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Recursive identification of an arterial baroreflex model for the evaluation of cardiovascular autonomic modulation

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ABSTRACT

The evaluation of the time-varying vagal and sympathetic contributions to heart rate remains a challenging task because the observability of the baroreflex is generally limited and the time-varying properties are difficult to take into account, especially in non-stationnary conditions. The objective is to propose a model-based approach to estimate the autonomic modulation during a pharmacological challenge.

A recursive parameter identification method is proposed and applied to a mathematical model of the baroreflex, in order to estimate the time-varying vagal and sympathetic contributions to heart rate modulation during autonomic maneuvers. The model-based method was evaluated with data from five newborn lambs, which were acquired during injection of vasodilator and vasoconstrictor drugs, on normal conditions and under beta-blockers, so as to quantify the effect of the pharmacological sympathetic blockade on the estimated parameters.

After parameter identification, results show a close match between experimental and simulated signals for the five lambs, as the mean relative root mean squared error is equal to 0.0026 ($\pm$ 0.003). The error, between simulated and experimental signals, is significantly reduced compared to a batch identification of parameters. The model-based estimation of vagal and sympathetic contributions were consistent with physiological knowledge and, as expected, it was possible to observe an alteration of the sympathetic response under beta-blockers. The simulated vagal modulation illustrates a response similar to traditional heart rate variability markers during the pharmacological maneuver. The model-based method, proposed in the paper, highlights the advantages of using a recursive identification method for the estimation of vagal and sympathetic modulation.

1. Introduction

During the first days of life, newborns may be exposed to various life threatening events, such as intracranial hypertension, neonatal septic shock or streptococcus b infection. These events induce physiological challenges that trigger protective autonomic autoresuscitation reflexes and the evolution of the newborn state directly depends on the responses of both vagal and sympathetic nervous activities. Monitoring the status of infants in the Neonatal Intensive Care Unit (NICU) provides data of physiological variables (arterial pressure, heart rate, etc.). Although the prognosis of the newborn will depend on the maturity of his or her autonomic nervous system, information about autonomic adaptation is difficult to access. As a consequence, robust tools are required to evaluate time-varying evolutions of vagal and sympathetic responses during newborn monitoring in NICU. In fact, evaluating sympathetic and parasympathetic tones will give precious information for the diagnosis and the choice of the most appropriate treatment.

Informations about the autonomic status are usually provided by Heart Rate Variability (HRV) analysis based time or frequency domaine indicators. In particular, the high-frequency (HF) components of the power spectrum of the HRV signal have been widely used as an indicator of the parasympathetic modulation and the low-frequency components (LF) are considered as a mix of sympathetic and parasympathetic modulations. Time-frequency analyses of heart rate (HR) series have also been applied to

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estimate these frequency-domain markers in non-stationary conditions [1]. Another approach is based on the application of blind source separation methods. Vetter et al. [2] have proposed a method based on independent component analysis (ICA) for the estimation of the sympathetic, parasympathetic and respiratory activities as three different, synchronous time-varying sources. Previous work of our team extended this approach to an asynchronous processing of the observables [3].

However, it is difficult to interpret the results of most of these methods in physiological terms, since no *a priori knowledge* about the underlying physiology is integrated into the analysis. For instance, it is difficult to separate the sympathetic and parasympathetic contributions to the LF marker or the mechanical respiratory effect from the parasympathetic modulation of the HF marker [4]. As a consequence, complimentary approaches are needed in order to improve of the evaluation of sympathetic and parasympathetic modulation and the interpretation of clinical data.

Yet another approach consists in the integration of physiological knowledge into the analysis, by means of physiological models, integrating not only the effect of ANS on HR, but also other physiological parameters. Several models of the baroreflex, based on adult data, have been already proposed. Those based on autoregressive representations are particularly adapted to study interactions between RR interval, arterial pressure and respiration [5–7]. Other models include an explicit representation of vagal and sympathetic nervous systems [8,9]. Transfer functions are largely used to represent the components of the baroreflex loop [10–12]. Most of them take into account the non-linear behavior of the autonomic modulation [13,14]. Some models have been employed to reproduce non-stationary clinical tests, such as the orthostatic stress [15–17] and Valsalva maneuvers [11,18]. However, most of these models rely on population-based parameters (not patient-specific parameters) or neglect their time-varying nature.

In this work, we propose an original approach, based on a model of the baroreflex function, introducing: (i) a phase of subject-specific model parameter identification and (ii) a phase of estimation of the time-varying sympathetic and parasympathetic modulations, through the use of a recursive evolutionary algorithm. The proposed approach was evaluated with cardio-respiratory data acquired from five newborn lambs, during non-stationary conditions, provoked by the injection of a vasodilator and a vasoconstrictor drug, in normal conditions and during sympathetic blockade. Results from the proposed approach were compared to traditional autonomic markers, extracted from time-frequency HRV analysis.

2. Methods

2.1. Data and experimental protocol

Experiments were performed on lambs aged 4–5 days. All lambs were full-term at birth and housed with their mother. The protocol was approved by the Committee for Animal Care and Experimentation of the University of Sherbrooke, Canada. Surgery was performed two days before the experiment under general anesthesia following the procedure detailed by Duvareille et al. [19] for catheter implanting. Systemic arterial pressure (AP) 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). Respiratory thoraco-abdominal movements were monitored with a respiratory inductance plethysmography (RIP) system (Respitrace; NIMS Inc., Miami, FL, USA). Two electrocardiogram (ECG) channels were acquired using a couple of ECG100 modules (Biopac Systems, Inc. Santa Barbara, CA, USA). All signals (ECG, AP and respiration) were sampled at 1000 Hz and recorded on a PC, using the MP100A data acquisition system and Acknowledge 3.7.3 software (Biopac Systems Inc. Santa Barbara, CA, USA).

Lambs were non-sedated and, throughout the recordings, were comfortably positioned in a sling with loose restraints and monitored with the above-mentioned recording system. 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 conditions, while during behaviorally defined quiet sleep, followed by a continuous perfusion of nitroprusside sodium ($12\ \mu g.kg^{-1}\cdot min^{-1}$) for 360 s.

In the standardization process, we aim to maintain the state of alertness (quiet sleep), which is quiet frequent but with short duration in full-term lamb. The 3-min duration is a good compromise between sufficient duration for the analysis and the preservation of quiet sleep. Subsequently, after a 30 min period of recovery, a bolus injection of nitroprusside ($20\ \mu g\cdot kg^{-1}$) was administrated and was followed, after 120 s, by a bolus injection of phenylephrine ($4\ \mu g\cdot kg^{-1}$) (Fig. 1). The same sequence of experimentations was repeated another day, starting 5 min after the intravenous bolus administration of metoprolol ($1\ mg\cdot kg^{-1}$) repeated each 30 mins. The metoprolol blocks the action of the sympathetic nervous system. The days, with and without beta-blockers, were randomized in order to minimize the residual effect of metoprolol. At the end of the experimentation, the beta-blockers administration is combined to an

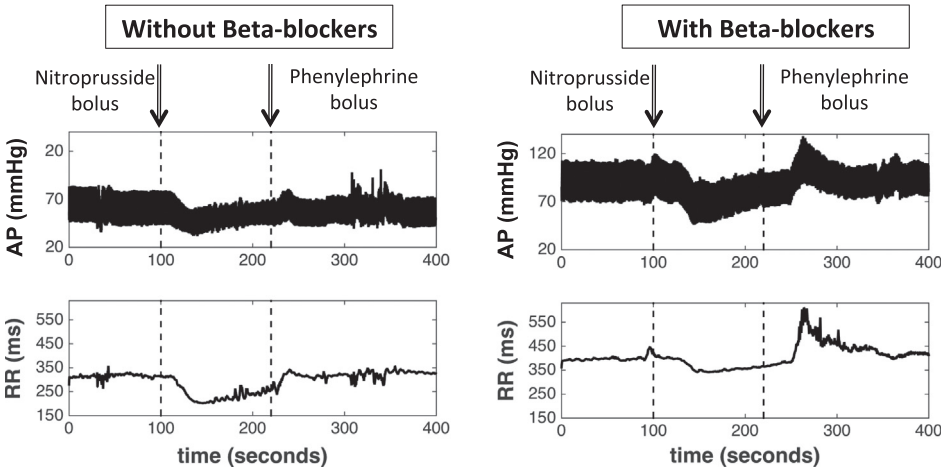

Fig. 1. Example of signals acquired with and without beta-blockers on two days. Arterial pressure (mmHg) and RR (ms) obtained during the perfusion of nitroprusside and after the bolus of phenylephrine.

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