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Effect of electroacupuncture on porcine cardiac excitability induced by left stellate ganglion stimulation

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ABSTRACT

Augmentation of cardiac sympathetic tone has been shown to induce ventricular arrhythmias. Acupuncture has been clinically used to treat hypertension, angina pectoris, and atrial arrhythmias. However, the effects of acupuncture on ventricular electrophysiology and autonomic tone remain unknown. We hypothesized that acupuncture attenuates cardiac excitability and corrects the imbalance of autonomic tone during sympathetic hyperactivity. Fourteen Yorkshire pigs were randomized to electroacupuncture (EA, 2 Hz, 0.3–0.5 mA, 0.5 ms duration) or control (without EA) groups. Animals were sedated with terazol. General anesthesia consisted of isoflurane and fentanyl during surgical preparation and was transitioned to α-chloralose during experimental protocols. Through a median sternotomy, the heart was exposed and fitted with an elastic epicardial 56-electrode sock. Cardiac excitability was measured via activation recovery interval (ARI) and dispersion of repolarization (DOR) while autonomic balance was evaluated by heart rate variability (HRV) power spectrum analysis at baseline and during left stellate ganglion stimulation (LSS) with and without EA delivered at P 5–6 acupoints. 30-min of EA did not alter the baseline ARI and DOR, but significantly suppressed cardiac excitability during LSS through attenuation of ARI shortening (EA 2.1 ± 0.3% vs. control 5.2 ± 0.7%, $P < 0.05$) and DOR (EA 74.3 ± 26.9% vs., control 110.1 ± 22.9%, $P < 0.05$). EA significantly attenuated the increase in LF/HF (EA 0.6 ± 0.1 vs. control 1.1 ± 0.2, $P < 0.05$). In conclusion, EA reduces the cardiac excitability induced by LSS through correction of cardiac sympathovagal balance. This study provides mechanistic insights underlying cardiac neuromodulation of EA during sympathoexcitation.

1. Introduction

The sympathetic nervous system plays an important role in arrhythmogenesis (Vaseghi and Shivkumar, 2008). Blockade of direct sympathetic stimulation via beta blockers reduces the risk of sudden cardiac death, while sympathectomy reduces ventricular arrhythmic episodes in both animal and human studies (Zipes, 1970; Kadowaki and Levett, 1986; Odero et al., 2010; Hofferberth et al., 2014). Direct sympathetic stimulation decreases effective refractory period and ventricular fibrillation threshold in animal study (Ng et al., 2007). Imbalances in the activity of the sympathetic and parasympathetic nervous systems have been strongly associated with ventricular tachyarrhythmias (Stein et al., 1999; Vaseghi and Shivkumar, 2008). While it is difficult to directly quantify the activity of the autonomic nervous system on the cardiovascular system, heart rate variability (HRV) is a noninvasive means to evaluate autonomic tone (Stein et al., 1994; Bailey et al., 1996). The low frequency (LF) oscillations represent sympathetic while the high frequency (HF) component represents parasympathetic nerve activity. Therefore, the ratio of LF to HF can reflect the balance of autonomic nervous system (Malliani et al., 1991).

Global and regional ventricular electrophysiology can be assessed by recording activation recovery intervals (ARI), a surrogate of action potential duration (APD), and dispersion of repolarization (DOR), an important determinant of cardiac excitability, wave stability, and arrhythmogenesis (Vaseghi and Shivkumar, 2008; Vaseghi et al., 2012a; Vaseghi et al., 2013). Left stellate ganglion stimulation (LSS) has been shown to increase sympathetic outflow with subsequent increases in cardiac sympathoexcitation and left ventricular inotropy. LSS was used in this study because it shortens ARI and increases the dispersions of repolarization (Vaseghi et al., 2012a; Vaseghi et al., 2012b; Ajijola et al., 2013), creating a proarrhythmic state for ventricular tachyarrhythmias in a unique model for evaluation of cardiac excitability and arrhythmogenesis.

Clinical evidence suggests that acupuncture may have salutary

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effects on coronary artery disease, arrhythmias, angina pectoris, and myocardial infarction (Bao et al., 1982; Ballegaard et al., 1986; Richter et al., 1991). The beneficial effects of acupuncture are partially mediated by sympathetic inhibition (Middlekauff et al., 2002; Li et al., 2004). In the present study, the Jianshi-Neiguan acupoints (P5–6) acupuncture were selected because it has been shown that stimulation of these acupoints affects the central cardiovascular regulation (Tjen-A-Looi et al., 2004; Tjen-A-Looi et al., 2006). P 5–6 acupoints located over the median nerve are commonly used in traditional Chinese medicine to treat coronary heart disease and hypertension (Bao et al., 1982; Cheng et al., 1983; Ballegaard et al., 1986; Ballegaard et al., 1993; Chiu et al., 1997; Zhou and Longhurst, 2006; Zhou and Longhurst, 2012). We have previously demonstrated that electroacupuncture (EA) at P5–6 significantly inhibits the cardiovascular sympathoexcitatory reflex responses through modulation of neuronal activity in the rostral ventrolateral medullar in the brain stem (Zhou et al., 2005a; Zhou et al., 2005b). In addition, EA at P5–6 reduces infarct size and decreases cardiac interstitial norepinephrine release in an ischemia reperfusion injury rabbit model (Zhou et al., 2012). However, little is known on cardiac neuromodulation by EA during sympathoexcitation.

The purpose of this study was to assess changes in regional myocardial repolarization and dispersion of repolarization as well as to evaluate the balance between sympathetic and vagal nerve activities during LSS with and without EA using high fidelity cardiac electrophysiology mapping and power spectral analysis of heart rate variability in a porcine model. We hypothesized that EA reduces cardiac excitability and corrects the imbalance of autonomic tone during LSS.

2. Methods

All animal experimental studies were performed in accordance with guidelines of the University of California Institutional Animal Care and Use Committee and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Pub. No. 85-23, Revised 1996).

2.1. Surgical preparation

Fourteen Yorkshire pigs (44 ± 2 kg, both male and female) were sedated with telazol (4–8 mg/kg, intramuscular). Following endotracheal intubation, general anesthesia was induced and maintained with inhaled isoflurane (1–2%). An intravenous bolus of fentanyl (20–30 μg/kg) was administered for analgesia before sternotomy; intermittent injections were used as required. A surface 12-lead electrocardiogram was obtained via a Prucka CardioLab system (GE Healthcare, Fairfield, CT). The left jugular vein was cannulated for fluid and drug administration, while the femoral artery was cannulated for blood pressure monitoring and sampling. A median sternotomy and pericardectomy were performed to expose the heart and the left stellate ganglia. Following completion of surgical preparation, anesthesia was changed to α-chloralose. Administration of α-chloralose began with a 50 mg/kg bolus followed by continuous intravenous infusion of 20–30 mg/kg/h. Animals were placed to maintain a core body temperature of at 37.0 °C, as measured by a thermistor probe placed in the esophagus. Arterial blood samples were analyzed using IRMA TRUpoint (ITC, Edison, NJ) hourly to assure adequate oxygenation and normocapnia.

Upon completion of the experimental protocol, animals were euthanized with a lethal dose of pentobarbital sodium (100 mg/kg).

2.2. Left stellate ganglion stimulation

The left stellate ganglion was stimulated via bipolar needle electrodes implanted in the ganglion, which was interfaced to a Grass S88 Stimulator (Grass Co, Warwick, RI) via PSIU6 constant current isolation units. Square wave stimulation pulses (4-Hz frequency, 4 ms in duration) were delivered. The stimulation threshold (control 5.9 ± 0.63 mA vs. EA 6.1 ± 0.64 mA, $P > 0.05$) was defined as the current required to induce a 10% increase in the left ventricular end-systolic pressure (LVESP) as we used previously (Zhou et al., 2013).

2.3. Electroacupuncture

32-gauge stainless steel acupuncture needles (Suzhou Medical Appliance) were inserted into Jianshi-Neiguan (P5–6) acupoints overlying the median nerve. Needles were inserted perpendicularly to a depth of 15–20 mm. The correct positioning of acupuncture needles in human subjects relies on their feeling of "heaviness" associated with electrical stimulation of the needles when properly positioned at the acupoint (Stux and Pomeranz, 1998). However, this information is not available in animals. Therefore, our criterion for correct needle positioning relied on our observation of a slight repetitive flexion of the paw during EA.

2.4. Experimental protocol

Animals were randomly divided into two groups: the control group ($n = 7$) and the EA group (n = 7). The experimental protocols are shown in Fig. 1.

2.5. Hemodynamic indices

A 5 Fr pig-tail 12-pole pressure-volume catheter (Millar Instruments, Houston, TX) was introduced into the LV chamber via the left carotid artery under ultrasound guidance and connected to an MPVS Ultra Pressure-Volume Loop System (Millar Instruments, Houston, TX). The position of the catheter was confirmed by echocardiography and appropriate pressure volume loops on LabChart. Heart rate (HR), LVESP, LV end diastolic pressure (LVEDP) and maximum rate rise of LV pressure (dP/dtmax) were measured in all protocols.

2.6. Ventricular electrophysiological recordings and analysis

A custom 56-electrode epicardial sock was placed around the heart to acquire unipolar ventricular epicardial electrograms recorded by a Prucka Cardio Lab system (GE Healthcare, Fairfield, CT) (Fig. 2). Ventricular activation time (AT) was measured from the onset of ventricular activation to the first minimum dV/dt of the QRS complex. Ventricular repolarization time (RT) was measured as the time interval between the onset of ventricular activation and the first maximum dV/dt of the T wave. The activation-recovery interval (ARI), a surrogate measurement of APD, was defined as AT subtracted from RT, as previously described (ARI = RT - AT) (Vaseghi et al., 2013). ARIs were analyzed using customized software, ScalDyn M (University of Utah, Salt Lake City, UT). Regional ARIs were measured in two predefined regions: the anterior and posterior walls of the ventricles (Fig. 2), which were verified visually. Whole heart epicardial dispersion of repolarization was calculated using the variance of all 56-electrode ARIs. Epicardial dispersion of repolarization is associated with heterogeneity

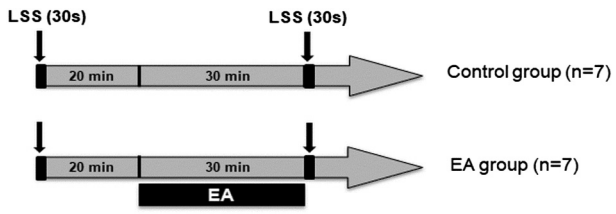

Fig. 1. Timeline of the experimental protocols. 14 animals were randomized to electroacupuncture (EA) group and control (without EA). Both control and EA groups underwent pre-EA left stellate ganglion stimulation (LSS), 30-min EA or time control and post-EA LSS. Left stellate ganglion was stimulated for 30 s.