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Virginie Le Rolle, David Ojeda, Alain Beuchee, Jean-Paul Praud, Patrick Pladys, et al.. A model-based approach for the evaluation of vagal and sympathetic activities in a newborn lamb.. Conference proceedings : .. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference, 2013, 2013, pp.3881-4. 10.1109/EMBC.2013.6610392 . inserm-00881084

**HAL Id: inserm-00881084**

**https://inserm.hal.science/inserm-00881084**

Submitted on 7 Nov 2013

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# *A model-based approach for the evaluation of vagal and sympathetic activities in a newborn lamb*

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## Abstract

**This paper proposes a baroreflex model and a recursive identification method to estimate the time-varying vagal and sympathetic contributions to heart rate variability during autonomic maneuvers. The baroreflex model includes baroreceptors, cardiovascular control center, parasympathetic and sympathetic pathways. The gains of the global afferent sympathetic and vagal pathways are identified recursively. The method has been validated on data from newborn lambs, which have been acquired during the application of an autonomic maneuver, without medication and under beta-blockers. Results show a close match between experimental and simulated signals under both conditions. The vagal and sympathetic contributions have been simulated and, as expected, it is possible to observe different baroreflex responses under beta-blockers compared to baseline conditions.**

## INTRODUCTION

Heart rate variability (HRV) is a commonly used indicator of the autonomic balance between the sympathetic and the vagal activities. Although HRV can be easily extracted from the electrocardiogram (ECG), its interpretation can be difficult because of the complex mechanisms involved in the autonomic regulation. Moreover, the evaluation of the sympathovagal balance is difficult, since the vagal and sympathetic nervous system responses can't be assessed directly. In this context, a model-based approach could ease the evaluation of the vagal and sympathetic activities from variations of RR intervals.

Several works in the literature have proposed a model-based analysis of the baroreflex response to variations of arterial pressure (AP). Some of them are based on a black-box approach, associating transfer functions with parametric identification [1,2]. Although this approach generates simulations that are close to experimental data, vagal and sympathetic pathways are not explicitly represented. On the other hand, several models are based on a realistic representation of the physiological structure, integrating explicitly the vagal and sympathetic pathways [3]. These models can be easily coupled with models of the cardiovascular system [4,6]. Although they proved their ability to reproduce physiological tests, such as valsalva maneuver [5,7] and orthostatic test [4,8], the modelling approach has not been used to estimate vagal and sympathetic activites. Moreover, HRV is not only due to blood pressure variations, but is also influenced by neuronal, humoral or other physiological control loops. HRV is also affected by respiration because of the mechanical thoracic coupling with the cardiovascular system (SCV) and the interaction between respiratory control centers and the autonomic nervous system (ANS) [9].

In this paper, a modeling approach is proposed in order to simulate experimental heart rate variability and to estimate the time-varying activities of vagal and sympathetic pathways. Although our previous works concern closed-loop models of the SCV including the autonomic regulation [4,5], this paper only focuses on the open-loop relationship between AP and HR in order to reduce the number of parameters to identify and to decrease the uncertainty on the estimation of AP. The complete process has been applied to analyze RR series acquired on one newborn lamb during the injection of a vasodilator and a vasoconstrictor. In the next section, the experimental protocol, the baroreflex model and the identification algorithm are described. Then, the results obtained are described and discussed.

## Materials and Method

### Experimental protocol

Experiments were performed on lambs aged 4–5 days. All lambs were born at term and housed with their mother. The protocol was approved by the Committee for Animal Care and Experimentation of the Universit de Sherbrooke, Canada. Surgery was performed two days before the experiment under general anesthesia following the procedure detailed by St Duvareille et al. [10]. Briefly, ECG Leads were subcutaneously positioned and an arterial catheter was inserted into the brachial artery for recording systemic arterial pressure. All lambs were returned to their mother after arousal from anesthesia. Leads from the electrodes were connected to a transmitter attached to the lambs back just prior to the experiment. The raw signals were transmitted by radiotelemetry. Systemic arterial pressure was obtained from

the brachial catheter using a pressure transducer (Trantec model 60–800, American Edwards Laboratories, Santa Anna, CA, USA) and pressure monitor (model 78342A Hewlett Packard, Waltham, MA, USA). Two ECG leads were also acquired using this monitor.

Throughout the recordings, the lambs were comfortably positioned in a sling with loose restraints and monitored with polygraphic recording. Ambient temperature was 22°C. An observer was always present in the laboratory to note all events. The sequence of experimentations started with a 3 min recording in basal condition while in quiet sleep, followed by a continuous perfusion of nitropussiate sodium for 360 secondes, subsequently, after a 30 min period of recovery, a second continuous perfusion of nitroprusside was started for 120 secondes and concluded by a single and bolus injection of phenylephrine. The same sequence of experimentations was repeated the following day started 5 minutes after the bolus administration of metoprolol 1 $mg.kg^{-1}$ repeated each 30 mins.

**Baroreflex Model**

The baroreflex is initiated by the stimulation of the baroreceptors, which are sensory receptors that respond to variations of pressure that are mainly located in the wall of atria, vena cava, aortic arch, and carotid sinus. The cardiovascular control center is the link between afferent and efferent pathways. This complex structure, located in the medulla, includes the Nucleus Tractus Solitarius (NTS) that is connected to afferent nerves, the vagal motor center (Vagal Dorsal Motor Nucleus DMN, the Nucleus Ambiguus, NA) and the origin of sympathetic nerve (Rostral Ventrolateral Medulla RVLM) [11]. The different elements of this structure depend on the output from baroreceptors and are also under the direct influence of different brain structures like central nervous system, the hypothalamus or the respiratory control center [12]. The variations initiated in cardiovascular control center are translated into corresponding effects on the efferent sympathetic and parasympathetic pathways. The sympathetic system has a global excitatory effect, increasing heart rate, ventricular contractility, peripheral vascular resistance, and so forth, during situations like hunger, fear, and physical activity. The parasympathetic system generally presents an opposite effect. The main effectors are the heart rate, myocardium contractility, peripheral resistance, and venous blood volume.

The baroreflex model is represented in figure 1. It includes the receptors (baroreceptors) and afferent pathways, the cardiovascular control center and the efferent pathways (including the vagal and sympathetic branches). All details on the constitutive elements of the model and some parameters values can be found in [4].

The baroreceptor input is the arterial pressure (*AP*) and its dynamical properties are represented by a first-order filter, which gain and time constant are noted *K* and *T*. The cardiovascular control center is represented by sigmoidal functions and two time-varying gains. Normalization and saturation effects are represented by sigmoidal input-output relationship :

$$N_x = a_x + \frac{b_x}{e^{\lambda_x (P_B - M_{x,0})} + 1}.$$

(1)

The generic parameter *x* stands for the vagal and sympathetic pathways, *P* is the baroreceptor output, the parameters *a*, *b*, λ and $M_0$ are used to adjust the sigmoidal shape. The links between cardiovascular control center and efferent nerves are modeled by two time-varying gains *C* (*t*) and *C* (*t*), representing respectively the vagal and sympathetic responses. These time-varying gains reflect the modulation of the vagal and sympathetic activities by the brain structures that interact with NTS and the influence of respiratory control center.

The efferent pathways are composed of two parts for the vagal and the sympathetic nerves. Each branch is composed of a delay (*R* and *R* are respectively the sympathetic and parasympathetic delays), and a first-order filter characterized by a gain (*K* and *K* for the sympathetic and the vagal gains) and a time constant (*T* and *T*). The output signal of the heart rate regulation model (*HR*) is continuous and is obtained by adding the contributions from the parasympathetic and sympathetic branches (V and S) and a basal (intrinsic) heart rate ($HR_0$), which is equal to average heart rate.

**Identification Method**

The identification process was performed using the experimental AP as input of the baroreflex model. The simulated RR interval signal is used as output and is compared to the experimental RR using the error functions described in this section. The identification procedure is composed of two steps: 1) the constant parameters are identified on a short period of the signal equal to *P*, 2) the time-varying parameters are identified recursively on the complete RR signal, of duration *T*. The ranges of the parameters values used to realize the identification were defined to approximate published values.

The first step consists in minimizing the following error function $\varepsilon_1$, in order to identify constant parameters [*T*, *K*, *T*, *R*, *K*, *T*, *R* ] :

$$\epsilon_1 = \sum_{t_{e1}=t_{e10}}^{t_{e10}+P_x} \left| \left(RR_{sim}(t_{e1}) - RR_{exp}(t_{e1})\right) \right|,$$

(2)

where $t_1$ corresponds to the time elapsed since the onset of the identification, $t_{10}$ is the beginning of the identification period. The variables $RR(t_1)$ and $RR(t_1)$ correspond to the experimental and simulated RR interval. The identification period duration is equal to 5 seconds, and was selected after the injection of phenylephrine in order to take into account rapid events. An evolutionary algorithm (EA) has been applied, as in our previous works [13], [14]. EA are stochastic search methods, inspired by the theories of evolution and natural selection, which can be employed to find an optimal configuration for a given system [15].

The second step consists in identifying recursively time-varying parameters [$C$, $C$ ]. At each step $i$ of the algorithm, the parameters are identified on intervals, which duration is equal to $T$, by minimizing an error function $\varepsilon_2$

$$\epsilon_{2i} = \sum_{t_{e2}=iT_L}^{iT_L+T_I} | (RR_{sim}(t_{e2}) - RR_{exp}(t_{e2})) |, i \in [0, N],$$

(3)

where $t_2$ corresponds to the time elapsed since the onset of the identification period, $T$ is the time lag between each interval and $N$ is the number of identification intervals, which is equal to integer part of $\frac{T_{tot}}{T_L}$. This error function is minimized on each interval $i$ using EA. Concerning the first interval, a set of random initial solutions was used to create the initial population. For the following intervals, the initial population was set equal to the population obtained from interval $i$-1 considering that the parameter variation between interval is limited. Although this approach of attribution of initial populations limits the parameters changes, a mutation operator wit probability $p$ = 0.2 helps the process to explore the entire search space and prevent from convergence to a local minimum.

## Results and Discussion

The baroreflex model was implemented under an object-oriented multiformalism modeling tool (M2SL) [16]. The first step of the identification was performed over a period $P$ of 5 seconds. The results obtained are the following (the time parameters are expressed in seconds) : $T$ = 0.13, $K$ = 0.848, $T$ = 0.01, $R$ = 0.01, $K$ = 0.7873, $T$ = 3.9 and $R$ = 8.3. Vagal time constant and delay have lower values compared to sympathetic ones and the difference between vagal and sympathetic parameter values is more significant than in human adult models [7,11]. This can be explained by the maturity of the autonomic nervous because parameters evolve rapidly during the first days of life. Identified parameters values were used in the second step of the identification.

The identification of cardiovascular control center parameters has been realized on the whole signal duration. The interval length $T$ and the time lag $T$ are respectively equal to 2 seconds and 0.3 seconds and have respectivelly the same orders of magnitude than the sympathetic and vagal time constants. The comparisons between experimental and simulated RR signals are shown in Fig. 2.a and Fig. 3.a. The beginning of the RR series corresponds to the nitroprusside injection, and the phenylephrine bolus is injected after 120 seconds. Fig. 2 depicts experimental arterial pressure and RR signals without any autonomic blocking drugs. Signals, illustrated in Fig. 3, were obtained after the injection of beta-blockers. The decrease of the RR interval, which can be observed in the first part of the signal, is the consequence of the vasodilatation induced by nitroprusside. Then, the RR increases following the baroreflex response and the injection of phenylephrine (at $t$=120 seconds) which induces a vasoconstriction.

The comparison between simulated (black lines) and experimental (red lines) RR intervals after recursive identification shows a close match between experimental and simulated RR intervals, since Root Mean Square Errors (RMSE) is equal to 0.0008 for the first day of experimentation (Fig. 2) and 0.0014 or the second day of experimentation (Fig. 3). In fact, the global morphology of the curve is reproduced since RR signals increase and decrease in response to nitroprusside and phenylephrine.

The estimated activities of vagal and sympathetic pathways, without any autonomic blockade drugs, is shown in Fig. 4. During the first 100 seconds, these signals are characterized by a decrease of vagal activity and an increase of sympathetic activity. Then, the parasympathetic contribution begins to rise and the sympathetic contribution falls because AP stabilizes. After the injection of phenylephrine occuring at 120 seconds, the vagal activity is maintained while sympathetic activity drops about 20 second after the injection.

Fig. 5 depicts the contributions of vagal and sympathetic pathways with beta-blockers. Although the injection of nitroprusside is realized at the beginning ($t$=0), vagal and sympathetic contributions are relatively stable until the injection of phenylephrine. After 120 seconds, parasympathetic activity rapidly increases and then stabilizes. Sympathetic activity falls to its minimum level few seconds after the phenylephrine injection.

The variations of vagal and sympathetic pathways show different behaviors in the absence of an autonomic blockade drug and with beat-blockers. In fact, the baroreflex activity allows a stabilization of AP in the first case and, as expected, vagal and sympathetic responses are reduced with beta-blockers. Moreover, the curves depicted in Fig. 4 and Fig. 5 show the variety of dynamics associated with vagal and sympathetic pathways.

## Conclusion

In this paper, a model-based approach is proposed in order to estimate the vagal and sympathetic contributions to heart rate. A recursive identification algorithm was used to obtain parasympathetic and sympathetic gains associated with cardiovascular control center. This method was applied to the analysis of a newborn lamb RR signal during the injection of nitroprusside and phenylephrine. Signals acquistions were realized under baseline conditions and beta-blockers. Results illustrate the similarity between experimental data and simulations following identification. The evolution of vagal and sympathetic activities shows the different responses associated with baseline conditions and beta-blockers. The results presented in this paper are encouraging for the use of this model-based approach for the estimation of parasympathetic and sympathetic activities. The proposed model-based method must now be further validated with signals obtained in additional lambs.

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**Fig. 1**

Block diagram of baroreflex control of arterial pressure. See text for abreviations.

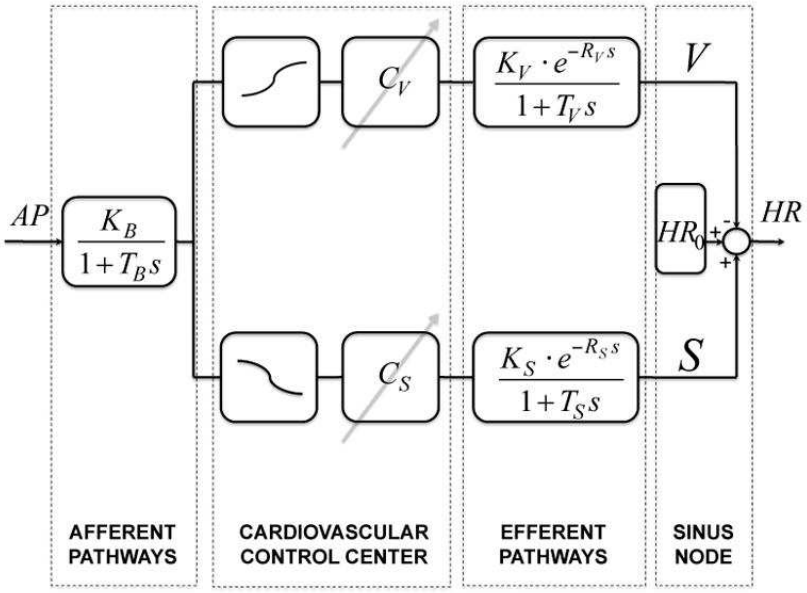


**Fig. 2**

First day of experimentation - without any autonomic blocking drugs - (a) Experimental arterial pressure, (b) Comparison of model simulations (black lines) with experimental RR interval (red lines)

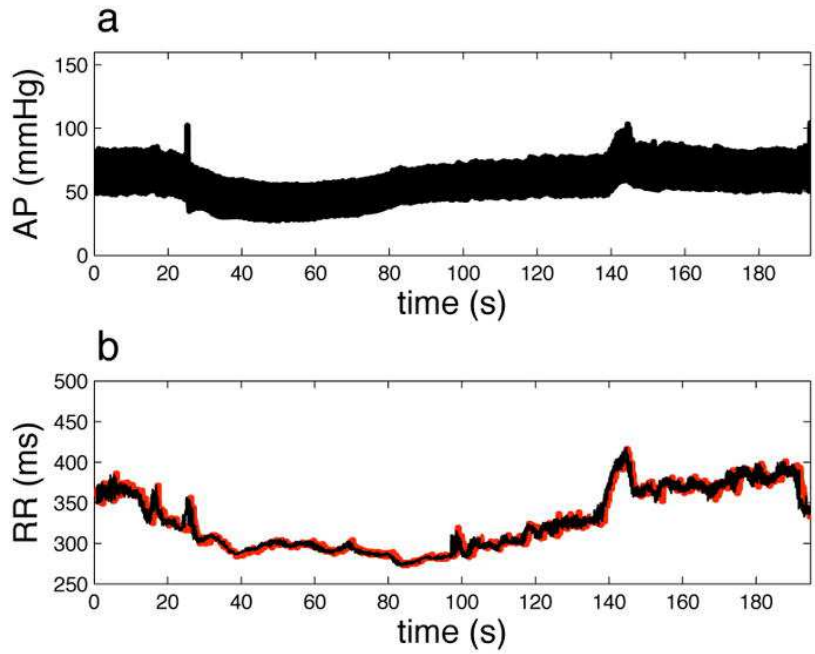



**Fig. 3**

Second day of experimentation - beta-blockers - (a) Experimental arterial pressure, (b) Comparison of model simulations (black lines) with experimental RR interval (red lines).

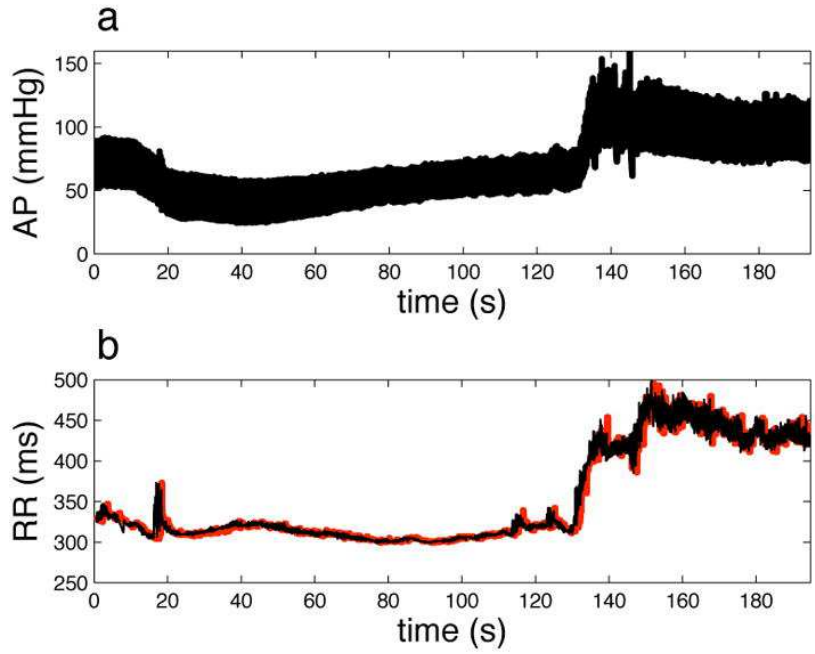


**Fig. 4**

Contributions of the vagal (V) and sympathetic (S) pathways without any autonomic blocking drugs (expressed in beat/s).

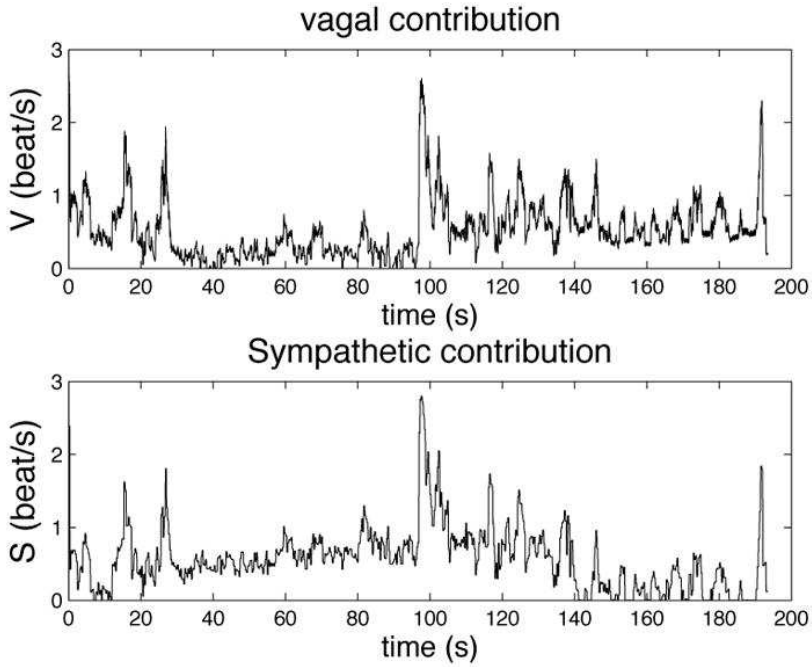



**Fig. 5**

Contributions of the vagal (V) and sympathetic (S) pathways with beta-blockers (expressed in beat/s).

