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Ventricular fibrillation mechanisms and cardiac restitutions: An investigation by simulation study on whole-heart model

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ABSTRACT

Background: The action potential duration (APD) and the conduction velocity (CV) restitution have been reported to be important in the maintenance and conversion of ventricular fibrillation (VF), whose mechanisms remain poorly understood. Multiple-wavelet and/or mother-rotor have been regarded as the main VF mechanisms, and APD restitution (APDR) and CV restitution (CVR) properties are involved in the mutual conversion or transition between VF and ventricular tachycardia (VT).
Methods and results: The effects of APDR (both its slope and heterogeneity) and CVR on VF organization and conversion were examined using a "rule-based" whole-heart model. The results showed that different organizations of simulated VF were manifestations of different restitution configurations. Multiple-wavelet and mother-rotor VF mechanisms could recur in models with steep and heterogeneous APDR, respectively. Suppressing the excitability either decreased or increased the VF complexity under the steep or shallow APDR, respectively. The multiple-wavelet VF changed into a VT in response to a flattening of the APDR, and the VT degenerated into a mother-rotor VF due to the APDR heterogeneity.
Conclusions: Our results suggest that the mechanisms of VF are tightly related to cardiac restitution properties. From a viewpoint of the "rule-based" whole-heart model, our work supports the hypothesis that the synergy between APDR and CVR contributes to transitions between multiple-wavelet and mother-rotor mechanisms in the VF.

1. Introduction

Sudden cardiac death (SCD) is a major clinical and public health problem in many countries. SCD claims over 300,000 lives annually in the United States alone [1]. Ventricular fibrillation (VF) is notorious as one of the most common causes of SCD [2], but knowledge about VF's underlying mechanisms remains incomplete [3]. It is generally considered that there are two major but contradictory hypotheses on the mechanisms of VF [3–4]: the multiple-wavelet [5] and mother-rotor [6] hypotheses. In addition, the mechanism(s) responsible for the degeneration from reentrant ventricular tachycardia (VT) to VF, conventionally believed to be due to a different mechanism, is not fully understood, either [7].

Weiss et al. [8] in 1999 hypothesized that both the action potential duration (APD) restitution and the conduction velocity (CV) restitution characteristics may be related to the wavelength oscillation that led to wave break, a phenomenon that may convert VT to VF. Clinical studies have either demonstrated [9] or implied [10] that the APD restitution (APDR) is also tightly related to the risk of VF induction. Based on Weiss et al.'s hypothesis, Wu et al. [11] further postulated that both APDR and CV restitution (CVR) were important in VF maintenance, and tested this supposition in experiments using rabbit hearts infused with methoxyverapamil (D600). They found that there were two distinct types of VF during the perfusion of D600 with increasing concentrations: starting from Type 1 VF, then to VT, and finally to Type 2 VF. The Type 1 VF is associated with a steep APDR and a flat CVR, comparable with multiple-wavelet VF. The VT was associated with a flat APDR and a flat CVR. The Type 2 VF was associated with a flat APDR and a steep CVR with a broader CV span, comparable with a mother-rotor VF. Each restitution configuration was associated with a perfusion of D600 at a given concentration. Wu et al. also simulated the transitions from Type 1 VF to VT, to Type 2 VF in a three-dimensional cardiac tissue slab [12].

Abbreviations: APD, action potential duration; APDR, action potential duration restitution; CV, conduction velocity; CVR, conduction velocity restitution; D600, methoxyverapamil; DF, dominant frequency; DI, diastolic intervals; ERP, effective refractory period; FFT, fast Fourier transform; FOI, frequency of interest; FPAZ, the *r*-value of the first peak after zero of the autocorrelation function; LR, Luo–Rudy model; MF, median frequency; RV, right ventricle; SCD, sudden cardiac death; SHD, structural heart diseases; SpW, spectral width; VF, ventricular fibrillation; VT, ventricular tachycardia

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Since the shape of the real heart is not a slab, the hypothesis tested by simulations in a cardiac tissue slab [12], that the space-time dependent APDR and CVR can significantly influence VF organization and conversion, needs further validation using whole-heart model with a realistic heart shape, because anatomical features can significantly influence wave instability [13]. If both APDR and CVR are indeed important determinants of VF behavior, the manifestations of VF induced in models with some APDR and CVR could reflect these restitution properties. Moreover, the multiple-wavelet VF and the mother-rotor VF and VT would be simulated in models with the corresponding restitution configurations. Furthermore, the transitions from multiple-wavelet VF to VT, to mother-rotor VF from restitution alterations could also be simulated.

Several studies based on whole-heart models investigated the relationship between cardiac restitutions and VF organization. Xie et al. [13] investigated the influence of the APDR slope on VF patterns in a canine ventricular model (by varying the parameter that controls the Ca^{2+} current amplitude, G_{si}), but didn't investigate the effect of the CVR on VF. ten Tusscher et al. [14] tested several factors, including excitability and APDR that determine the number of rotors during VF. Nevertheless, the effects of these factors were only studied individually without investigating the combined action of APDR and CVR in influencing the VF organization. Keldermann et al. [15] have successfully reproduced both multiple-wavelet and mother-rotor VF in a detailed human ventricular model. However, they only investigated the effects of APDR heterogeneity and VF-induction sites on the VF dynamics. To the best of our knowledge, few simulation studies based on a human whole-heart model have been implemented so far to verify the deduction that multiple-wavelet VF, VT, and mother-rotor VF are probably just the different appearances of corresponding APDR and CVR properties, and their mutual conversions are due to changes in restitution. The purpose of this study was to check the role of APDR and CVR in exploring the mechanism of VF [8].

2. Method

We used a "rule-based" model, the Wei–Harumi whole-heart model that contains a detailed description of cellular electrophysiology and cardiac anatomy [16–17] in this study. Its effectiveness is proved by many recognized publications based on this model [18–19]. We enhanced this model's spatial resolution to a finer level 0.5 mm × 0.5 mm × 0.5 mm. Unlike the models reviewed in the previous session, our model included the His–Purkinje system, which is considered to play an important role in the initiation and maintenance of VF [20–21]. Details and features of this model are provided in the Appendix.

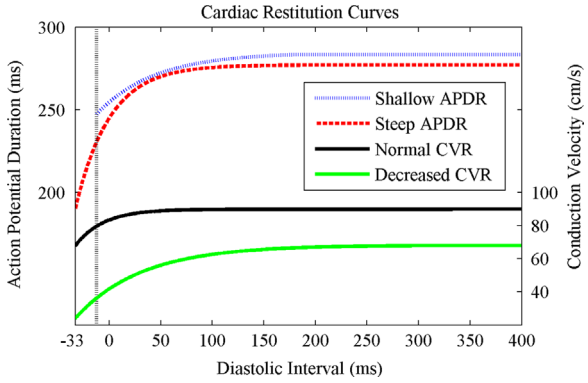

Fig. 1. The action potential duration (APD) and conduction velocity (CV) restitution curves adopted. The dashed lines represent shallow/steep APD restitutions (APDR) at the apex with maximum slope of 0.55/1.85, and the solid lines represent CV restitutions (CVR). The vertical dotted line denotes the minimum diastolic interval (DI) of a shallow APDR.

2.1. Electrophysiological settings

We used the APDR and CVR curves in previous publications as an "input" into the Wei–Harumi model. During the simulations, the model cells are assigned time-varying APD and CV according to their APDR, CVR, locations in the model, and the diastolic intervals (DI). The validation of these restitution settings was carefully performed by simulating cardiac processes consistent with clinical reports [22]. The APDR and CVR inputted are described below.

The APDR curves were derived by fitting the clinical discrete data published by Selvaraj et al. [9] to a mono-exponential function [23], as shown below in Eq. (1):

$$\mathrm{APD} = \mathrm{APD}_{ss} - A\exp(-DI/B) \quad (1)$$

where APD_{ss} is the steady-state APD, A and B are the fitting parameters, and DI is the preceding diastolic interval defined as the amount of time spent recovering prior to an applied stimulus.

Selvaraj et al. defined two data sets recorded from two patients designated as "High-Risk" and "Low-Risk" [9], with each set containing APDR at the apex, middle, and base of the right ventricular (RV) endocardium. Hereinafter, the APDR fitted from the High-Risk and Low-Risk patient data sets will be referred to as "steep" or "shallow" APDR, respectively (see Fig. 1; only the APDR curves at the apex are shown, whose maximum slopes are 1.85 and 0.55, respectively). During the simulation, the effective refractory period (ERP) was part of the APD as introduced in the ERP part of the Appendix, and a ventricular model cell could not be excited by its neighboring model cells if it was in its ERP.

The CVR curves were also depicted using a mono-exponential function similar to Eq. (1). The sources for the CVR were data from the results of ten Tusscher et al. [24] obtained from simulations using a strain of human myocyte model. There were three curves provided in Ref. [24], and two of them were adopted in this study: the standard I_{Na} and the LR I_{Na} CVR curves (obtained from simulations using models with standard and Luo–Rudy (LR) fast I_{Na} dynamics [24], respectively). Both curves were left-shifted by about 56 ms in the abscissa so that the minimum DI value in the later simulations was aligned with the minimum DI value of the steep APDR curve (−33 ms). In addition, the LR I_{Na} restitution curve was scaled up by a factor of 30% to make its steady-state value become 90 cm/s. The transformed LR I_{Na} or standard I_{Na} CVR data (resembling a steep CVR with a broader span or a flat CVR in Ref. [11]) represent physiologically normal excitability or decreased excitability of the cells. Hereinafter, these two CVR will be referred to as "normal" and "decreased" CVR, respectively. During the simulation, the CVR determines the myocyte longitudinal CV dynamically, and the value of CV of an excited cell determined the extent that it could influence (See the "The Propagation Strategy" part in the Appendix). The two solid lines in Fig. 1 show both transformed CVR curves used in the simulation. Note that these two curves are comparable to the CVR acquired from clinical trials [25].

2.2. Models with different restitutions

Table 1 lists the cardiac restitution settings of six different models used in our simulations. It is known that there are different types of electrophysiological heterogeneities in human ventricles, such as the apicobasal gradient, the transmural gradient, and the left–right ventricular heterogeneity [23,25]. These heterogeneities have been proven to play an important role in developing ventricular tachyarrhythmia [15]. The settings of the apicobasal gradient and the transmural gradient have been discussed in the Appendix, and the left–right ventricular heterogeneity was modeled in a simplified manner by assigning different sets of APDR to