Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Structural Barrier Increases QT-peak Dispersion in Swine Left Ventricle *in Vivo*

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Abstract--QT dispersion (QTD) is thought to represent the regional nonuniformity of ventricular repolarization and can serve as a prognostic marker for vulnerability to ventricular arrhythmias and risk for sudden cardiac death (SCD). In this study, we used an *in vivo* swine model to investigate the change of QT-peak dispersion before and after the introduction of a left-ventricular (LV) free-wall structural barrier (SB). Baseline and post-ablation pacing were delivered to: (i) the epicardial LV base, (ii) the epicardial LV apex, and (iii) the right ventricular (RV) endocardium. Four unipolar electrograms were measured from LV free wall epicardial sites referenced to an intrathorax electrode. An SB (~4 x 1 x 1 cm (length, width, depth)) was created by cryoablation in the middle of the two electrode pairs. QTD was computed as the difference between QT-peak intervals for each beat from two electrodes across the SB region from one another. A significant increase of QTD occurred ($p<0.05$) after the introduction of the SB in all six animals. These results may reflect the accentuation of anatomical repolarization heterogeneity due to SB disruption of electrotonic coupling. Given the link between dispersion of repolarization and initiation of reentry, these findings are consistent with the increased arrhythmia risk of structural heart disease.

Keywords—QT-peak dispersion, Ventricular arrhythmia, Structural barrier, Cryoblation.

I. INTRODUCTION

Increased heterogeneity of ventricular repolarization facilitates and provides a substrate for reentry and the development of ventricular arrhythmias [1-3]. A noninvasive way to assess increased dispersion of repolarization is the measurement of QT dispersion (QTD). QTD is measured as the difference between the maximal and minimal QT intervals from a standard 12-lead ECG [4-5]. A number of studies have shown that an increased QT dispersion is a risk indicator for arrhythmic events and sudden cardiac death [6-10], and also a marker for cardiovascular disease [11-14].

It has been reported that QTD is related to the amount of dysfunctional but viable myocardium [15]. A recent study of patients with ischemic cardiomyopathy showed that QTD was significantly greater in cases with larger amounts of nonviable scar tissue [16]. Experimentally, it has been reported that spatial dispersion of ventricular repolarization increases with the introduction of a structural barrier (SB) in guinea pig hearts *in vitro* [17]. However, the direct relationship between QTD and scar tissue (or SB) has not been investigated *in vivo* and/or in large animals.

The dispersion of ventricular repolarizaton was recently investigated in swine *in vivo* [18]. Epicardial ventricular repolarization dispersion was observed, reflecting the presence of anatomical ventricular repolarization heterogeneity. These findings are consistent with anatomical repolarization heterogeneities known to exist in other species. Uncoupling of such heterogeneities may explain the increase in repolarization heterogeneity after introduction of an SB in the aforementioned guinea pig study [17].

In this study we investigated the relationship between the introduction of an SB and the change of QTD in an *in vivo* swine model. We use cryo-ablation in an open chest model. We investigate QTD, before and after ablation, at a range of heart rates to investigate whether ventricular repolarization dispersion is independent of heart rate [19-20].

II. METHODOLOGY

1) Experimental procedure:

We investigated the variability of QT-peak dispersion before and after the introduction of an SB in six ~100 lb Yorkshire pigs. All procedures were approved by the institutional Animal Care and Use Committee of Weill Medical College of Cornell University.

Animals were sedated with an intramuscular injection of telazol (200mg) and xylazine (100mg). The right common femoral vein was surgically exposed. A 7FR sheath was inserted into the femoral vein over a 0.035-inch guide wire. A quadripolar electrophysiology catheter (Bard EP, Billerica, MA) was advanced to the right ventricular endocardial surface under fluoroscopic guidance. The heart was exposed via median sternotomy. Baseline pacing, (square pulse stimuli of 2 ms duration and 2 mA or 2 x diastolic threshold current, whichever is greater), for 128 beats at cycle lengths (CL) of 400, 350, 325, 300, 290, 280, 270, 260, 250 ms was delivered to three separate sites. The three sites were: (1) LV epicardial apex via mid-myocardial bipolar stimulation electrodes, (2) LV epicardial base via mid-myocardial bipolar stimulation electrodes, (3) RV endocardium via two poles of the quadripolar catheter. The order of pacing sites was randomized.

Four unipolar electrograms were measured (locations annotated by 'x' in Fig. 1) from LV free wall epicardial sites referenced to an intrathorax electrode. After baseline pacing, an SB (~4 x 1 x 1 cm (length x width x depth)) was cryoblated in the middle of the two electrode pairs (location shown Fig. 1). Cryoablation was applied for 3 min. using a Frigitronics CCS 200 cardiac cryosurgical system at -65C using a cylindrical CCSA-200 Maze Linear Probe (diameter: 0.5 cm; length: 3.5 cm) placed on the tissue. 15 minutes post-ablation, the pacing protocol was repeated. All signals were bandpass filtered at 0.05-400 Hz and digitized at 1000 Hz by a PCI-DAS 1602-16 16-bit data acquisition board and recorded on an AMD K6-II computer running our custom Real-Time Linux experiment interface system [27].

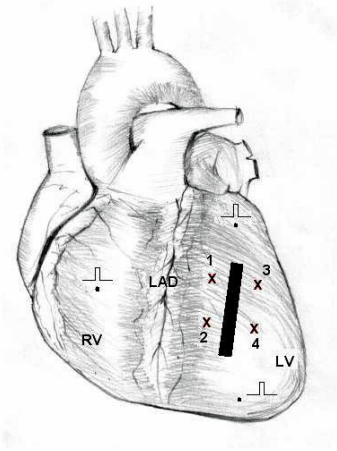

Fig. 1: Schematic of electrode and cryoablation lesion (i.e., structural barrier; SB) positions. Black rectangular bar indicates the position of SB, electrode pairs (1 vs 3, 2 vs 4, labeled with 'X') are on the either side of the SB. Pacing sites on LV epicardial apex, base and RV endocardial surface are annotated with ⊓. Stimulus sites and electrode locations varied slightly for different animals.

2) Histological analysis

6 transmural sections (Each section has a well demarcated area of myocardial hypereosinophilia which measures 0.9 x 0.3 cm), each oriented perpendicular to the linear cryoablation lesion, were taken. The first section was taken from the basal end of the lesion and the sixth was taken from the apical end of the lesion. Histological analysis was performed on each section.

3) Data analysis and computational method

QT-peak interval was measured as the time between the stimulus artifact and the T-wave apex. QT-peak interval examples, QT1 and QT2, are shown in Fig. 2. QT-peak intervals were automatically detected (with manual correction) in Matlab. QT-peak dispersion, labeled as ΔQT in Fig. 2, was computed as the difference between QT1 and QT2. Student's T-test analysis was performed to show the significance of the difference of QTD before and after the introduction of the SB. $p<0.05$ is considered to be significant.

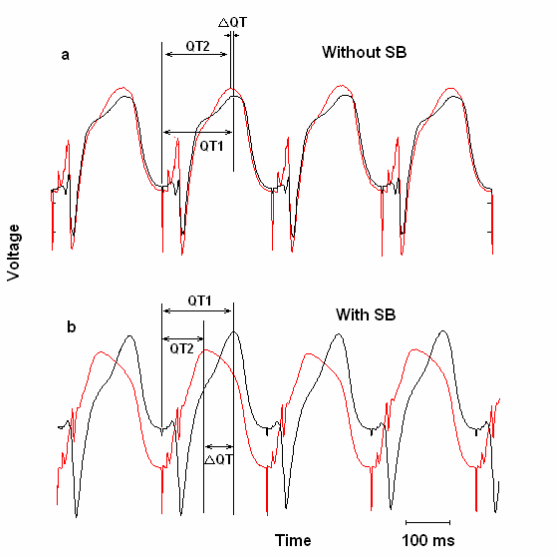

Fig. 2: Four-beat sequences from one experiment (pig 2). Pacing was delivered to LV base at CL=250 ms. Panel (a) shows the electrograms from Lead 1 (black) and Lead 3 (red) at baseline before the introduction of SB, panel (b) shows the signals from the same positions with the presence of the SB. QT1 is the QT-peak interval of Lead 1, QT2 is the QT-peak interval of Lead 3, ΔQT is the QT-peak dispersion, which is the difference between QT1 and QT2 .The increase in the interval between the T-wave peaks from Lead 1 and 3 after introduction of the SB is clear.

It is important to note that in the literature, QT dispersion is extracted from 12-lead surface ECG signals. Here, QTD was calculated from unipolar electrograms measured directly from the left ventricular epicardial surface.

III. RESULTS

1) Histology

A ~3.9 x 0.9 x 1.0 cm (length, width, depth) linear, reddish-brown lesion was noted. Each of the 6 transverse sections had a well demarcated area of myocardial hypereosinophilia extending from the epicardial surface downward into the myocardium (about ~0.8 cm. i.e., resulting from the cryo-ablation). Compared to the adjacent non-affected myocardium, affected myofibers in the hypereosinophilic area were characterized by heterochromatic nuclei and hypereosinophilic fibers (Fig. 3). In some fibers, normal cross striations are apparent while in others, tightly contracted cross striations or no cross striations are noted. In addition, at the junction

between affected and non-affected myocardium, the myofibers are pale and vacuolated.

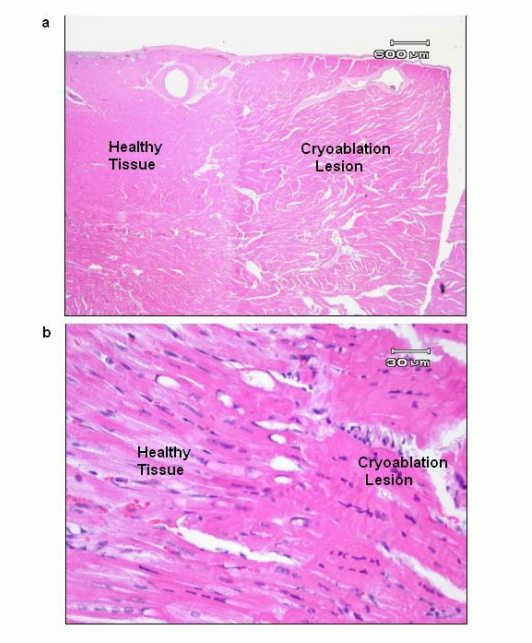

Fig. 3: Panels (a) and (b) show the histological difference between normal tissue and the cryoablation lesion region in low and high resolution, respectively. Compared to the adjacent non-affected myocardium (left side of both panels), affected myofibers in the cryoablated lesion (right side of both panels) are characterized by heterochromatic nuclei and hypereosinophilic fibers. In some fibers, normal cross striations are apparent while in others, tightly contracted cross striations or no cross striations are noted. At the junction between affected and non-affected myocardium, the myofibers are pale and vacuolated.

2) Electrophysiology

Fig. 2 shows example electrophysiological recordings, taken from pig 2 at CL=250 ms. Fig. 2a shows the electrograms from Lead 1 and Lead 3 (location as shown in Fig. 1) before the introduction of SB. The Black and red curves represent signals from Lead 1 and Lead 3, respectively. Fig. 2b shows the signals from the same positions after cryoablation of the SB. The increase of the interval between the Lead 1 and 3 T-wave peaks after SB introduction is clear.

Fig. 4 shows the QT-peak interval and cycle length (CL) relationship for pig 2. The decrease of QT-peak interval with decreasing CL, is consistent with action potential duration restitution, as would be expected given that the QT-peak interval approximates the cardiac depolarization and repolarization time. In the example in Fig. 4, at shorter CL, the dispersion of QT-peak intervals with SB is larger than for its counterpart without SB.

Typically, especially with higher pacing CL, QTD after the introduction of the SB is significantly larger than at baseline (results not shown).

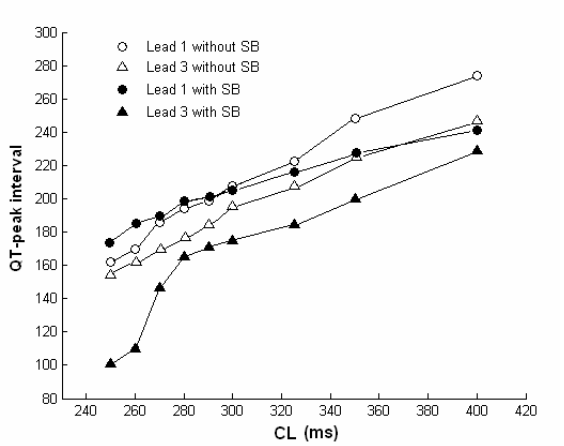

Fig. 4 shows the QT-peak interval and cycle length (CL) relationship for pig 2.

IV. DISCUSSION AND CONCLUSION

It has been reported that the dispersion of the QT interval, as well as other measures of ventricular repolarization dispersion, are independent of heart rate [19, 20]. In this study, in the presence of an SB, increased QTD was observed at moderate pacing rates. QTD either plateaued or decreased as pacing rate was further increased in the presence of an SB; at baseline (without an SB), the increase was not as obvious, although it was observed in several cases. This finding might reflect increased risk for structural heart disease patients at increased heart rates.

In this study, a significant increase of QT-peak dispersion was detected after the introduction of a structural barrier. These results may reflect the accentuation of anatomical repolarization heterogeneity as a result of structural barrier disruption of electrotonic coupling. Given the link between dispersion of repolarization and initiation of reentry, these findings are consistent with the increased arrhythmia risk of structural heart disease.

ACKNOWLEDGEMENT

This research was supported by grants from the National Institutes of Health (R01HL073644), the Whitaker Foundation (RG-02-0369) and the Kenny Gordon Foundation. Dr. Y. Gong is supported by the American Heart Association Heritage Affiliate award #0525855T.

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