Influence of Vagus Nerve Stimulation parameters on Chronotropism and Inotropism in Heart Failure

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Abstract — **Vagus Nerve Stimulation (VNS) has been shown to be useful in heart failure patients, including antiarrhythmic effects, improvement of cardiac function and reduction of the mortality. However, the optimal configuration of VNS can be a difficult task, since there are several adjustable parameters, such as current amplitude (mA), pulse width (ms), burst frequency (Hz), number of pulses and, in the case of cardiac-triggered VNS, the delay (ms) between the R-wave and the beginning of the stimulation. The objective of this paper is to analyse the effect of these parameters, and their interaction, on the chronotropic and inotropic responses to vagal stimulation. 306 VNS sequences were tested on 12 sheep with induced heart failure. Autonomic markers of the chronotropic (changes in RR interval) and inotropic (changes in dP/dt_{max}) effects were extracted from the observed data. In order to analyse the influence of stimulation parameters on these markers, a sensitivity analysis method was applied. Results illustrate the strong interaction between the delay and the others parameters. The number of pulses, the current and the frequency seem to be particularly influent on chronotropism and inotropism although the effect of the frequency is highly non-linear or it depends on other parameters.**

I. Introduction

In heart failure (HF), the balance of the autonomic nervous system is disrupted by an increased sympathetic system activity and a reduced parasympathetic tone [1]. This reduction of the vagal activity, in patients with heart failure, is associated with an increased mortality [2]. Vagus nerve stimulation (VNS) offers an alternative therapy in heart failure patients who do not respond to resynchronization therapy and a large part of those who are not eligible for cardiac resynchronization therapy (CRT). In fact, VNS has been extensively studied for its effect on cardiac arrhythmia and ischemia [3-5]. Several studies have demonstrated an improved cardiac function in particular on left ventricular performance and a decrease in cardiac volumes with VNS [6-8]. The beneficial effects of VNS in HF include reduction of heart rate, increased heart rate variability and antiarrhythmic effects [9].

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Despite the beneficial effects of VNS in HF, the stimulation parameters induce a high variability of responses. The choice of the parameters configuration is an essential step to optimize physiological responses to VNS and to obtain favourable outcomes. The combination of VNS parameters could also affect the functional selectivity of these physiological responses and should take into account the power consumption of the stimulation device. In fact, several configurations of parameters could induce similar responses, while involving different energy consumption.

Stimulation parameters have been evaluated in previous studies: pulse train, frequency (1–100 Hz), current (0.1–15mA) and pulse width (0.1–2ms) [8, 10-12]. Most papers deal with asynchronous pulse trains, not related to cardiac activity. Other parameters have been introduced, such as the "duty cycle", which allows to program sequences of alternating VNS and non-VNS. Studies have shown that several parameters have significant effects on the role of VNS including pulse width, frequency, pulse voltage and the duration of VNS [12, 13]. However, few studies investigate the interaction between the different stimulation parameters and the effect on heart rate or blood pressure.

In this paper, the relation between stimulation parameters and their effect on the physiological response to VNS is investigated in the anesthetized sheep. Two different autonomic markers were observed (changes in RR interval and changes in dP/dt_{max}) under different VNS parameter configurations. Using a database of several stimulation sequences and their observed autonomic markers, a sensitivity analysis method was used to assert qualitatively the influence of the stimulation parameters on the chronotropic and inotropic responses to VNS.

The experimental protocol and signal processing methods used in this work are described in Section II. In section III, the paper discuses the results obtained on the database. Finally, conclusions are given in section IV.

II. Methods

A. Experimental protocol

Experiments were performed on 12 sheep with a myocardial infarction provoked by ligatures on three marginal coronary arteries. The French ethics committee for animal experimentation approved the protocol. Two interventions under general anesthesia (isoflurane or etomidate) were performed. The first one, about 7 days after the infarction, is focused on device implantation, which includes *i)* a lead in the right ventricle for QRS detection and stimulation of the heart in case of severe bradycardia,

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(SonRTip™ lead, Sorin CRM, Clamart, France) *ii)* a stimulation cuff (Cuff electrode C4D3-1, Obélia, Vallauris, France) which is a bipolar cuff placed on the right vagus nerve, and *iii)* a prototype device delivering vagal nerve stimulation (VNS) with programmable parameters. The second intervention is performed 3 months later.

During the two experiments, left ventricular pressure was measured with a probe (Millar Instruments, Inc., Houston, USA) inserted temporarily into the left ventricle. With this sensor, an intracardiac electrogram (EGM) was measured in addition to an external ECG. All signals were acquired by a BIOPAC system (Biopac system Inc., CA, USA) with a sampling rate of 1250 Hz and recorded for further analyses.

B. Explored VNS configurations

Several sequences of VNS were carried out during each experiment. One sequence of stimulation consists of a pulse train, triggered by an R-wave and characterized by a given VNS configuration, which represents a set of adjustable parameters. Pulses are delivered at a programmable preset delay from the R-wave. Only some cardiac cycles may be stimulated, according to a defined ratio, so that a stimulation is delivered to one for every four cardiac cycles (ratio=1/4) or for every cardiac cycle (ratio=1/1). Selected parameters for this study are: current (P_{Cur}, mA), pulse width (P_{Width}, ms), pulse train frequency (P_{Freq}, Hz), number of pulses (P_{Num}) and delay (P_{Delay}, ms). The value of each parameter is selected in predefined ranges, which have been chosen according to the stimulator capabilities: P_{Cur}=[1, 1.5, 2, 2.5, 3]; P_{Width} = [0.12, 0.24, 0.37, 0.49]; P_{Freq} = [25.6, 32, 42.7]; P_{Num} = [1, 2, 3, 4]; P_{Delay} = [16, 47, 63, 86,109].

In total, 306 different sequences were considered in this study; 219 obtained during the first experiment and 87 three months later. These sequences correspond to 99 different VNS configurations.

C. Signal processing

The RR intervals, systolic and diastolic pressures were first extracted from the ECG and the left ventricular pressure, respectively. The rate dP/dt_{max} was then computed as the maximum derivative of the left ventricular pressure signal, on a beat-to-beat basis. This index reflects the contractile function of the heart and is recognized as an indicator of inotropism [14]. In order to quantify the influence of VNS on chronotropism and inotropism, two indices were extracted from the RR and dP/dt_{max} signals for each sequence.

The first one, ΔRR_n, is the percentage of RR interval variation between VNS period and a rest period just before the stimulation. It is calculated as follows:

$$\Delta RR_n = 100 \frac{\overline{RR}_{stim} - RR^*_{baseline}}{RR^*_{baseline}} \quad (1)$$

where $\overline{RR}_{stim}$ is equal to the median of seven stimulated RR after removing the transient part (first three stimulated RR) and $RR^*_{baseline}$ is the average of the three cycles before beginning stimulation. The transient response of the RR was removed in order to have the same number of stimulated RR intervals for the entire database, independently of the duration of the stimulation.

Equation (2) defines the second index, $\Delta dPdt_n$, which is obtained from dP/dt_{max}. It is a measurement of the change in dP/dt_{max} between a VNS period and a rest period. For the VNS period, the minimum of dP/dt_{max}, $mindPdt_{stim}$, is used to characterize this period. For rest period, the calculation $dPdt^*_{baseline}$ is the same as $RR^*_{baseline}$:

$$\Delta dPdt_n = 100 \frac{\min dPdt_{stim} - dPdt^*_{baseline}}{dPdt^*_{baseline}} \quad (2)$$

where $dPdt^*_{baseline}$ is the average of the dP/dt_{max} in baseline and $mindPdt_{stim}$ is the minimum value of dP/dt_{max} during VNS.

Figure 1 shows an example of the method used to calculate ΔRR_n and $\Delta dPdt_n$ during a VNS sequence.

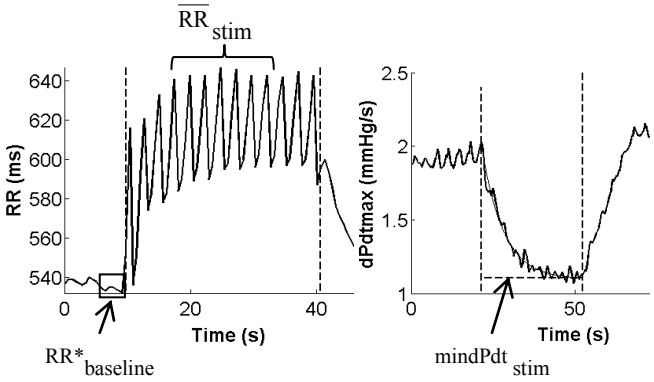

Figure 1: Example of the evaluation of ΔRR_n and $\Delta dPdt_n$. Dotted lines correspond to the beginning and the end of the VNS period.

D. Sensitivity analysis of the stimulation parameters

The approach used to analyse the influence of the stimulation parameters on chronotropism and inotropism is largely inspired on well-known sensitivity analysis methods [15]. A screening method was chosen because *i)* it provides more information about interactions between parameters than local methods and *ii)* it requires fewer observations than global sensitivity analyses methods. The objective is to study the influence of one parameter perturbation Δ_X on the value of the autonomic marker *Y*, where $Y \in \{\Delta RRn, \Delta dPdtn\}$ and X_i = [P_{cur}(i), P_{Width}(i), P_{Freq}(i), P_{Num}(i), P_{Delay}(i)]. One evaluation of the autonomic marker Y_i depends directly on the value of the parameters programmed in the stimulator, i.e. $Y_i = Y(X_i)$. The chosen sensitivity method has the particularity to provide no quantification (in contrast to global methods) but a rank of importance concerning these parameters.

A normalized measure of parameter sensitivity, the *elementary effect*, or $EE_{x,i}$, is thus defined as the fractional change of variable *Y* after a perturbation of parameter P_x, scaled by the corresponding parameter perturbation Δ_x ($x \in$ {current, pulse width, frequency, number of pulses, delay}). For example, the elementary effects associated with the VNS burst frequency parameter are thus defined as:

$$EE_{freq,k} = \frac{Y(X_i) - Y(X_j)}{\Delta_{Frequency}} \quad (3)$$

where X_i=[P_{Cur}(i), P_{Width}(i), P_{Freq}(i), P_{Num}(i), P_{Delay}(i)] and X_j=[P_{Cur}(i), P_{Width}(i), P_{Freq}(j), P_{Num}(i), P_{Delay}(i)]. In this

example, the only difference between the vector X_i and X_j is the value of the frequency parameter P_{Freq}. Careful attention was paid to the comparison of autonomic markers associated with the same anesthetic agent (isoflurane or etomidate) and the same VNS ratio ('1/1' and '1/4'). $\Delta_{frequency}$ is the normalized variation associated with the frequency, which can be computed as:

$$\Delta_{frequency} = \frac{P_{freq}(i) - P_{freq}(j)}{\max(P_{freq}) - \min(P_{freq})} \quad (4)$$

Such estimation of the elementary effects $EE_{x,k}$ can be computed for all the parameters $x \in$ {current, pulse width, frequency, number of pulses, delay}.

The resulting estimates of the value of the mean μ_x and the standard deviation σ_x of the $EE_{x,k}$, are indicators of which input parameters are most sensitive in terms of chronotropic or inotropic response. A large value of μ_x indicates that the parameter x has a significant overall effect on the output Y, while a large value of σ_x is associated with the presence of non-linear effects or with strong interactions with other parameters. Results from this sensitivity analysis can be represented graphically on the $\mu-\sigma$ plane.

III. Results

A. Chronotropic and Inotropic response to VNS

Modifications of VNS parameters show a variable effect on RR interval and dP/dt_{max}. As an example, Figure 2 shows typical RR and dP/dt_{max} evolutions during several VNS sequences. In these sequences, only one parameter is changed (the number of pulses, the burst frequency and the current), in order to illustrate the independent influence of the chosen parameters.

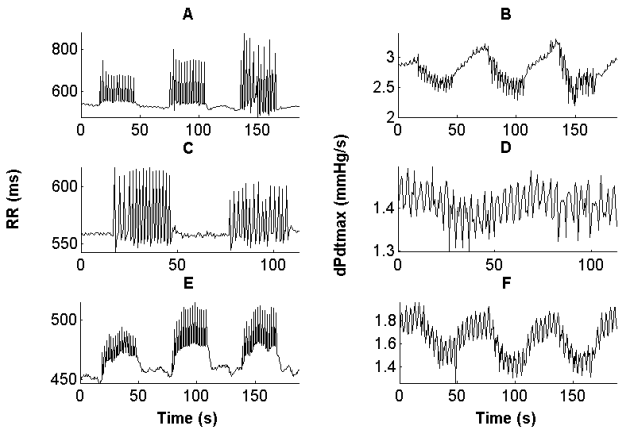

Figure 2: Example of RR and dP/dt_{max} evolutions while changing of one VNS parameter. A and B, P_{Cur}=2mA, P_{Width}=0.12ms, P_{Freq}=32Hz, ¼, P_{Delay}=16ms and **P_{Num}=1, 2 or 4**; C and D; P_{Cur}=3mA, P_{Width}=0.24ms, P_{Freq}=**25.6Hz or 42.7Hz**, ¼, P_{Delay}=16ms and P_{Num}=3; E and F; P_{Cur}=**1mA, 2mA or 3mA**, P_{Width}=0.49ms, P_{Freq}=25.6Hz, ¼, P_{Delay}= 6ms and P_{Num}=3

In the stimulation sequences presented in figures 2.A and 2.B, the influence of the number of pulses is clearly observed, since the RR and the dP/dt_{max} respectively rises and decreases with the number of pulses. The influence associated with the frequency is illustrated in figures 2.C and 2.D. As the frequency rises, the variation of RR falls and the dP/dt_{max} increases. In figures 2.E and 2.F., the current rises between 1 and 3 mA. Influence of current is clearly visible in this figure with an increase in RR and a decrease in dP/dt_{max}.

According to the sequences shown below, these three parameters seem to be particularly interesting to explore, when defining an optimal VNS configuration. However, it is difficult to formally analyse the influence of each parameters and the interaction between them.

B. Sensitivity analysis of VNS parameters

The elementary effects method has been applied on the database composed of the 306 sequences that have been acquired on 12 sheep. Figures 3 and 4 depict respectively the $\mu-\sigma$ plane obtained with the autonomic markers ΔRR_n and $\Delta dPdt_n$. The abscissa and the ordinate are respectively the mean value μ and the standard deviation σ associated with the elementary effects computed for each parameter x.

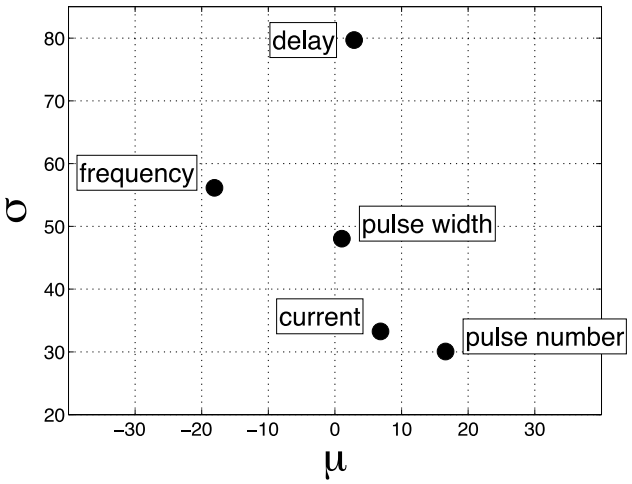

Figure 3: Sensitivity $\mu-\sigma$ plane used to represent the influence of the stimulator parameters on ΔRR_n.

Figure 3 depicts the influence of each stimulation parameter on ΔRR_n. It is possible to observe that the delay and the pulse width have a low μ and are associated with elevated value of σ. This indicates that the delay and the pulse width have a low overall effect on ΔRR_n, but there are strong interactions between them and the other parameters. The low influence of pulse width can be explained by the values chosen for this study, which are greater than the chronaxie of vagus fibers [16]. The burst frequency also presents a high σ value, which indicates strong interactions with other parameters or non-linear effects. However, the average of elementary effects μ of the burst frequency parameter is high and negative. In fact, as the frequency rises, the ΔRR_n decreases. As a consequence, the frequency has a significant and non-linear influence on the ΔRR_n. Finally, the current and the number of pulses are associated with a relatively low σ, which means that their influences on the ΔRR_n are less dependent on the other parameters. While the μ related with the current is relatively small compared with other parameters, the value of μ associated the number of pulses is significant. It is important to precise that the important values of σ are also due to the high variability of the data, which include several sheep and two different anesthesia.

The first observation on the $\mu-\sigma$ plane obtained for the $\Delta dPdt_n$, concerns the signs of μ and σ, which are reversed compared to those computed for ΔRR_n, as expected from the physiology of the chronotropic and inotropic effects. VNS provokes negative inotropic and chronotropic effects. Thus, when the current rises, the ΔRR_n increases and $\Delta dPdt_n$ decreases.

Globally, the standard deviations of all parameters, except the delay, are lower than those computed for the ΔRR_n. Therefore, the influences of the frequency, number of pulses, pulse width and current are more linear, while the effect of their interactions are less important. The delay presents a high σ and a μ close to zero. This parameter is highly non-linear and dependent of other parameters but its individual sensitivity is almost non-existent. The influence of the number of pulses and the current are similar because their μ and σ are very close.

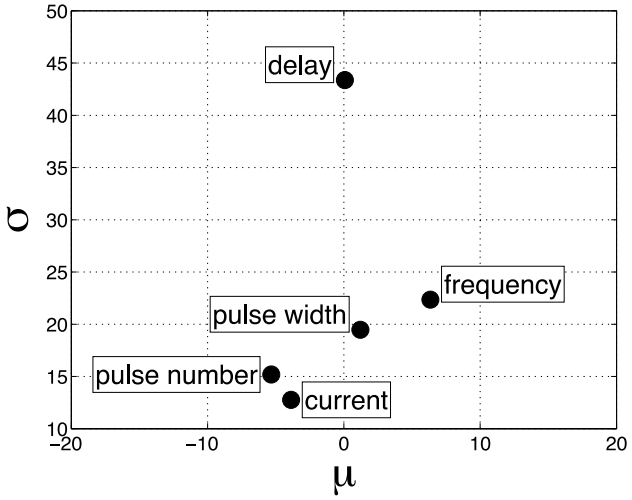

Figure 4: Sensitivity μ-σ plane used to represent the influence of the stimulator parameters on $\Delta dPdt_n$.

The evaluation of the effect of VNS on the chronotropic and inotropic response provides a qualitative estimation of the importance of each stimulation parameter. In particular, the burst frequency, number of pulses and current appear interesting due to their individual overall effects. This information can be used to determine which stimulation parameters are the most important in order to design an optimal VNS configuration that *i)* induces a greater physiological response, *ii)* produces a selective chronotropic or inotropic response, or *iii)* minimizes device power consumption.

IV. Conclusion

Although the beneficial effects of VNS in heart failure are now recognized, the stimulation parameters induce a high variability of responses. In this paper, the effect of a configurable stimulation on the chronotropic and inotropic response to VNS was studied using an original approach to analyze the sensitivity associated with each stimulation parameter. This permitted to identify qualitatively the stimulation parameters that show a linear effect and which parameters show non-linear or interactive effects. From the sensitivity analysis results on the RR interval and dP/dt_{max}, three parameters (number of pulses, current and frequency) produce an important effect on the physiological response to VNS. These results can guide and provide important information for the design of optimal VNS configurations. Further work will be directed towards i) the inclusion of more stimulation sequences in order to confirm these results, ii) the quantification of the parameter effects using a statistical or computational model, and iii) the investigation of VNS configurations that induce a selective chronotropic or inotropic response.

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