Heart Rate Control through Vagal Nerve Stimulation

Tosato M 1, Toft E 1,2, Yoshida K 1, Nekrasas V 2, Struijk JJ 1

1 Center for Sensory-Motor Interaction, Dept of Health Science and Technology, Aalborg University, Fredrik Bajers 7D, DK 9220 Aalborg Øst, Denmark.
2 Aalborg Sygehus, Aarhus University Hospital, Hobrovej 18-22, DK 9000 Aalborg, Denmark.

Abstract

The aim of this study is to determine whether closed loop (PI) controlled Vagal Nerve Stimulation (VNS) can be used to control heart rate. This novel type of FES system may be a suitable option in some cases of drug resistant malignant tachycardia and the prevention of Sudden Cardiac Death. The preliminary results from two experiments in the porcine model are presented. We attempted to quantify the stimulus amplitude influence of VNS by analysis of the Vagal Compound Action Potential (VCAP). It showed that not only did the B-fibres have an inhibitory cardiac effect, but there may also be an action by faster, putative Aγ fibres. Second, left VNS was found to be as effective as right VNS for the task of automatic external R-R interval control. Although bilateral stimulation elicited a faster response, it did not result in greater accuracy of control of the R-R interval. It appears that either one side or the other dominates with no increase in performance with bilateral stimulation.

1 Introduction

Although Vagal Nerve Stimulation (VNS) has long been known to have strong cardiac effects [1] and its deployment has been suggested as a therapy for treating drug resistant Myocardial Infarction (M.I.) patients and for preventing Sudden Cardiac Death (SCD) [2], there are still many issues to be addressed and optimised. When malignant tachycardia cannot be cured with β-blockers, another way of preventing SCD in M.I. patients may be to continuously monitor R-R interval and keep it in a safe range through VNS. Instead of using doses of VNS in an open-loop fashion [2], its powerful influence on the sinoatrial (SA) and atrioventricular (AV) nodes may be taken advantage of and modulated using an external close-loop controller. An FES system where the ventricular rhythm or blood pressure is used as feedback signal to modulate the frequency or amplitude of electrical stimulation can be realized.

Similar experiments have been performed on the canine model during Atrial Fibrillation (AF) [3][4], and several patents have been registered [5][6][7]. In the present study, the porcine animal model was used to determine the proof of principle of closed loop FES control over the heart via VNS with special focus on laterality and diameter of the nerve fibers involved.

2 Methods

The study was conducted under the approval granted by the Ethical Committee of the County of North Jutland. Two 7-months-old pigs (~90 kg) were anaesthetised with an IV injection of Ketalar. The femoral artery was cannulated to monitor arterial blood pressure. Surface electrodes were applied to monitor standard lead I and II and precordial lead V2. A midline incision in the neck and blunt dissection were used to expose both vagi. The sympathetic adventitial bundle was separated from the vagus-sympathetic trunk. The identity of each bundle was assessed by stimulation with a hook electrode and monitoring the effect on the HR. Two sets of custom-made silicon tripolar cuff-electrodes were placed around each vagus nerve, displaced by 4-5 cm. One electrode set was used for stimulation and the other for recording.

ECG and ENG signals were acquired to a PC (PCI-MIO4E, National Instruments) and recorded for later analysis. Lead II was used to compute the instantaneous R-R interval. A second controller routine took the computed instantaneous R-R interval and generated a pulse train frequency regulated by a Proportional Integral (PI) control law. Current pulses were used with duration fixed at 0.3ms. The amplitude was selected according to the desired class of vagal fibers (based on fiber diameter). Stimulation was delivered from two
independent stimulus isolation units separately connected to each stimulating cuff-electrode.

The study protocol was based on the repetition of three 5-minutes-long test periods:
1. establish the baseline R-R interval (control)
2. target set first to 118% baseline
3. target set to 133% of baseline

This 15 minutes basic unit was repeated while the side of stimulation and the types of activated nervous fibers were randomly selected. The RMS of the difference between target and actual R-R interval over the 5-minutes bin was used to quantify the effectiveness of the control. In each case, it was normalized by dividing it with the RMS of the difference between target and baseline value. This normalized RMS difference will be 1 when the control action is not applied or it has no effect, and will be 0 in the ideal case, when the R-R interval duration immediately reaches the target and remains constant.

3 Results

All Vagal Compound Action Potentials (VCAPs), at supramaximal stimulation for myelinated fibers, show three peaks, although their absolute peak-to-peak values differ (an example in Figure 1).

Figure 1: A typical Vagal Compound Action Potential (VCAP) (top) and its recruitment curves: pk-to-pk amplitude vs. stimulation current (bottom).

Varying stimulation strength resulted in an inverse recruitment order, with the fastest myelinated fibre recruited first and ending with the slowest myelinated fibre. Excitation thresholds for the 3 components of the VCAP were as follows: 0.088 ±0.038mA, 0.14 ±0.088mA and 1.2 ±0.38mA. Saturation thresholds were: 0.48±0.13mA, 0.85 ±0.20mA and 4.0 ±1.8mA respectively. Conduction velocities were estimated to be in the range of 50, 25 and 10 m/sec respectively. In both experiments it was possible to achieve a satisfactory degree of control when the stimulus current was set above the saturation value for the third peak of the VCAP and the target R-R interval was set to 118% of the baseline. The average values for the normalized RMS differences are: 0.37 ±0.019 for the right, 0.43 ±0.067 for the left and 0.40 ±0.029 for the bilateral stimulation. When the target was set to 133%, it was seldom possible to reach the desired value and achieve stable control. The average normalized RMS values are: 0.82 ±0.18 for right, 0.65 ±0.28 for left and 0.58 ±0.059 for bilateral stimulation. In the first experiment, control was attempted by exciting only the two fastest types of fibers. Values for the normalized RMS of the difference in this case are: 0.92 for right, 0.59 for left and 0.66 for bilateral stimulation. In Figure 2, the dynamics of two representative responses are shown.

Figure 2: An example of the dynamic response of the R-R interval for a target of 118% (top) and 133% (bottom).

4 Discussion and Conclusions

The outcome of these comparison experiments is that heart rate control through cervical VNS is indeed feasible and more research is needed to find the best strategy. Several different approaches have been implemented and reported on [3][4][8] or patented [5][6][7]. Waninger et al. [3] used a cumulative sum controller and obtained good preliminary results in controlling ventricular rhythm by left cervical stimulation during AF, but the reaction
time and the oscillations of their system are quite different from ours. Zhang et al. [4] stimulated the fat pad on the AVN with a synchronous fixed train of stimuli, whose amplitude was regulated by a PI controller. They found the target for sinus cycle length optimal for hemodynamics improvement during AF. In both studies, the site of stimulation was fixed and the type of excited fibers was not taken into account; as these two topics are controversial, a comparison is needed.

From a qualitative analysis of axon calibres, VCAPs and conduction velocities, we ascribed the first peak to Aβ-fibers, the second to Aγ and the third to B. Unmyelinated fibers are the largest component of the vagus nerve, but they require very high stimulation amplitudes for activation, and have, thus far, not been investigated. It is widely accepted that A-fibers don’t exert any cardiac effect, while the B fibres have a powerful, short latency effect. The C-fibers have a somehow smaller but longer lasting effect [9]. In their study, Middleton et al. [1] confirmed the effects of B-fibers, and reported that in a few experiments stimulation of what they call Aδ did result in a small bradycardia. In our first experiment, a similar situation occurred, as the third peak of the VCAP was absent. A small number of B-fibers may have been excited anyway, and they might be responsible for what we saw; hence further trials are needed to validate this specific result. C-fibers, although not necessary, might be beneficial for improving the dynamics of the heart rate response.

The left vagus is thought to have little effect on heart rate [10] compared to the right side. Classical physiological studies and applications are usually on the right [2][8], whereas more recent ones focus on the left or both [3][5][6]. In [11] evidence is produced that rules out any side difference in slowing the heart through VNS. Our results, so far, appear to be consistent with the hypothesis of no absolute side predominance [12], since right seems more powerful for the 118% target but left performs better for the 133%. Probably, depending upon ganglionic differences among species and individuals, left and right may be equally effective. On the other hand, bilateral stimulation doesn’t seem to improve the overall RMS of the error, but it does produce a faster and stronger variation of the RR interval, as it may be expected. Our system has a fast response and relatively small oscillations around the target value, but when the baseline R-R interval is physiologically high or the variation needed to reach the target is too high, then it might fail. If the compliance is low and the error builds up, the controller output saturates, the R-R interval goes back to its baseline value and control is not reached. If the heart rate locks in, it happens within a few seconds after the start. This all or none response is due to the fast dynamics of the designed system, as compared to existing patents [5][6][7].

References


Acknowledgements

This work was supported by the European Commission for the NeuralPRO Network (FP5-Program, Research and Training Network).