Mechanisms linking electrical alternans and clinical ventricular arrhythmia in human heart failure

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BACKGROUND Mechanisms of ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients with heart failure (HF) are undefined.

OBJECTIVE The purpose of this study was to elucidate VT/VF mechanisms in HF by using a computational-clinical approach.

METHODS In 53 patients with HF and 18 control patients, we established the relationship between low-amplitude action potential voltage alternans (APV-ALT) during ventricular pacing at near-resting heart rates and VT/VF on long-term follow-up. Mechanisms underlying the transition of APV-ALT to VT/VF, which cannot be ascertained in patients, were dissected with multiscale human ventricular models based on human electrophysiological and magnetic resonance imaging data (control and HF).

RESULTS For patients with APV-ALT k-score >1.7, complex action potential duration (APD) oscillations ($\geq$2.3% of mean APD), rather than APD alternans, most accurately predicted VT/VF during long-term follow-up (+82%; −90% predictive values). In the failing human ventricular models, abnormal sarcoplasmic reticulum (SR) calcium handling caused APV-ALT (>1 mV) during pacing with a cycle length of 550 ms, which transitioned into large magnitude (>100 ms) discordant repolarization time alternans (RT-ALT) at faster rates. This initiated VT/VF (cycle length <400 ms) by steepening apicobasal repolarization (189 ms/mm) until unidirectional conduction block and reentry. Complex APD oscillations resulted from nonstationary discordant RT-ALT. Restoring SR calcium to control levels was antiarrhythmic by terminating electrical alternans.

CONCLUSION APV-ALT and complex APD oscillations at near-resting heart rates in patients with HF are linked to arrhythmogenic discordant RT-ALT. This may enable novel physiologically tailored, bioengineered indices to improve VT/VF risk stratification, where SR calcium handling and spatial apicobasal repolarization are potential therapeutic targets.

KEYWORDS Alternans; Arrhythmia; Heart failure; Computational modeling; Simulation

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Introduction

Emergence of low-amplitude action potential voltage alternans (APV-ALT) at near-resting heart rates precedes life-threatening ventricular arrhythmias in patients with heart failure (HF).[1] APV-ALT during slow rates is the consequence of calcium transient (CaT) alternans (CaT-ALT) caused by abnormal sarcoplasmic reticulum (SR) calcium handling in HF.[2] However, the mechanisms linking APV-ALT in HF with arrhythmogenesis remain undefined.

Local repolarization time in the ventricles is activation time (AT) plus action potential duration (APD). In structurally normal animal hearts, CaT-ALT at rapid pacing rates produces arrhythmogenic repolarization time alternans (RT-ALT), for example, adjacent ventricular regions exhibiting RT-ALT 180° out of phase.[3] Discordant RT-ALT steepens repolarization gradients to promote unidirectional block and reentry[4] and is attributed to electrophysiological heterogeneities[3] and/or slowed conduction.[5]

Patients with HF are at risk of ventricular tachycardia (VT) and ventricular fibrillation (VF). Notably, failing human hearts exhibit widely remodeled electrophysiological parameters[6,7] and conduction slowing.[8] This could produce detectable APV-ALT at near-resting heart rates that transition into discordant RT-ALT to initiate VT/VF at faster rates. However, this is unestablished in the failing human ventricles and is this research's hypothesis.

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This hypothesis was tested using a computational-clinical approach. First, a clinical study established the relationship between APV-ALT and VT/VF outcome on long-term follow-up in patients with HF. To determine the mechanisms of this transition, which cannot be ascertained in vivo, multiscale computational human ventricular models (HVMs) were developed using human electrophysiological and magnetic resonance imaging (MRI) data. These HVMs, one without (control) and one with HF electrophysiology, were used to determine: (1) pacing threshold and spatial distribution of APV-ALT and RT-ALT; (2) mechanistic relationship between APV-ALT, RT-ALT, and arrhythmogenesis; and (3) key components of electrophysiological remodeling and spatial heterogeneity underlying arrhythmogenesis.

Methods

See Online Supplemental Table 1 for abbreviations.

Computational

HVMs

Anatomically accurate HVMs were derived from a high-resolution MRI scan of an adult human heart geometry and fiber orientation (Online Supplemental Section 2). They simulated transmural and apicobasal electrophysiological heterogeneity in nonfailing and failing human ventricles. The failing HVM featured a reduced transmural APD gradient from epicardial APD prolongation,[6] reduced amplitude and slow recovering CaT from deranged calcium handling,[7] and slow conduction from fibrosis and/or reduced connexin 43 expression.[8] These features make the HVM the most complete model of human ventricular electrophysiology to date (Online Supplemental Sections 2–6).

Electrical alternans pacing protocol

HVMs were preconditioned by pacing the left ventricular (LV) endocardial apex at a cycle length (CL) of 1000 ms for 20 beats with 5-ms-long stimuli at twice capture amplitude. The LV apex was then dynamically paced with a CL of 550 m and shortened by 50-ms decrements until loss of 1:1 capture or reentry. Each pacing CL lasted for 32 beats since stable electrical alternans occurred after 20–24 beats for all CLs.

APV-ALT and CaT-ALT analyses

APV-ALT was analyzed using spectral methods for each CL's last 8 beats in the electrical alternans pacing protocol.[1] APV-ALT in the failing HVM was recorded when absolute voltage alternation (V_{alt}) was more than twice the maximum control HVM V_{alt} with a pacing CL of 1000 ms. CaT-ALT was analyzed by modifying the APV-ALT spectral method to compute absolute CaT alternation (C_{alt}):

$$C_{alt} = \sqrt{\frac{\sum T}{\text{CaT duration}}} \quad (1)$$

CaT duration was computed according to Lou et al,[7] but at 90% recovery. Spectral magnitude was computed at 0.5 cycles/beat (ΣT) from peak CaT to 90% recovery. CaT-ALT in the failing HVM was recorded when C_{alt} was more than twice the maximum control HVM C_{alt} with a pacing CL of 1000 ms. Since ΣT is computed over the entire CaT, C_{alt} takes into account changes in both CaT peak amplitude and duration.

Discordant RT-ALT analysis

Spatial ventricular repolarization maps (Rmaps) were computed for each CL's last 8 beats in the electrical alternans protocol:

$$\text{Rmap}(b, i) = \text{AT}(b, i) + \text{APD}_{90}(b, i) \quad i = 0 \rightarrow n \quad (2)$$

where APD_{90} is APD at 90% repolarization, i is the HVM node, n is the total of HVM nodes, and b is the beat number. The difference in subsequent Rmaps (Rdiff) was

$$\text{Rdiff}(b, i) = \text{Rmap}(b, i) - \text{Rmap}(b-1, i) \quad b = 2 \rightarrow 8 \quad (3)$$

Discordant RT-ALT was present at i when Rdiff magnitude was >1 ms (temporal V_m resolution) and changed sign between subsequent beats. The gradient of each repolarization map was computed [∇Rmap(b, i)] to quantify repolarization gradient steepening from discordant RT-ALT.

Discordant RT-ALT mechanisms were identified using published criteria.[3,9] Nodal lines for electrical alternans, Rdiff(b, i) = 0, were calculated for each CL's last beat in the electrical alternans pacing protocol. When nodal lines approached the pacing site as CL shortened, discordant RT-ALT resulted from dynamically slowed conduction. When nodal line behavior was independent of the pacing site, discordant RT-ALT resulted from electrophysiological heterogeneities. To verify which mechanism is needed, the alternans pacing protocol was executed with different pacing sites.

Electrical alternans spatial distribution

APV-ALT, CaT-ALT, and RT-ALT distributions were determined by subdividing the HVM into 4 regions (Figure 1) using the apicobasal direction (Φ_{ab}) and transmural direction (Φ_{tran}), which are defined in Online Supplemental Section 4. Apical and basal regions were defined as HVM nodes with Φ_{ab} values below and above the midpoint Φ_{ab} value, respectively. Endocardial and epicardial regions were defined as nodes with Φ_{tran} values below and above the midpoint Φ_{tran} value, respectively. For each region, the percentage of HVM nodes with electrical alternans was calculated for each CL.

HF parameter analysis

Each HF parameter in Online Supplemental Tables 2, 5, and 6 was switched to its control value, and the alternans pacing protocol and analyses were repeated for each.