Role of suppression of the inward rectifier current in terminal action potential repolarization in the failing heart

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BACKGROUND The failing heart exhibits an increased arrhythmia susceptibility that is often attributed to action potential (AP) prolongation due to significant ion channel remodeling. The inwardly rectifying K^+ current (I_{K1}) has been reported to be reduced, but its contribution to shaping the AP waveform and cell excitability in the failing heart remains unclear.

OBJECTIVE The purpose of this study was to define the effect of I_{K1} suppression on the cardiac AP and excitability in the normal and failing hearts.

METHODS We used electrophysiological and pharmacological approaches to investigate I_{K1} function in a swine tachy-pacing model of heart failure (HF).

RESULTS Terminal repolarization of the AP (TRAP; the time constant of the exponential fit to terminal repolarization) was markedly prolonged in both myocytes and arterially perfused wedges from animals with HF. TRAP was increased by 54.1% in HF myocytes ($P < .001$) and 26.2% in HF wedges ($P = .014$). The increase in TRAP was recapitulated by the potent and specific I_{K1} inhibitor, PA-6 (pentamidine analog 6), indicating that I_{K1} is the primary determinant of the final phase of repolarization. Moreover, we find that I_{K1} suppression reduced the ratio of effective refractory period to AP duration at 90% of repolarization, permitting re-excitation before full repolarization, reduction of AP upstroke velocity, and likely promotion of slow conduction.

CONCLUSION Using an objective measure of terminal repolarization, we conclude that I_{K1} is the major determinant of the terminal repolarization time course. Moreover, suppression of I_{K1} prolongs repolarization and reduces postrepolarization refractoriness without marked effects on the overall AP duration. Collectively, these findings demonstrate how I_{K1} suppression may contribute to arrhythmogenesis in the failing heart.

KEYWORDS Arrhythmia; Pentamidine; PA-6; Effective refractory period; Inward rectifier; Repolarization instability; Andersen syndrome

(Heart Rhythm 2017;■:1–7) Published by Elsevier Inc. on behalf of Heart Rhythm Society.

Introduction

I_{K1}, the inwardly rectifying K^+ current, is responsible for the maintenance and stability of the diastolic potential and rapid repolarization of the cardiac action potential (AP), but this current has not been fully characterized in heart failure (HF). Strong rectification mediated by intrinsic polyamines and intracellular Mg^{2+} (Reference[1]) serves to suppress spontaneous depolarizations, which can trigger delayed afterdepolarizations (DADs) and possibly lethal arrhythmias.[2] Indeed, suppression of I_{K1} conductance due to a mutation in the *KCNJ2* gene product Kir2.1 causes Andersen syndrome,[3] characterized by premature beats and ventricular arrhythmias.

I_{K1} is reduced in human end-stage HF[4–8] and animal models of tachy-pacing induced HF.[9,10] We hypothesize that diminished I_{K1} plays a significant role in mediating ventricular arrhythmias associated with HF because of the accompanying delay and destabilization of terminal repolarization. Here, we show in a pig model of HF that terminal repolarization is significantly prolonged in HF and that suppression of I_{K1} may be responsible. Moreover, a specific inhibitor of I_{K1}, PA-6 (pentamidine analog 6),[11] reproduces the prolonged terminal repolarization in HF and shortens the effective refractory period (ERP) of ventricular

This work was supported by the Department of Defense (grant nos. R0832486 and R083330216). **Address reprint requests and correspondence:** Dr Michael G. Klein, Division of Cardiology, Department of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Bethesda, MD 20814. E-mail address: michael.klein@usuhs.edu.

1547-5271/$-see front matter Published by Elsevier Inc. on behalf of Heart Rhythm Society. http://dx.doi.org/10.1016/j.hrthm.2017.04.001

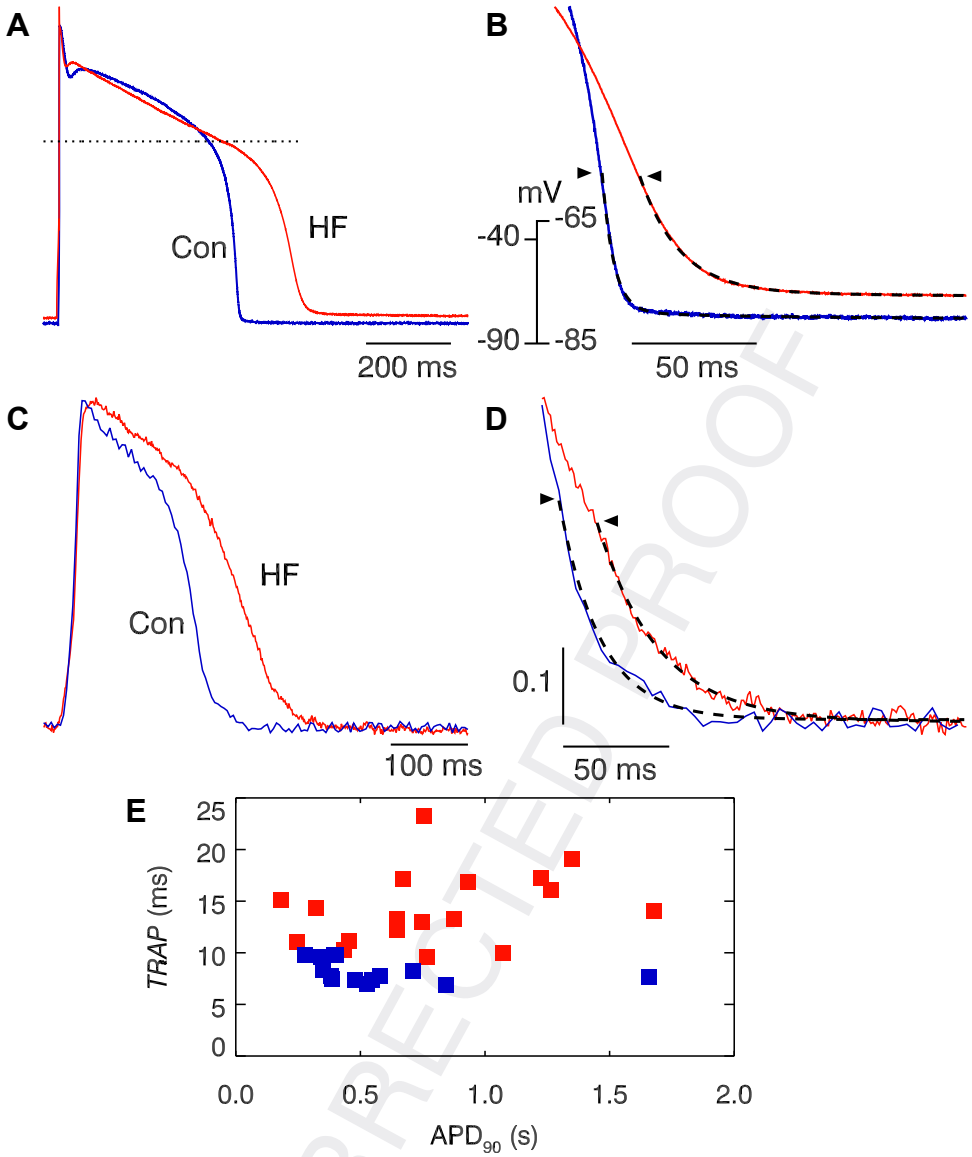

Figure 1 Terminal repolarization of the AP and TRAP are prolonged in HF. **A:** APs recorded from isolated ventricular myocytes from HF and non-HF (Con) hearts. The APs have been aligned at the rising phase. Note the significant prolongation of the plateau (phase 2) as well as the terminal (phase 3) repolarization. **B:** The terminal repolarizations from panel A are shown on expanded voltage and timescales, shifted so as to be aligned at −40 mV. TRAP was determined as the faster time constant (τ_1) of the fit of a 2-exponential plus constant function to the terminal repolarization and is significantly prolonged in HF as compared with Con. The fit is shown (black dashed lines) superimposed on each data record, starting at the points indicated by arrowheads. Fit parameters: Con: $A_1 = 22.7$ mV, $\tau_1 = 9.2$ ms, $A_2 = 1.1$ mV, $\tau_2 = 65.1$ ms, C = −80.9 mV, $\chi^2 = 0.038$; HF: $A_1 = 19.2$ mV, $\tau_1 = 15.8$ ms, $A_2 = 1.6$ mV, $\tau_2 = 215.1$ ms, C = −78.3 mV, $\chi^2 = 0.0083$. **C:** APs recorded as the normalized fluorescence of a voltage-sensitive dye, di-4-ANEPPS, in Con and HF ventricular wedge preparations, showing that TRAP is similarly prolonged in HF. **D:** Terminal repolarization of APs from panel C, with superimposed fits to an exponential function. Values of TRAP from the fits are 19.6 and 28.9 ms in Con and HF, respectively. **E:** The time course of terminal repolarization, as given by TRAP, is independent of AP duration. TRAP was relatively unchanged over a 9-fold range of APD_{90}, obtained by varied pacing frequency in Con (blue squares) and HF (red squares) myocytes.

myocytes relative to the AP duration (APD), leading to a destabilizing susceptibility to early reentrant beats.

Methods

All animal studies conform to the *Guide for the Care and Use of Laboratory Animals* and were performed under a protocol that was approved by the Institutional Animal Use and Care Committee of the Uniformed Services University. Detailed methods for induction of HF in swine, isolation of ventricular myocytes, cellular electrophysiology and optical recording techniques, solutions and drugs, and data analysis are provided in the Online Supplement.

Results

Terminal repolarization of the AP is prolonged in the failing heart

Figure 1A shows APs recorded from isolated ventricular myocytes from control and failing pig hearts using whole-cell electrophysiological recording. Significant prolongation during the plateau (phase 2) portion of HF myocytes is evident