Differential Modulation of Electrocardiographic Indices of Ventricular Repolarization Dispersion Depending on the Site of Pacing During Premature Stimulation

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Differential Modulation of ECG Indices of Dispersion. ***Introduction:*** **Dispersion of ventricular repolarization has been shown to increase with premature stimulation. Moreover, a straight correlation between the amount of dispersion of repolarization and the vulnerability to ventricular fibrillation was reported. On the other hand, differences between right ventricular (RV) and left ventricular (LV) fibrillation threshold have been reported. However, no data exist regarding the influence of the site of stimulation on modulation of dispersion of repolarization.**

Methods and Results: **In the present study, several ECG indices of dispersion of repolarization, as a function of the coupling interval and the site of stimulation, were evaluated in a modified Langendorff-perfused rabbit heart (n = 12), with a 5 × 8 array of a simulated body surface unipolar lead system. As the coupling interval was shortened, a biphasic modulation of dispersion of repolarization was found when stimuli were elicited at the LV. In contrast, when the heart was paced from the RV, the dispersion increased monotonically as coupling interval was shortened.**

Conclusion: **A differential behavior of the modulation of dispersion of repolarization was found as a function of the site of stimulation.**

electrocardiography, QT interval, JT interval, QT dispersion, JT dispersion, mapping, pacing

Introduction

Dispersion of ventricular repolarization is a measure of nonhomogeneous recovery of excitability during the repolarization process. Under normal conditions, this variable parallels dispersion of refractoriness. Differences in activation time and action potential duration (APD) were considered determinants of the dispersion of repolarization.[1,2] An inverse relationship between these two variables, associating greater conduction time with shorter APD, has been shown only under control conditions.[3] Moreover, increments in the dispersion of ventricular repolarization have been shown to play a significant role in the genesis of ventricular arrhythmias.[4-8] In this regard, both clinical and experimental studies[9-15] demonstrated that programmed ventricular stimulation significantly increased the dispersion of ventricular repolarization and that these changes were markedly associated with an increase in the induction of ventricular arrhythmias. Also, dispersion of either the JT or QT interval has been shown to correlate with dispersion of APD.[16] Laurita et al.[17,18] showed that APD was monotonically shortened as single premature stimuli were introduced at progressively shorter coupling intervals. These authors also showed that the dispersion of APD, in contrast, decreased to a minimum at short critical coupling intervals and then, at even shorter coupling intervals, increased sharply. Modulation of APD was attributed to coupling interval-dependent changes in the magnitude and direction of ventricular APD gradients, which in turn were explained by systematic heterogeneity of APD restitution across the epicardial surface. Moreover, it has been demonstrated that modulation of repolarization gradients by single premature stimuli significantly influences vulnerability to ventricular fibrillation. Vulnerability also is modulated in a biphasic fashion,[18] in parallel with modulation of the dispersion of repolarization, and both variables are highly related to each other.

On the other hand, ventricular vulnerability, as assessed by the ventricular fibrillation threshold technique, was reported to be different when evaluated at the right ventricle (RV) or left ventricle (LV). Horowitz et al.[19]

showed that LV epicardium exhibited a significantly higher ventricular fibrillation threshold as compared with LV endocardium and RV (endocardium and epicardium).

Because a different vulnerability to fibrillation may exist between both ventricles, we hypothesized that there also would be a different behavior in the modulation of dispersion of repolarization depending on the site where premature stimuli were elicited (RV or LV stimulation). Hence, ECG indices of APD dispersion, such as JT or QT dispersion, also should be modulated, whether or not in a biphasic manner, by the site of premature stimulation.

The main purposes of the present study were twofold: (1) to demonstrate that modulation of APD dispersion found by others could be reproduced measuring JT or QT dispersion during premature stimulation; and (2) to evaluate if the modulation of these variables, if any, is dependent on the site where the stimuli were applied.

Methods

Isolated Rabbit Heart Preparation

Twelve New Zealand white male rabbits (2.8 to 3.8 kg) were heparinized (500 U/kg IV) 10 minutes before being killed and were anesthetized by intramuscular injection of a combination of ketamine (35 mg/kg) and lidocaine (5 mg/kg). The animals were killed by cervical dislocation. The chest was opened via a median sternotomy, and the heart quickly removed with scissors and immediately arrested by immersion into ice-cold Tyrode's solution. After removal of the remaining connective tissue, lungs, and pericardium, the heart was mounted on a vertical Langendorff apparatus through cannulation of the aorta and immersed in a tissue bath filled with Tyrode's solution. Simultaneously, the heart was retrogradely perfused through the aorta with Tyrode's solution. Time from chest opening to cannulation of the aorta ranged from 2 to 3 minutes. The composition of Tyrode's solution was (in mM) NaCl 140, KCl 5, $MgCl_2$ 1, NaH_2PO_4 0.33, HEPES 5, glucose 11.1, and $CaCl_2$ 2. The pH of the Tyrode's solution was adjusted to 7.4 with NaOH. The temperature of both the perfusion and the reservoir Tyrode's solutions was fixed at 38° ± 0.5°C and gassed with 100% O_2. The flow rate for aortic perfusion was adjusted using a variable speed roller pump (Extracorporeal, M2102 Infusion Pump) to 700 to 900 mL/hour to maintain a perfusion pressure of at least 70 mmHg. The sinus node was crushed, and the hearts were paced from the RV or LV at a basic cycle length of 400 msec to override spontaneous activity below the AV node.

Experimental Setup

The heart was completely immersed into a cylindrical chamber containing warmed Tyrode's solution that was thermally equilibrated with the myocardial perfusion fluid. The chamber was 7 cm in diameter and 7 cm high to simulate the thorax of the rabbit. Silver-silver chloride electrodes 2 mm in diameter were mounted in the wall of the chamber distributed in an array of five rows (inter-electrode distance 10 mm) and eight columns (angular distance between electrodes 45°). Another set of four electrodes were positioned in an "Einthoven" configuration, two beneath the heart and the other two in the chamber wall as arm electrodes. The sole purpose of these electrodes was to serve as an electrical reference configuring the Wilson central terminal. We previously demonstrated higher accuracy in the evaluation of QT interval dispersion using a multiple external electrode recording system compared with 12-lead standard ECG in an in vitro model.[20]

Care was taken to always place the hearts at the same relative position with respect to the set of electrodes. Figure 1 shows the arrangement of electrodes used.

Use of an isolated perfused rabbit heart model allowed us to study the effects of different cycle lengths during extrastimulation on cardiac repolarization, independent of interactions due to the autonomic nervous system. All results and conclusions are limited by the assumption that volume-conducted electrograms have a similar behavior in the intact animal, so care must be taken to extrapolate the data directly.

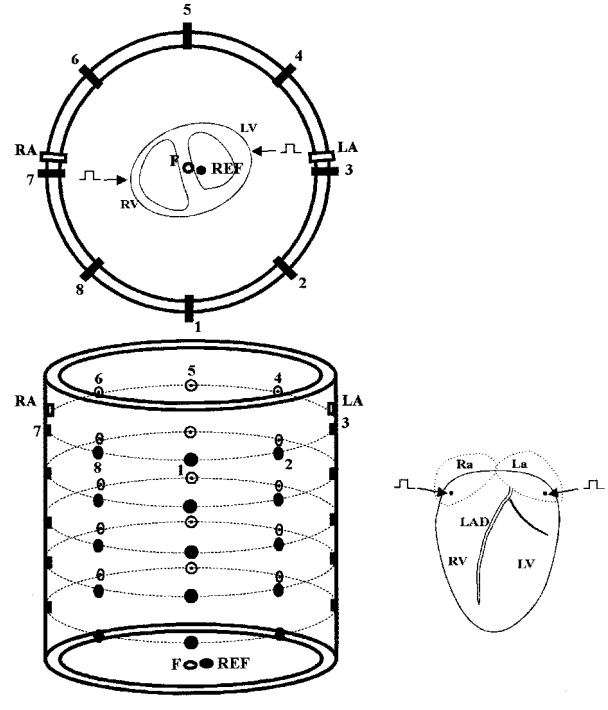

Figure 1. *Schematic diagram with top and side views of the chamber showing the distribution of all electrodes used for ECG recordings, including the 5 × 8 electrode array and the electrodes used for standard ECG. F = foot; LA = left arm; RA = right arm; REF = reference. The diagram also shows the relative position of both stimulating electrodes located in the base of the left ventricle (LV) and right ventricle (RV) below the atrial appendages. La = left atrium; LAD = left anterior descending coronary artery; Ra = right atrium.*

Experimental Protocol

An equilibration period was allowed for the heart to be free of arrhythmias before the protocol was started, which usually was within 30 minutes of perfusion with normal Tyrode's solution. The RV and LV were stimulated at twice diastolic threshold (0.4 to 0.7 mA) with rectangular pulses of 20-msec duration, with bipolar electrodes of Teflon-coated stainless-steel wires. The stimulation electrodes were carefully hooked at the midpoint of the base of each ventricle, below the atrial appendage, as shown in Figure 1.

The hearts were driven by trains of stimuli at a basic cycle length of 400 msec over a period sufficient to reach steady-state conditions (50-beat pulse trains). Single premature stimuli (S2) were applied after pulse trains, at four different S1-S2 coupling intervals of 300, 250, 200, and refractoriness + 5 msec. The stimulus train (S1) and the premature stimulus (S2) were delivered by a programmable stimulator (DTU 101, Bloom Associates Ltd., Reading, PA, USA).

To measure the effective refractory period (ERP), premature coupling intervals (S1-S2) were decreased progressively in steps of 5 msec until ventricular refractoriness was reached. The preparations were stable and exhibited normal ECG signals for more than 3 hours of perfusion, although typically the experiments were concluded in <1 hour.

ECG Variables

From each measured electrogram, the following ECG duration variables were measured. Associated dispersion was calculated from each duration variable as the difference between the maximum and the minimum (expressed as Δ) or as the standard deviation (SD) of the variables considered.

QRS: Interval measured in milliseconds from the onset of the Q wave to the offset of the S wave

JTpeak: Interval measured in milliseconds from the J point to the peak of the T wave (J point to T peak)

JTend: Interval measured in milliseconds from the J point to the end of the T wave (J point to T end)

QTpeak: Interval measured in milliseconds from the beginning of the QRS complex to the peak of the T wave (Q onset to T peak)

QTend: Interval measured in milliseconds from the beginning of the QRS complex to the end of the T wave (Q onset to T end)

Tp-e: Interval measured in milliseconds from the peak of the T wave to the end of the T wave (T peak to T end).

Data Acquisition

The signals were amplified by custom-built amplifiers with a gain between 1,000 and 10,000×, and a bandwidth between 0.05 and 300 Hz. Recordings were digitized at 1 kHz and 12-bit resolution, with a digital acquisition board (LabPC+, National Instruments, Austin, TX, USA). The signals, if necessary, were digitally filtered for 50-Hz noise. All data were processed using custom-built software made in Borland C++ 5.01 running under Windows 98. Fifty consecutive beats, including the premature beat, for the 40-electrode array were acquired simultaneously and stored on hard disk. This process was repeated for each coupling interval. The stimulation protocol was performed for the RV and LV as many times as necessary to obtain a complete set of high-quality signals. Normally this procedure requires one or two sequences of stimulation.

For the purpose of analysis, the 48th and 49th beats from each of the 50 pulse basic drive trains were averaged as control. Variables were measured for these selected beats and for each of the premature beats at the different coupling intervals. This sequence was repeated for each of the 40 recording electrodes. For each experiment, the duration variables are expressed as the mean values of the 40 leads and the dispersion variables are expressed as either SD or Δ of the same recording electrodes. Data from the 12 experiments are expressed as mean $\pm$ SEM.

The software allowed us to monitor and store all the channels on a hard disk. Analysis of the ECG variables was carried out manually by two experimented observers using a calibrated cursor. The end of the T wave was defined as the intersection of the tangent of the T wave downslope with the baseline.

This process requires manual measurement of $>14{,}000$ beats. The software allowed measurement of variables with a time resolution of 1 msec. The background noise level was <20 μV.

To verify the reproducibility of the measurement methodology, 1,000 randomly selected recordings were analyzed by a third observer. Interobserver differences between both groups were not significant and were $<5\%$.

Statistical Analysis

Data from the 12 experiments were averaged. Variables were analyzed by one-way analysis of variance, and comparisons between control and other groups of data were performed using Bonferroni post-hoc test. $P < 0.05$ was considered statistically significant.

Results

To determine the influence of the site of stimulation on ventricular dispersion of repolarization, the heart was stimulated from both the RV and LV in a randomized sequence. Premature stimulation was introduced at different coupling intervals. The longest S1-S2 was equal to the basic cycle length (400 msec), and the shortest S1-S2 was equal to refractoriness + 5 msec (165 $\pm$ 7.5 msec and 170 $\pm$ 12.9 msec for RV and LV, respectively; P = NS).

A representative experiment is shown in Figure 2. This figure shows the dispersion of repolarization, expressed as the SD of both JTend and JTpeak intervals as a function of the coupling interval. From an S1-S2 of 300 msec, coupling intervals were shortened in steps of 10

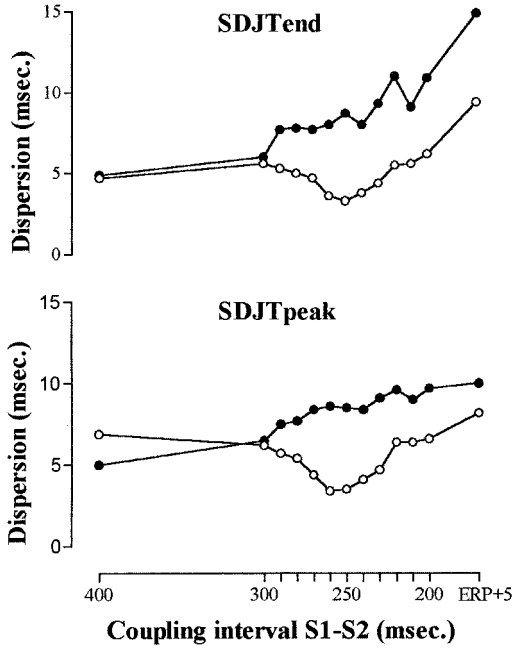

Figure 2. *Data from a single experiment showing mean values for standard deviation of JTend (top) and JTpeak (bottom) when stimulated from the left ventricle (open circles) and the right ventricle (closed circles). The coupling intervals were varied in 10-msec steps between 300 and 200 msec to demonstrate the modulated response in more detail.*

msec until S1-S2 was 200 msec. When premature stimuli were applied to the LV (open circles), a biphasic behavior in the dispersion variables was observed. Both SDJTend and SDJTpeak decreased progressively as the coupling interval was decreased between 300 and 250 msec. However, when premature stimuli were decreased further (from 250 to ERP + 5 msec), an increase in both variables was observed, attaining levels that were even greater than control. In contrast, when stimuli were applied to the RV (filled circles), both variables increased monotonically.

Figure 3 shows mean ± SEM of both JTpeak and JTend intervals (open squares) measured during the premature beat elicited at different S1-S2 intervals. Repolarization duration variables decreased monotonically as the coupling interval was shortened, either during RV or LV pacing. Mean ± SEM of both SDJTend and SDJTpeak also are plotted in the figure (filled circles). Dispersion of repolarization was significantly decreased at a coupling interval of 250 msec, only when stimuli were applied to the LV. With further decrease of the S1-S2 interval, the dispersion values increased to higher levels than those measured during basic cycle length. In contrast, when the heart was paced from the RV, as the S1-S2 interval was shortened, dispersion of repolarization was monotonically increased, exhibiting the trend to be greater at shorter S1-S2 coupling intervals. Mean ± SEM values of the duration and dispersion of QRS are shown at the bottom of Figure 3. The depolarization process did not seem to be different when stimuli were

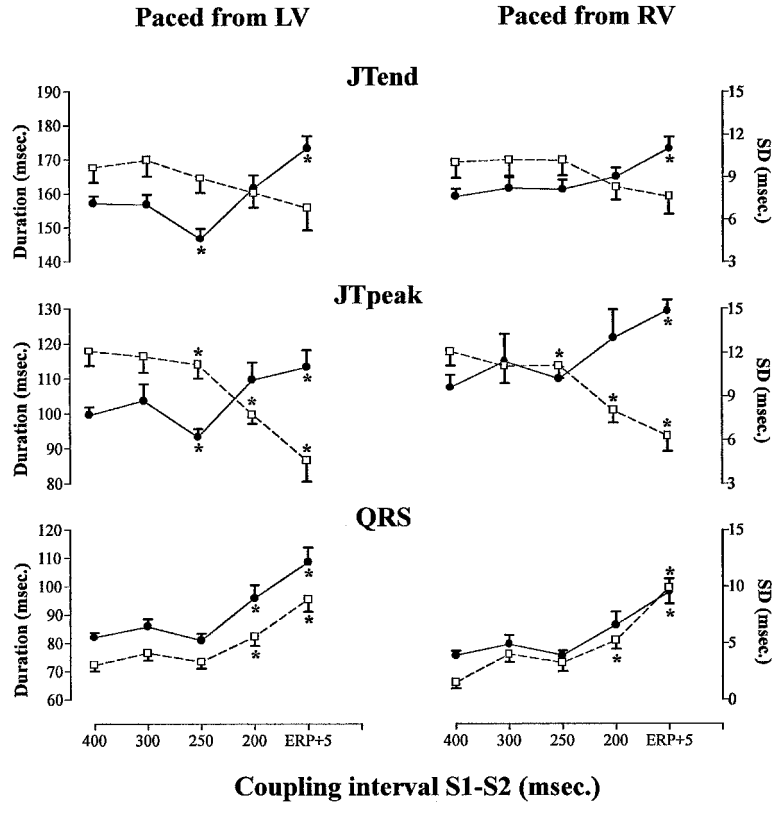

Figure 3. *Data from 12 experiments showing mean ± SEM for duration (open symbols) and standard deviation (solid symbols) of JTend (top), JTpeak (middle), and QRS (bottom) intervals, when hearts were paced at 400 msec from the left ventricle (LV) and right ventricle (RV) at various coupling intervals. *P < 0.05 compared with control (400-msec coupling interval).*

applied from either the LV or the RV, because both variables exhibited a similar behavior as the S1-S2 interval was shortened.

Figure 4 shows the spatial distribution of JTend duration at three different coupling intervals for stimuli applied at the LV and RV. Data are from a single experiment. A more homogeneous spatial distribution of JTend intervals at S1-S2 = 250 msec can be seen when the stimuli were applied at the LV.

Mean ± SEM of all the variables measured are summarized in Table 1. All the dispersion variables calculated when the heart was paced from the LV showed the same biphasic modulation, achieving the minimum value at S1-S2 = 250 msec. This also was true when dispersion variables were calculated as the difference between extreme values. SDQTpeak, ΔJTpeak, and ΔQTpeak also exhibited a minimum value at a coupling interval of 250 msec; however, these changes were not significantly different from control.

In contrast, when stimuli were applied at the RV, all dispersion variables increased as the S1-S2 interval was shortened.

Discussion

The most important finding of the present study is the differential behavior in the modulation of dispersion of repolarization depending on whether premature stimuli were elicited at the RV or the LV. When stimuli were applied to the RV, the dispersion of repolarization increased monotonically as the S1-S2 interval was shortened. In contrast, when stimuli were elicited at the LV, a biphasic behavior of the dispersion of repolarization exhibiting a dip at a critical coupling interval was found. This differential response according to the site of stimulation was not previously reported. Our data are concordant, in part, with those reported by Laurita et al.[17,18] These authors showed that premature stimulation caused biphasic modulation of dispersion in APD optically recorded from the guinea pig ventricle. This analogy may support further the fact that dispersion of APD would be reflected accurately by dispersion of either the JT or QT interval.

Our data showed that analysis of QRS duration, when stimulated from the RV or the LV, followed almost the same pattern, without evidence of differences in activa-

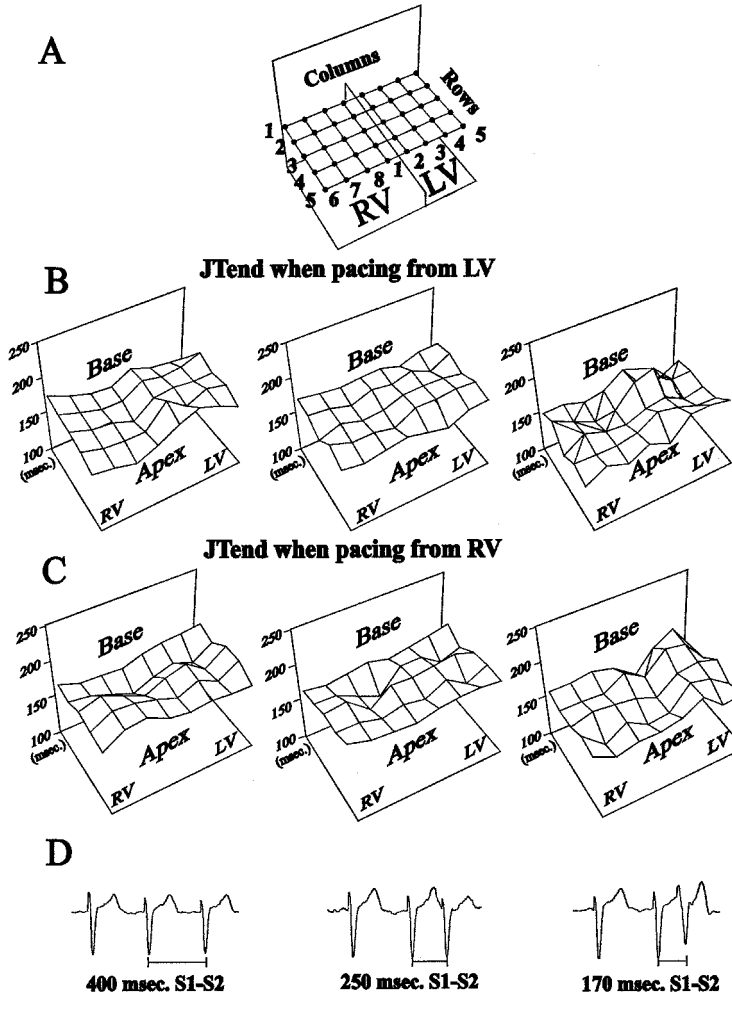

Figure 4. *Electrode recording system used to obtain the spatial distribution three-dimensional maps of repolarization duration. (A) Distribution of the 40 recording electrodes used and its spatial location with respect to the heart. JTend duration is shown on the y-axis. On the z-axis, electrodes in rows 1 and 5 correspond to the heart base and apex, respectively. On the x-axis, columns 2–5 and 6–1 show the left ventricle (LV) and right ventricle (RV), respectively. (B,C) Spatial distribution of repolarization duration measured during stimulation at three different coupling intervals (400, 250, and 170 msec) applied at the LV and RV for a single experiment. The lowest dispersion, illustrated by the smoother pattern of the three-dimensional map, is achieved for S1-S2 = 250 msec (middle column), when premature stimuli were applied at the LV. (D) Representative electrograms for each of the S1-S2 premature stimuli, when pacing from the LV.*

TABLE 1

Influence of Shortening Coupling Interval on Dispersion Variables Depending on Site of Stimulation

Dispersion Variable (msec)	Coupling Interval (msec)							
	Stimulus from Right Ventricle				Stimulus from Left Ventricle			
	400	300	250	200	ERP + 5	400	300	250	200	ERP + 5
SDJTpeak	9.6 ± 0.88	11.4 ± 1.88	10.2 ± 0.84	13.0 ± 1.96	14.9 ± 0.73*	7.7 ± 0.55	8.7 ± 1.13	6.2 ± 0.55*	10.1 ± 1.20	11.0 ± 1.16*
SDJTend	7.6 ± 0.55	8.2 ± 0.86	8.1 ± 0.70	9.0 ± 0.63	11.0 ± 0.83*	7.1 ± 0.52	7.0 ± 0.73	4.6 ± 0.72*	8.0 ± 0.90	11.0 ± 0.86*
SDQTpeak	9.6 ± 1.01	11.9 ± 1.80	10.1 ± 0.90	13.6 ± 1.93	16.9 ± 1.13*	7.8 ± 0.60	8.8 ± 1.03	7.2 ± 0.63	10.4 ± 1.00	12.8 ± 1.23*
SDQTend	8.0 ± 0.66	8.8 ± 1.00	8.4 ± 0.70	10.5 ± 0.93	13.4 ± 1.43*	7.9 ± 0.50	7.7 ± 0.73	5.4 ± 0.66*	9.8 ± 1.10	12.8 ± 1.33*
SDTp-e	9.0 ± 0.95	10.8 ± 1.56	10.6 ± 0.75	12.9 ± 1.53	14.8 ± 0.80*	8.3 ± 0.78	8.7 ± 1.20	6.3 ± 0.69*	10.1 ± 1.03	13.6 ± 1.10*
ΔJTpeak	39.9 ± 3.81	44.1 ± 7.20	43.6 ± 3.47	54.1 ± 8.77	56.4 ± 4.10*	32.4 ± 2.48	43.3 ± 7.3	28.3 ± 3.00	42.0 ± 4.50	44.0 ± 5.20
ΔJTend	35.8 ± 2.48	38.3 ± 5.13	36.9 ± 3.44	38.2 ± 2.77	52.2 ± 4.50*	31.8 ± 2.25	29.8 ± 3.66	20.5 ± 3.11*	35.6 ± 3.43	43.6 ± 3.26*
ΔQTpeak	40.3 ± 4.10	50.2 ± 7.63	44.3 ± 3.58	60.6 ± 10.90	68.2 ± 4.50*	33.9 ± 2.82	46.1 ± 7.56	33.6 ± 3.78	43.4 ± 3.60	47.9 ± 5.43
ΔQTend	36.3 ± 2.82	41.2 ± 5.10	39.4 ± 3.66	48.2 ± 5.96	63.7 ± 7.93*	34.5 ± 2.14	35.6 ± 3.73	24.9 ± 3.35*	41.3 ± 4.13	56.5 ± 6.30*
ΔTp-e	38.6 ± 4.24	43.9 ± 6.90	41.8 ± 3.38	53.2 ± 7.40	58.1 ± 3.90*	35.6 ± 3.26	41.3 ± 6.33	27.2 ± 2.94*	47.0 ± 5.96	48.3 ± 3.73

Mean values ± SEM of the 12 experiments showing all dispersion variables measured for different coupling intervals when stimuli were applied to the left and right ventricle. ERP + 5 = effective refractory period + 5 msec.

* $P < 0.05$ vs 400 msec.

tion time or conduction during the depolarization phase of the heart.

All dispersion variables exhibited a minimum value at an S1-S2 interval of 250 msec, as shown in Table 1. However, the minimum value measured for SDQTpeak, ΔJTpeak, and ΔQTpeak was not statistically different from control. Therefore, we could speculate that the dispersion of early repolarization was less affected by extrastimulation. On the other hand, our data also show that a clear difference exists in the behavior of Tp-e dispersion depending on the site of stimulation. The final portion of the T wave, as that measured by the Tp-e interval, has been proposed to reflect transmural dispersion of repolarization.[21]

The mechanism responsible for differential modulation of dispersion of repolarization by premature stimulation depending on the site of pacing is not clearly explainable with our current data. Systematic heterogeneities of APD restitution across the epicardial surface accounted for the modulated biphasic response found by Laurita et al.[17,18] These authors found that faster restitution kinetics were closely associated with longer baseline APD. These results also would help explain the presence of a dip in the amount of dispersion when stimuli were applied from the LV. However, it would be difficult to explain why this behavior disappeared when stimuli were applied from the RV. Differences in the anatomic properties of the RV and LV, specifically their dissimilar three-dimensional structures, could be considered an explanation of the results. It could be hypothesized that different anisotropic properties of both ventricles, associated with dissimilar wall thickness and fiber orientation, partially contribute to the explanation of our data. The sequence of propagation could be altered by differences in anisotropic properties; hence, electrotonic influences must change accordingly. Mendez[22] demonstrated a strong influence of electrotonus in APD. Thus, it is at least theoretically possible that APD is affected by this modification in the electrotonus secondary to changes in activation pattern, as shown by Lesh et al.[23] These authors showed that, in a modeled anisotropic bidimensional syncytium, the APD was dependent on the direction of propagation. Moreover, a greater degree of heterogeneity in APD, that is, an increase in dispersion of repolarization, was found when propagation proceeded across, rather than along, the fiber axis.

Finally, the use of ECG data to measure dispersion of repolarization must be considered a methodologic restriction, and the analysis may be limited only to this experimental model. Additional studies are needed to determine the mechanisms of this differential behavior in the modulation of dispersion of repolarization depending on the site of stimulation.

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