Intermittent Vagus Nerve Stimulation Reflexively Modulates Heart Rate Variability in Rats with Chronic Ischemic Heart Failure

Joseph Ippolito, Xueyi Xie, Bruce H. KenKnight, Elena G. Tolkacheva

Department of Biomedical Engineering
University of Minnesota

1 Background

Heart disease is the leading cause of death in the developed world. Despite major strides made in the past decade regarding the treatment and prevention of heart disease, cardiac injury due to acute myocardial infarct (MI) remains a difficult and complicated problem to solve. When enough tissue damage occurs in the myocardium, the ability of the heart to circulate blood is reduced and the organ changes shape in a maladaptive attempt to compensate for its lack of pumping capacity, ultimately leading to an even greater lack of circulatory output known as heart failure. Such tissue damage begins for a great number of patients the downward spiral termed ‘heart failure’ - which culminates almost certainly at death.

At rest, the heart rate of healthy individuals exhibits spiral termed 'heart failure' - which culminates almost at death. Such tissue damage begins for a great number of patients the downward spiral termed ‘heart failure’ - which culminates almost certainly at death.

Depressed parasympathetic activity within the autonomic nervous system resulting from cardiovascular disease has been linked to significantly diminished HRV in humans suffering with chronic heart failure (CHF). CHF is associated with autonomic dysregulation characterized by a sustained increase in sympathetic activity and decrease in parasympathetic activity [1]. Mainstream methods of nervous system modulation include beta-blockers, aldosterone antagonists, and ACE inhibitors. Recently, modulation of parasympathetic activity through cardiac vagal nerve stimulation (VNS) has emerged as a potential therapy for CHF. VNS has been shown to prevent cardiac remodeling, eventually leading to an improved prognosis of HF rats after initial MI [2]. VNS also inhibited sudden cardiac death in dogs with MI [3] and markedly suppressed arrhythmias in conscious rats [4]. Chronic VNS may even improve quality of life and LV function in CHF patients with severe systolic dysfunction [5]. Recently, low-level VNS was implemented to reduce atrial tachyarrhythmia in ambulatory dogs [6]. Implantable VNS stimulators are currently undergoing human clinical trials for possible future use as a CHF therapy [8]. While human trials may be advancing, little is still known about the underlying anti-arrhythmic mechanisms of VNS. VNS may indeed present a very promising future therapy for patients suffering from CHF, but further work is necessary to develop a reliable and efficacious treatment. Here we investigated changes induced in in-vivo MI heart rat model by means of chronic VNS. Specifically, we focused on changes in heart rate, and HRV. The objective of this paper was to investigate the changes induced in in-vivo MI heart rat model by means of chronic VNS. Specifically, we focused on changes in heart rate, and HRV that followed after chronic stimulation in 8-week animal study. Because VNS will soon be used for human CHF therapy, we must know how clinically relevant parameters such as HRV respond to VNS therapy and specifically, how they may change over time.

2 Methods

2.1 In-vivo CHF Model

All experiments conformed to the Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1996) and the University of Minnesota guidelines regulating the care and use of animals. Sprague-Dawley rats (275–300 g, N=9) were used for this study, and they were randomly placed in Active (n=5) and Control (n=4) groups. The CHF phenotype was first created by performing in-vivo surgery to induce acute MI in rat hearts. Accordingly; the rats were anesthetized with Ketamine and Xylazine (35 mg/kg and 5 mg/kg, respectively). The rats were then intubated, and ventilated with a rodent ventilator (model 683, Harvard Apparatus); a median sternotomy was then performed. Subsequently, at most two 6-0 silk sutures were ligated around the proximal LAD artery until the vessel was fully occluded and the myocardial color changed to blue; after which the chest was closed [7].

2.2 Vagal Nerve Stimulation

Vagal nerve stimulators (Cyberonics Model 103, Houston TX) were implanted below the epidermis dorsally, and bipolar cuff electrodes were implanted on the right-hand side cervical vagus nerve. Non-functional stimulators of were implanted in Control rats. Active MI rats received chronic VNS starting week 2 postoperative, while Control rats did not receive any stimulation. Parameters of VNS stimulation were as follows: stimulation frequency was 20 HZ; pulse width was 500 microseconds; and stimulation current was either 0.5 mA or 1mA. The stimulator was active for 7 sec every 1 min., representing a duty cycle of roughly 12%.

2.3 Data analysis

ECG was recorded in both Active and Control lightly anesthetized rats weekly, for ~30 min per animal using the iWorx IX-ECG-12 recording system. The acute effect of VNS was estimated for Active rats from multiple 21-sec ECG traces representing the before (PRE, 7-sec), during (ON, 7-sec) and after (POST, 7-sec) episodes of VNS stimulation (see Fig. 2). HRV was defined as a ratio of the standard deviation of RR interval to the mean RR interval over corresponding 7-sec interval. Chronic effect of VNS was estimated for both Active and Control rats over 10-weeks period. For each week, the last 2-min of ECG recording was analyzed, and mean heart rate and HRV were calculated.

2.3 Statistical Analysis

Statistical comparison between Active and Control groups for chronic VNS effect were performed using ANOVA (Origin Software, Northampton, MA) with p<0.1 considered significant. Statistical analysis of the acute effect of VNS in
the Active rats was performed using a paired student’s t-test. Values of $p < 0.05$ were considered statistically significant.

3 Results

3.1 Acute effect of VNS
Several experiments were undertaken where we attempted to isolate the threshold current required for VNS to lower heart rate in healthy animals. As a result of these experiments we found that our threshold current lied between .75mA and 1.0mA. We then looked at the effect on that sub-threshold and super-threshold stimulation would have on heart rate and HRV. As such, Figure 2 illustrates the acute effect of VNS on threshold (1 mA) stimulation current.

For VNS stimulation strength of 0.5 mA, the HRV between all periods as well as heart rate were statistically similar. Interestingly, for or stimulation strength of 1mA we determined that mean HRV decreases during the ON periods compared to both PRE (0.419± 0.04 vs. 0.91± 0.16, p <0.05) and POST (0.419± 0.04 vs. 0.745±0.13, p <0.05) periods.

3.2 Chronic effect of VNS
The chronic effect of VNS on heart rate and HRV is shown in Figure 3, where weekly HR data is plotted. Here we have applied supra-threshold stimulation (current strength is 1mA) for the entire 8-week period. Note that average heart rate of VNS Active rats over 8 weeks (343.6128 ± 9.0 bpm ) is significantly higher than that of Control rats (318.0361 ± 9.9 bpm, p <0.001), suggesting that VNS increase heart rate in MI hearts over time. Also, for 6 of the 8 weeks of our study, the Active rats had higher HR compared to Control. There was no significant difference in chronic HRV over the 8 week study.

4 Interpretation
Here we demonstrated that VNS is a threshold phenomenon, and that the threshold current value lies between 0.50mA and 1.0mA. We demonstrated that acute VNS stimulation leads to significant decrease of HRV. It is possible that the instantaneous reduction of HRV may be due to a filtering out of the RSA as a result of overstimulation of the cholinergic neuronal targets of the parasympathetic nervous system in and around the heart. Interestingly, no statistically significant changes in heart rate were observed as a result of acute VNS stimulation. Our results also demonstrate that chronic VNS leads to a significant increase of average heart rate between groups in MI rats, and that for 6 of the 8 weeks of the experiment the heart rates between groups are statistically different. Given the use of HRV as a clinical marker for heart disease, we believe that further investigation of the effects of VNS on HRV must take place.

5 Acknowledgment
This work was supported by grant from Cyberonics, Inc.

6 References