Lack of Effect of Conduction Direction on Action Potential Durations in Anisotropic Ventricular Strips of Pig Heart

GUILLERMO BERTRAN, B.Sc., MARCELO O. BIAGETTI, B.Sc., ESTEBAN VALVERDE, E.Eng., PEDRO D. ARINI, E.Eng., and RICARDO A. QUINTEIRO, M.D., Ph.D.

From the Department of Physiology, Favaloro University, Buenos Aires, Argentina

Anisotropy and Repolarization. ***Introduction:*** **The influence of activation sequence on the rate of rise of the depolarization phase of action potentials in atrial or ventricular muscles has been well established. However, whether myocardial fiber orientation is important in modulating the repolarization process is unclear.**

Methods and Results: **We examined the influence of activation sequence on the repolarization phase of action potentials in epicardial tissues from the right and left ventricles of domestic pigs. Whereas cells from the right ventricle exhibited direction-dependent differences in action potential duration at 30%, 50%, and 90% of full repolarization (190.6 ± 31.1 msec vs 181.8 ± 32.8 msec, 240.3 ± 23.5 msec vs 236.7 ± 25.4 msec, and 291.3 ± 23.7 msec vs 287.4 ± 25.1 msec for longitudinal and transverse propagation, respectively; $P < 0.001$), a similar duration of repolarization during both directions of propagation was observed in cells from the left ventricle at 50% and 90% of full repolarization (241.4 ± 39.4 msec and 285.5 ± 39.5 msec vs 240.4 ± 38.9 msec and 284.9 ± 39.6 msec for longitudinal and transverse propagation respectively; P = NS). A slight but significant difference was found at 30% of full repolarization in cells from the left ventricle (190.4 ± 39.0 msec vs 187.0 ± 38.0 msec for longitudinal and transverse propagation, respectively; $P < 0.05$). In the left ventricle, the duration of repolarization did not change as the distance between the recording site and stimulation site increased.**

Conclusion: **The direction of wavefront propagation with respect to fiber orientation may not play an important role in modulating the duration of repolarization in epicardial cells from the left ventricle.**

electrotonus, action potential duration, anisotropic conduction, repolarization

Introduction

The anisotropic nature of myocardial structures has marked effects on the propagation of transmembrane action potentials (APs). Isochronal activation maps have revealed that epicardial stimulation elicited elliptical activation patterns, with the major axis aligned with the longitudinal axis of epicardial fibers and the conduction velocity (θ) being faster when propagation is parallel to the anatomic fiber orientation.[1-10] Moreover, an important effect of activation sequence and anisotropic cellular geometry on the rate of rise of the depolarization phase of APs was demonstrated by different investigators.[6-10] On the other hand, it has been shown that the distribution of epicardial potentials measured over extensive epicardial regions during paced beats reflects the direction of superficial and intramural fibers through which excitation spreads.[11] In contrast, repolarization showed a relatively uniform pattern, independent of pacing site, that began at the apex and spread anisotropically to the base.[12] However, whether myocardial fiber orientation is important in modulating the repolarization process has not been well established. It was shown recently that activation sequence and anisotropic cellular geometry substantially affect action potential duration (APD), with APs being shorter when propagation proceeded transverse to myocardial fiber orientation.[13,14] However, these data were recorded from tissues obtained from the right ventricle (RV). Because differences in the electrophysiology of the RV and left ventricle (LV) have been reported, it seems reasonable to look for differences in the modulation of repolarization in both ventricles.

In the present study, we analyzed the influence of activation sequences on AP configuration, especially in the repolarization phase in RV and LV tissue of the pig heart.

Methods

General

Domestic pigs of either sex (weight 15 to 20 kg) were anesthetized with sodium thiopental 20 mg/kg and ketamine 15 mg/kg intravenously and ventilated mechanically. The hearts were rapidly removed through a left thoracotomy and immersed in cool oxygenated Tyrode's solution. Strips of 3 cm × 2.5 cm × 1 mm were shaved from the epicardial surface of either the RV or LV. Tissues were removed so that myocardial fiber orientation was approximately parallel to the long axis of the strips. Immediately after removal, the slices were placed in a tissue bath with the epicardial surface facing upward, superfused with warmed Tyrode's solution gassed with 95% O_2 and 5% CO_2, and equilibrated at pH 7.4. Temperature was held constant at 37° ± 0.5°C. The Tyrode's solution was of the following composition (in

mM): NaCl 120, $NaHCO_3$ 30, KCl 2.7, $MgCl_2$ 0.5, NaH_2PO_4 0.9, $CaCL_2$ 1.8, and glucose 5.5. The tissues were driven at 1,000-msec pacing cycle length using rectangular pulses of 2-msec width and twice diastolic threshold. Pulses were delivered using a programmable stimulator and stimulus isolation units. Two thin bipolar Teflon-coated silver wire pacing electrodes were used to drive the tissues.

Standard glass microelectrodes filled with 3M KCl with a tip resistance of 10 to 20 MΩ and connected through an Ag/AgCl interface to an amplifier with high input impedance and capacitance neutralization (dual microprobe system K-S700; World Precision Instruments [WPI], Sarasota, FL, USA) were used to record APs from surface cells. The separate reference electrodes were Ag/AgCl electrodes (RC-1; WPI) positioned at least 4 cm from the recording site. The microelectrodes were positioned using micromanipulators (ML-8; Narishige) assisted by an optical micrometer with 50-μm resolution.

Experimental Protocol

The preparations were allowed to equilibrate in Tyrode's solution for 1 hour while being driven at a pacing cycle length of 1,000 msec before AP recordings were made. A roving extracellular electrode was positioned at each point of a 7 × 7 array so that isochronal activation maps were obtained. Activation sequence isochronal maps were generated to define the axes parallel and transverse to the assumed fiber orientation and to confirm the absence of irregularities in activation. The total duration of the experiments was approximately 3 hours. Tissues were sequentially stimulated with electrodes ST1 and ST2 to assess the effect of propagation direction on APD and the spatial distributions of AP shapes. The effects of propagation direction on AP characteristics were assessed with the microelectrode impaled in the same cell during both longitudinal (LP) and transverse (TP) propagation and positioned at a distance of 7 mm from either ST1 and ST2 (Fig. 1). To assess the spatial distributions of AP shapes, APs were recorded at every 1-mm point through a distance of 10 mm from the stimulating electrode along the axes oriented parallel and transverse to the anatomic fiber orientation (Fig. 1).

The following variables were measured at each recording site: activation time, which was defined as the interval (in milliseconds) between the stimulus artifact and the maximum derivative of phase 0 of the AP; resting membrane potential (in millivolts); AP amplitude (in millivolts); maximal rate of rise of the AP upstroke (V_{max}; in V/sec); APD, which was defined as the interval (in milliseconds) from the maximum derivative of phase 0 of the AP to either 30% (APD_{30}), 50% (APD_{50}), or 90% (APD_{90}) of full repolarization; and θ, which was estimated as 1/slope of the plot of activation time against distance in both the LP (θ_L) and TP (θ_T) directions.

Recordings with resting membrane potential more positive than −75 mV or with V_{max} <90 V/sec were considered as depressed responses and rejected.

Data Acquisition and Analysis

Signals were displayed on a variable persistence screen oscilloscope (dual beam storage 5113; Tektronix, Beaverton, OR, USA) and digitized at 10 kHz and 12-bit accuracy with an analog-to-digital acquisition board (LabPC+; National Instruments, Austin, TX, USA). The signals were processed on-line using custom-built software written in Borland C++ 5.01, running under Windows 98, and stored on computer hard disk.

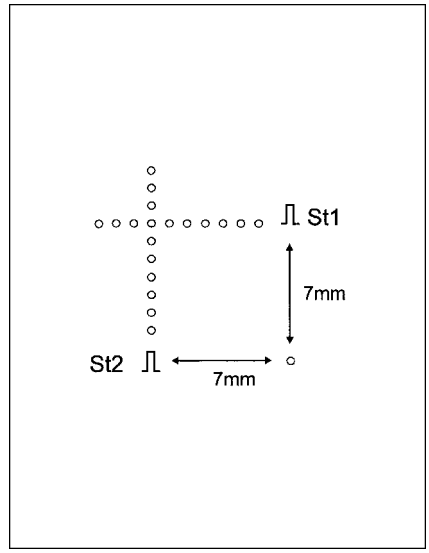

Figure 1. *Schematic diagram of microelectrode recording sites (open circles) and stimulating electrodes (ST1 and ST2). A cell located 7 mm from both ST1 and ST2, as indicated, was continuously impaled during both longitudinal and transverse propagation to analyze action potential characteristics. Action potentials also were recorded every 1 mm from ST1 and ST2 during longitudinal and transverse propagation.*

Statistical Analysis

Group data are given as mean ± SD. Paired *t*-tests were used for comparison of AP parameters in the same cell during both LP and TP. APDs also were evaluated at each 1-mm distance from the stimulating site. Differences between LP and TP were assessed by paired *t*-test. To evaluate the spatial distribution of APD as a function of distance, linear regression analysis and one-factor repeated measures analysis of variance were used for each direction of propagation. $P < 0.05$ was considered statistically significant.

Results

Effects of Activation Sequence on AP Characteristics

We examined the influence of activation sequence on the AP configuration in epicardial tissues obtained from the RV (4 tissues) and LV (11 tissues). An average of 14 APs were obtained, from an area <1 mm^2 located 7 mm from either ST1 and ST2, in each of the 4 RV tissues. Similarly, at least 3 APs were averaged from each of the 11 LV tissues. Cells were continuously impaled while tissues were driven at a cycle length of 1,000 msec. Stimulation from ST1 induced an activation wavefront that approached the recording site parallel to fiber orientation, whereas stimulation from ST2 induced an activation wavefront that approached the recording site transverse to fiber orientation. These activation sequences caused marked differences in the upstroke phase of APs despite similar resting membrane potentials during both directions of propagation. V_{max} was significantly greater during TP (Fig. 2). In this example, a faster rising

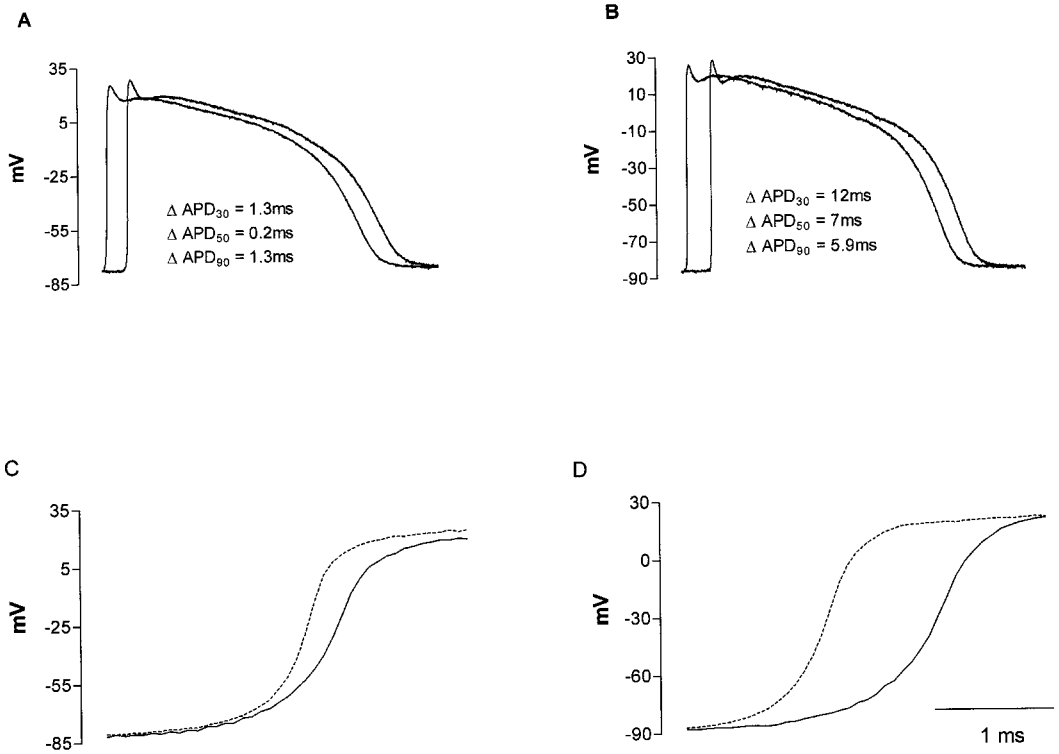

Figure 2. *Effect of changing the orientation of activation wavefronts on the shape of action potentials (APs). Superimposed APs were obtained from the same cell during continuous impalement. (A) APs (left ventricular tissue) obtained from a single experiment during both longitudinal and transverse propagation exhibited similar durations as indicated by* $\Delta APD < 2$ *ms at* APD_{30}, APD_{50}, *and* APD_{90}. *(B) APs from the right ventricle exhibited different durations depending on the direction of propagation at 30%, 50%, and 90% of full repolarization, as indicated by* ΔAPD *between 6 and 12 msec. The depolarization phase during both directions of propagation is plotted on an expanded time base in the lower panel. The rate of depolarization is faster during transverse propagation in both the left ventricle (C) and the right ventricle (D).*

phase of APs during TP (dotted lines) than during LP (solid lines) in either the RV or LV is clearly seen. Activation time also was significantly greater during TP, even though the recording site was equidistant from both stimulating electrodes, indicating a slower θ during TP. APD exhibited a different behavior as a function of activation sequence, which was dependent on the source of epicardial tissue. APs exhibited a shorter duration at APD_{30}, APD_{50}, and APD_{90} in RV tissues, whereas APD in LV, except for APD_{30}, was not affected by the activation sequence. The results are summarized in Table 1.

Spatial Distribution of Activation Times and APDs

To further characterize the lack of effects of propagation direction on APDs from the LV epicardial surface, we analyzed the spatial distribution of activation time and APD as follows.

Activation time increased progressively in both propagation directions as the recording site was moved farther from the stimulating electrodes. A linear relationship with a high correlation was found between activation time and distance ($r^2 = 0.95 \pm 0.06$ and 0.99 ± 0.01 for LP and TP, respectively). The slopes during TP were significantly greater than the slopes during LP (1.7 ± 0.4 and 5.6 ± 1.0 for LP and TP, respectively; $P < 0.0001$). Estimated θ was 0.61 ± 0.15 m/sec during LP and 0.19 ± 0.04 m/sec during TP. These differences also were significant ($P < 0.0001$), with θ_L/θ_T ratio $= 3.5 \pm 1.2$. Figure 3 shows the linear fits of the 11 experiments during both LP and TP. These results are compatible with the characteristics of uniform anisotropic

TABLE 1

Action Potential Characteristics of Right and Left Ventricles During LP and TP

	Right Ventricle		Left Ventricle	
	LP	**TP**	**LP**	**TP**
Activation time (msec)	17.8 ± 3.3¶	49.7 ± 11.0*¶	12.5 ± 4.2	37.9 ± 10.6*
Resting potential (mV)	−86.9 ± 7.8¶	−86.6 ± 8.2¶	−82.5 ± 4.1	−82.4 ± 4.1
V_{max} (V/sec)	129.7 ± 26.1	154.2 ± 28.1*	156 ± 43	179 ± 41†
APA (mV)	109.8 ± 8.7	112.4 ± 9.1*	112 ± 5	113 ± 4
APD_{30} (msec)	190.6 ± 31.1	181.8 ± 32.8*	190.4 ± 39.0	187.0 ± 37.8‡
APD_{50} (msec)	240.3 ± 23.5	236.7 ± 25.4†	241.4 ± 39.4	240.4 ± 39.0
APD_{90} (msec)	291.3 ± 23.7	287.4 ± 25.1*	285.5 ± 39.5	284.9 ± 39.6

*$P < 0.0001$ longitudinal propagation (LP) vs transverse propagation (TP); †$P < 0.01$ LP vs TP; ‡$P < 0.05$ LP vs TP; ¶$P < 0.05$ against left ventricle.

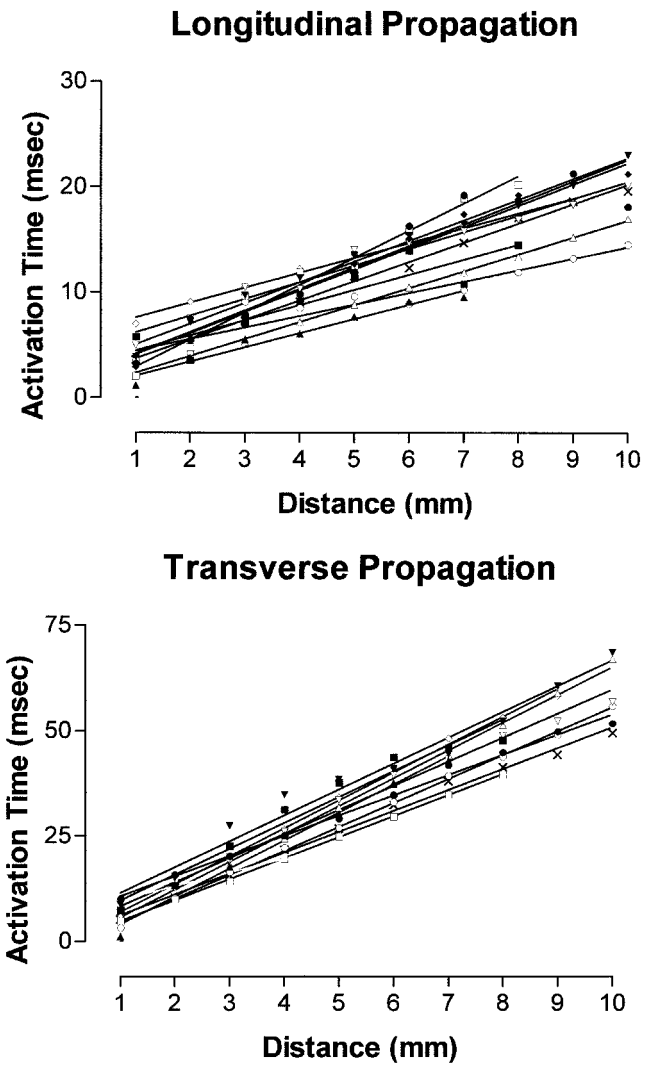

Figure 3. *Relationship between activation time and distance in the 11 experiments during longitudinal propagation (top) and transverse propagation (bottom). See text for results.*

propagation in ventricular epicardium reported previously.[1-10]

APD_{30}, APD_{50}, and APD_{90} were evaluated between 1 and 10 mm from the stimulating electrodes. Only experiments where APs were obtained during both LP and TP were considered for analysis. No significant differences in APD_{30}, APD_{50}, and APD_{90} were observed between LP and TP for each of the 10 recording sites, as indicated by paired *t*-tests. No significant differences were found in APDs among the 10 recording sites for each direction of propagation, as indicated by one-factor analysis of variance for repeated measures. Data are summarized in Table 2. In 7 experiments in which APs were successfully recorded from all 10 recording sites during both LP and TP, the relationship between APD and distance for each of the three levels of repolarization was modeled as a separate line for each direction of propagation. Pooled data exhibited regression lines with slopes for both LP and TP that were not significantly different from 0. These slopes were not significantly different from each other. The results are given in Figure 4 and Table 3.

Influence of Activation Sequence on Dispersion of Repolarization

We assessed the effect of activation sequence on dispersion of repolarization by comparing the standard deviation of the APD (SDAPD) obtained between 1 to 10 mm from the stimulating electrodes during LV propagation in each direction. We did not find significant differences in SDAPD, determined at either 30% ($SDAPD_{30}$; 19.8 ± 7.6 msec vs 16.9 ± 6.9 msec for LP and TP, respectively; P = NS), 50% ($SDAPD_{50}$; 18.0 ± 8.7 msec vs 15.8 ± 7.7 msec for LP and TP, respectively; P = NS), and 90% of full repolarization ($SDAPD_{90}$; 15.9 ± 8.6 msec vs 15.2 ± 7.3 msec for LP and TP, respectively; P = NS).

Because it previously was reported that the direction-dependent differences in APD were greater at low temperatures, in three additional LV tissues we looked for APD direction-dependent changes induced by sequentially reducing the temperature from 37°C to 31°C and increasing K^+ concentration in the perfusion solution from 2.7 to 8.1 mEq/L. In each experiment, we recorded an average of five APs from a central area of <1 mm^2 that was approximately equidistant from both ST1 and ST2 stimulating electrodes. θ during LP changed from 0.52 ± 0.16 (37°C ,K^+ 2.7 mEq/L) to 0.57 ± 0.09 (37°C, K^+ 8.1 mEq/L), 0.36 ± 0.06 (31°C, K^+ 8.1 mEq/L), and 0.35 ± 0.08 (31°C, K^+ 2.7 mEq/L). During TP, θ changed from 0.16 ± 0.01 (37°C, K^+ 2.7 mEq/L) to 0.27 ± 0.01 (37°C, K^+ 8.1 mEq/L), 0.12 ±

TABLE 2
Action Potential Duration as a Function of Distance

Distance (mm)	*N*	APD_{30} (msec)		APD_{50} (msec)		APD_{90} (msec)	
		LP	TP	LP	TP	LP	TP
1	11	195.4 ± 43.7	194.9 ± 28.8	248.3 ± 42.5	248.6 ± 34.2	295.0 ± 41.6	293.1 ± 36.7
2	11	194.9 ± 44.5	202.5 ± 30.6	247.3 ± 43.0	256.1 ± 37.4	293.2 ± 41.2	297.6 ± 39.7
3	11	198.4 ± 38.3	205.0 ± 31.9	250.8 ± 39.3	256.5 ± 37.5	294.6 ± 38.1	296.9 ± 39.6
4	11	198.2 ± 33.4	198.1 ± 32.5	251.1 ± 34.7	250.6 ± 35.8	295.0 ± 34.3	291.9 ± 36.4
5	11	207.3 ± 35.3	200.1 ± 28.2	256.2 ± 34.3	251.4 ± 30.2	298.7 ± 33.7	293.3 ± 30.8
6	11	200.5 ± 41.4	189.4 ± 23.9	254.0 ± 41.0	243.1 ± 24.8	296.9 ± 39.8	286.5 ± 26.6
7	11	196.4 ± 34.2	187.1 ± 26.6	248.2 ± 36.0	240.7 ± 27.0	290.3 ± 36.5	286.0 ± 26.8
8	10	198.4 ± 31.6	183.5 ± 19.9	247.4 ± 32.8	237.6 ± 26.2	288.4 ± 36.3	283.5 ± 27.3
9	8	201.5 ± 32.0	197.9 ± 26.8	248.3 ± 34.9	249.7 ± 29.7	288.5 ± 36.3	290.7 ± 30.6
10	7	196.9 ± 36.4	190.1 ± 18.8	241.8 ± 40.1	246.1 ± 28.3	281.4 ± 40.5	289.4 ± 32.0

LP = longitudinal propagation; TP = transverse propagation.

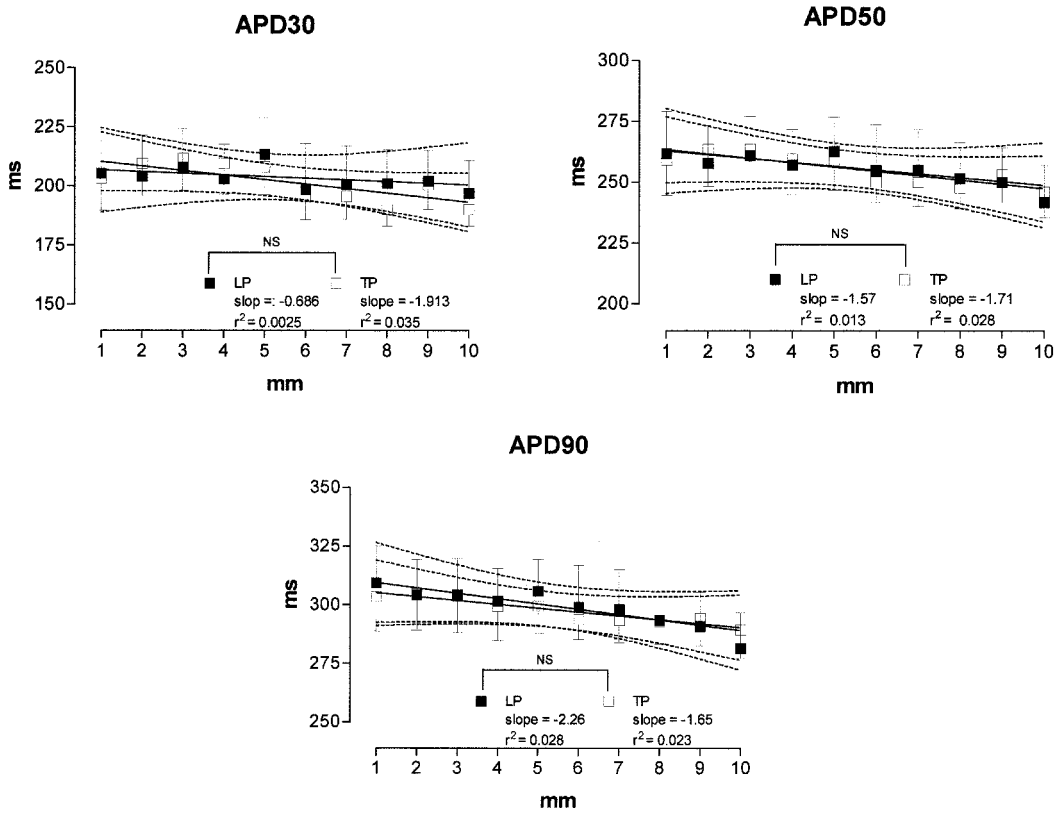

Figure 4. *Relationship between action potential duration (APD) and distance during both longitudinal propagation (LP) and transverse propagation (TP). Data were obtained from seven experiments in which APs were successfully recorded every 1 mm between 1 to 10 mm from the stimulating electrodes. Solid lines represent the least square fits of all the data points (not shown for clarity). Dotted lines represent the 95% confidence intervals for each direction of propagation. Mean ± SD of both LP (filled squares) and TP (open squares) from the seven experiments are superimposed.*

0.01 (31°C, K^+ 8.1 mEq/L), and 0.13 ± 0.01 (31°C, K^+ 2.7 mEq/L). However, no direction-dependent differences were found in APDs, although a significant increase in APDs was observed after temperature reduction. The results are shown in Figure 5.

Discussion

Our data mainly indicate that the duration of repolarization of cells from the LV epicardial surface was not modulated by the direction of propagation. In contrast, cells from the RV epicardial surface exhibited shorter APDs during transverse propagation.

APs recorded from the same cell during both directions of propagation exhibited faster depolarization phases during TP compared with LP, indicating clear modulation of the rate of depolarization by the sequence of activation in both ventricles (Fig. 2 and Table 1). In addition, θ values in the LV, estimated as 1/slope of the plot of activation time against distance during both LP and TP, are characteristic of epicardial anisotropic conduction.[1-10] In contrast, repolarization exhibited a differential behavior depending on the ventricle from which the tissue was obtained. Whereas APs obtained from cells of the RV surface exhibited significantly shorter APD_{30}, APD_{50}, and APD_{90} during TP, similar durations of APs were found during both directions of propagation in LV cells. Two observations further support the independence of APD with regard to the direction of wavefront activation with respect to fiber orientation in the LV: a nearly homogeneous spatial distribution of APDs with no significant differences between LP and TP and between each of the 10 recording sites during both directions of propagation (as shown in Table 2), and a nonsignificant linear trend across distance with no differences among LP and TP (Fig. 4). In contrast, activation sequence-induced differences in the spatial distributions of APDs have been demonstrated in computer simulations. Lesh et al.[15] showed that cellular uncoupling unmasks APD dispersion. Unfortunately, these authors did not report isolated tissue studies to support their theoretical observations. Moreover, we showed that dispersion of APD_{30}, APD_{50}, or APD_{90} in the LV epicardial surface did not exhibit significant direction-dependent differences, although we did not test the presence of changes in APD dispersion under conditions of increased axial resistivity, as simulated by Lesh et al.

TABLE 3
Linear Regression Analysis of APD Versus Distance

	APD30		APD50		APD90	
	LP	TP	LP	TP	LP	TP
Slope	−0.69	−1.91	−1.58	−1.79	−2.26	−1.65
r^2	0.0025	0.0378	0.0135	0.0283	0.0288	0.0229
Deviation from 0?	NS	NS	NS	NS	NS	NS
Are the lines different?	P = 0.5493		P = 0.9189		P = 0.7683	

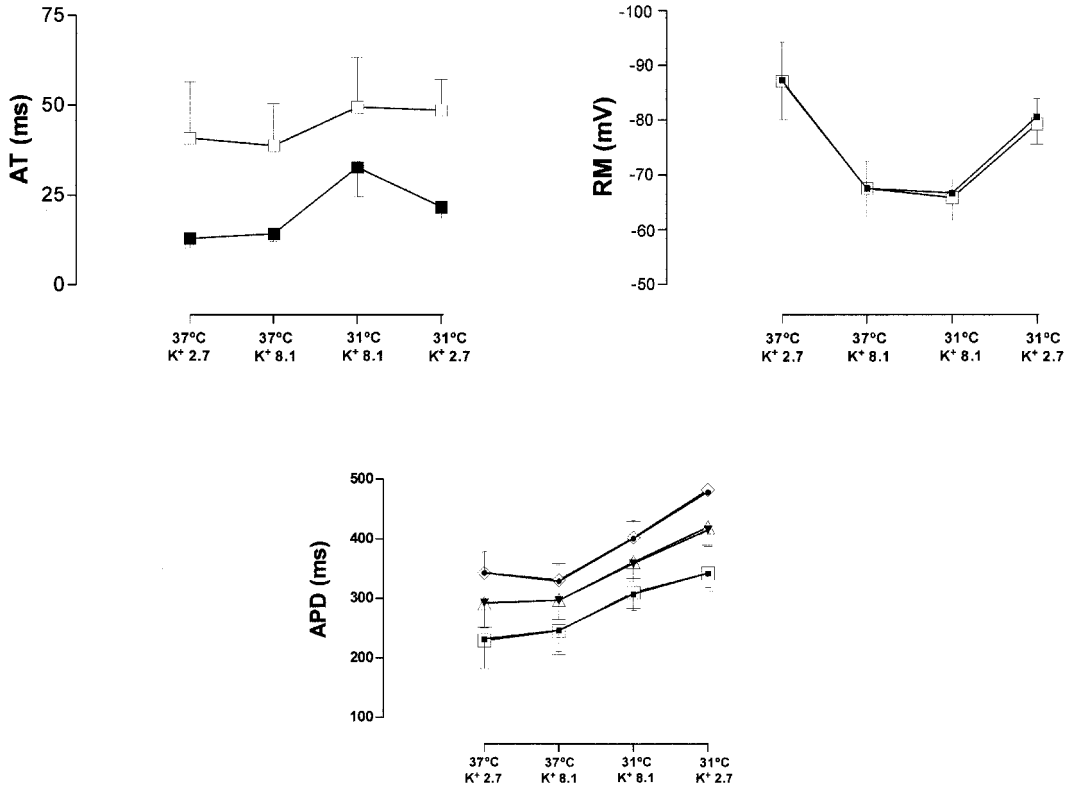

Figure 5. *Variations of electrophysiologic parameters during sequential changes of temperature and K^+ concentration in the perfusion solution. Shown are changes observed in activation time (AT; left upper panel) and membrane resting potential (RM; right upper panel) during longitudinal propagation (filled symbols) and transverse propagation (open symbols). Changes observed in the duration of repolarization at 30% (squares), 50% (triangles), and 90% (diamonds) during longitudinal propagation (filled symbols) and transverse propagation (open symbols) are shown in the lower panel.*

Our results from the LV are in concordance with those previously reported by Laurita et al.,[16] who showed that both restitution kinetics and APD are largely determined by membrane ionic kinetics at each recording site and not by electrotonic loading and fiber orientation. However, expression of repolarization properties in different regions of the ventricles is a complex interaction between the spatial distribution of the intrinsic properties of the cells and the spatial distribution of the coupling resistances among cells of the cardiac syncytium. In this regard, it is well accepted that the parameters measured from a single cell penetration in the electrical syncytium (e.g., V_{max}, AP, APD, and resting membrane potential) reflect not only the properties of that cell but also the electrotonic interactions with other cells to which the recorded cell is electrically coupled.

Only a limited number of studies in isolated ventricular tissues from different animal species have shown important effects of activation sequence and anisotropic cellular geometry on ventricular repolarization. Osaka et al.[13] and Gotoh et al.[14] reported significant modulation of repolarization depending on the direction of the activation wave with respect to fiber orientation. These authors postulated an electrotonic interaction between neighboring cells in tissues having anisotropic cellular geometry to account for their findings. Interestingly, these data were obtained in epicardial tissues from the RV of either dogs and pigs. Our data from the RV are in concordance with those reported by these authors, although a lesser degree of APD shortening during TP was found in the present study. Several possibilities might account for our results.

First, electrical coupling is essential for expression of electrotonic interactions between cells.[17-20] Under normal propagation conditions, a different phase relationship occurs between neighboring myocytes due to the different activation patterns (LP and TP). However, it is questionable whether such a phase shift is sufficient to trigger electrotonic interactions at any measurable level. Therefore, timing of repolarization among myocytes is crucial for expression of electrotonic interactions, because the magnitude of these effects is inversely related to θ. Given that a slow θ would be associated with a greater probability for expression of electrotonic interaction, it could be postulated that the differences in θ reported in the present study compared with those of Osaka et al.[13] and Gotoh et al.[14] may be responsible for the different behavior of repolarization as a function of propagation direction. These authors reported epicardial θ values during LP and TP that were slower than those reported in the present study. We reported estimated $\theta_L = 0.61 \pm 0.15$ m/sec and estimated $\theta_T = 0.19 \pm 0.05$ m/sec, which are in agreement with values of about 0.59 and 0.21 m/sec for LP and TP, respectively, reported in the literature for adult ventricular myocardium (weighted average for N = 91 from references 1 to 10). Osaka et al.[13] reported $\theta_L = 0.35 \pm 0.01$ and $\theta_T = 0.15 \pm 0.01$ at 30°C that increased to $\theta_L = 0.47 \pm 0.02$ and $\theta_T = 0.19 \pm 0.01$ at 35°C. In contrast, despite the observation of a significant

reduction of θ during both LP and TP, no significant direction-dependent differences in APDs were found when the temperature was reduced from 37°C to 31°C. On the other hand, the relatively slower θ values reported by Gotoh et al.[13] ($\theta_L = 0.35$ and $\theta_T = 0.16$ at a basic cycle length of 500 msec and θ_L of 0.34 and θ_T of 0.17 at a basic cycle length of 1,000 msec) might be due to a more depolarized resting membrane potential, because those authors used a higher potassium concentration than we did. However, as we showed, no differences in APDs were found between both directions of propagation after increasing the K^+ concentration from 2.7 to 8.1 mEq/L.

Second, the animal species used in the experiments might be important because the histologic structures of porcine and canine hearts are known to be different, especially because of the proliferation of Purkinje fibers in pig myocardium that is absent in dog myocardium. It can be speculated that these differences have some effect on the electrotonic properties of epicardial tissues. However, Osaka et al.[13] and Gotoh et al.[14] obtained similar results using different animal species, whereas we obtained different results with the same animal species. Thus, this last possibility probably can be ruled out.

Finally, differences in the electrical properties of myocytes between the RV and LV have been described.[21,22] In this regard, different I_K densities among M cells of both ventricles have been reported.[21] On the other hand, heterogeneity of I_K has been linked to dispersion of repolarization and danger of torsades de pointes.[23] Thus, it can be postulated that differences in the electrophysiologic properties leading to different anisotropic properties in both ventricles might be responsible for the differences in direction-dependent changes in repolarization. Moreover, an interventricular difference in the dispersion of repolarization, facilitated by the differential anisotropic modulation of repolarization, can be postulated. These data might be in agreement with the lower ventricular fibrillation threshold reported by Horowitz et al.[24] for the RV compared with the LV. Our data from the RV and those from Osaka et al. and Gotoh et al. also are in keeping with these results.

These findings may have important clinical implications. Anisotropy has been proposed as a major factor in the development of ventricular arrhythmias. Reentrant circuits caused by anisotropy might be classified as functional because they occur without a defined anatomic pathway. Unlike the leading circle type of reentry where the functional characteristic is a difference in refractory periods in adjacent areas caused by inhomogeneous repolarization, the functional characteristic in anisotropic reentry is the difference in effective axial resistance to impulse propagation that is dependent on fiber orientation. However, under conditions of nonuniform anisotropy where the θ_L/θ_T ratio is significatively increased, the electrotonic influences enhanced by very slow conduction may play a significant role in increasing APD dispersion. Hence, another arrhythmogenic factor would exist and enhancement of θ, through an increase in junctional conductance, would be a rational therapy.

Conclusion

It is likely that fiber orientation per se is not an important factor in determining repolarization characteristics in ventricular epicardium. Further clarification of anisotropic modulation of repolarization should involve not only the activation sequence in relation to the structural characteristics of cardiac tissue but also the anatomic source from which the tissues are obtained (RV or LV) and the degree of depression in conduction velocity.

References

1. Sano T, Takayama N, Shimamoto T: Directional differences in conduction velocity in the cardiac ventricular syncytium studied by microelectrodes. Circ Res 1959;7:262-267.
2. Roberts DE, Hersh LT, Scher AM: Influence of cardiac fiber on wavefront voltage, conduction velocity and tissue resistivity in the dog. Circ Res 1979;44:701-712.
3. Spear JF, Michelson EL, Moore EN: Cellular electrophysiologic characteristics of chronically infarcted myocardium in dogs susceptible to sustained ventricular tachyarrhythmias. J Am Coll Cardiol 1983;1: 1099-1110.
4. Balke CW, Lesh MD, Spear JF, Kadish A, Levine JA, Moore EN: Effects of cellular uncoupling on conduction in anisotropic canine ventricular myocardium. Circ Res 1988;63:879-892.
5. Kadish A, Shinnar M, Moore EN, Levine JH, Balke CW, Spear JF: Interaction of fiber orientation and direction of impulse propagation with anatomic barriers in anisotropic canine myocardium. Circulation 1988;78:1478-1494.
6. Spach MS, Miller WT III, Geselowitz DB, Barr RC, Kootsey JM, Johnson EA: The discontinuous nature of propagation in normal canine cardiac muscle. Evidence for recurrent discontinuities of intracellular resistance that affect the membrane currents. Circ Res 1981; 48:39-54.
7. Tsuboi N, Kodama I, Toyama J, Yamada K: Anisotropic conduction properties of canine ventricular muscles. Influence of high extracellular K^+ concentration and stimulation frequency. Jpn Circ J 1985;49: 487-498.
8. Kadish A, Spear JF, Levine JH, Moore EN: The effects of procainamide on conduction in anisotropic canine ventricular myocardium. Circulation 1986;74:616-625.
9. Quinteiro RA, Biagett MO, de Forteza E: Effects of lidocaine on V_{max} and conduction velocity in uniform anisotropic canine ventricular muscle. Possible role of its binding rate constants. J Cardiovasc Pharmacol 1990;15:29-36.
10. Quinteiro RA, Biagetti MO, de Forteza E: Relationship between V_{max} and conduction velocity in uniform anisotropic canine ventricular muscle. Differences between the effects of lidocaine and amiodarone. J Cardiovasc Pharmacol 1990;16:931-939.
11. Taccardi B, Macchi E, Lux RL, Ershler P, Spaggiari S, Baruffi S, Vyhmeister Y: Effect of myocardial fiber direction on epicardial potentials. Circulation 1994;90:3076-3090.
12. Efimov IR, Ermentrout B, Huang DT, Salama G: Activation and repolarization patterns are governed by different structural characteristics of ventricular myocardium: Experimental study with voltage sensitive dyes and numerical simulations. J Cardiovasc Electrophysiol 1996;7:512-530.
13. Osaka T, Kodama I, Tsuboi N, Toyama J, Yamada K: Effects of activation sequence and anisotropic cellular geometry on the repolarization phase of action potential of dog ventricular muscles. Circulation 1987;76:226-236.
14. Gotoh M, Uchida T, Fan W, Fishbein M, Karagueuzian H, Chen P: Anisotropic repolarization in ventricular tissue. Am J Physiol 1997; 272:H107-H113.
15. Lesh MD, Pring M, Spear JF: Cellular uncoupling can unmask dispersion of action potential duration in ventricular myocardium. A computer modeling study. Circ Res 1989;65:1426-1440.
16. Laurita KR, Girouard SD, Rosenbaum DS: Modulation of ventricular repolarization by premature stimulus. Role of epicardial dispersion of repolarization kinetics demonstrated by optical mapping of the intact guinea pig heart. Circ Res 1996;79:493-503.

17. Tan RC, Joyner RW: Electrotonic influences on action potentials from isolated ventricular cells. Circ Res 1990;67:1071-1081.
18. Zaniboni M, Pollard AE, Yang L, Spitzer KW: Beat-to-beat repolarization variability in ventricular myocytes and its suppression by electrical coupling. Am J Physiol 2000;278(Heart Circ Physiol):H677-H687.
19. Huelsing DJ, Spitzer KW, Cordeiro JM, Pollard AE: Modulation of repolarization in rabbit Purkinje and ventricular myocytes coupled by a variable resistance. Am J Physiol 1999;276:H572-H581.
20. Joyner RW: Modulation of repolarization by electrotonic interactions. Jpn Heart J 1986;27(Suppl 1):167-183.
21. Volders PGA, Sipido KR, Carmeliet E, Spätjens R, Wellens HJJ, Vos MA: Repolarizing potassium currents are larger in right than in left canine ventricular epicardium. Circulation 1999;99:206-210.
22. DiDiego JM, Sun ZQ, Antzelevitch C: I_{to} and action potential notch are smaller in left vs. right canine ventricular epicardium. Am J Physiol 1996;271:H548-H561.
23. Gintant GA: Regional differences in I_K density in canine left ventricle: Role of I_{Ks} in electrical heterogeneity. Am J Physiol 1995;268:H604-H613.
24. Horowitz LN, Spear JF, Moore EN: Relation of the endocardial and epicardial ventricular fibrillation thresholds of the right and left ventricles. Am J Cardiol 1981;48:698-701.