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Preliminary Results on the Importance of Vagus Nerve Stimulation Parameters for its Chronotropic Effects in Vagotomized Rabbits

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Abstract— **A sensitivity analysis of the main parameters of cardiac-synchronized vagus nerve stimulation was performed to determine their importance on the acute provoked chronotropic effects in bilaterally vagotomized rabbits. The preliminary results suggest a preeminent importance of current amplitude and pulse width, while other parameters may play a minor role.**

Clinical Relevance— **Our work aims to better understand the influence of vagus nerve stimulation on the provoked acute chronotropic effects.**

I. INTRODUCTION

In recent years, vagus nerve stimulation (VNS) is gaining interest for the treatment of cardiac diseases. Therefore, cardiac-synchronized stimulation is often applied to the right vagus nerve, delivering a burst of stimuli at a certain point in each cardiac cycle. This leads to five typical main stimulation parameters, namely the current amplitude (CA), pulse width (PW), number of pulses (NP), inter-pulse period (IPP), and the stimulation onset delay (D). A previous study [1] has already investigated the importance of these stimulation parameters for the provoked acute cardiac effects in anesthetized sheep with intact vagus nerves. In this case, however, parameter sensitivity is determined for concurrently evoked afferent and efferent responses together. Therefore, to determine the importance of stimulation parameters on vagal efferent cardiac effects only, we conducted a sensitivity analysis of the VNS parameters in bilaterally vagotomized animals.

II. METHODS

Six adult rabbits were used in the study under approval of the Institutional Animal Care and Use Committee of the city of Vienna (BMBWF 2020-0.016.858 – GZ 2020-0.016.858).

The animals were anesthetized, and the right and left vagus nerves were exposed at the cervical level, implanting a bipolar stimulation electrode on the right side. A bilateral vagotomy was performed, transecting both nerves cephalad to the stimulation electrode. The electrocardiogram (ECG) and the arterial pressure were continuously monitored and recorded throughout the experiments. Cardiac-synchronized stimulation was performed using cathodic-anodic charge-balanced biphasic rectangular current pulses which were triggered by the R-peaks in the ECG signal.

A total of 100 value combinations of the five main VNS parameters were generated using Latin Hyper Cube sampling. The value ranges were CA = [0.5 to 2] mA, PW = [50 to 500] µs, NP = [1 to 6], IPP = [25 to 200] ms and D = [0 to 300] ms.

For each combination, stimulation was applied for 30 s, separated by a pause of at least 30 s to allow the heart rate and blood pressure to recover.

The chronotropic responses were quantified as the relative difference between the mean RR-interval at baseline and the last 10 s of each stimulation phase.

The data was used to train a gaussian process regression model. The model was then applied to calculate first-order effects and interactions using Sobol's variance decomposition [2] for 10,000 random parameter value combinations.

III. RESULTS

The preliminary results of the sensitivity analysis highlight the preeminent importance of the CA and secondly the PW, together explaining more than 85% of the observed variability in the chronotropic responses. Together accounting for less than 10% of variability, the NP, IPP, and D seem to play a subordinate role. The differences between total- and main-effect indices were all well below 10%, suggesting no clear interactions between the stimulation parameters

IV. DISCUSSION & CONCLUSION

The preliminary results highlight the major importance of CA and PW in VNS-induced chronotropic effects in bilaterally vagotomized rabbits. Although the first-order effect ranking is qualitatively the same as previously found in sheep with intact vagus nerves [1], the interactions between the stimulation parameters are substantially less. Further studies are needed to determine the role of vagal deafferentiation and possible inter-species differences

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REFERENCES

[1] D. Ojeda et al., "Sensitivity Analysis of Vagus Nerve Stimulation Parameters on Acute Cardiac Autonomic Responses: Chronotropic, Inotropic and Dromotropic Effects" in *PlosOne*, 2016, 11(9): e0163734

[2] I. Sobol et al., "Estimating the approximation error when fixing unessential factors in global sensitivity analysis," Reliability engineering & systems safety, vol. 92, no. 7, pp. 957–60, 2007.