Effect of Wenxin Keli and quinidine to suppress arrhythmogenesis in an experimental model of Brugada syndrome

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BACKGROUND Wenxin Keli (WK), a Chinese herb extract, is reported to be effective in the treatment of atrial and ventricular cardiac arrhythmias. Recent studies suggest that WK inhibits the transient potassium outward current (I_{to}).

OBJECTIVE To examine the effectiveness of WK, alone and in combination with quinidine, to suppress arrhythmogenesis in an experimental model of Brugada syndrome (BrS).

METHODS Action potential and electrocardiographic recordings were obtained from epicardial and endocardial sites of coronary-perfused canine right ventricular wedge preparations. The I_{to} agonist NS5806 (10–15 μM) was used to pharmacologically mimic a genetic predisposition to BrS.

RESULTS The I_{to} agonist induced Phase 2 reentry (P2R) in 13/19 preparations and polymorphic ventricular tachycardia (pVT) in 11/19 wedge preparations. WK (10 g/L) suppressed P2R and pVT in 100% (3/3) of preparations. A lower concentration of WK (5 g/L) suppressed P2R in 60% (3/5) and pVT in 50% (2/4), but in combination with a low concentration of quinidine (5 μM), was 100% effective in suppressing P2R and pVT. Quinidine alone suppressed P2R and pVT in 60% (3/5) and 50% (2/4), respectively, and in combination with WK (5 g/L) suppressed P2R and pVT by 80% (4/5) and 75% (3/4), respectively. WK reduced I_{to}, the L-type calcium current, and contractility in single cardiomyocytes, but dose-dependently increased contractility in intact wedge preparations, an effect mimicked by tyramine.

CONCLUSIONS Our data provide support for the hypothesis that WK, particularly in combination with quinidine, effectively suppresses arrhythmogenesis in an experimental model of BrS via inhibition of I_{to} and indirect adrenergic sympathomimetic effects.

KEYWORDS Transient outward potassium channel current; Positive inotropic effect; Cardiac arrhythmias; Sudden death

ABBREVIATIONS AP = action potential; **BrS** = Brugada syndrome; **ECG** = electrocardiographic/electrocardiogram; **Epi** = epicardial; **I_{Ca}** = L-type calcium current; **I_{Na}** = transient outward sodium current; **I_{to}** = transient outward potassium current; **LRII** = Luo-Rudy II; **NcBe** = nardostachys chinensis batal extract; **P2R** = phase 2 reentry; **pVT** = polymorphic ventricular tachycardia; **RV** = right ventricle/ventricular; **WK** = Wenxin Keli

(Heart Rhythm 2013;10:1054–1062)

Introduction

Wenxin Keli (WK), a Chinese herb extract composed of 5 components (Nardostachys chinensis batal extract [NcBe], Codonopsis, Notoginseng, Amber, and Rhizoma Polygonati), is reported to be effective for the treatment of cardiac arrhythmias and heart failure.[1,2] WK has been reported to block the transient outward potassium channel current (I_{to}), transient outward sodium current (I_{Na}), and L-type calcium current (I_{Ca}) in rat and rabbit ventricular cardiomyocytes.[3–5] The mechanism by which WK improves cardiac function is not well established.

Brugada syndrome (BrS) is an inherited cardiac disorder associated with a high incidence of sudden death because of the development of life-threatening polymorphic ventricular tachycardia (pVT) and ventricular fibrillation. Previous studies performed in the canine ventricular wedge preparation have demonstrated that the Brugada electrocardiographic (ECG) phenotype can be induced by an outward shift in the balance of currents active at the end of phase 1 of the ventricular epicardial (Epi) action potential (AP) via inhibition of I_{Na} or I_{Ca} or augmentation of I_{to} or IK-ATP.[6–11] Inhibition of the I_{to} was first identified by our group as a therapy for BrS more than 13 years ago.[6,12]

The present study evaluates the potency with which WK inhibits I_{to} as well as other currents, contributing to the

This study was supported by a grant from the Buchang group, National Heart, Lung, and Blood Institute grant HL47678, National Research Service Award fellowship grant #F32-HL107029, NYSTEM grant #C026424, Grant-in-Aid (10GRNT4210016) from the American Heart Association, and the Masons of New York, Florida, Massachusetts, and Connecticut. This study was in part supported by Buchang Group, who markets Wenxin Keli.
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balance of currents active during the early phases of the cardiac AP, as well as tests the hypothesis that WK can suppress the electrocardiographic and arrhythmic manifestations of BrS in an experimental model of BrS.

Methods

Wedge preparations

Detailed methods for isolation, perfusion, and recording of transmembrane activity from coronary-perfused canine right ventricular wedge preparations have been reported previously[7,13] and are briefly described in the Online Supplement.

Voltage-clamp studies using canine cardiomyocytes

Cardiomyocytes were isolated as described previously.[14] I_{to} was measured in isolated left ventricular Epi and M cells at 36.5ºC by using whole-cell patch clamp techniques.[15] Details of the protocol are presented in the Online Supplement.

Unloaded cell shortening in isolated myocytes

Myocytes were isolated from canine midmyocardium as described above, and unloaded cell shortening was recorded by using a charge-coupled device camera and a video-based edge detector as detailed in the Online Supplement.

Simulation of ventricular Epi APs

Right ventricular (RV) Epi APs were simulated by using a Luo-Rudy II (LRII) AP model, which is modified to include I_{to} as described previously.[16,17] Details are provided in the Online Supplement.

Statistical approaches and drugs used are described in the Online Supplement.

Results

Figure 1 depicts APs and ECG recordings obtained from an RV coronary-perfused wedge preparation under control conditions (Figure 1A) after the addition of 15 μM of NS5806 (Figure 1B) and the addition of 10 g/L of WK to the perfusate (Figure 1C). The I_{to} agonist NS5806 was used to mimic a presumed genetic predisposition to BrS. NS5806 caused loss of the AP dome at Epi2 but not Epi1. Phase 2 reentry (P2R) developed as the Epi AP dome propagated from Epi1 to Epi2, leading to the development of pVT. The addition of 10 g/L of WK to the perfusate reduced the AP notch throughout the preparation, leading to the recovery of the AP dome at Epi1, normalization of the ST segment, and suppression of pVT in 3 of 3 preparations (Figure 4A). Online Table 1 shows composite data of 3 to 6 RV wedge preparations. Neither NS5806 nor the combination of NS5806 plus WK affected transmural conduction time, as estimated by width of the R wave. NS5806 (10–15 μM) significantly prolonged Epi action potential duration at 90% repolarization secondary to a dramatic increase in the I_{to}-mediated AP notch. Online Table 1 also shows that WK (10 g/L) significantly shortened the action potential duration at 90% repolarization owing to the normalization of the Epi AP notch.

Figure 2 shows AP and ECG recordings obtained from an RV wedge preparation under control conditions (Figure 2A) after perfusion with 12 μM of NS5806 (Figure 2B) and after addition of 5 g/L of WK (Figure 2C). Figure 2D illustrates the effect of WK (5 g/L) in the presence of a relatively low concentration of quinidine (5 μM). In this example, WK (5 g/L) alone did not prevent P2R (Figure 2C), although this arrhythmia mechanism was effectively suppressed when quinidine (5 μM) was added to the perfusate. The lower concentration of WK effectively suppressed P2R and pVT in

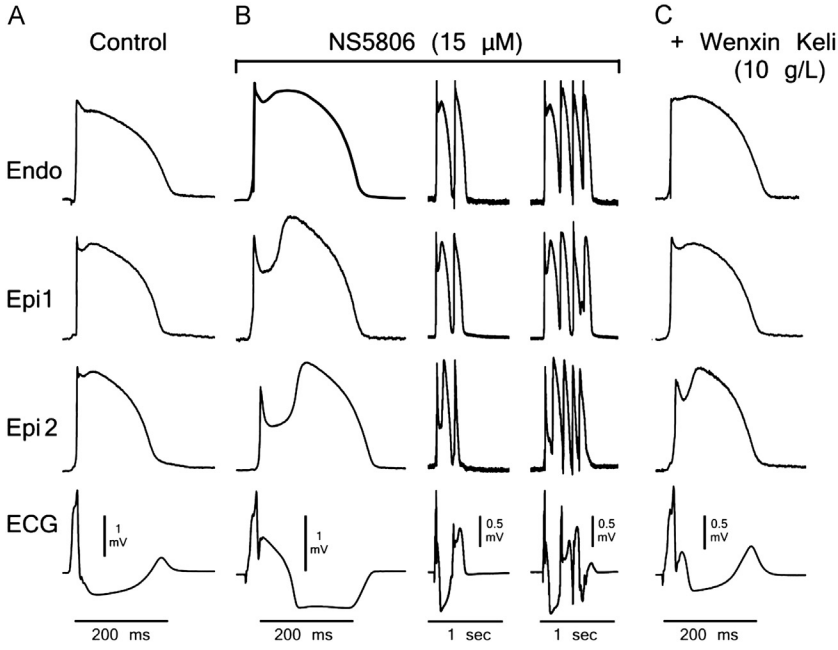

Figure 1 Wenxin Keli (10 g/L) suppression of NS5806-induced Brugada syndrome phenotype. Shown are transmembrane action potentials (APs) recorded simultaneously from 2 sites on the epicardial (Epi) surface and 1 site on the endocardial (Endo) surface of a coronary-perfused right ventricular wedge preparation. The bottom trace is the pseudo-electrocardiogram (ECG) recorded across the bath. **A:** Control. **B:** The transient outward potassium channel current agonist NS5806 (15 μM) accentuates the Epi AP notch and electrocardiographic J wave, leading to the loss of the AP dome at Epi2 but not Epi1. Heterogeneous loss of the dome leads to the development of a closely coupled phase 2 reentrant extrasystole, which precipitates a polymorphic ventricular tachycardia. **C:** Wenxin Keli (10 g/L) suppresses NS5806-induced phase 2 reentry and ventricular tachycardia/ventricular fibrillation and restores the AP dome, thus restoring homogeneity and aborting all arrhythmic activity. Basic cycle length = 2000 ms.