Published in final edited form as:

J Cardiovasc Electrophysiol. 2009 January ; 20(1): 85–92. doi:10.1111/j.1540-8167.2008.01273.x.

Membrane Time Constant During Internal Defibrillation Strength Shocks in Intact Heart:

Effects of Na⁺ and Ca²⁺ Channel Blockers

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Abstract

Na⁺ and Ca²⁺ Channel Blockers on Kinetics of Shock-Induced Response.

Introduction—We assessed defibrillation strength shock-induced changes of the membrane time constant (τ) and membrane potential (ΔV_m) in intact rabbit hearts after administration of lidocaine, a sodium (Na⁺) channel blocker, or nifedipine, a L-type calcium (Ca²⁺) channel blocker.

Methods and Results—We optically mapped anterior, epicardial, electrical activity during monophasic shocks (± 100 , ± 130 , ± 160 , ± 190 , and ± 220 V; 150 μ F; 8 ms) applied at 25%, 50%, and 75% of the action potential duration via a shock lead system in Langendorff-perfused hearts. The protocol was run twice for each heart under control and after lidocaine (15 μ M, n = 6) or nifedipine (2 μ M, n = 6) addition. τ in the virtual electrode area away from the shock lead was approximated with single-exponential fits from a total of 121,125 recordings. The same data set was used to calculate ΔV_m . We found (1) Under all conditions, there is inverse relationship between τ and ΔV_m with respect to changes of shock strength, regardless of shock polarity and phase of application: a stronger shock resulted in a larger ΔV_m , which corresponded to a smaller τ (faster cellular response); (2) Lidocaine did not cause appreciable changes in either τ or ΔV_m versus control, and (3) Nifedipine significantly increased both τ and ΔV_m in the virtual cathode area; in contrast, in the virtual anode area, this effect depended on the phase of shock application.

Conclusion— τ and ΔV_m are inversely related. Na⁺ channel blocker has minimal impact on either τ or ΔV_m . Ca²⁺ blocker caused polarity and phase-dependent significant changes in τ and ΔV_m .

Keywords

membrane time constant; transmembrane potential; defibrillation shock; lidocaine and nifedipine

Introduction

The mechanism of defibrillation remains poorly understood. It has been shown that highly nonuniform shock-induced transmembrane potential changes (ΔV_m) in the heart are a critical factor in determining the success or failure of defibrillation.¹ Shock-induced ΔV_m have been extensively characterized in the cultured strands of myocytes,^{2–6} isolated myocytes,^{7–10} cardiac tissue,^{11–14} and intact hearts.^{15,16} Roles of ionic currents and channel blockers on ΔV_m have also been investigated in cell culture² and single myocytes.¹⁷

The membrane time constant (τ) can be derived from the shock-induced ΔV_m by fitting it to a resistor-capacitor network. τ is useful for optimizing and for predicting the efficiency of defibrillation waveforms.¹⁸ Theoretical modeling has been commonly used to assess τ .¹⁹⁻²¹ There are limited reports of assessments of τ in cardiac tissue and whole heart preparations.^{11,22,23} However, no data on shock-induced changes in τ and in colocalized ΔV_m in intact hearts under Na^+ and Ca^{2+} channel blockers are available. Such data are important to understanding τ changes in response to defibrillation strength shocks, as most patients with implantable cardioverter defibrillators (ICD) receive adjunctive pharmacologic therapies such as ionic channel blockers.²⁴ The information gained from the measurement of τ under channel blockers can further serve as an important basis for validating and refining various modeling efforts for defibrillation.

In this study, we set out (1) to quantify the effects of lidocaine, a selective Na^+ channel blocker or nifedipine, a selective Ca^{2+} channel blocker on τ during defibrillation strength shocks applied by a coil electrode in the right ventricle (RV) of the intact heart, as in clinical settings and (2) to elucidate the relationship between τ and the variables of ΔV_m , shock strength, shock polarity, and phase of shock application under conditions of controls and ionic channel blockers.

Methods

The experimental protocol was approved by the Institutional Animal Care and Use Committee of Cleveland Clinic. All animals used in this study received humane care in compliance with the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals*.

Experimental Preparation

Isolated intact rabbit hearts ($n = 17$) were Langendorff-perfused with modified Tyrode solution.^{15,23,25,26} Cytochalasin D (Cyto D, 20 μM , Sigma) was used to eliminate the motion artifact caused by muscle contraction.²⁷ We have reported that compared with 2, 3-butanedione monoxime (15 mM), Cyto D at 20 μM caused much less alternation of action potential (AP) shape or AP duration (APD) in rabbit hearts.²⁸ A 1 cm coil shock electrode was placed in the RV and the return electrode was placed posterior to heart in the perfusion chamber filled with modified Tyrode solution. A photograph of the preparation is shown in Figure 1A.

Staining with Potentiometric Dye

To record electrical activity, the heart was stained with the potential-sensitive dye di-4-ANEPPS (Invitrogen-Molecular Probes) through slow coronary perfusion via a custom made micro-pump. The signal-to-noise ratio typically steadily decreases due to washout of the dye during an experiment.²⁹ Periodic additional dye staining and/or a continuous dye infusion at submicromolar concentration were performed to offset washout of the dye in order to maintain a high signal-to-noise ratio throughout the experiment.

Optical Mapping

A photodiode array (C4675, Hamamatsu, Hamamatsu City, Japan) measured fluorescence above 610 nm from 256 sites at a spatial and temporal resolution of 970 μm and 528 μs , respectively. The field of view (FOV) was depicted by the square in Figure 1A and was kept at 17.5×17.5 mm in all experiments. Typical data scans were 1.5 seconds in duration that included optical APs before, during and after the shocks. Transmembrane voltage was calculated from fluorescent recordings with the use of a pseudo-mV calibration.^{30,31} We assumed that the normal AP has a 100-mV amplitude and a -85-mV resting potential. There are some differences of ΔV_m and τ as assessed by optical mapping compared to microelectrode method (See Study Limitations Section).

Experimental Protocol

The protocol used has been described previously.²³ Briefly, the heart was continuously paced at a basic cycle length of 300 ms. Truncated exponential monophasic shocks of 8 ms duration and strengths of ± 100 , ± 130 , ± 160 , ± 190 , and ± 200 V were delivered from a 150 μ F capacitor clinical defibrillator (HVS-02, Ventritex, Sunnyvale, CA, USA). The shocks were applied at 25%, 50%, and 75% of the APD.^{22,23} For each heart, the protocol was first carried out with no drug infusion (control) and then repeated with the addition of either lidocaine (15 μ M, $n = 6$) or nifedipine (2 μ M, $n = 6$). In addition, we have conducted a time-dependent experiment ($n = 5$) to assess stability of electrical properties throughout the experiment. In this case, after the control, the protocol was repeated with a pseudo ionic channel blocker, that is, no blocker in the perfusate.

Time Constants of Cellular Response to Shocks

The effects of lidocaine, nifedipine, and pseudo channel blocker on τ were quantified and compared with the respective control. The method used to calculate τ has been previously used by others¹¹ and by us.^{22,23} Namely, the membrane response curve, $V(t)$, between the beginning and the end of the shock was fitted by the Levenberg-Marquardt method³² to the following exponential equation: $V(t) = a(1 - e^{-t/\tau}) + c$, where a is the maximum transmembrane response (mV); t is the time (ms); τ is the cellular time constant (ms); c is the DC offset (mV). A program was developed using Microsoft Visual C++ to automate the processing of large amounts of data with the ability for manual review and correction. The τ was calculated only in the virtual electrode areas at least 6–10 mm away from the shock electrode because electroporation created near the shock lead^{33–36} could contaminate the cellular response. The areas away from shock lead are either virtual cathode areas (positive or depolarizing polarization) induced by anodal shock or virtual anode areas (negative or hyperpolarizing polarization) induced by cathode shock.²⁵ In this study, the shock electrode was in the RV and seen at the left edge of the FOV (Fig. 1A); τ was therefore calculated from the optical traces at the right side of FOV only (see Fig. 3B). In order to accurately and objectively define virtual electrode areas away from shock lead and to improve fidelity of τ measurement, the following criteria were incorporated into the data analysis program: (1) the virtual electrode areas away from shock lead were selected by defining a virtual electrode border with selected area including only those traces with more than a 10mV change in amplitude during the shock and (2) within selected virtual electrode areas, only traces with a signal-to-noise ratio of greater than 75 were selected for calculation of τ .

We analyzed a total of 121,125 individual responses to a total of 1,020 shocks: 63,450 during controls and 57,675 during lidocaine, nifedipine, or pseudo ionic channel blocker perfusion. In each heart, we applied 30 test shocks during the control (10 shocks each at 25%, 50%, and 75% of APD) and 30 test shocks after perfusion of either channel blockers or pseudo blocker. In addition, ΔV_m changes induced by shock (the difference between the membrane potential just before shock and the membrane potential at the end of shock) were measured automatically via the same Microsoft Visual C++ program from the same raw data set used for τ measurement.

Statistical Analysis

Data are expressed as mean $\pm$ SD. We used a two-way repeated-measures analysis of variance test to assess the effect of channel blockers or pseudo channel blocker presence and shock strength on dependent variables (τ , ΔV_m). If an effect was significant, post hoc Scheffe testing was used to assess the effect of channel blockers or pseudo channel blocker presence at individual shock strength level. Wilcoxon matched pairs tests were used to assess electrical property changes (APD50, APD90, etc.) in the channel blockers or pseudo channel blocker groups with respective control group. A P value of less than 0.05 is considered as statistically significant.

Results

Effects of Channel Blockers and Pseudo Channel Blocker on Electrical Properties

We first characterized the effects of lidocaine, nifedipine, and pseudo channel blocker on electrical properties in our intact rabbit heart model. Lidocaine at 15 μM had minimal effect on AP morphology or duration (see Fig. 1B and Table 1). However, the conduction time (CT) across a FOV (latest activation time in FOV —earliest activation time in FOV) was significantly slowed by lidocaine due to blockage of Na^+ channel (Table 1). This resulted in a reduction of conduction velocity (CV: FOV/CT) within a FOV by 23.3%. These findings illustrate that the lidocaine at 15 μM is effective in our preparation. As a result of slowing of CV, lidocaine significantly shortened the wavelength (λ $\text{APD}_{90} \times \text{CV}$) by 21.6%. In contrast, nifedipine at 2 μM resulted in AP triangulation and significant shortening of APD due to blockage of L-type Ca^{2+} channels (Fig. 1C and Table 1). However, neither CT nor CV was significantly affected by nifedipine. As a result of the shortening of APD_{90} , λ was also significantly shortened. Our data are consistent with previous studies regarding reduction of CV by lidocaine³⁷ and shortening of APD by nifedipine³⁸ in rabbit hearts. For the time-dependent control group, all parameters remained steady over the course of the experiment (Table 1).

Typical Optical Traces in Response to a Shock

Figure 2A represents 256 optical APs in response to a +160-V, 8-ms shock delivered at 50% of APD during control. Delivery of a shock in the heart created a virtual electrode polarization pattern with the adjacent positive (depolarizing) and negative (hyperpolarizing) polarization areas. In this case, a +160-V, 8-ms shock creates a virtual anode (negative polarization) near the shock electrode in the left portion of the FOV, and a virtual cathode (positive polarization) away from the shock electrode in the right portion of the FOV. We have shown previously that the reversal of shock polarity will result in the reversal of virtual electrode polarization pattern.^{25,26} The isopotential map of transmembrane polarization by this shock is depicted in the Figure 3, upper panel A. Figure 2B expands the five highlighted traces spanning the transition from the virtual anode to virtual cathode. The colors and locations correspond with the traces in Figure 2A. The dark blue trace shows a relatively strong negative polarization. A similar but much weaker response is seen in the light blue trace. The green trace does not show negative polarization, but responds with a weak positive polarization. In the purple and the red traces, the cells strongly positively polarize. As defined in the methods section, only the virtual electrode area away from the shock lead, in this case the purple and the red traces were included in the analysis of this particular shock. In this example, one can see that the resting potential does not recover after shock in recording sites close to the shock electrode (Fig. 2A, left columns), suggesting shock-induced electroporation occurred. These areas were subsequently not included in the τ measurement (Fig. 3, upper panel). Figure 2C shows the red trace with an expanded time scale. The black line is the fitted exponential function. Note that both the first and last sample points during the shock were not included to ensure the accuracy of the fit.

Effect of Lidocaine on Cellular Responses to Shocks

We obtained lidocaine data from six rabbits. Figure 3, upper panel A, shows a representative example of the transmembrane voltage map at the end of a + 160-V, 8-ms shock delivered at 50% of APD during the control, and in the presence of lidocaine. Overall, lidocaine did not alter the pattern of transmembrane voltage distribution. τ maps from the same shocks are shown in Figure 3, upper panel B. Black represents those traces that were not fitted. The τ ranged from 0.9 ms to 2.3 ms. Again, similar τ maps were observed between lidocaine and control. Figure 3, upper panel C, shows an example of raw optical traces of the fastest cellular response (τ_{max} , blue trace) and the slowest cellular response (τ_{min} , green trace) to the shock. We then assessed the relationship between τ and ΔVm with respect to shock intensity, shock polarity

and phase of shock application in both control and lidocaine conditions (Fig. 4). For both control and lidocaine groups, it was evident that regardless of shock polarity and phase of shock application, there was inverse relationship between τ and ΔV_m in response to changes of shock intensity: the stronger the shock strength, the larger the magnitude of ΔV_m and the smaller the τ (the faster the cellular response). Further, for both groups, τ and ΔV_m in a virtual anode were larger than those in a virtual cathode. This asymmetric attribute was most evident at lower shock intensities when shocks were delivered at 25% and 50% of APD (note y-axis scale differences between virtual cathode and virtual anode). For shocks applied at 75% of APD, this asymmetry became less evident due to the active response. Finally, it was evident that despite some cases of small yet statistically significant increases of τ and ΔV_m in lidocaine versus control, overall distribution patterns of τ and ΔV_m in lidocaine closely follow their respective control.

Effect of Nifedipine on Cellular Responses to Shocks

Nifedipine data were obtained from six hearts. Figure 3, lower panel A, shows a representative example of transmembrane voltage maps at the end of a +160-V, 8-ms shock delivered at 50% of APD during the control, and in the presence of nifedipine. As with lidocaine, the overall pattern of transmembrane voltage distribution was not significantly altered by nifedipine. However, the τ maps differed between control and nifedipine (Fig. 3, lower panel B). τ was larger in nifedipine than that in control. Raw optical traces of the fastest cellular response ($\tau_{\max}$, blue trace) and slowest cellular response ($\tau_{\min}$, green trace) were shown in Figure 3, lower panel C. The relationship between τ and ΔV_m in respect to shock intensity, shock polarity, and phase of shock application was shown in Figure 5. Again, as with lidocaine, for both control and nifedipine groups, τ and ΔV_m were inversely related to changes of shock strength, regardless of shock polarity and phase of shock application. However, contrary to lidocaine, both τ and ΔV_m in the virtual cathode area were significantly larger in nifedipine than that in control for all shock strengths and times of shock application. In contrast, in the virtual anode area, the increase in either τ or ΔV_m at early phase (25%) of shock application was reversed to decrease when shock was applied at late (75%) phase. As a result of a significantly increased τ and ΔV_m in virtual cathode by nifedipine, nifedipine reduced asymmetry of τ and ΔV_m observed between virtual cathode and virtual anode when shocks were applied at 25% and 50% of APD (note the difference of y-axis scales). At 75% of APD, this asymmetry was reversed by nifedipine.

Effect of Pseudo Channel Blocker on Cellular Responses to Shocks

In this study, shocks were applied repeatedly to the same heart over the course of the experiment. Repeated shocks may cause some tissue injury. It is necessary to clarify whether multiply shocks contribute to some of the observations made. Thus, we have performed a time-dependent control experiment to assess the changes of τ and ΔV_m over the entire course of the experiment. After taking control data, an ~30-minutes waiting period similar to that before either lidocaine or nifedipine data were collected was ensured. This was followed by taking a second data set from the same heart. The experiments were repeated in five hearts. The summarized results are shown in Figure 6. There were some cases of small yet statistically significant increase in ΔV_m in pseudo channel blocker versus that in control. However, overall distribution patterns of τ or ΔV_m in pseudo channel blocker closely followed the ones observed under respective control. These distribution patterns of τ and ΔV_m over range of shock strengths at various shock phase application are also similar to the ones observed in controls of lidocaine and nifedipine studies. In addition, as described in Table 1, other electrical characteristics did not alter substantially either between control and pseudo channel blocker application. These results illustrate the stability of our heart preparation and consistency of measured parameters over the course of entire experiment despite multiply shock applications in this model.

Discussions

In this study, for the first time, we performed measurement of the cardiac membrane time constant in response to defibrillation strength shocks in intact heart under the selective Na⁺ channel blocker lidocaine and the L-type Ca²⁺ channel blocker nifedipine. We examined the relationship between τ and variables of shock-induced ΔV_m changes, shock strength, polarity, and phase of shock application. The main findings are: (1) under all conditions (controls, lidocaine and nifedipine), in respect to increase of shock strength, τ and ΔV_m are inversely related, regardless of shock polarity and phase of shock application. A stronger shock results in larger changes of ΔV_m , which corresponds to smaller τ (faster cellular response); (2) lidocaine does not have appreciable effects on either τ or ΔV_m ; and (3) nifedipine significantly increases both the τ and ΔV_m in the virtual cathode area; in contrast, in the virtual anode area, this effect depends on the phase of shock application.

A number of factors may play a role in membrane time constant of shock-induced transmembrane polarization: (1) shock waveform; (2) ionic channel kinetics; (3) passive myocardial structure (resistor-capacitor component); and (4) electroporation. In this study, we aimed to focus on ionic channel kinetics for realistic shock waveforms and myocardial structure, although our protocol excluded electroporation as described in the methods section. We examined the effects of blockage of fast Na⁺ channel and the L-type Ca²⁺ channel on τ using a clinically relevant truncated exponential waveform in intact heart. Some of our findings from these settings are in agreement with findings from previous studies under ionic channel blocker free media in nonintact heart preparation or with rectangular shock waveforms in uniform electric field. Our observed correlations between changes of τ and ΔV_m in this study are consistent with previous reports obtained from ionic channel blocker-free media of guinea pig papillary muscle¹¹ and intact rabbit heart with rectangular shock waveforms in the uniform electric field.³⁹ An asymmetrical distribution of ΔV_m with a large ratio of negative to positive ΔV_m in control and decreased such asymmetry by nifedipine when shock applied at early and plateau phase of APD (Figs. 4 and 5) are also consistent with previous report by Cheek *et al.*² in cultured monolayer strand of rat myocytes when uniform-field shocks were applied.

In our experiment, we chose to use lidocaine at 15 μM concentration and nifedipine at 2 μM , since similar concentrations have also been used in other experiments with rabbits.⁴⁰⁻⁴³ We chose such concentrations for their relevance to this model and for consistency with respect to the prior literature. Our results with lidocaine suggest that Na⁺ channels play only a limited role in shock-induced polarization in this model, when the shock is applied during 25%, 50%, and 75% of APD under paced conditions. There is only a slight slowing of τ caused by lidocaine. Although it reached statistical significance for some combinations of phases and shock strength, these changes are unlikely to play a major role. Given the rapid activation and subsequent inactivation of the Na⁺ current, this is perhaps not surprising. However, this lidocaine effect was observed under paced conditions when shocks were delivered at certain phases of APD in the structurally normal heart. The effect of lidocaine may be different, based on the fact that the Na⁺ channel availability may be different during ventricular fibrillation in the structurally abnormal heart. Future study will be needed to clarify effect of lidocaine under those conditions. In contrast, nifedipine caused significant slowing of τ as well as an increase in the amplitude of ΔV_m in the virtual cathode area for any phase and shock strength. This suggests an important role for L-type Ca²⁺ channels in shock-induced positive, depolarizing polarization. The role of L-type Ca²⁺ channels in the virtual anode area is not as pronounced.

Study Limitations

There are number of limitations in this study: (1) The recorded optical traces during shock application represent an average transmembrane responses from a large number of cells. Thus,

actual maximum τ may be faster than the measured τ . (2) A clinically indicated defibrillation shock is applied to the fibrillating myocardium, which has all possible phases of electrical activity at a partially depolarized membrane state. Our protocol excluded the resting state of the myocardium, which usually has a multiphasic response to a shock. Such responses are difficult to fit with a single exponential function. (3) This study was conducted under the structurally normal heart while the majority of defibrillation shocks are delivered to the patients with structural heart disease, such as myocardial infarctions. It is a challenge to measure τ reliably from infarct border zone areas since the quality of signal is normally not as good as those from structurally normal hearts.

Conclusions

There is inverse relationship between membrane time constant and transmembrane potential changes with respect to changes of shock strength. This inverse relationship is observed at various conditions: control, lidocaine and nifedipine for both shock polarity and different phase of shock delivery. Blockage of fast sodium current has little impact on either membrane time constant and transmembrane potential changes. Blockage of L-type calcium current causes polarity and phase dependent changes in membrane time constant and transmembrane potential changes.

Acknowledgments

We thank Mei-Ling Chang Liao, MS, for her excellent technical support. We are grateful to Dr. Zoran B. Popović for assistance with statistical analysis.

This study was supported by American Heart Association grants 9960384 V and 0235172 N to Dr. Cheng, and NIH R01-HL67322 and R01-HL074283 to Dr. Efimov.

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Figure 1.

Experimental preparation and effects of lidocaine and nifedipine on APD. (A) Photograph of the preparation. Hollow black box, 17.5×17.5 mm field of view. Solid black square, recording site illustrated in B and C. The bipolar electrode used for pacing was placed at the posterior apex of the heart. The shock electrode was inserted in the right ventricle cavity (white wire), positioned at the left edge of the field of view. (B) Superimposed optical recordings of action potentials during control and $15 \mu\text{M}$ lidocaine taken from the same recording site but from different heart shown in A. (C) Superimposed optical recordings of action potentials during control and $2 \mu\text{M}$ nifedipine taken from the same site and the same heart shown in A.

Figure 2.

Raw optical traces illustrating the results of a +160-V shock delivered at 50% of APD during control. (A) 256 optical traces; (B) Expanded traces highlighted in A. The box indicates the timing of the shock; (C) The exponential approximation (black line) to the red trace.

Figure 3.

Representative voltage maps, τ maps and optical traces to a +160-V, 8-ms shock applied at 50% of APD before and after administration of lidocaine or nifedipine. (A) Representative voltage maps at the end of the shock; (B) τ maps during the shock; Colored squares indicate corresponding recording sites illustrated in C. Black represents those traces that were not fitted; (C) Superimposed optical traces of maximum (blue trace) and minimum (green trace) cellular responses to the shock taken from the recording sites shown in B.

Figure 4.

Relationship between the cellular time constant (τ) and transmembrane voltage changes by shocks (ΔV_m) in respect to changes of shock strength during the control and in the presence of lidocaine. τ and ΔV_m were plotted against shock intensities of ± 100 , ± 130 , ± 160 , ± 190 , and ± 220 V delivered at 25%, 50%, and 75% of the APD ($n = 6$ hearts). *, #: Significant difference between lidocaine and corresponding control ($P < 0.05$). See text for details.

Figure 5.

Relationship between τ and ΔV_m in respect to changes of shock strength during the control and in the presence of nifedipine. τ and ΔV_m were plotted against shock intensities of ± 100 , ± 130 , ± 160 , ± 190 , and ± 220 V delivered at 25%, 50%, and 75% of the APD ($n = 6$ hearts). *, #: Significant difference between nifedipine and corresponding control ($P < 0.05$). See text for details.

Figure 6.

Evaluation of stability of heart preparation over time: control versus pseudo ionic channel blocker. τ and ΔV_m were plotted against shock intensities of ± 100 , ± 130 , ± 160 , ± 190 , and ± 220 V delivered at 25%, 50%, and 75% of the APD ($n = 5$ hearts). #: Significant difference between pseudo blocker and corresponding control ($P < 0.05$). See text for details.

TABLE 1
Comparison of Electrical Characteristics: Controls Versus Lidocaine or Nifedipine or Pseudo Channel Blocker

	APD50 (ms)	APD90 (ms)	CT (ms)	CV (m/s)	λ (cm)
Pre-lidocaine	152.7 $\pm$ 4.7	173.5 $\pm$ 4.6	44.6 $\pm$ 7.8	0.43 $\pm$ 0.05	7.4 $\pm$ 0.7
Lidocaine, 15 μ M	150.4 $\pm$ 7.3	173.0 $\pm$ 7.0	53.8 $\pm$ 10.3	0.33 $\pm$ 0.05	5.8 $\pm$ 1.0
P-value	0.17	0.46	<0.05	<0.05	<0.05
Pre-nifedipine	149.1 $\pm$ 8.6	172.4 $\pm$ 7.3	45.6 $\pm$ 5.5	0.39 $\pm$ 0.04	6.7 $\pm$ 0.7
Nifedipine, 2 μ M	102.1 $\pm$ 3.8	127.6 $\pm$ 5.0	45.8 $\pm$ 7.6	0.39 $\pm$ 0.05	5.0 $\pm$ 0.7
P-value	<0.05	<0.05	0.68	0.60	<0.05
Pre-pseudo blocker	163.1 $\pm$ 9.4	182.4 $\pm$ 9.3	45.7 $\pm$ 4.9	0.39 $\pm$ 0.04	7.1 $\pm$ 1.0
Pseudo blocker	163.6 $\pm$ 11.0	184.2 $\pm$ 10.1	47.9 $\pm$ 8.2	0.37 $\pm$ 0.06	6.9 $\pm$ 1.4
P-value	0.69	0.14	0.50	0.35	0.50

Heart was paced via steady state ventricular pacing at cycle length of 300 ms. Values are mean $\pm$ SD. Pre-lidocaine, control data in lidocaine group (n = 6); Pre-nifedipine, control data in nifedipine group (n = 6). Pre-pseudo blocker, control data in time-dependent group (n = 5). APD50 and APD90, AP at 50% and 90% repolarization, respectively; CT = conduction time across the field of view; CV = conduction velocity across the field of view; λ = wavelength.