Linear and Nonlinear Parametric Model Identification to Assess Granger Causality in Short-Term Cardiovascular Interactions

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Abstract

We assessed directional relationships between short RR interval and systolic arterial pressure (SAP) variability series according to the concept of Granger causality. Causality was quantified as the predictability improvement (PI) of a time series obtained when samples of the other series were used for prediction, i.e. moving from autoregressive (AR) to AR exogenous (ARX) prediction. AR and ARX predictions were performed both by linear and nonlinear parametric models. The PIs of RR given SAP and of SAP given RR, measuring baroreflex and mechanical couplings, were calculated in 15 healthy subjects in the resting supine and upright tilt positions. Using nonlinear models we found a bilateral interaction between the two series, unbalanced towards the mechanical direction at rest and balanced after tilt. The utilization of linear AR and ARX models led to higher prediction accuracy but comparable trends of predictability and causality measures.

1. Introduction

Characterization of directional interactions between heart period (RR interval) and arterial pressure (AP) variability is becoming a very important problem among those addressed by cardiovascular time series analysis. In the recent years many studies have indeed focused on the assessment of causality in cardiovascular interactions, providing evidence that variations of the reciprocal influence between RR and AP often reflect modifications of the regulatory mechanisms related either to diseases or experimental interventions [1-4].

Among the multiple available definitions of causality and practical algorithms developed to quantify directional influences between two simultaneously measured signals, a prevailing notion is that formulated by Granger in the context of linear stochastic modeling [5] and recently extended to nonlinear systems [6]. According to Granger's definition, a series is called causal to another if we can better predict the second series by using the past information from the first one than by using the information without it. Albeit methods quantifying linear and nonlinear Granger causality are recommended for the study of complex physiological systems such as the cardiovascular one, their application to short-term cardiovascular interactions requires formulations that guarantee applicability to time series which are stationary only over short epochs (typically a few minutes).

In the present study, we formalize the Granger's definition of causality in the context of parametric modeling of time series, and assess linear and nonlinear causality between short-term RR interval and systolic AP (SAP) series measured in healthy subjects in the resting supine position and in the upright position after passive head-up tilt. To describe the dynamics and the interactions between the two series, we make use of linear autoregressive (AR) and AR exogenous (ARX) models, as well as of nonlinear AR (NAR) and nonlinear ARX (NARX) models, and combine the resulting prediction errors to provide linear and nonlinear Granger causality measures. This approach, that exploits the advantages of the parametric representation of bivariate time series (e.g., robustness of parameter estimation for limited sample size and compact representation of linear and nonlinear systems), has been recently proposed and thoroughly validated on simulated dynamics [7].

2. Methods

Fifteen young healthy subjects (25±3 years old) were considered for the study. The surface ECG (lead II) and the noninvasive arterial pressure signals (Finapres) were acquired with subjects in sinus rhythm during spontaneous breathing. The experimental protocol consisted of 15 minutes of data collection in the resting supine position followed by another 15 minutes with subjects in the upright position using a motorized tilt table at 60º body position.

After digitization of the continuous signals with a 1 kHz sampling rate and 12 bit precision, the beat-to-beat series of the RR intervals and of the SAP values were determined as the temporal interval between two consecutive R peaks in the ECG and as the local maximum of the AP wave within each detected cardiac cycle, respectively. After removing artifacts and slow trends, two stationary segments of N=300 points were selected for each subject, one in the supine and one in the upright position.

For each selected data segment, the RR and SAP series were normalized by subtracting the mean and dividing by the standard deviation, thus obtaining the dimensionless series $r(n)$ and $s(n)$, n=1,…,300. To describe the heart period dynamics, the series s and r were considered respectively as input and output of a closed-loop time-invariant NARX model as

$$\begin{aligned} r(n) = c_0 &+ \sum_{i=1}^{P_1} a_1(i) r(n-i) + \sum_{j=0}^{Q_1} b_1(j) s(n-j) + \\ &+ \sum_{i=1}^{P_2} \sum_{j=i}^{P_2} a_2(i,j) r(n-i) r(n-j) + \\ &+ \sum_{i=0}^{Q_2} \sum_{j=i}^{Q_2} b_2(i,j) s(n-i) s(n-j) + \\ &+ \sum_{i=1}^{P_2} \sum_{j=0}^{Q_2} c_2(i,j) r(n-i) s(n-j) + e(n) \end{aligned} \quad (1)$$

The same model, implemented reversing the roles of the two series, i.e. using r as input series and s as output series, was considered to describe the systolic pressure dynamics. In the NARX model, the coefficients c_0,$\{a_1(i)$; $b_1(j)\}$, and$\{a_2(i,j)$; $b_2(i,j)$; $c_2(i,j)\}$ represent constant (zero-th order), linear (first order), and nonlinear (second order) contributions to $y(n)$, respectively, while $e(n)$ is the prediction error. The model orders P_1 and P_2 determine the maximum lags for linear and nonlinear autoregressive (AR) influences, respectively, while the maximum lags for linear and nonlinear exogenous (X) effects are indicated by the orders Q_1 and Q_2. It is worth noting that the formulation in (1) allowed us to perform either linear or nonlinear representation of the dynamics of the output series, respectively removing from the model the coefficients relevant to nonlinear interactions (i.e., forcing P_2=0 and Q_2=-1) or keeping them within the model (i.e., allowing P_2>0 and Q_2>-1).

Estimation of the model coefficients was performed by the Optimal Parameter Search algorithm [8], a recently proposed identification method that has been shown to outperform the traditional least squares approach, and to

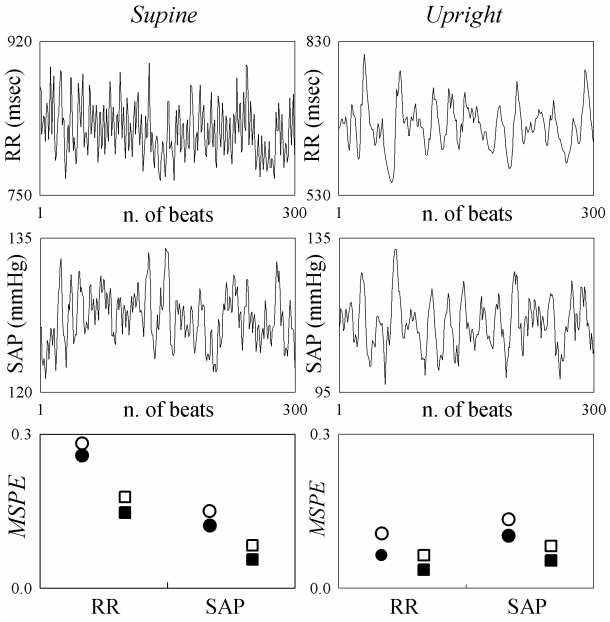

Figure 1. Causal analysis of cardiovascular interactions for a subject in the supine and upright positions. Upper and middle panels show RR interval and SAP series measured in the two body positions. Lower panels show the MSPE yielded for the two series by AR prediction (empty circles), ARX prediction (empty squares), NAR prediction (filled circles), and NARX prediction (filled squares).

be suitable for model order selection even in nonlinear systems. The reader is referred to Refs. [8] and [7] for the detailed description of the algorithm and for the analysis of its performance on cardiovascular variability signals. After model identification, the estimated coefficients were used to forecast the output series, thus obtaining the predicted series $\hat{r}(n)$ and $\hat{s}(n)$. The unpredictability of the two series was then quantified as mean squared prediction error (MSPE):

$$\begin{aligned} MSPEr &= \frac{1}{N} \sum_{n=1}^{N} \left(r(n) - \hat{r}(n) \right)^2 \\ MSPEs &= \frac{1}{N} \sum_{n=1}^{N} \left(s(n) - \hat{s}(n) \right)^2 \end{aligned} \quad (2)$$

Prediction was performed both by a pure NAR model, i.e. forcing Q_1=Q_2=-1 in (1), and by a NARX model (Q_1>-1, Q_2>-1). Accordingly, the output series was predicted only from its own past for a NAR (or AR) model, yielding the prediction errors $MSPEr|r$ and $MSPEs|s$, and from both its own past and the past and present of the input series for a NARX (or ARX) model, yielding the prediction er-

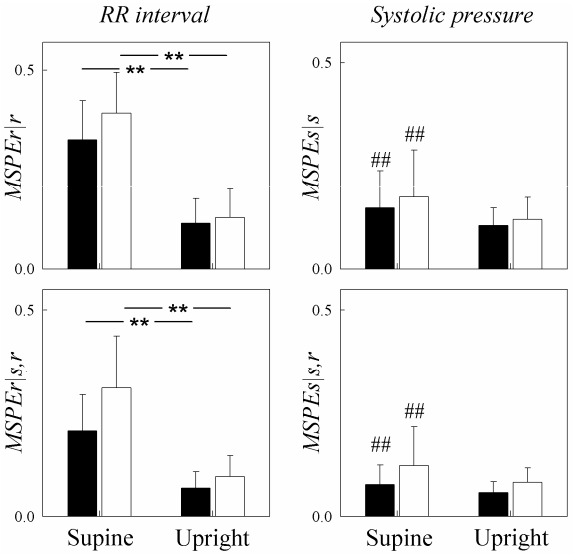

Figure 2. Results of predictability analysis of RR interval and SAP series in the supine and upright positions. Plots show the MSPE (mean+SD over 15 subjects) obtained by linear (white) and nonlinear model identification (black) using AR models (*MSPEr|r* and *MSPEs|s*) and ARX models (*MSPEr|s,r* and *MSPEs|s,r*). Student t-test for paired data: ** p<0.01 Supine vs. Upright; ## p<0.01 RR interval vs. Systolic pressure.

rors *MSPEr|s,r* and *MSPEs|s,r*. Finally, Granger causality from the input to the output series was quantified calculating the normalized predictability improvement (NPI) obtained by the NARX (or ARX) model compared to the NAR (or AR) model prediction

$$NPIr \mid s = \frac{MSPEr \mid r - MSPEr \mid s,r}{MSPEr \mid r}$$
$$NPIs \mid r = \frac{MSPEs \mid s - MSPEs \mid s,r}{MSPEs \mid s} \quad (3)$$

3. Results

Fig. 1 depicts an example of the cardiovascular variability series measured in the supine and upright positions, along with the values of the MSPE index obtained for linear and nonlinear model identification using only the AR part or including also the X part of the model. At rest, the predictability was better for the SAP series than for the RR interval series (*MSPEs|s* < *MSPEr|r*). Tilt position resulted in a marked reduction of *MSPEr|r* that became slightly lower than *NMSPEs|s*. The improvements in predictability with the use of ARX or NARX models for the tilt position were less marked than in the supine position. For all models, linear prediction led to less predictable series than nonlinear prediction.

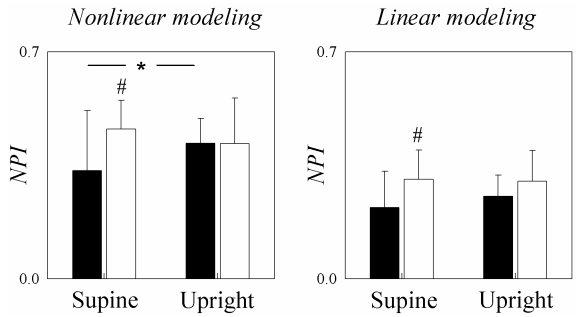

Figure 3. Results of causality analysis of RR interval and SAP series in the supine and upright positions. Plots show the normalized predictability improvement (*NPI*, mean+SD over 15 subjects) obtained by linear and nonlinear model identification in the direction from SAP to RR (*NPIr|s*, black) and from RR to SAP (*NPIs|r*, white). Student t-test for paired data: * p<0.05 Supine vs. Upright; # p<0.01 *NPIr|s* vs. *NPIs|r*.

Fig. 2 summarizes the results of predictability analysis of the 15 subjects In the supine position, the SAP was significantly more predictable than the RR interval, as evidenced by the lower MSPE yielded by AR and NAR prediction (upper panels), as well as by ARX and NARX prediction (lower panels). After tilt, the predictability of the RR interval improved significantly using all four models. There was also a tendency of the predictability of the SAP to be increased when the body position was changed from supine to tilt, although not significant. In all RR interval and SAP series, nonlinear model prediction yielded a better predictability (i.e. lower MSPE) than linear prediction.

The results of linear and nonlinear Granger causality analysis are summarized in Fig. 3. With nonlinear modelling, in the supine position the NPI index was significantly higher in the direction from RR interval to SAP than in the reverse direction. The tilt position resulted in a significant increase of the NPI in the feedback direction: from SAP to RR interval, while the NPI value relating RR interval to SAP did not change with alteration in the body position. The analysis performed by linear AR and ARX models yielded similar results, indicating unbalancing of NPI in the two causal direction at rest, and recovering of the unbalance after tilt. The only difference with nonlinear analysis was that the increase of *NPIr|s* from the supine to the upright position, though documented, was not statistically significant.

4. Discussion

In this paper we made use of a method to evaluate Granger causality in short bivariate variability series [7], based on NARX model identification through an efficient

optimal parameter search algorithm [8], for assessing linear and nonlinear predictability and directional interactions between RR interval and SAP series measured in healthy subjects during a head-up tilt testing protocol. Our main results were well interpretable according to the known cardiovascular physiology, thus confirming the suitability of the model-based approach. The higher predictability of SAP with respect to RR observed in the supine position, documented by all prediction models, is compatible with the hypothesis that the numerous mechanisms responsible to the regulation of heart rate exhibit at rest a low degree of synchronization that results in an increased complexity of the RR series [9]. With assumption of the upright position, both RR and SAP became more predictable, mainly as a consequence of the rise of a regular dominant low frequency oscillation induced by the activation of the sympathetic nervous system related to tilt [10].

The result indicating higher PI from RR interval to SAP than in the reverse direction during supine position (Fig. 3) reflects an imbalance of the cardiovascular regulation towards mechanisms operating along the pathway from heart rate to arterial pressure. This finding confirms, from the point of view provided by Granger causality analysis, the prevailing role of mechanical feedforward interactions in the cardiovascular regulation of supine humans [2,4]. Moreover, the increase of the PI from SAP to RR interval in the upright position, responsible for the recovery of a balanced cardiovascular regulation, can be explained by the activation of the baroreflex control pathway as a consequence of tilt-induced sympathetic activation [10].

With respect to linear model identification, the implementation of nonlinear models always led us to a better prediction of the cardiovascular variability series. This higher prediction accuracy may be interpreted either as a consequence of the contribution of nonlinear dynamics and nonlinear interactions to cardiovascular variability, or simply as an indication of the fact that optimal parameter identification of nonlinear models leads to select a larger number of significant model terms, ultimately improving the fit of the time series. Further analysis, e.g. involving surrogate time series in which nonlinear dynamics are destroyed and linear properties are preserved, is required to be explanatory about this point. Nevertheless, we observe that almost all the behaviours of predictability and Granger causality indices (e.g., in response to tilt or comparing the values of the indices for RR and SAP) were obtained similarly using linear and nonlinear model identification. This finding confirms the suitability of linear tools for assessing directionality to be applied for the investigation of directionality in short-term cardiovascular variability. As an example, utilization of the causal coherence [11] in the same experimental protocol considered in this study evidenced a similar imbalance of RR-SAP coupling with prevalence of mechanical interactions at rest, as well as the enhancement of the feedback regulation from SAP to RR after tilt [4,11].

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