Slow Adaptation of Ventricular Repolarization as a Cause of Arrhythmia?

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Summary
Introduction: This article is part of the Focus Theme of Methods of Information in Medicine on “Biosignal Interpretation: Advanced Methods for Studying Cardiovascular and Respiratory Systems”.

Background: Adaptation of the QT-interval to changes in heart rate reflects on the body-surface electrocardiogram the adaptation of action potential duration (APD) at the cellular level. The initial fast phase of APD adaptation has been shown to modulate the arrhythmia substrate. Whether the slow phase is potentially proarrhythmic remains unclear.

Objectives: To analyze in-vivo human data and use computer simulations to examine effects of the slow APD adaptation phase on dispersion of repolarization and reentry in the human ventricle.

Methods: Electrograms were acquired from 10 left and 10 right ventricle (LV/RV) endocardial sites in 15 patients with normal ventricles during RV pacing. Activation-recovery intervals, as a surrogate for APD, were measured during a sustained increase in heart rate. Observed dynamics were studied using computer simulations of human tissue electrophysiology.

Results: Spatial heterogeneity of rate adaptation was observed in all patients. In-homogeneity in slow APD adaptation time constants ($\Delta t_s$) was greater in LV than RV ($\Delta t_s^{LV} = 31.8 \pm 13.2$, $\Delta t_s^{RV} = 19.0 \pm 12.8$ s, $P < 0.01$). Simulations showed that altering local slow time constants of adaptation was sufficient to convert partial wavefront block to block with successful reentry.

Conclusions: Using electrophysiological data acquired in-vivo in human and computer simulations, we identify heterogeneity in the slow phase of APD adaptation as an important component of arrhythmogenesis.

Monophasic action potential (AP) recordings by Franz et al. highlighted a large variability in the slow phase of APD adaptation in humans [5]. The high variability in their measurements might be due to either inter-subject variability or spatial heterogeneity in APD adaptation, as reported in animal species [6, 7]. The underlying ionic mechanisms of APD adaptation also have been investigated, showing that its slow phase is primarily driven by intracellular Na$^+$ handling and the Na$^+$/K$^+$ pump in particular [8], while the fast phase is mainly modulated by Ca$^{2+}$ and K$^+$ currents [9].

We hypothesized that spatial differences in the slow phase of APD adaptation may significantly modulate dispersion of repolarization following changes in heart rate. This paper presents a detailed combined analysis of in-vivo data and computer simulations to examine the contribution of this component to arrhythmogenesis in the human ventricle.

2. Methods

2.1 Patients and Data Acquisition

Fifteen patients (4 females; aged 35 to 72 years, median 61) with healthy ventricles were studied prior to atrial ablation, as described in [10].

Unipolar electrograms were recorded using two decapolar electrode catheters. Catheters were positioned in a base-to-apex orientation, one on the postero-inferior endocardial left ventricle (LV) wall and the other on the antero-septal right ventricle (RV) wall. Special care was taken in positioning the arrays in similar endocardial locations in all patients. Pacing was estab-
lished from the RV apex (pulse width of 2 ms, strength 2 × diastolic threshold). A period of 2 minutes was recorded from each patient following a sustained change in heart rate from intrinsic rhythm (median 767.5 ms) to a faster rate (median 500 ms).

### 2.2 Signal Analysis

Activation-recovery intervals (ARIs), defined as the difference between repolarization and activation times, were acquired from unipolar electrograms as a surrogate for APD using the Wyatt method [11], incorporated in an automated system with manual verification [12]. Local time constants of the fast and slow phases of adaptation were calculated by fitting each ARI series to a double exponential decay.

Statistical data are presented as mean ± SD. The Mann-Whitney U-test was used to determine statistical significance.

### 2.3 Human Ventricular Tissue Simulations

Computer simulations were based on the human ventricular AP model presented in [10], which allows the independent control of the slow APD adaptation phase. Model parameters were selected to replicate human endocardial AP morphology; APDs in the range of our measured ARIs, and APD restitution from our experimental recordings [10]. Tissue simulations were conducted using an isotropic monodomain model of 6 × 6 cm in size (200 × 200 mesh points, see [10]).

### 3. Results

#### 3.1 Heterogeneity in Slow Phase of APD Adaptation in the Human Ventricle

Estimated time constants of the slow phase of APD adaptation (τₘ) are shown in Figure 1A, for all recording sites and patients of the study. Inhomogeneity in slow APD adaptation, expressed as either the total range of variation (Δτ = τₘax - τₘin) or standard deviation σ(τₘ) of local time constants within each of the patients’ ventricles, was larger in LV compared to RV (ΔτₘLV = 31.8 ± 13.2 s, ΔτₘRV = 19.0 ± 12.8 s; P < 0.01; σ(τₘLV) = 11.0 ± 5.1 s, σ(τₘRV) = 7.4 ± 5.1 s, P < 0.05). Spatial heterogeneity of rate adaptation (as quantified by Δτₘ or σ(τₘ)) was observed in all patients, with 80% of patients showing more homogeneous RV than LV. No statistical differences were found in terms of the fast phase between both ventricles (data not shown).

The considerable inter-subject variability and intra-ventricular heterogeneity in the slow APD adaptation phase can be further appreciated in Figure 1B (different patients shown to highlight same inter-patient signal quality).

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**Figure 1** Variability in slow APD adaptation in the human ventricles. A: Slow APD adaptation time constants (τₘ) in LV and RV. Each dot represents one electrode in the arrays. B: Inter-subject and apico-basal differences in slow APD adaptation.
Figure 2  Generation of transient patterns of APD dispersion. A: APD adaptation after abrupt change in pacing (750 to 400 ms), for different slow adaptation time constants. Bottom panel shows steady-state APs at different pacings. B: APD dispersion due to heterogeneous APD adaptation (change in pacing as in A). Contour maps show dispersion of repolarization times (ΔRT) for the beats indicated in the top panel.

Figure 3  Unidirectional block due to transient patterns of APD dispersion. A: Small heterogeneity in adaptation (τs = 20 vs 80 s) is able to partially block wavefront propagation, but not to sustain reentry. B: Successful initiation of reentry due to a larger heterogeneity in adaptation (τs = 10 vs 100 s). Times indicated from ectopic stimulus (ms), colorbar denotes transmembrane potential (mV).
3.2 Dispersion of Repolarization by Heterogeneous Slow Phase of APD Adaptation

Based on these experimental results, a simulation study was conducted to investigate potential proarrhythmic consequences of spatial heterogeneity and variability in the slow phase of APD adaptation.

Localized areas of protracted slow adaptation were modeled as circular regions with larger $\tau_s$ than the surrounding tissue (Figure 2A), similar to optical mapping results in rabbit [7]. Selected values of adaptation time constants were in the range of our reported values of $\tau_s$ in human.

Figure 2B shows the temporal evolution of APD dispersion ($\Delta$APD = APD$_{max}$ - APD$_{min}$) due to inhomogeneities in the slow phase of adaptation, following a sudden change in pacing. APD dispersion first increases, and then goes back to zero as the tissue approaches its new steady-state. Larger differences in slow APD adaptation result in an amplification of maximum APD dispersion and its change over time.

3.3 Conduction Block/Reentry by Heterogeneous Slow Phase of APD Adaptation

It has been hypothesized that transient patterns of repolarization heterogeneity may affect the onset of arrhythmia during a series of ectopic beats [6]. We simulated this scenario by applying ectopic stimulation in the repolarization wake, in the beat of maximum transient dispersion. A small transient dispersion of repolarization was able to partially block wavefront propagation, but not to sustain reentry (Figure 3A). However, when dispersion was accentuated by increasing the difference between slow adaptation time constants, reentry was observed in the tissue (Figure 3B), solely due to heterogeneity in the slow phase of APD adaptation.

5. Conclusions

In this work, we report an in-depth examination of the slow phase of APD adaptation following an abrupt change in heart rate in the human ventricles. We identify spatial heterogeneity in the slow phase of APD adaptation as a significant moderator of transient dispersion of repolarization. These transient adaptive responses may contribute to repolarization inhomogeneities, therefore increasing vulnerability to ventricular arrhythmia.

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References