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Cardiac Repolarization Instability During Normal Postnatal Development

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Abstract

Long QT Syndrome (LQTS) is a disease characterized by abnormal lengthening of the QT interval and by sudden cardiac death. LQTS is a disease of development with the incidence of a sudden event increasing during childhood. Repolarization instability during postnatal development could make the substrate susceptible to a fatal arrhythmia. Dynamic changes in repolarization that occur on a beat-to-beat basis, known as alternans, are a hallmark of electrical instability. T-wave alternans (TWA) in the ECG correlates with arrhythmia risk and long-term survival in adults. We determined TWA properties longitudinally *in vivo* in seven propofol-sedated NZW rabbits using transesophageal pacing weekly from 2 to 10 weeks of age. Also, TWA induction following the onset of rapid pacing was characterized *in vitro* in six infant (2 week) and six adolescent (7 week) isolated, arterially-perfused rabbit hearts. *In vivo*, TWA amplitude was maximum at 2 weeks and declined with age. Isoproterenol increased TWA at 8 weeks (adolescence). *In vitro*, large amplitude TWA was induced with rapid pacing in both infant and adolescents but decreased to low, steady-state levels in infants. We conclude that TWA properties are age-dependent in rabbit. Significant TWA is induced in rabbit at the onset of rapid pacing.

Keywords

repolarization; ontogeny; alternans; neonate; arrhythmia; adolescent

Introduction

Infants and children die suddenly from arrhythmias due to genetic diseases of cardiac repolarization, such as Long QT Syndrome (LQTS) (1). However, the age at which an arrhythmia develops is variable – despite the presence of a genetic repolarization defect prior to birth. This suggests age-dependent mechanisms are present which alter the stability of the heart's rhythm during postnatal development. Recent research in the mature heart has shown that one mechanism for destabilizing the normal periodic rhythm is linked to intrinsic, non-linear, rate-dependent properties of repolarization (2). This destabilization is manifest as repolarization alternans, a cyclic change of cardiac action potential duration that occurs on a beat-to-beat basis. Repolarization alternans at the cellular and tissue-levels is manifest on the

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body-surface as electrocardiographic T-wave alternans (TWA). Clinical observation in LQTS patients has shown that TWA is a hallmark of severe electrical instability preceding arrhythmias (3).

After birth, dramatic changes occur which could affect the dynamic properties of repolarization. Gap junctional distribution, electrotonic interactions, and cell size change with postnatal age (4-7). Developmental changes in the expression and function of ion channels governing the duration of the action potential occur, including I_{to} (8-10), I_K (10-12), I_{Ca-L} (13,14), and $I_{Na/Ca}$ (15-17). Calcium handling in the infant, also, differs at the subcellular level. The cytosolic calcium transient appears to be more dependent upon transmembrane calcium flux rather than the SR calcium cycle (13,18). We hypothesize that normal postnatal development of these electrophysiologic components alters repolarization dynamics such that there are periods during which there is an increased susceptibility to alternans. In the presence of LQTS, this susceptibility may be particularly increased.

In this paper, we present the results of two animal studies to determine if properties of TWA change during normal postnatal development from infancy to adolescence in the rabbit. The first study is an *in vivo* longitudinal investigation to determine if the onset and amplitude of TWA in response to persistent transesophageal rapid pacing changes with age under normal conditions and during β -adrenergic stimulation or blockade. The second study is an *in vitro* investigation to determine the time-dependence of TWA amplitude in response to an abrupt onset of rapid pacing in neonatal and adolescent rabbit myocardium. An example is given of how this response may change in the presence of LQTS (LQT type 2), induced by blockade of I_{Kr} after perfusion with E4031.

Methods

All animal studies were approved by the Duke University Animal Care and Use Committee.

T-wave Alternans in the Developing Rabbit, *In Vivo*

Transesophageal atrial pacing was performed weekly from 2-10 weeks of age in seven New Zealand White infant rabbits. Pregnant, late gestation, rabbits were purchased and housed in the Duke University Vivarium until parturition. Alternatively, mothers with one week old kits were also purchased. The mother and rabbit kits were housed together in a quiet environment. Starting at approximately 10 days of age, individual infant kits were removed, studied, and returned to the cage weekly. Following weaning, the young rabbits were housed separately.

On the day of study, the infant rabbit was removed from the cage and placed in a comfortable, warm environment. Small areas of skin were shaved free of hair from the right and left forelegs and hindlegs, anterior chest, and posterior thorax in the midline. Small ECG recording electrodes (Blue Dot) were placed at these sites and secured with tape. Each electrode site was marked on the skin with a permanent marker so the same electrode positions could be located in subsequent studies. Intravenous access was obtained. The rabbit was sedated with an initial IV bolus of propofol (1 mg/kg infused over 20-30 sec) followed by an infusion at a rate of 0.1 mg/kg/min. The rate was increased by 0.05 to 0.1 mg/kg/min every few minutes as needed to maintain comfort during placement of the esophageal electrode and during pacing. Blow-by oxygen was administered throughout the study. Periodic capillary blood gas measurements were made to ensure adequate oxygenation and ventilation. After sedation was achieved and maintained, the animal was placed in the supine position on a small surgical table. Body temperature was monitored with a skin probe and maintained at 37-38°C with a warming blanket and heat lamp. A multipolar esophageal probe was placed orally to provide the largest atrial signal on the recorded electrogram from its tip.

Transesophageal atrial pacing was performed starting at basic cycle length (BCL) which was 10 msec less than sinus rhythm RR interval. The BCL was reduced by 10 msec every 5 minutes until 1:1 AV conduction could no longer be maintained. The protocol was repeated during esmolol and during isoproterenol infusion. The sequence of drug conditions was reversed with each study.

The electrocardiogram was recorded simultaneously from three near-orthogonal body surface leads (lead I, II, and approximately V2). The ECG was amplified and band-pass filtered (10^3 amplification, 0.1-500Hz, Iso-Dam8, World Precision Instruments, WPI, Inc), digitized and sampled (12-bit A/D, 1kHz), and stored to a computer hard drive using customized acquisition software (LabView, National Instruments, Inc). The ECG was recorded for three minutes after two minutes of steady pacing at the test BCL.

Spectral analysis of the recorded electrograms was performed to detect and quantify the amplitude of T-wave alternans as described previously(19). Briefly, each recording was divided into sequential epochs of 128 consecutive beats. Within an epoch, the waveforms from each beat were time aligned according to the S1 pacing artifact preceding each beat. Spectral analysis was performed on each time point in the T-wave using the fast Fourier transform (FFT) to determine the beat-to-beat frequency characteristics at that time-point. The spectral energies for each sample in the T-wave were added to determine the summed spectral energy distribution for the entire T wave. The total alternans energy for the T-wave was taken as the summed energy at the alternans frequency (0.5 cycles/beat) adjusted for baseline noise (noise band 0.44 to 0.47 cycles/beat). The K-score was calculated as the total alternans energy divided by the standard deviation of the baseline noise. K-scores greater than three were considered indicative of significant alternans. The root mean square alternans amplitude was calculated as twice the square root of the alternans energy. Alternans analysis was performed for each of the three orthogonal leads. The alternans vector magnitude was calculated as the square root of the summed squared alternans amplitudes of each of the leads. The overall alternans amplitude was taken as the median of all epochs in a recording.

T-wave Alternans in the Developing Rabbit, *In Vitro*

The hearts of six 2-week old (infant) and six 7-week old (adolescent) New Zealand White rabbits were isolated and arterially-perfused (20). Briefly, the rabbits were pre-medicated with intramuscular ketamine (35 mg/kg) and xylazine (5 mg/kg) and then given a bolus of intravenous heparin (800 U/kg), followed by thiopental sodium (20 mg/kg). The hearts were rapidly excised and perfused with cold, high-potassium, Tyrode's solution following aortic cannulation. Both atria were removed and the atrioventricular node was cauterized. The tissue was then placed in a heated bath and perfused with oxygenated normal Tyrode's solution at 37-38°C. A constant-flow perfusion system was used with no recirculation of perfusate. Perfusion pressure was maintained between 45 and 60 mmHg by adjusting the flow rate. Tissue was allowed to equilibrate for 90 minutes prior to study.

A custom-built, bipolar pacing electrode was placed within the left ventricular cavity for endocardial pacing. Three pairs of Ag/AgCl pellet electrodes were placed in the bath to form three orthogonal ECG recording leads around the heart. The ECGs were amplified, filtered, digitized, and stored on a computer hard drive as described above, with the exception that sampling was performed at 2 kHz.

Pacing was performed with twice-diastolic threshold rectangular current pulses of 2 msec duration. Pacing trials were performed as follows: Recording of the ECG began with pacing at BCL = 1000 msec. The BCL was abruptly decreased to 500 msec for two minutes. The BCL was then reset to 1000 msec and the tissue was allowed to equilibrate for several minutes. The next trial was performed in the same manner, but with a target BCL of 300 msec. Subsequent

trials were performed with target BCLs decremented by 20 msec until 1:1 capture could no longer be accomplished following the jump to rapid pacing. In some preparations, 50 μ M E4031 (Wako Chemicals) was infused to block IKr. The pacing trials were then repeated after the tissue stabilized for 30 minutes.

Spectral analysis of the recorded bath ECGs was performed to detect and quantify TWA amplitude, as described previously(19). For the purpose of this study, TWA amplitude was determined for each sequential series of 64 beats following the abrupt transition to the target BCL in each trial.

Statistical Analysis

Statistical analysis was performed using repeated measures analysis of variance (SAS Version 9.1, Cary, NC). A p-value less than 0.05 was considered significant.

Results

T-wave Alternans in the Developing Rabbit, *In Vivo*

Baseline, unsedated, heart rate (HR) increased during the first month then gradually declined (HR in bpm, mean $\pm$ sd. (age): 268 $\pm$ 31 (1 wk), 311 $\pm$ 21 (2wk), 321 $\pm$ 29 (3wk), 311 $\pm$ 28 (4wk), 294 $\pm$ 19 (5wk), 282 $\pm$ 13 (6wk), 253 $\pm$ 36 (7wk), 229 $\pm$ 27 (9wk)). Esophageal pacing was accomplished in all rabbits, and TWA was easily inducible in all rabbits at each age. In the first month, there were no significant changes in TWA threshold heart rate (THR) as a function of age (THR in bpm, mean $\pm$ sd. (age): 377 $\pm$ 81 (2wk), 389 $\pm$ 55 (3wk), 378 $\pm$ 38 (4 wk)). THR also did not change as a function of age in the first month with the addition of either isoproterenol or esmolol infusions. However, β -blockade with esmolol significantly ($p < 0.01$) lowered the THR in the first month compared to both baseline and isoproterenol (*Baseline*: 386 $\pm$ 54 bpm, *Esmolol*: 340 $\pm$ 43 bpm, *Isoproterenol*: 399 $\pm$ 45 bpm).

TWA amplitude was age-dependent. Figure 1 shows the mean TWA amplitude for all animals as a function of age. TWA amplitude was greatest two weeks of age and then declined to significantly lower levels ($p < 0.05$) by 8 weeks. β -blockade did not substantially affect TWA amplitude at any of the ages. However, interestingly, β -stimulation with isoproterenol significantly amplified TWA amplitude at 8 weeks.

T-wave Alternans in the Developing Rabbit, *In Vitro*

Spectral analysis of the electrograms recording following a jump to rapid pacing from a basic cycle length (BCL) of 1000 msec revealed induction of both transient and steady-state TWA in each age groups. TWA induction profiles were created by plotting TWA amplitude as function of both BCL and time. An example of the TWA induction profile for one infant and one adolescent preparation is shown in Figure 2 (panels A and B, respectively). For both infant and adolescent myocardium, abrupt decreases in BCL resulted in initial large-amplitude TWA. With continued stimulation at the same cycle length, the time-dependent TWA response differed between the two age groups. The infant myocardium tended to have a large maximal TWA response followed by relative rapid decay to significantly lower TWA amplitude by the end of the two-minute pacing run. In the adolescent myocardium, there was an initial large-amplitude TWA response, as in the infant preparation. However, the adolescent myocardium had a tendency for less-rapid decay of TWA amplitude and persistence of significant TWA at steady-state, two minutes after initiating rapid pacing.

Both maximum and steady-state TWA amplitudes were measured and compared between age-groups. These results are presented in Table 1. The mean maximum TWA amplitude in adolescent myocardium was greater than in the infant, but the difference was not statistically

significant ($p=0.05$). However, at steady-state, TWA amplitude was significantly greater for adolescent preparations compared to the infant myocardium.

The TWA response to E4031 perfusion was variable. However, in some animals, there was a prominent increase in TWA inducibility. An example of one of these instances in infant myocardium is shown in Figure 3. Here the TWA profile is shown for both baseline and E4031, using the same TWA scale. Although not apparent due to the scale, the TWA profile was similar to that for an infant shown in Figure 2A. With the addition of E4031, TWA was induced at longer cycle lengths and there was a dramatic increase in TWA amplitude compared to baseline. This example illustrates how ion-channel blockade can amplify electrical instability that is present at baseline in the infant myocardium under normal conditions.

Discussion

In this paper, we present the results of two studies in which age-dependent changes in TWA properties are investigated. Previously, it has been shown that TWA is inducible in normal newborn canine myocardium(19). The results of the current study show, in a longitudinal *in vivo* rabbit model, that rapid pacing induces large-amplitude TWA in an age-range from infancy to adolescence. These results are significant given that TWA, a hallmark of electrical instability, is induced in normal, but immature, myocardium. Interestingly, the amplitude of induced-TWA was maximal at the youngest ages and decreased with development while there were no significant differences in the threshold heart rate. This suggests different mechanisms governing induction of TWA and its amplitude. This may also indicate that the most immature myocardium has the most potential for electrical instability. These data are also significant in that beta-adrenergic receptor stimulation, with the addition of isoproterenol, substantially increased TWA intensity – specifically in the pre-adolescent/adolescent age range. Therefore, it is apparent in Figure 1, that normal, but immature, myocardium, can be electrically unstable at different periods of postnatal development.

Our *in vitro* studies explore a different facet of TWA – the induction of TWA after the abrupt onset of rapid pacing. Our findings reveal that in both normal infant and adolescent myocardium, large amplitude TWA is induced with a sudden rate change. It is interesting that in the infant, TWA amplitude decreases to much smaller steady-state levels, but can be amplified with potassium-channel blockade (Figure 3). These age-dependent differences in the TWA induction profiles over time may be related to underlying developmental differences in the intrinsic dynamics of the cardiac tissue. We have recently shown that action potential short-term memory has different rate-dependent characteristics between infant and adolescent rabbit myocardium (21,22). Short-term memory, also known as accommodation, can significantly affect the initiation of alternans (23), and changes in this intrinsic property of the myocardium during development may, in part, explain the age-related differences in TWA that we report here.

Beat-wise alternation of the T-wave has been recognized as a sign of electrical instability for a century(24). More recent research has established a link between alternans of the T-wave and alternans of action potential duration in the underlying myocardium (25). The presence of action potential duration alternans enhances susceptibility for reentry by generating spatial gradients of repolarization. The severity of these gradients is dependent on the relationship of alternans phase between adjacent regions of myocardium. Spatially-concordant alternans is present when regions of myocardium alternate in-phase with each other. However, in the presence of spatial discordance – where one region is alternating out of phase with an adjacent region – large gradients of repolarization are generated and arrhythmia vulnerability is particularly increased. An increase in these dynamic beat-to-beat repolarization gradients may be reflected as an increase in TWA amplitude.

In the *in vivo* study, we demonstrated larger TWA at younger ages after three minutes of rapid pacing. Without direct action potential recordings within the myocardium, we can only speculate that spatial discordance may have been present in the younger animals. Furthermore, the electrical substrate in the infant may be less stable over time resulting in larger TWA after three minutes of pacing. In the *in vitro* study, we demonstrated that the maximum TWA amplitude, occurring soon after the onset of pacing, was significantly greater in the adolescent compared to the infant. However, this difference was substantially less by two minutes of pacing. Again, we can only speculate that the electrical substrate in the adolescent may be more prone to spatial discordance at the onset of rapid pacing.

The identification of T-wave alternans as a marker of arrhythmia susceptibility, and the refinement of techniques for detecting its presence at the microvolt-level, have had substantial impact on the care of adult patients at risk of sudden cardiac death(26). However, less is known about TWA in pediatric patients. Detection of microvolt-TWA using a commercially-available system, which was created for risk-stratification in adults, has not been entirely useful for the same purpose in children(27,28). This is perhaps the result of differences in TWA properties between young and adult myocardium, and the need for age-specific methods of detection and analysis. Sudden death risk stratification in children, based upon the detection of electrical instability, manifest as TWA in the ECG, may be achievable after characterizing and understanding age-dependent changes in the dynamic properties of repolarization.

The most common current clinical technology focuses on detecting microvolt-level TWA at steady heart rates in adults(26). However, the utility of this detection scheme may be limited in detecting electrical instability and vulnerability in the young. Transient TWA at the onset of a fast heart rate in the infant may be just as destabilizing and lead to fibrillation, despite the reduction of TWA as the tachycardia progresses for minutes. Transient electrical instability of this type may explain age-dependent differences in the mechanism of arrhythmia onset in infant patients with LQTS(3). Our data highlight the importance of understanding how non-linear dynamic repolarization properties change with age. Studies in children utilizing TWA detection with continuous recordings, such as with Holter monitoring (29), without the requirement of steady heart rates, need to be performed to elucidate the dynamic temporal characteristics of TWA in infants and children.

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Figure 1.
Average TWA amplitude as a function of age for both baseline and isoproterenol infusion conditions. Error bars = s.e.m.

Figure 2.

TWA amplitude as a function of BCL and time after transition to BCL from BCL=1000 msec. In Infant (top), an abrupt transition to BCL=140 and BCL=150 induces large amplitude TWA. With continued pacing, TWA reduces to lower steady-state levels by 80 seconds. In contrast, in Adolescent (bottom), large amplitude TWA is also induced with an abrupt cycle-length transition; however, a slower decay of TWA amplitude is observed with continued pacing to steady-state.

Figure 3.

TWA amplitude as a function of BCL and time after transition to BCL from BCL=1000 msec in adolescent at baseline and after blockade of IKr with E4031 perfusion. E4031 results in TWA induction at longer BCLs and with larger amplitude compared to baseline.

Table 1

Maximum and Steady-state TWA Amplitude

<i>TWA Amplitude</i>	<i>Infant</i>	<i>Adolescent</i>
Maximum	$48 \pm 34 \text{ uV}^{\S}$	$168 \pm 42 \text{ uV}$
Steady-state	$4 \pm 8 \text{ uV}^*$	$36 \pm 10 \text{ uV}$

[§]
p=0.05*
p=0.03