Beta-Adrenergic Receptor Blockade Attenuates the Electronic Uncoupling Induced by Coronary Artery Occlusion

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Abstract

Nine dogs (n=9) with healed anterolateral (LADa) infarction, were chronically instrumented for myocardial electrical impedance (MEI) measurements, and subjected to brief (2min) LCXa occlusions with (BETA) and without (CTRL) beta-adrenergic receptor blockade.

Scar tissue (LADa) had significantly lower MEI (373.5±58.8Ω) than normal (LCXa) myocardium (CTRL: 548.8±49.0Ω, BETA: 532.2±34.1Ω). MEI increased significantly after 2min LCXa occlusion (CTRL and BETA). However, beta-adrenergic receptor blockade significantly attenuated the magnitude of such increase. In control conditions (CTRL) MEI increased 4.5±1.8% (21.3±7.0Ω), while with beta-blockade it changed only by 3.4±1.8% (15.6±6.7Ω). In a 1-D cable model of propagating action potentials (Luo-Rudy formulation), such reduction of the ischemic electronic uncoupling prevented conduction block at the ischemic/scar interface.

1. Introduction

Sudden cardiac death due to ventricular fibrillation (VF) is the leading cause of death in most industrially developed countries, killing more that 300,000 Americans each year [1,2]. A potential mechanism underlying these arrhythmias depends on the temporary electrotonic depression of intrinsically viable tissue (e.g. by ischemia) that leads to conduction slowing and block in surviving myocardial layers [3]. Furthermore, electronic uncoupling between neighboring regions of myocardium has been shown to facilitate the development of discordant T-wave alternans (TWA) closely associated with spatial dispersion of repolarization, a substrate for functional block and reentrant VF [4].

Recently, beta-adrenergic receptor blockade (β-blockade) was shown to significantly reduce TWAs [5]. Interestingly, β-blockers are the only class of antiarrhythmic drugs that offers significant protection against sudden death [2]. These findings suggest that β-blockade protection is achieved, at least partially, by attenuation of cell-to-cell electrical uncoupling. However, studies investigating this hypothesis are lacking.

Myocardial electrical impedance (MEI), a passive electrical property of the heart muscle, has been found to detect cell-to-cell electrical uncoupling, as induced by myocardial ischemia [6]. Hence, this experiment was designed to study the effects of β-blockade on the MEI changes induced by acute left circumflex coronary artery (LCXa) occlusion in a canine model of healed myocardial infarction.

2. Methods

Animal protocols were approved by the Institutional Lab Animal Care and Use Committee (ILACUC) at this institution, and adhered to the statutes of the Animal Welfare Act and the guidelines of the Public Health Service.

2.1. Animal preparation

The surgical preparation of this model has been previously described [7]. Briefly, isoflurane anesthetized heartworm-free mongrel dogs had a large antero-lateral infarction created by ligature of the distal left anterior descending coronary artery (LADa). At the time of infarction the animals were chronically instrumented with a LCXa 20 MHz Doppler-flow probe (Crystal Biotech, Northborough, MA), and a hydraulic coronary artery occluder (In Vivo Metrics, Ukiah, CA). Additionally, four temporary pacing electrodes (Medtronic Streamline™, 8mm^2), were sutured (~1cm apart) into the myocardial walls of the LCXa and LADa distributions (1pair/each) for MEI measurements.

Subsequently, the animals were allowed to recover for 3 weeks, and were subjected to brief (2min) LCXa occlusions at rest (awake and unsedated) with and without β-blockade (BETA and CTRL, respectively). Beta-adrenergic receptor blockade was achieved with propranolol HCL (1.0 mg/kg, i.v, Sigma Chemical Co., St. Louis, MO). MEI was measured every 3s throughout

the experiment in a fashion previously described [6].

In short, a computer controlled circuit stimulated the myocardium with a sub-threshold zero mean bipolar current, consisting of two alternating rectangular pulses (±5μA, 100μs wide) generated 10ms apart. The (positive) current stimulus and the respective voltage response of the myocardium were band-pass filtered (0.27 – 5.90 kHz), digitized (@ 22.0 kHz) and transformed into the frequency domain by a radix-2 Fast Fourier Transformation (FFT). The complex MEI spectrum was calculated as the voltage to current ratio at each frequency component. Here, MEI is reported as the ensemble average (10 measurements) of the mean MEI modulus in the 0.5 kHz to 5.0 kHz range.

Results are presented as means with standard deviations (mean ± sd). Differences between MEI values were analyzed using one-way analysis of variance (ANOVA) with repeated measures. For multiple comparisons the Tukey post hoc test was used. In all cases, $P<0.05$ was considered statistically significant.

2.2. PAP Simulation

Cable theory was used to simulate propagating cardiac action potentials (PAPs) in a one dimensional (1D) structure, as described by the following partial differential equation (PDE):

$$\left(\frac{a}{2\cdot R_i}\right)\frac{\partial^2}{\partial x^2}V_m = C_m\cdot\frac{\partial}{\partial t}V_m + I_{ionic}(V,t) \qquad (1)$$

where R_i is the cell-to-cell coupling (or axial) resistivity (Ω·cm), V_m is the transmembrane potential (mV), and I_{ionic} is the nonliner membrane ionic current density (μA/cm^2), which here, followed the Luo-Rudy formulation [8,9]. The cable equation (1) was solved using the implicit Crank-Nicholson method described by Joyner et al. [10], while the differential equations describing the ionic current kinetics were solved using the hybrid integration method. Additionally, symmetric propagation (stimulus-end) and sealed-end (far-end) boundary conditions were used [11]. The length (Δx=100μm) and time (Δt=10μs) increments were set as in [12], for a cable of N=40 segments and T=40ms (i.e., 4000 iterations). The rest of the parameters were 2.5μm for the cable radius (a), and 1 μF/cm^2 for the membrane capacitance (C_m).

The passive electrical properties of the boundary between ischemic myocardium and scar were modeled by means of a spatially heterogeneous coupling resistance R_i [12]. Three regions (normal, ischemic, and infarcted) were defined along the cable, and previously reported MEI values were used as estimates of R_i for each region (Fig. 2a). Recently, Dzwonczyk et al. measured the MEI of normal myocardium (530.1±190.02Ω) during beating heart revascularization in humans [13], while Howie et al. showed (in anesthetized dogs) that MEI increases 22.5±7.5% from baseline after a 15min coronary artery occlusion (i.e., 1.5%/min) [6]. In addition, Schwartzman and colleagues [14] reported the MEI of border-zone and densely infarcted myocardium (380±60 and 160±80 Ω·cm, respectively). Thus, for this model the cell-to-cell coupling resistivities of normal, ischemic and scarred myocardial regions were set to 550, 630 and 160 Ω·cm (respectively), assuming a 10 min ischemic insult.

PAPs were studied during three scenarios: baseline (pre-ischemic), LCXa occlusion (CTRL), and LCXa occlusion under β-blockade (BETA). The β-blocked ischemic region was modeled by a 30-50% reduction of the control ischemic MEI increase (i.e., by 0.8-1.0%/min, or 590-605Ω·cm), in accordance with the reported beneficial effects of β-blockers on the energy metabolism of ischemic myocardium [15].

3. Results

Nine (n=9) animals had viable electrodes in normal (LCXa) and scarred (LADa) myocardium at the time of the experimental ischemic insults (CTRL: 22.6±2.78 days, and BETA: 21.1±0.99 days, respectively). As expected [14], healed myocardial infarct tissue (scar) had significantly ($P<0.001$) lower MEI (373.5±58.8Ω) than normal myocardium (540.5±41.8Ω).

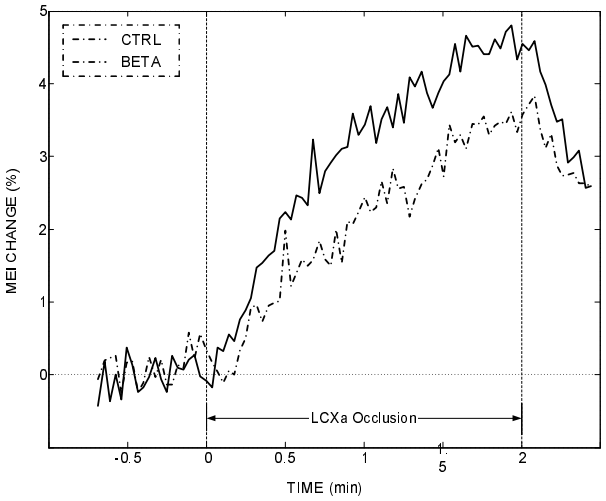

Figure 1. MEI changes during acute LCXa occlusion (2min) with and without β-blockade (BETA and CTRL, respectively) in dogs (n=9).

In all cases (CTRL and BETA), MEI increased significantly (see Fig.1) after 2 min LCX occlusion. However, β-blockade significantly (P=0.003) attenuated the magnitude of this increase. In control conditions (CTRL), MEI increased 4.5±1.8% (21.3±7.0Ω) after 2 min of LCXa occlusion, while under β-blockade, MEI reached only 3.4±1.8% (15.6±6.7Ω) after a comparable ischemic insult. No significant differences (P=0.757) in MEI pre-ischemic values were observed between control and β-blocked (CTRL: 548.8±49.0Ω, BETA: 532.2±34.1Ω).

Simulated PAPs under baseline and ischemic conditions (CTRL and BETA) are shown in Fig. 2 (panels (b)-(d)). In control conditions (CTRL), the MEI rise of ischemic myocardium adjacent to scar, resulted in unidirectional block (panel (c)). However, moderate reductions (30-50%, panel (d)) of such ischemic uncoupling, as measured under β-blockade, allowed bidirectional conduction.

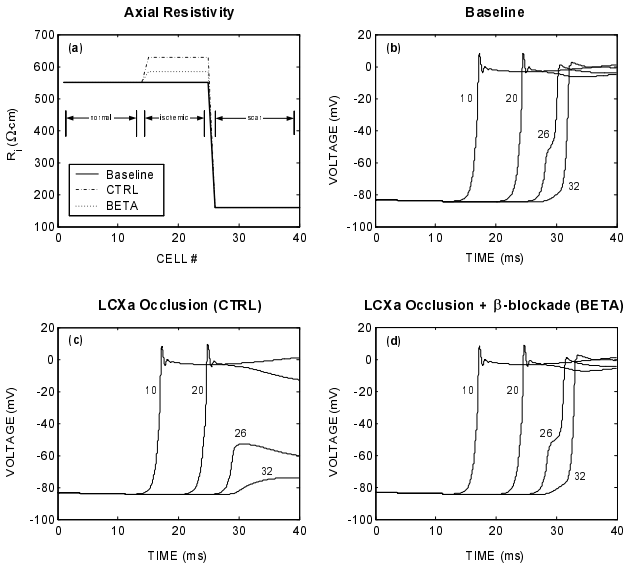

Figure 2. The modeled non-uniform cell-to-cell coupling (axial) resistivity at the ischemic/scar interface (panel (a)) changes significantly the PAPs characteristics: LCXa occlusion without β-blockade results in unidirectional block (panel (c)). Panels (b)-(d) show PAPs in four cable segments (cells # 10, 20, 26 and 32).

4. Discussion and conclusions

In this report, beta-adrenergic receptor blockade decreased (29.3±13.7%) the electrical uncoupling (induced by coronary artery occlusion) between neighboring regions of myocardium. In an applicable (see Table I) 1D cable model of PAPs, a similar attenuation of uncoupling (30%) prevented conduction block at the boundary between ischemic cells and scar, a known mechanism of malignant arrhythmias.

In addition, the present study demonstrates that myocardial electrical impedance, a passive electrical property of the myocardium (measured from temporary pacing leads), can detect of myocardial ischemia in the chronic setting (3 weeks after implantation).

Table 1. Measured MEI parameters, and values used for 1D cable model of propagating action potentials (PAPs).

MEI Parameters		Measured	Cable Model
Baseline (Ω)	CTRL	548.8±49.0	550
	BETA	532.2±34.1	550
Ischemic Rise (%/min) †	CTRL	2.3±0.9	1.5
	BETA	1.7±0.9	0.8-1.0
Scar (Ω)	-	373.5±58.8	160

†: P<0.05 between CTRL and BETA

Acknowledgements

These studies were supported, in part, by a grant from the National Institutes of Health HL 68609.

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