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Mechanisms underlying the development of the electrocardiographic and arrhythmic manifestations of early repolarization syndrome

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ABSTRACT

Early repolarization pattern in the ECG has been associated with increased risk for ventricular tachycardia/fibrillation (VT/VF), particularly when manifest in inferior leads. This study examines the mechanisms underlying VT/VF in early repolarization syndrome (ERS). Transmembrane action potentials (APs) were simultaneously recorded from 2 epicardial sites and 1 endocardial site of coronary-perfused canine left-ventricular (LV) wedge preparations, together with a pseudo-ECG. Transient outward current (I_{to}) was recorded from epicardial myocytes isolated from the inferior and lateral LV of the same heart. J wave area (pseudo-ECG), epicardial AP notch magnitude and index were larger in inferior vs. lateral wall preparations at baseline and after exposure to provocative agents (NS5806 + verapamil + acetylcholine (ACh)). I_{to} density was greater in myocytes from inferior vs. lateral wall (18.4 ± 2.3pA/pF vs. 11.6 ± 2.0pA/pF; $p < 0.05$). A combination of NS5806 (7 μM) and verapamil (3 μM) or pinacidil (4 μM), used to pharmacologically model the genetic defects responsible for ERS, resulted in prominent J-point and ST-segment elevation. ACh (3 μM), simulating increased vagal tone, precipitated phase-2-reentry-induced polymorphic VT/VF. Using identical protocols, inducibility of arrhythmias was 3-fold higher in inferior vs. lateral wedges. Quinidine (10 μM) or isoproterenol (1 μM) restored homogeneity and suppressed VT/VF. Our data support the hypothesis that 1) ERS is caused by a preferential accentuation of the AP notch in the LV epicardium; 2) this repolarization defect is accentuated by elevated vagal tone; 3) higher intrinsic levels of I_{to} account for the greater sensitivity of the inferior LV wall to development of VT/VF; and 4) quinidine and isoproterenol exert ameliorative effects by reversing the repolarization abnormality.

1. Introduction

Early repolarization (ER) pattern in the ECG is characterized by a J point and ST segment elevation, sometimes manifest as a notch or slur on the QRS (J wave). The ER pattern, long thought to be benign, was recently proposed to have a malignant component on the basis of the association of ER with the development of ventricular tachycardia and fibrillation (VT/VF) in an experimental model consisting of canine ventricular wedge preparations, thus identifying the ER syndrome (ERS) [1,2]. Validation of this hypothesis came several years later with the demonstration that patients with ER, particularly in the inferior or infero-lateral ECG leads are at a higher risk for VT/VF [3–5]. The co-occurrence of a J point elevation in the right precordial leads (V1–V3) has been linked to a more severe phenotype often associated with the development of electrical storms [4,6].

Recent studies have demonstrated that gain of function mutations in *KCNJ8*, the gene responsible for the pore forming subunit of the ATP-sensitive potassium channel (K_{ATP}), is associated with ERS [7–9]. Loss of function mutations in the α1, β2 and α2δ subunits of the cardiac L-type calcium channel (*CACNA1C*, *CACNB2*, and *CACNA2D1*) have also been identified as causative in patients with ERS [10]. Watanabe et al. [11] described loss of function mutations in *SCN5A* in patients with idiopathic ventricular fibrillation associated with early repolarization. Sodium channel blocker challenge resulted in an accentuation of early repolarization and development of VT/VF.

Vagal activity has long been implicated in the development of an ER pattern in the ECG [12,13] and recent clinical observations suggest that

Abbreviations: ACh, acetylcholine; AP, action potential; BrS, Brugada syndrome; EDR, epicardial dispersion of repolarization; ER, early repolarization; ERS, early repolarization syndrome; I_{Ca}, calcium inward current; I_{to}, transient outward current; IVF, idiopathic ventricular fibrillation; K_{ATP}, ATP-sensitive potassium channel; LV, left ventricle; RV, right ventricle; TDR, transmural dispersion of repolarization; VT/VF, ventricular tachycardia/ventricular fibrillation.

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Table 1
Effects of provocative agents on transmural and epicardial (Epi) dispersions of repolarization and on action potential (AP) parameters in perfused left ventricular wedge preparations.

	Endo APD_{90} (ms)	Epi1 APD_{90} (ms)	Epi2 APD_{90} (ms)	Endo APD_{50} (ms)	Epi1 APD_{50} (ms)	Epi2 APD_{50} (ms)	Notch magnitude (% of Ph0)*	Notch index†	TDR (ms)	EDR (ms)
Control	223.2 ± 2.1	199.7 ± 5.9	201.8 ± 3.9	177.8 ± 3.9	169.5 ± 7.6	170.7 ± 4.2	14.0 ± 3.1	255.2 ± 54.3	17.0 ± 3.5	14.7 ± 2.8
NS5806 (7 μM)	226.2 ± 5.1	203.7 ± 6.5	207.2 ± 2.6	176.5 ± 7.4	169.3 ± 8.0	176.1 ± 2.5	31.7 ± 4.0	780.8 ± 116.0	17.7 ± 5.3	13.3 ± 2.8
Verapamil (3 μM)	227.0 ± 7.9	225.9 ± 8.3[a]	222.5 ± 4.6[a]	167.9 ± 6.9	188.8 ± 7.9	186.5 ± 3.8[a]	38.9 ± 5.0[b]	2551.9 ± 182.8[b]	21.3 ± 4.4	14.6 ± 6.4
Acetylcholine (3 μM)‡	217.3 ± 3.1	129.9[c] ± 17.2	246.3 ± 26.6	157.1 ± 2.1	69.1[c] ± 17.8	202.7 ± 26.4	42.2 ± 5.1	4654.5 ± 894.0	80.8[c] ± 15.5	111.2[c] ± 24.1

APD_{90}; APD_{50} = action potential durations at 90% and 50% repolarization. Results are mean ± S.E.M. a = $p < 0.05$, b = $p < 0.01$ vs control, c = $p < 0.05$ vs NS5806 + verapamil combination. Basic cycle length = 1000 ms; n = 5.

* Epicardial AP notch data (notch magnitude and notch index) measured before loss of the AP dome at epicardial sites.

† Notch index = Notch magnitude × (Ph 0 to Ph 2 interval) which approximates the area of the notch.

‡ Epicardial dispersion of repolarization (EDR) and transmural dispersion of repolarization (TDR) reported here were measured in cases at which the addition of Acetylcholine caused loss of the AP dome at EPI 1 site but no EPI 2, with the development of phase 2 reentry.

parasympathetic tone contributes to the electrocardiographic and arrhythmic manifestations of ERS [14,15]. Sleep is commonly associated with spontaneous VF in patients with ERS [16]. Indeed heart rate spectral analysis has identified a sudden rise in vagal activity just before the development of VF in patients diagnosed with cases of idiopathic VF (IVF) [17].

A number of studies have shown that an ER pattern in the inferior ECG leads (II, III and aVF) is associated with a much higher risk for the development of VT/VF [18,19]. The electrophysiological basis for this distinction is not known and presents a critical gap in our knowledge.

The present study was designed to probe the mechanisms underlying the development of the electrocardiographic and arrhythmic manifestations of ERS, to elucidate the role of vagal influences, and to better understand the basis for the greater susceptibility to VT/VF when the ER substrate resides in the inferior region of the ventricular myocardium. The study was specifically designed to test the hypothesis that an outward shift in the balance of current contributing to the early phase of the left ventricular (LV) epicardial action potential (AP) either via an increase in $I_{K\text{-}ATP}$ or transient outward current (I_{to}) or via a decrease in calcium inward current (I_{Ca}) in LV wedge preparations can recapitulate the ECG and arrhythmic manifestations of ERS. Thus, we sought to test the hypothesis that pharmacologic modeling of the genetic defects associated with ERS, using pinacidil and NS5806 to increase $I_{K\text{-}ATP}$ and I_{to} and verapamil and acetylcholine (ACh) to reduce I_{Ca} or pilsicainide to reduce $I_{Na,}$ could give rise to a substrate capable of inducing phase 2 reentry and polymorphic VT/VF. Finally, we test the hypothesis that increased levels of I_{to} sensitize the ventricular epicardium to induce development of ER and ERS and those higher levels of I_{to} in the inferior wall can explain why an ER pattern in the inferior ECG leads is associated with a higher risk for sudden cardiac arrest.

2. Methods

All experiments were carried out in compliance with the *Guide for Care and Use of Laboratory Animals published by the National Institutes of Health* (NIH publication No 85-23, Revised 1996) and approved by the Institutional Animal Care and Use Committee. Adult dogs (20–35 kg) of either sex were used in this study.

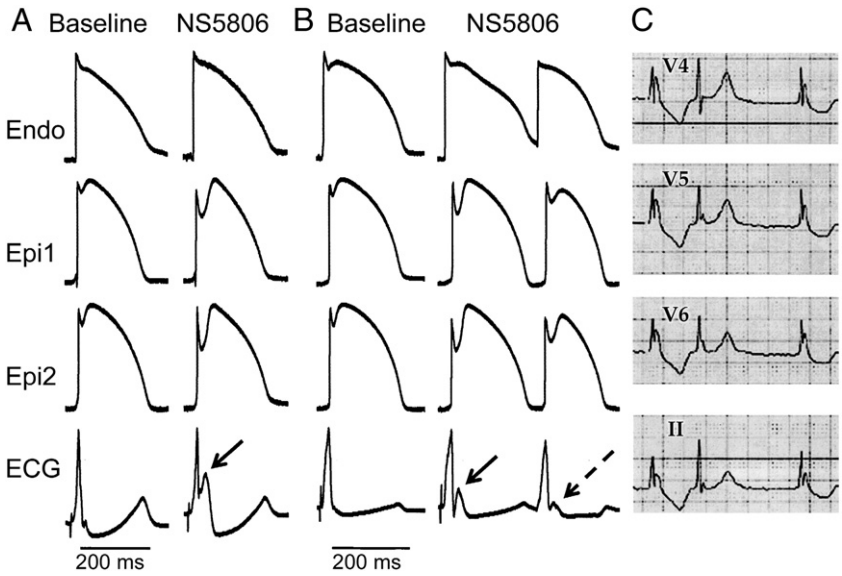

Fig. 1. Augmentation of the transient outward current (I_{to}) promotes early repolarization and J wave manifestation in left ventricular (LV) wedge preparations from the inferior wall of the LV of the canine heart. Each panel shows simultaneous recordings from one endocardial (Endo) and two epicardial (Epi) sites together with a pseudo-ECG. **A**: Recorded under control conditions and 35 min following addition of NS5806 (7 μM); Basic Cycle Length (BCL) = 1000 ms. **B**: Recorded from another wedge preparation under control conditions and 30 min after addition of NS5806 (7 μM); BCL = 2000 ms. The I_{to} agonist gives rise to prominent J waves (solid arrows) secondary to accentuation of the Epi action potential (AP) notch. A much diminished Epi AP notch and ECG J wave (dashed arrow) is associated with a closely coupled premature beat. **C**: Clinical example of accentuated J wave in a patient with early repolarization syndrome and atrial fibrillation. Note the marked attenuation of the J wave attending the abbreviated RR interval.