The Electrocardiogram Restitution Portrait Quantifying Dynamical Electrical Instability in Young Myocardium

JA Bell, NC Rouze, W Krassowska, SF Idriss

Duke University, Durham, NC, USA

Abstract

Novel methods need to be developed to detect electrical instability in children. The dynamical properties of action potential restitution play an important role in the development of instability leading to arrhythmias. A new method, the Restitution Portrait (RP), was developed to visualize and quantify these properties at the action potential level. Here, we apply the RP method using the activation-recovery interval (ARI) from the ECG to detect, in vitro, repolarization abnormalities in neonatal and preadolescent rabbit myocardium with drug-induced Long QT Syndrome (LQTS Type 1 or Type 2). The ECG was recorded during programmed endocardial pacing to record the RP. The ECG RP demonstrated significant changes in dynamical restitution components during drug-induced LQTS compared to baseline. This study shows that the ECG RP may be an important noninvasive diagnostic tool for detecting electrical instability in the young.

1. Introduction

Long QT Syndrome (LQTS) is a genetic disorder that is characterized by episodes of syncope, ventricular arrhythmias, and sudden death in infants, children, and adolescents. LQTS is estimated to affect approximately 1 in 5000 to 10000 people. It is further implicated as one cause of Sudden Infant Death Syndrome (SIDS), the leading cause of death during infancy.[1] While the QT interval, corrected for cycle length (QTc), is an electrocardiographic (ECG) measure used to screen patients for the presence of LQTS, it is neither sensitive nor specific enough to confirm the diagnosis independently or to determine the risk of sudden death. For example, a child can have a normal QTc, yet have an ion channel mutation that creates electrical instability and risk of sudden death. Other children can have QTc prolongation without the presence of LQTS. Methods for assessing the electrical phenotype in children with LQTS must be developed. Such methods will allow determination of risk in order to guide appropriate therapy in this population.

The QTc interval is a measurement typically obtained at a steady heart rate. However, arrhythmogenesis has been linked to dynamic beat-to-beat characteristics of repolarization. Beat-wise alternation of the T-wave, T-wave alternans (TWA), is a marker of electrical susceptibility, and alternans of action potential duration (APD) has been identified as a precursor to fibrillation.[2] The mechanism for the initiation of alternans is not completely known. However, the property of APD changing as a function of rate – APD restitution – has been linked to the development of alternans.[3]

Restitution is the relationship that determines the APD in response to the length of the preceding diastolic interval (DI) and in response to the prior history of stimulation. There are several types of restitution responses, including: 1) response to pacing at a constant rate at steady-state (Steady-state restitution), 2) response to an extrastimulus (S1-S2 restitution), and 3) transient response after an abrupt change in pacing rate (Short-term memory).

Steady-state restitution is the relationship between steady-state APD values at different basic cycle lengths (BCL) and their preceding diastolic intervals (DI). The Steady-state Restitution Curve (Steady-state RC) is determined by fitting a function to the steady-state APD data plotted versus DI. One example of a fit is to an exponential function of the form: $APD=A-B*e^{(-DI/\tau)}$.

S1-S2 restitution is determined by first pacing at a constant BCL until steady-state is achieved (S1). A single extrastimulus (S2) is then applied. For one BCL, the S1-S2 coupling interval is varied to determine the response to premature and postmature extrastimuli. Traditionally, an S1-S2 restitution curve is determined by testing a range of S1-S2 coupling intervals for a single BCL. For each BCL, a different S1-S2 RC exists.

Short-term memory (STM) is the transient response when the APD changes from one steady-state value to a new steady-state value after an abrupt change in BCL. This response is also known as "accommodation" or "adaptation."

Our group has developed an algorithm to measure,

analyze and display all of these APD restitution properties as a composite "Restitution Portrait" (Figure 1).[4] This algorithm includes a custom pacing protocol (the Perturbed Downsweep Pacing, PDP) to elicit each type of restitution response. Certain restitution parameters can be determined from the RP. For the steady-state RC, the maximum slope and long-BCL asymptote of the curve are determined. For the S1-S2 restitution responses, the PDP protocol (see below) determines a segment of the full S1-S2 RC. Segments are determined for a range of BCLs and these are quantified and compared based on maximum slope of the segment, after linear regression is performed. To quantify the STM transient, the data are fit to an exponential function: $APD=A-B*e^{(-TIME/\tau)}$. Comparisons are then made based on the time constant (τ) for APD to reach a new steady-state value. These parameters of the RP, and others, have been used previously to formulate a criterion to predict stability in mathematical models of cardiac dynamics.[4]

The RP is a tool based on APD measurement, and, therefore, is not easily measured in the clinical setting. Future applicability of this technique to determine characteristics of repolarization in patients requires translation of the RP from APD measurements to electrocardiographic (ECG) measurements.

The purpose of this study was to determine if the RP created from an ECG-derived "correlate" of APD, the activation-recovery interval (ARI), can be used to detect dynamic restitution changes in young myocardium with drug-induced LQTS.

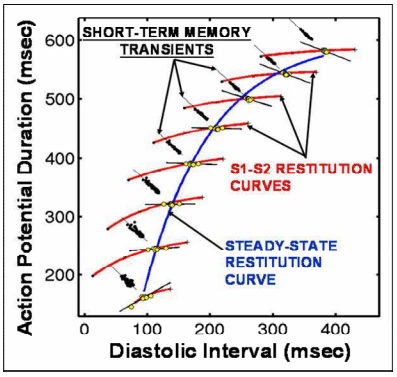

Figure 1: Restitution Portrait. *Figure based on data from Kalb et al.*[4]

2. Methods

Six neonatal (1-2 week) and four preadolescent (7 week) New Zealand White rabbits were studied. All animal studies were approved by the Duke Institutional Animal Care and Use Committee. The details of rabbit sedation, anesthesia, heart excision and perfusion have been described previously.[5] Briefly, following heart excision, aortic cannulation, and initial perfusion with a cold cardioplegia solution, the heart was submerged in a heated bath and perfused with a 37-38°C oxygenated Tyrode's solution. A constant-flow perfusion system was used with no recirculation of perfusate. Perfusion pressure was maintained between 35-45 mmHg by adjusting the flow rate. The tissue equilibrated for at least 90 minutes prior to data acquisition. A bipolar Ag/AgCl pacing electrode was used for endocardial pacing. Pacing stimulus strength was set to twice the diastolic pacing threshold.

Electrocardiograms were recorded in the bath using six Ag/AgCl electrodes configured as three orthogonal lead pairs around the heart. The recorded signals were amplified, filtered (0.1-500 Hz bandpass), sampled at 2 kHz, digitized at 14-bit resolution (PXI/SCXI data acquisition system, National Instruments, Austin, TX), and stored on a hard drive for post-processing.

Two drug-induced LQTS models were used. In some preparations, tissue was perfused with Chromanol-293b (31 μM) to block IKs and model LQT-1. In other preparations, LQT-2 was modeled by perfusing with E4031 (0.5 μM) to block IKr. In either case, data was obtained after at least 30 minutes of perfusion with the ion channel-blocking compound.

Pacing was performed using the Perturbed Downsweep Pacing Protocol (PDP protocol). The PDP protocol consisted of steady-state pacing at an initial basic cycle length (BCL0) of 1000 msec followed by a step decrease to BCL1 with inserted early (BCL1 minus 20 to 50 msec) and late (BCL1 plus 20 to 50 msec) beats (S2) at the end of two minutes of pacing (see Figure 2). In each successive run of the PDP protocol, BCL1 was decremented until persistent T-wave alternans or 2:1 capture was observed (BCL1 range: 500 msec to 200 msec). The PDP protocol was performed under normal ("control") conditions, and then repeated with either LQT-1 or LQT-2 model.

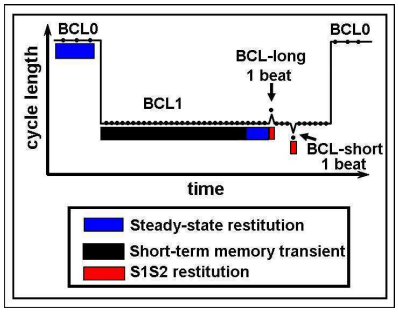

Figure 2: Perturbed Downsweep Pacing (PDP) Protocol. See text for details.

Each beat of the recorded ECG was analyzed to determine activation and recovery time and the QT interval. Activation time was defined as the time of the first maximum slope of the QRS complex. Recovery

time was defined as the time of the maximum slope of the upstroke (positive T-wave) or of the minimum slope of the downstroke (negative T-wave). The activation-recovery interval (ARI) for a beat was defined as the recovery time minus the activation time (see Figure 3).[6] The recovery-activation interval, the ECG diastolic interval, was defined as the activation time of the beat minus the recovery time of the preceding beat (RAI). The ECG RP was created by plotting ARI as a function of RAI for each of the three types of restitution responses. Steady-state slopes were determined by fitting the steady-state ARI data to an exponential, as described above. The slopes of the S1-S2 RC segments were determined through linear regression. For STM, the ARI transients were fit to an exponential function of time, as described above.

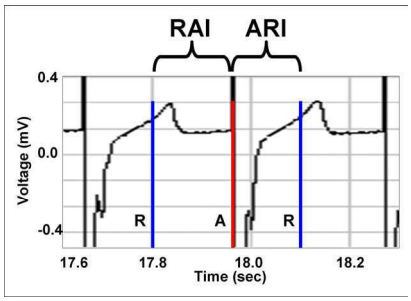

Figure 3: Measurement of activation-recovery interval (ARI) and recovery-activation interval (RAI). See text for details.

3. Results

Figure 4 shows the average QTc intervals for two age groups when pacing at BCL = 1000 msec for each state: normal, LQT-1, or LQT-2. The QTc interval did not significantly change with the addition of Chromanol-293B (LQT-1). In infant, QTc intervals were significantly longer for LQT-2 than for Normal or LQT-1 ($p<0.05$).

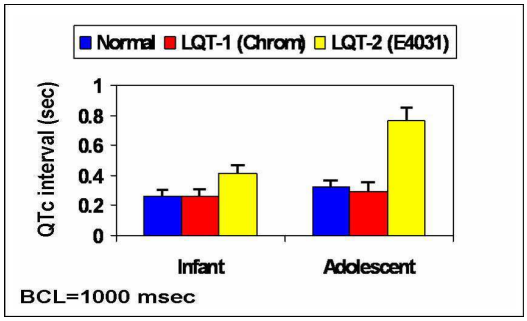

Figure 4: QTc intervals in infant and adolescent myocardium for normal, LQT-1, and LQT-2 conditions.

An example of the ECG RP for an infant preparation under normal and LQT-1 conditions is shown in Figure 5. The RP revealed underlying differences in repolarization. At the longest RAI (BCL = 1000 msec), there was no substantial difference in ARI between normal and LQT-1. However, at shorter RAI, the two RPs diverged. For LQT-1, in this example, two components of the RP, the steady-state RC and the short-term memory responses were different compared to normal. The S1-S2 RC segments were not substantially-different between Normal and LQT-1 (slope range: -0.02 to 0.15, Normal versus -0.23 to 0.26, LQT-1).

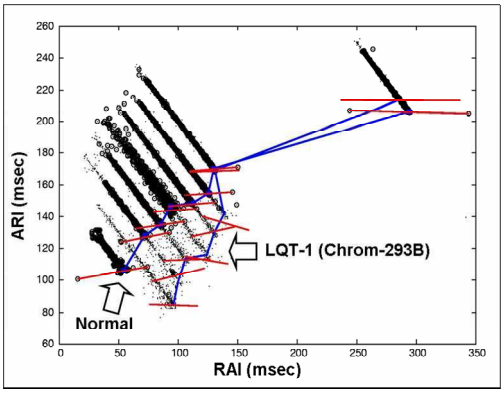

Figure 5: Example of ECG RP in infant myocardium. Steady-state RC, S1-S2 RC segments and STM transients are shown for both Normal and LQT-1conditions.

The steady-state RC for LQT-1 was steeper (maximum slope LQT-1 = 1.97 versus Normal = 0.93). The STM transients had similar characteristics as that seen in STM transients using APD.[5] The STM time constant was long (tens of seconds), indicating that relaxation of the ARI to steady-state takes minutes. STM τ increased slightly with decreasing BCL for both Normal and LQT-1 conditions (Figure 6).

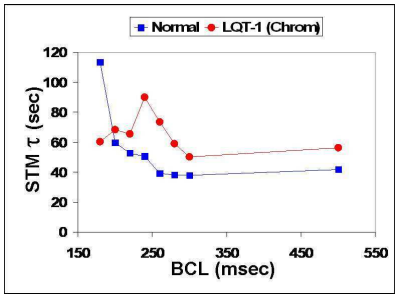

Figure 6: STM τ vs. BCL for infant ECG RP example in Figure 5.

An example of the ECG RP for an infant preparation under normal and LQT-2 conditions is shown in Figure 7. The ECG RP is significantly shifted for LQT-2 compared to Normal. ARI is prolonged for LQT-2 over all tested BCLs. The steady-state RC was steeper for LQT-2 compared to Normal (maximum slope 1.62 versus 0.77, respectively). As with the LQT-1 model, the S1-S2 RC

segments were shallow and were not substantially different (slope range: -0.02 to 0.0 for Normal; 0.11 to 0.15 for LQT-2).

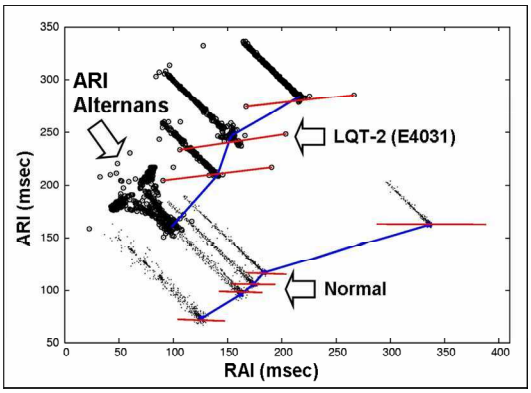

Figure 7: Example of ECG RP in infant myocardium under Normal and LQT-2 (E4031) conditions. Steady-state RC, S1-S2 RC segments and STM transients are shown for both Normal and LQT-2.

For the shortest tested BCL (260 msec) in the LQT-2 condition, alternans of the ARI was induced at the beginning of the STM transient (Figure 7). The amplitude of ARI alternans was large for over 70 beats after the change to BCL = 260 msec (Figure 8). This is in contrast to the normal condition where ARI alternans was not present. The observation of ARI alternans under LQT-2 conditions indicated loss of dynamical stability in the tissue.

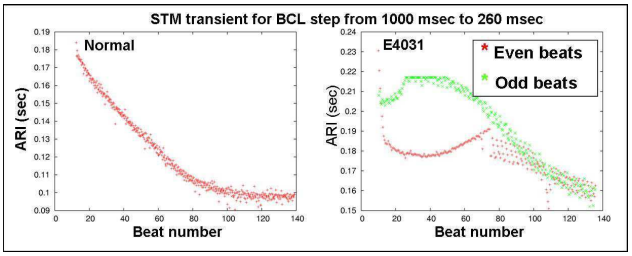

Figure 8: ARI plotted as a function of beat number after the transition from BCL = 1000 msec to 260 msec for the example ECG RP in Figure 7. ARI alternans (odd/even beat separation) is observed under E4031 (LQT-2) conditions whereas it was not present under normal conditions in the same preparation.

4. Discussion and Conclusions

In this *in vitro* tissue model, the ECG RP, determined using ARI measurements, was qualitatively similar to RPs determined using cellular measurements of action potential duration. The steady-state RC of the ECG RP had similar shape and slope values as that previously reported for AP RPs in adult rabbit myocardium [5]. The slope ranges of the S1-S2 RC segments were also similar. The time-constant for STM also was similar using ARI measurements as compared to APD measurements. The findings support the ECG RP as a reflection of the AP RP of the underlying myocardium.

In this study, the ECG RP revealed significant dynamic restitution changes in infant and adolescent myocardium under LQTS conditions (LQT-1 or LQT-2). In the case of LQT-1, these changes were evident despite lack of significant differences in the QTc. These preliminary findings suggest that the ECG RP may be a more sensitive tool to detect repolarization abnormalities under these two LQTS conditions.

Further studies should be performed to determine the utility of the ECG Restitution Portrait in assessing repolarization function in humans.

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Address for correspondence

Jamie Bell
PO Box 97230
Duke University
Durham, NC 27707
jamie.bell@duke.edu