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Rate-dependent force, intracellular calcium, and action potential voltage alternans are modulated by sarcomere length and heart failure induced-remodeling of thin filament regulation in human heart failure: A myocyte modeling study

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ABSTRACT

Microvolt T-wave alternans (MTWA) testing identifies heart failure patients at risk for lethal ventricular arrhythmias at near-resting heart rates (<110 beats per minute). Since pressure alternans occurs simultaneously with MTWA and has a higher signal to noise ratio, it may be a better predictor of arrhythmia, although the mechanism remains unknown. Therefore, we investigated the relationship between force alternans (FORCE-ALT), the cellular manifestation of pressure alternans, and action potential voltage alternans (APV-ALT), the cellular driver of MTWA. Our goal was to uncover the mechanisms linking APV-ALT and FORCE-ALT in failing human myocytes and to investigate how the link between those alternans was affected by pacing rate and by physiological conditions such as sarcomere length and heart failure induced-remodeling of mechanical parameters. To achieve this, a mechanically-based, strongly coupled human electromechanical myocyte model was constructed. Reducing the sarcoplasmic reticulum calcium uptake current (I_{up}) to 27% was incorporated to simulate abnormal calcium handling in human heart failure. Mechanical remodeling was incorporated to simulate altered thin filament activation and crossbridge (XB) cycling rates. A dynamical pacing protocol was used to investigate the development of intracellular calcium concentration ($[Ca]_i$), voltage, and active force alternans at different pacing rates. FORCE-ALT only occurred in simulations incorporating reduced I_{up}, demonstrating that alternans in the intracellular calcium concentration (CA-ALT) induced FORCE-ALT. The magnitude of FORCE-ALT was found to be largest at clinically relevant pacing rates (<110 bpm), where APV-ALT was smallest. We found that the magnitudes of FORCE-ALT, CA-ALT and APV-ALT were altered by heart failure induced-remodeling of mechanical parameters and sarcomere length due to the presence of myofilament feedback. These findings provide important insight into the relationship between heart-failure-induced electrical and mechanical alternans and how they are altered by physiological conditions at near-resting heart rates.

1. Introduction

Ventricular arrhythmias are the most common cause of sudden cardiac death, resulting in >300,000 US deaths annually (Lloyd-Jones et al., 2009). The standard procedure for preventing sudden cardiac death is to implant a cardioverter defibrillator (ICD), which delivers a strong electric shock to terminate arrhythmias. Since current methods for identifying patients who require ICDs have only been partially successful (Bardy et al., 2005), there is a need for noninvasive predictors with high sensitivity and specificity. Indeed, robust methods for stratifying the risk of lethal cardiac arrhythmias

Abbreviations: APV-ALT, action potential voltage alternans; APV-ALTM, action potential voltage alternans magnitude; $[Ca]_i$, free intracellular calcium concentration; CA-ALT, $[Ca]_i$ alternans; CA-ALTM, $[Ca]_i$ alternans magnitude; CL, cycle length; $[Ca]_{Troponin}$, total calcium bound to Troponin C; FORCE-ALT, active force alternans; FORCE-ALTM, active force alternans magnitude; RU, regulatory unit; SL, sarcomere length; XB, crossbridge.

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would decrease morbidity and mortality in patients with cardiovascular disease and reduce health care costs (Goldberger et al., 2011). Approaches for stratifying risk of cardiac arrhythmias involve testing for abnormalities in the ECG, then using the results to identify patients who would benefit from ICD therapy. ECG-based risk stratification methods scan for abnormalities in ventricular depolarization (late potentials (Kuchar et al., 1987), fractionated QRS complexes (Das et al., 2006)) and repolarization (T-wave alternans (Rosenbaum et al., 1994), and QT variability, dispersion, and instability (Berger et al., 1997; Chen et al., 2011, 2013; Chen and Trayanova, 2012; Couderc et al., 2007)). However, the mechanisms underlying these ECG indices, and their relationship to lethal cardiac arrhythmias, are not fully understood. This lack of knowledge likely explains why results of clinical trials to correlate surface EGG indices to lethal cardiac arrhythmias are often contradictory (Goldberger et al., 2011).

Of the above ECG indices, T-wave alternans have received possibly the most attention. Research has reported a strong correlation between increased arrhythmia risk and the presence of T-wave alternans (Narayan, 2006; Qu et al., 2010), defined as the beat-to-beat alternation of the timing or shape of the repolarization wave of the ECG. In the clinical setting, testing for Microvolt T-wave Alternans (MTWA) has been found to be a risk marker for lethal ventricular arrhythmias and sudden cardiac death (Cutler and Rosenbaum, 2009), to have high negative predictive power (Narayan, 2006) and to be particularly promising in dichotomizing patients that would and would not benefit from ICD therapy (Bloomfield et al., 2006; Hohnloser et al., 2009). However, the mechanistic basis of MTWA preceding lethal ventricular arrhythmias has long been under debate. Until the last decade, it was believed that a steep action potential duration (APD) restitution (>1) at rapid heart rates (Weiss et al., 2006) produces alternans in APD that underlie T-wave alternans and the genesis of fibrillation (Pastore et al., 1999). However, MTWA is most successful in stratifying risk in patients at near-resting heart rates <110 bpm, where APD restitution is flat (Narayan et al., 2007). Computational models of the LV wall in combination with clinical data revealed that abnormal handing of intracellular calcium underlies alternans in action potential voltage (APV-ALT), defined as the oscillation of the plateau voltage of the action potential, which results in MTWA at moderate heart rates, i.e. <110 bpm (Bayer et al., 2010; Narayan et al., 2008). Thus APV-ALT is the cell-level driver of MTWA at these rates under the conditions of heart failure.

Alternatively, noninvasively measured pressure alternans, defined as the beat-to-beat oscillation of the amplitude of systolic pressure, has been found to be a predictor of worsening heart failure and increased cardiac mortality (Hirashiki et al., 2010, 2006; Ito et al., 2012; Kashimura et al., 2014; Kim et al., 2014; Selvaraj et al., 2011). Pressure alternans also occurs simultaneously with MTWA in patients at near resting heart rates, thus indicating that pressure alternans, which have higher signal-to-noise ratio (Selvaraj et al., 2011), may be a better predictor of the propensity for ventricular arrhythmias and sudden cardiac death, however the mechanisms remain unknown.

At the cellular level, pressure alternans arises from force alternans (FORCE-ALT), defined as the beat-to-beat oscillation in the strength of active force production in cardiac muscle. APV-ALT at heart rates <110 bpm has been found to be driven by beat-to-beat fluctuations in the amplitude of the intracellular calcium concentration (CA-ALT) (Bayer et al., 2010; Narayan et al., 2008). CA-ALT has also been shown to underlie force alternans (FORCE-ALT), in animal experiments with cardiac muscle preparations (Kihara and Morgan, 1991; Kotsanas et al., 1996; Lab and Lee, 1990; Orchard et al., 1991) and perfused hearts (Brooks et al., 1994; Lee et al., 1988), but only at fast pacing rates. Clearly, to date, no studies have investigated FORCE-ALT in human myocytes at rates <110 bpm, and although calcium dysregulation is a likely candidate, the exact mechanistic link between APV-ALT and FORCE-ALT in the failing human myocyte at the clinically important near-resting heart rates remains unknown. Therefore, our goal was to investigate the mechanisms linking FORCE-ALT to APV-ALT in the human failing myocyte, with emphasis on those acting at the clinically-relevant pacing rates of <110 bpm, and to uncover how the link between FORCE-ALT and APV-ALT is affected by various physiological conditions such as sarcomere length (SL) and heart failure induced-remodeling of mechanical parameters.

2. Methods

2.1. Human electromechanical myocyte model

To uncover the mechanism linking FORCE-ALT to APV-ALT, a mechanistically-based human electromechanical myocyte model was used. The electromechanical model combined the human endocardial ventricular membrane kinetics model by ten Tusscher et al. (ten Tusscher and Panfilov, 2006) and the myofilament dynamics model by Rice et al. (Rice et al., 2008). The 2006 ten Tusscher et al. formulation was used because it incorporated an extensive description of intracellular calcium handling, which was found to be critical in the development of APV-ALT in previous studies of human heart failure (Bayer et al., 2010; Narayan et al., 2008). The Rice et al. model, which describes the activation of the thin filament by intracellular calcium binding to Troponin C as well as thin filament binding to thick filament crossbridges (XBs) using a 5 state Markov model, was chosen because it was computationally efficient while incorporating important biophysical detail and cooperativity mechanisms. Since the Rice et al. myofilament model was developed based on rabbit data we adjusted it to match human force data. This was done by modifying XB cycling and calcium-based thin filament activation parameters following the approach in de Oliveira et al. (de Oliveira et al., 2013). To account for the differences between the ionic model used by de Oliveira et al. (the 2004 formulation of the ten Tusscher et al. model (ten Tusscher et al., 2004)) and by us (ten Tusscher and Panfilov, 2006), additional modifications to calcium-based thin filament activation were made. Specifically, we decreased thin filament activation by reducing k_{on}, a parameter regulating the binding affinity of Ca to high and low regulatory sites on Troponin C, to 95% of the baseline value used in Rice et al., in order to increase the time to peak force value so that it fell in the physiological range of human values (Mulieri et al., 1992; Pieske et al., 1996).

The ionic and myofilament models were strongly coupled by incorporating myofilament feedback on calcium dynamics (Fig. 1); this was done by incorporating a dynamic term for troponin buffering of intracellular calcium ($[Ca]_{Troponin}$) using the approach in Rice et al. Strongly coupling the models with a dynamic representation of $[Ca]_{Troponin}$ was important and necessary, because it has been shown to be crucial for accurately reproducing contractile experiment data in myocyte simulations (Ji et al., 2015). This $[Ca]_{Troponin}$ term represents the amount of calcium bound to troponin and incorporates the cooperativity of calcium–troponin binding due to strongly bound nearby XBs. However, in the 2006 ten Tusscher and Panfilov model, troponin buffering of calcium is combined with calmodulin buffering of calcium and is represented using a steady state approximation. Therefore, to incorporate feedback from the myofilament model to the ionic model, we separated the combined buffering term in ten Tusscher and Panfilov into two terms. The $[Ca]_{Troponin}$ term from Rice et al., calculated using ordinary differential equations, was used for troponin buffering of calcium, and a steady state approximation was used for