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Ventricular hypertrophy amplifies transmural dispersion of repolarization by preferentially increasing the late sodium current in endocardium☆

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Abstract

Background: The late sodium current ($I_{Na\text{-}L}$) contributes importantly to rate-dependent change in action potential duration (APD) and transmural dispersion of repolarization (TDR). However, little is known about the mechanisms of increased APD rate-dependence and amplified TDR in left ventricular hypertrophy (LVH) and failure. The purpose of this study was to investigate the role of $I_{Na\text{-}L}$ in rate-adaptation of transmural APD heterogeneity.
Methods: APD, its rate-dependence and $I_{Na\text{-}L}$ current were examined in myocytes isolated from the endocardium and epicardium of the control and LVH rabbits. AP was recorded using the standard microelectrode technique, and $I_{Na\text{-}L}$ was recorded using the whole-cell patch clamp technique.
Results: Early afterdepolarizations (EADs) were frequently recorded in the isolated myocytes of the LVH rabbits but not in those of controls. LVH prolonged APD more significantly in the endocardial myocytes than in the epicardium (31.7 ± 3.4 *vs.* 21.6 ± 1.5% n = 6, $p < 0.05$), leading to a marked increase in TDR. LVH endocardial myocytes exhibited a greater rate-dependent change in APD compared to the epicardial myocytes. $I_{Na\text{-}L}$ densities were significantly increased in both LVH endocardium and epicardium. However, LVH increased the $I_{Na\text{-}L}$ density preferentially in the endocardial myocytes compared to the epicardial myocytes (54.5 ± 4.8% *vs.* 39.2 ± 3.3%, n = 6, $p < 0.05$).
Conclusions: Our results demonstrate that LVH increased the $I_{Na\text{-}L}$ preferentially in the endocardium over the epicardium, which contributes importantly to the stronger rate-dependent change in repolarization and longer APD in the endocardium. This results in an amplified TDR capable of initiating EAD and ventricular arrhythmias.
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Keywords: Left ventricular hypertrophy; Action potential duration; Late sodium current; Rate dependence; Transmural dispersion of repolarization

Introduction

Left ventricular hypertrophy (LVH) and failure afflicts approximately 2–2.5 % of the population worldwide, and claims millions of lives annually [1,2]. Of the patients with LVH and failure who die, up to 50% of the deaths are sudden and unexpected, and in most cases it is assumed that the underlying cause of sudden cardiac death is due to ventricular tachycardia [3,4]. Despite its importance, our understanding of the molecular mechanism of the underlying life-threatening arrhythmias in patients with heart failure is poor.

The most striking electrophysiological change in the failing heart is the action potential duration (APD) or QT interval prolongation, which has been observed in isolated myocytes and intact ventricular preparations [3,5,6], respectively. Myocytes isolated from the hypertrophied ventricle, which shows a prolonged APD, are associated with an increased susceptibility to early afterdepolarization (EAD), especially in the presence of APD prolonging agents [5,7,8]. It has been suggested that an increased transmural dispersion of repolarization (TDR) in LVH and heart failure contributes to the genesis of ventricular arrhythmia [6,9]. Our previous studies have also shown that LVH produced a significant APD prolongation in endocardium over epicaridium, resulting in a marked increase of

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TDR that plays a critical role in the genesis of phase-2 EAD and ventricular arrhythmias [7]. However, the precise mechanism of increased TDR underlying LVH and failure is largely unknown.

Most recently, studies have suggested that a late Na^+ current ($I_{Na\text{-}L}$), which exceeded the duration of action potential (AP), plays an important role in the determination of AP rate adaptation and reverse use-dependence of the APD prolonging agents [10,11]. Our recent results also demonstrated that LVH results in an increased $I_{Na\text{-}L}$ that plays an important role in the genesis of atrial arrhythmias in LVH rabbits [12]. We hypothesize that LVH not only causes an increased $I_{Na\text{-}L}$ current in ventricular myocytes, but also preferentially increase the $I_{Na\text{-}L}$ current in the endocardium over the epicardium, leading to a marked prolongation of APD in the endocardium. Preferential APD prolongation in the endocardium would increase the TDR across ventricular wall of the LVH rabbit. The present study was designed to investigate and compare the LVH-induced changes in APD rate-dependence and $I_{Na\text{-}L}$ density in the endocardium and epicardium, and their potential roles in the generation of arrhythmias associated with LVH and failure.

Methods

Experimental animals and LVH model

Male New Zealand rabbits (1.4–1.8 kg) underwent unilateral nephrectomy with contralateral renal artery banding to produce left ventricular hypertrophy (LVH) using techniques reported previously [13]. Rabbits with one kidney plus unilateral renal artery banded in this way uniformly develop LVH within three months. This group rabbits will be referred to as “LVH rabbits”. Control rabbits were matched for age, and will be referred to as “control group”. Data were collected from 12 LVH rabbits and 12 normal rabbits. Animal care and use was in accordance with institutional guidelines and approved by Institute Animal Care and Use Committee of Lankenau Institute for Medical research.

Heart weight, atrium weight and wall thickness measurement

Rabbits were heparinized (800 u/kg IV) and then anesthetized with overdose ketamine 40 mg/kg IV. When deep anesthesia was achieved, the heart was excised. Hearts were washed in cold bicarbonate-based Ca^{2+}-free solution (in mM): NaCl 125, KCl 3.5, KH_2PO4 1.5, $MgCl_2$ 1, NaHCO3 20, glucose 10 and saturated with 95% O_2/5% CO_2 to clear the chambers of blood. After a quick blotting, the heart and ventricle were weighted. The LV posterior wall thickness was measured using calipers positioned at the level of the papillary muscles.

Myocytes isolation

Single myocytes were isolated enzymatically from control and LVH rabbits of either sex using a method described previously [13]. After enzyme perfusion, thin layers (<0.5 mm) of tissue were dissected from epicardial and endocardial surfaces using fine scissors. Tissues from each region were placed into separate beakers. Myocytes isolated from epicardial and endocardial layers using above methods were defined as epicardial and endocardial myocytes, respectively. Myocytes were stored at 10 °C in Tyrode’s solution containing 1 mM Ca^{2+}. Only quiescent rod-shaped cells showing clear cross-striations were used.

Single myocyte action potential recording

Single myocytes action potential (AP) was recorded at 36.0 ± 0.3 °C using standard microelectrode techniques. Microelectrodes had a resistance of 25 to 40 MΩ when filled with 3 M KCl. Cells were superfused with a bath solution containing (mM): NaCl 137, KCl 5, $MgCl_2$ 1, $CaCl_2$ 2, glucose 10, and HEPES 10, and pH was adjusted to 7.4 with NaOH. AP was recorded at a steady state with various stimulus frequencies. APD was measured at 90% repolarization (APD_{90}).

$I_{Na\text{-}L}$ recording

Aliquots of cell-containing solution (about 0.1 ml) were added to a 1.5 ml bath chamber on a stage of an inverted microscope and $I_{Na\text{-}L}$ was recorded at 36.0 ± 0.5 °C using a whole-cell patch-clamp technique. Cells were superfused at 2 ml/min with a bath solution containing (mM): NaCl 140, CsCl 5, $MgCl_2$ 2.0, $CaCl_2$ 1.8, HEPES 5, Glucose 5, Nicardipine 0.002 (pH was adjusted to 7.4 with CsOH). Command pulses were generated by a Digidata 1320A (Axon Instruments, Foster City, CA, USA) controlled by pClamp 8 software (Axon Instruments, Foster City, CA, USA). Pipettes (made using Model P80 puller, Sutter Instrument, Novato, CA, USA) with 2–3 MΩ resistance after filling with pipette solution were selected. The composition of the filling solution was the following (in mM): NaCl 10, CsCl 130, EGTA 5, HEPES 5, ATP-Mg 5 (pH adjusted to 7.2 with CsOH). Liquid junction potentials were zeroed before the formation of the membrane-pipette seal, and passing to the whole-cell mode was obtained by applying a light suction by mouth aspiration. The series resistance was compensated electronically 70–80%. $I_{Na\text{-}L}$ currents were recorded using a 2000 ms depolarizing pulse from −140 mV to −20 mV at the stimulating rate of 0.1 Hz (holding potential is −140 mV). The amplitude of $I_{Na\text{-}L}$ was measured at 200 ms after membrane depolarization.

Data analysis

Data were expressed as mean ± SEM. Student’s T test or two-way ANOVA was used to determine the statistical significance of differences between control and test conditions. Significance was defined as a value of $p < 0.05$.

Results

Electrical abnormalities in left ventricular myocytes from LVH rabbits

Approximately 3 months after the surgery (unilateral nephrectomy with contralateral renal artery banding), rabbits developed significant LVH. LVH is manifested as an increased left ventricular wall thickness and heart weight. We measured the left ventricular wall thickness and the heart weight immediately after the heart was taking out from the chest. The mean left ventricular wall thickness was 0.52 ± 0.02 cm in LVH group versus 0.36 ± 0.01 cm in control group (n = 8, $p < 0.01$) after 3 months of surgery. The

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