quinidine in SQT1 patients increases the QT interval and ventricular effective refractory period and renders ventricular arrhythmia noninducible.[10, 24] Proven efficacy of quinidine and failure of class IC and III antiarrhythmic drugs in SQT1 is primarily related to a secondary effect of the N588K mutation in *KCNH2*. The N588K missense mutation induces +90 mV shift in the voltage-dependence of inactivation of HERG channels. The inactivated state of the channel normally stabilizes the interaction of the channel with most I_{Kr} blockers.[6, 17] Loss of inactivation accounts for the ineffectiveness of most I_{Kr} blockers in N588K KCNH2 channels. Quinidine is effective in SQT1 by the virtue of its interaction with the open state of the channel, whereas drugs like sotalol and dofetilide that have a higher affinity for the inactivated state of channel are largely ineffective.

I_{Kr} agonists have attracted the interest of the pharmaceutical industry because of their ability to suppress arrhythmogenesis encountered under long QT conditions. PD-118057 has been shown to be effective in reversing the long QT intervals and suppressing early afterdepolarization activity induced by I_{Kr} blockers.[13] The present study highlights the proarrhythmic potential of I_{Kr} agonists and provides additional support for the arrhythmogenic potential QT abbreviation. Our data also extend the proarrhythmic potential of reversing the direction of activation of the ventricular wall to include the short QT syndrome. This finding has direct relevance to biventricular pacing and resynchronization therapy, commonly used in the treatment of congestive heart failure.

Limitations

As with any experimental study, extrapolation of our results to the understanding of the clinical syndrome must be approached with caution. While PD-118057 is effective in augmenting I_{Kr}, it does not precisely mimic the gain of function produced by the mutations in *KCNH2* thus far uncovered. This notwithstanding, we take comfort in the fact that the model reproduces many of the characteristics of the clinical syndrome, as well as the response to drugs such as quinidine.

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Glossary

Abbreviations

ANOVA
analysis of variance

APD
action potential duration

APD$_{90}$
APD measured at 90%

BCL
basic cycle lengths

DMSO
Dimethyl Sulfoxide

Epi
epicardial

Endo
endocardial

ERP
effective refractory period

ICDs
implantable cardioverter defibrillators

I$_{K1}$
inward rectifier potassium channel current

I$_{K-ATP}$
ATP-sensitive potassium current

I$_{Kr}$
rapidly activating potassium channel currents

I$_{Ks}$
slowly activating potassium channel currents

I$_{to}$
transient outward current

M
subendocardial

MAP
monophasic action potentials

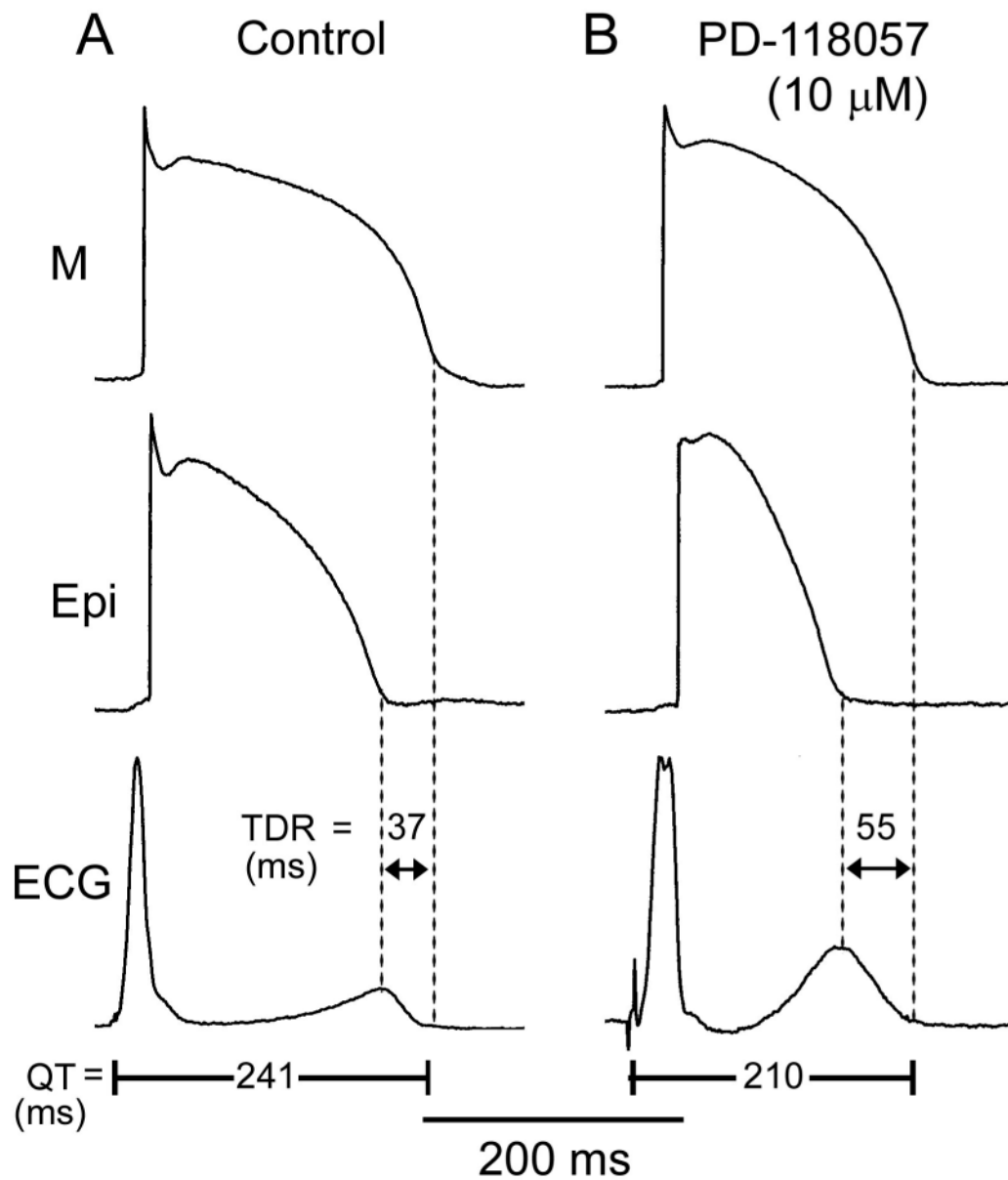**pVT**
Polymorphic ventricular tachycardia

SQTS

Short QT syndrome

TDR

transmural dispersion of repolarization

VT
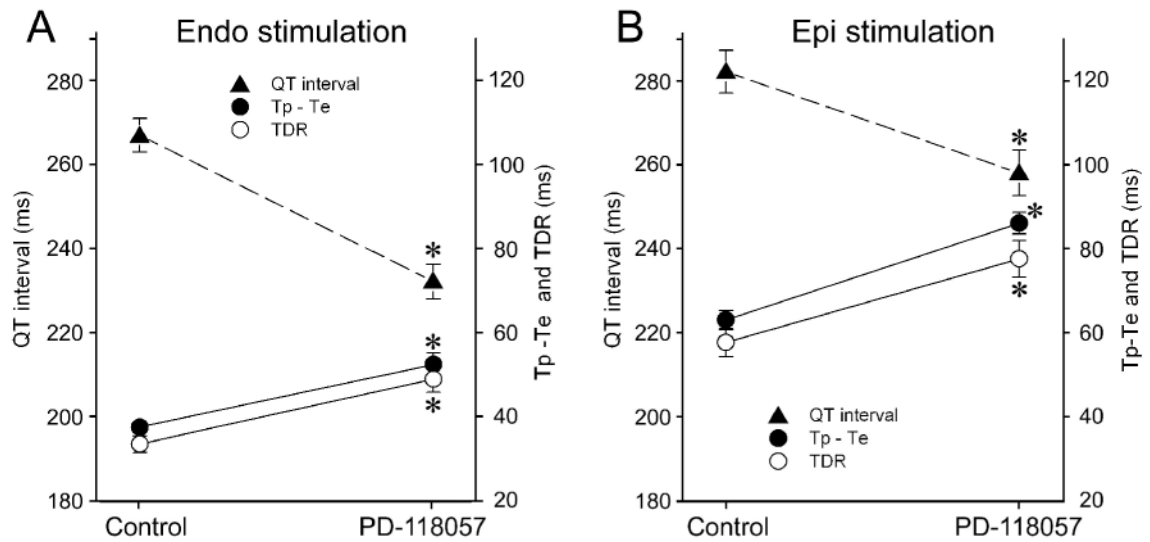
ventricular tachycardia

Figure 1.
The effect of an I_{Kr} agonist to abbreviate action potential duration and QT interval and augment transmural dispersion of repolarization (TDR). **A**: Control. **B**: PD-118057 (10 µmol/L). Each panel shows transmembrane action potentials simultaneously recorded from an epicardial (Epi) and a deep subendocardial M-cell in an arterially perfused LV wedge preparation, together with a pseudo-ECG. Basic cycle length (BCL) =2000 ms.
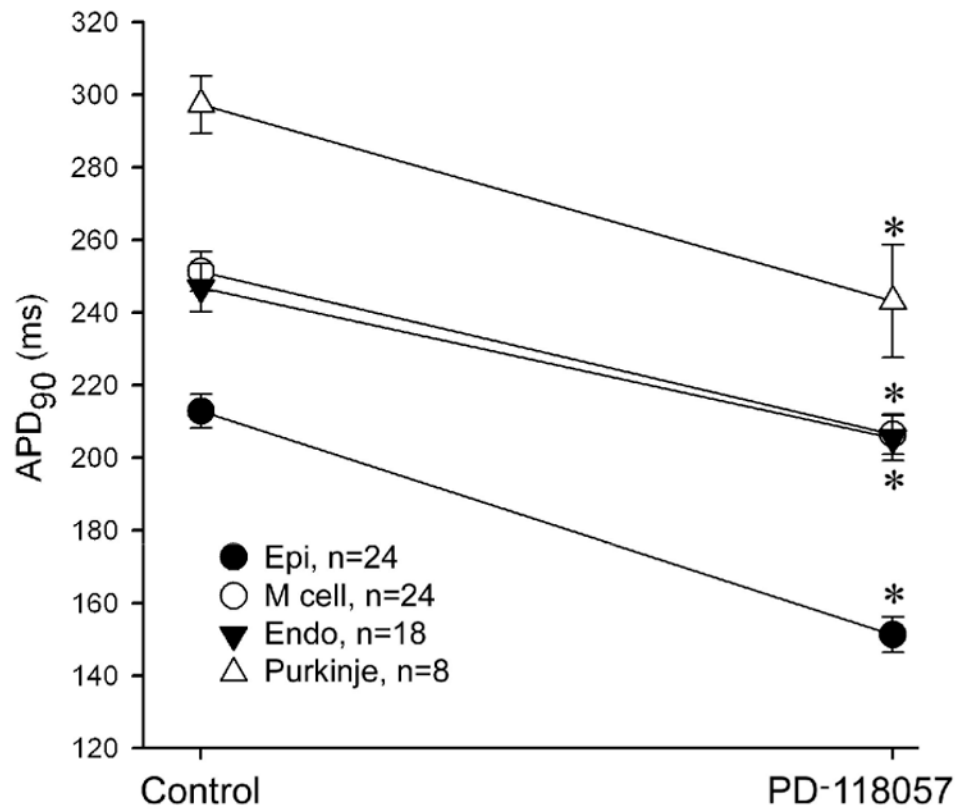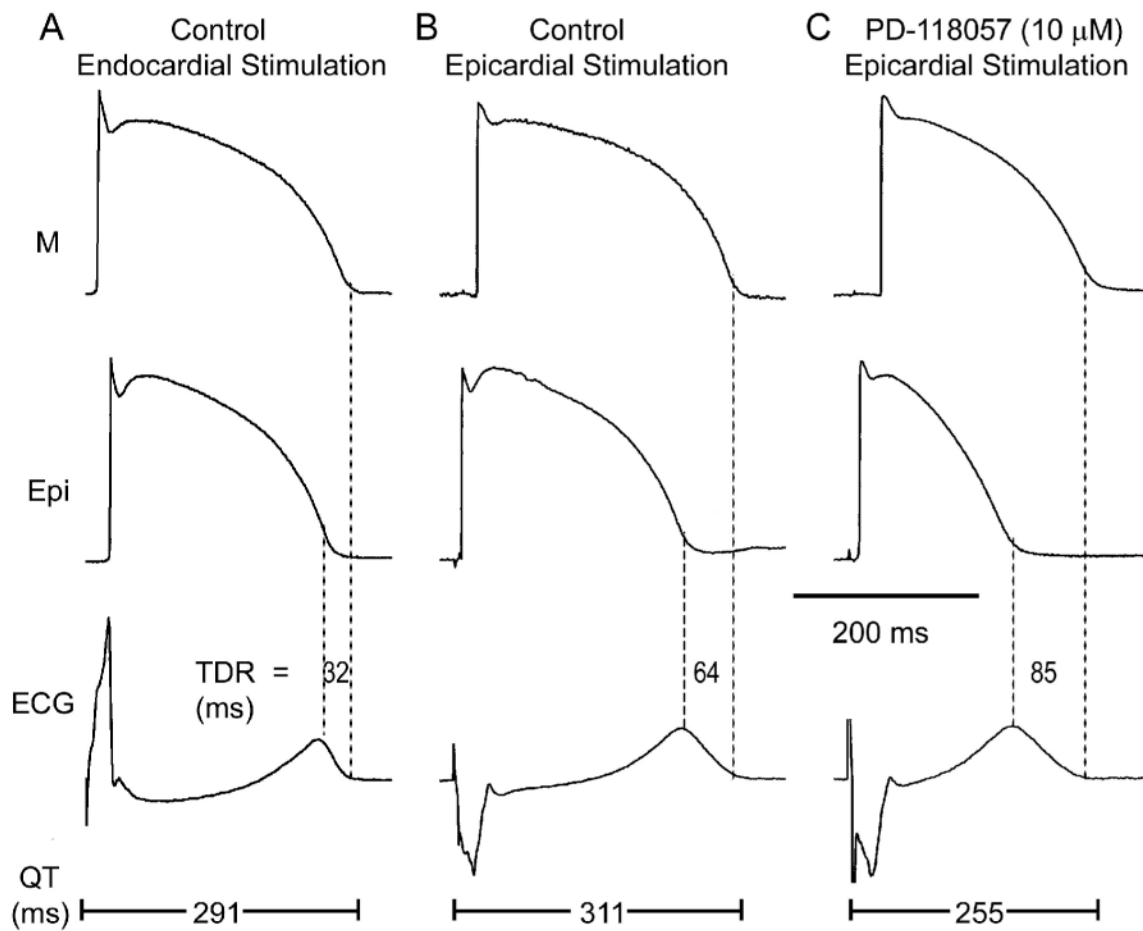
Figure 2.
Effect of the I_{Kr} agonist PD-118057 10 µmol/L on APD_{90} of epicardial (Epi), M, endocardial (Endo) and Purkinje cell action potentials recorded from arterially-perfused LV wedge preparations. BCL=2000 ms. Endo Stimulation. * p<0.001, PD-110857 vs Control.

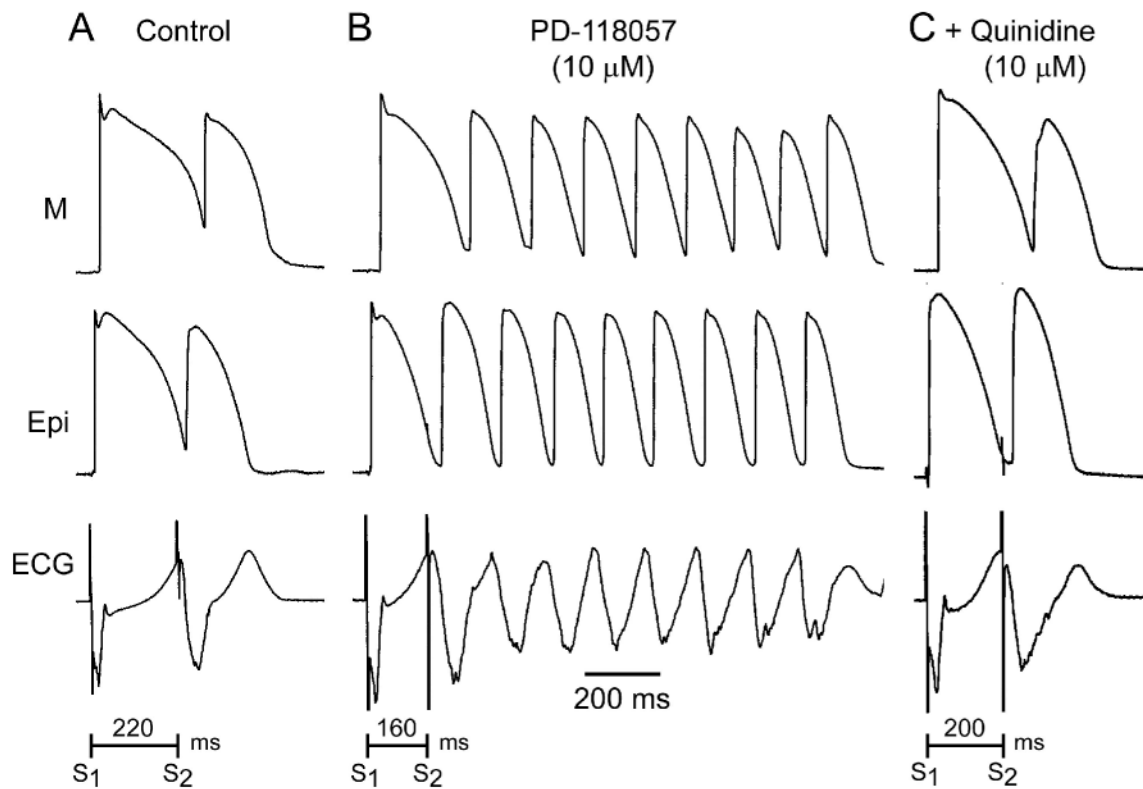**Figure 3.**
Composite data of the effects of PD-118057 10 µmol/L on QT, TDR, T_{peak}-T_{end} interval when basic stimuli (S_1) is delivered from endocardium (A. Endo stimulation, n= 20) or from epicardium (B. Epi stimulation, n=16). Shifting S_1 from Endo to Epi increased QT, TDR and T_{peak}-T_{end}. PD-118057 abbreviated QT interval and increased TDR and T_{peak}-T_{end} in both cases. BCL= 2000 ms. * p <0.001, PD-118057 vs Control.
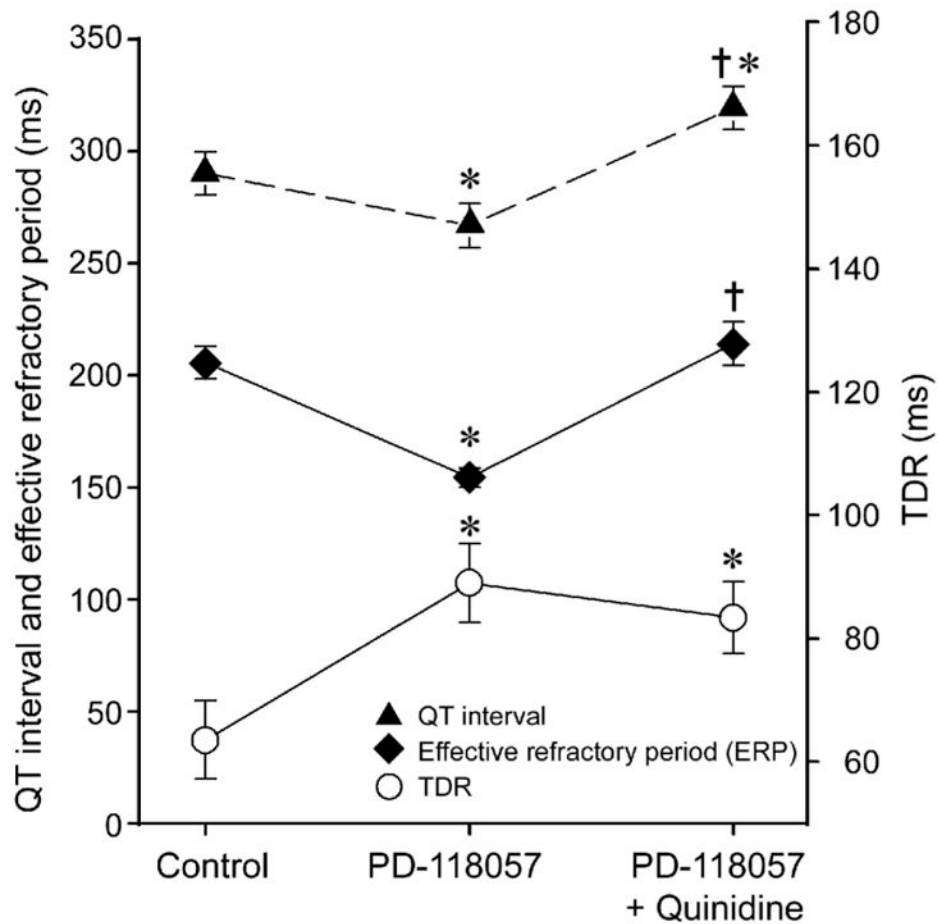
Figure 4.
Effect of reversal of the direction of activation of the left ventricular wall on action potential morphology, QT interval and transmural dispersion of repolarization (TDR) in the absence and presence of the I_{Kr} agonist. **A**: Control (Endocardial stimulation). **B**: Control (Epicardial stimulation). **C**: Effect of PD-118057 (10μM; Epicardial stimulation). BCL = 2000 ms.

Figure 5.
I_{Kr} agonist-induced short QT and polymorphic ventricular tachycardia (pVT). **A**: Control **B**: PD-118057 (10 µmol/L). **C**: PD-118057 (10 µM)+ quinidine (10 µM). Programmed electrical stimulation applied to the LV wedge preparation induced pVT when the QT interval and the effective refractory period were abbreviated with the I_{Kr} agonist, but not under baseline conditions or after the addition of quinidine. BCL = 2000 ms.

Figure 6.
Quinidine (10 µmol/L) reverses the effects of PD-118057 to abbreviate QT interval and effective refractory period, but not its effects to augment transmural dispersion of repolarization (TDR). Basic cycle length = 2000 ms. Epicardial stimulation. * $p<0.05$ vs. Control. † $p<0.001$ vs. PD-118057.

Table 1

Effect of the I_{Kr} agonist PD-118057 on QT interval, TDR, pVT inducibility in the absence and presence of quinidine

	QT interval (ms)		TDR (ms)		pVT	
	Endo Stimulation	Epi Stimulation	Endo Stimulation	Epi Stimulation	Endo Stimulation	Epi Stimulation
Control (n=16–20)	269.2±4.8	282.2±5.1*	34.1±2.0	57.7±3.3*	0/20	0/20
PD-118057 (n=16–20)	232.3±4.1†	258.1±5.4*†	46.9±3.7†	77.6±4.3*†	0/20	10/20
Control (n=7)	277.7±8.8	290.2±9.6*	36.4±4.3	63.6±6.4*	0/7	0/7
PD-118057 (n=7)	242.9±8.1†	266.9±9.9*†	55.1±5.2†	89.0±6.4*†	0/7	5/7
PD-118057 + Quinidine (n=7)	298±11.2‡	319.3±9.7*†‡	46.9±3.5	83.4±5.8*†	0/7	0/7

pVT = polymorphic ventricular tachycardia. TDR = transmural dispersion of repolarization. BCL = 2000 ms.

*
$p<0.05$ vs. Endo Stimuli

†
$p<0.05$ vs. Control

‡
$p<0.05$ vs. PD-118057.