Quantifying the Autonomic Nervous System Influence on Heart Rate Turbulence using Partial Least Squares Path Modeling

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Abstract

Heart rate turbulence (HRT) is a physiological phenomenon used for cardiac risk stratification. Its alteration or absence indicates a significantly increased likelihood of mortality. However, the influence of the autonomic nervous system (ANS) on HRT needs to be further investigated. We propose a cause-effect relationship model to quantify the influence of the ANS. A set of 481 Holter-monitor recordings from different medical conditions were used, from THEW: acute myocardial infarction, coronary artery disease and end-stage renal disease. We proposed to model the relationship between HRT and ANS using Partial Least Squares Path Modeling (PLS-PM), a method for structural equation modeling that allows analyzing the relationships between the observed data and the latent variables. HRT parameters were estimated on individual ventricular premature complex (VPC) tachograms. ANS was assessed by heart rate variability indices computed from 3-min before VPC tachograms. The data set was split into low-risk and high-risk subgroups. $SDNN$, P_{LF}, TS *and* TO *were the most relevant variables. In low-risk, ANS activity was negatively related to HRT, while correlation between coupling interval and HRT on high-risk depends on the pathology. PLS-PM suggests that the influence of physiological variables on HRT is broken on high-risk. Results of the model are in agreement with the baroreflex hypothesis.*

1. Introduction

Heart Rate Turbulence (HRT) is the physiological response to a spontaneous ventricular premature complex (VPC). In normal subjects, it consists of an initial acceleration and subsequent deceleration of the sinus heart rate. Heart rate variability (HRV) reflects the regulation of the heart rate by the autonomic nervous system (ANS). Both, HRT and HRV, have been shown to be strong risk stratification predictors in patients with cardiac disease [1–3]. However, the influence of the ANS on HRT in different cardiac pathologies needs to be further investigated.

It has been documented in the literature the influence of several physiological factors on the HRT [2]. The heart rate affects the strength of the HRT response, in a way that HRT is reduced at high heart rate. VPC prematurity also influences the HRT response [4, 5]. As well, it has been studied in the literature some interaction effect between sex and age on HRT [6, 7]. Finally, there are evidences of correlation between HRT and HRV on 24-hour Holters, since both are under the influence of the ANS, but the studies only compare long-term averages [8].

In this work, we propose to model the cause-effect relationship between ANS and HRT using latent-variables estimated, in turn, using Partial Least Squares Path Modeling (PLS-PM). We tested the model on several cardiac diseases, namely acute myocardial infarction (AMI), coronary artery disease (CAD) and end-stage renal disease (ESRD), using RR-intervals from Holter monitoring.

The structure of the paper is as follows. In Section 2, HRT and HRV assessment is detailed. In Section 3, BRT model is explained. In Section 4, data sets are detailed. In Section 5, results are reported. Finally, in Section 6, conclusions are presented.

2. Heart Rate Turbulence and Heart Rate Variability

HRT is usually quantified by two parameters, Turbulence Onset (TO) and Turbulence Slope (TS). Both parameters are usually computed on an averaged VPC tachogram built using all available individual VPC tachograms from 24-hour Holters [2]; even though there exist some other approaches to assess HRT [9, 10]. TO assesses the amount of sinus acceleration following a VPC, and it is defined as the percentage difference between the heart rate immediately following the VPC and the heart rate immediately preceding the VPC. TS represents the rate of sinus deceleration that follows sinus acceleration, and it is defined as the maximum positive regression slope assessed over any 5 consecutive sinus rhythm RR-intervals within the first 15 sinus rhythm RR-intervals after the VPC [2]. In this work, we are going to analyze individuals

Table 1. HRT and HRV indices use to characterize each individual VPC tachogram.

HRT index	Description
TO [%]	Turbulence onset.
TS [ms/RR-int]	Turbulence slope.
SCL [ms]	Sinus cycle length.
CP [ms]	Compensatory pause.
CI [ms]	Coupling interval.
HRV index	Description
$AVNN$ [ms]	Average NN-intervals.
$SDNN$ [ms]	Standard deviation NN-intervals.
$pNN50$ [%]	Percentage of pairs of adjacent NN-intervals differing more than 50 ms.
$RMSSD$ [ms]	Square root of the mean of the sum of the squares difference between adjacent NN-intervals.
$SDSD$ [ms]	Standard deviation of differences between adjacent NN-intervals.
$SD1$	The standard deviation of points in Poincaré plot across the identity line.
P_{lf} [ms^2]	Power low freq. band $[0.04, 0.15]$ Hz
P_{hf} [ms^2]	Power high freq. band $[0.15, 0.4]$ Hz
LF/HF	Ratio P_{lf}/P_{hf}

VPC tachograms [5], so apart from $T0$ and TS, the HRT is characterized also by the sinus cardiac length (SCL [ms]) computed as the average of the three RR-intervals previous the VPC, the compensatory pause (CP [ms]) which is the RR-interval just right after the VPC, and the coupling interval (CI [ms]) which isthe RR-interval corresponding to the VPC (see Table 1).

HRV is usually assessed by time-domain and frequency-domain indices, which are computed on NN-interval time series from 24-hour Holter recordings. In this work, HRV indices are computing on 3-min segments before each individual VPC tachogram, only segments with more than 90% of NN intervals (sinus beats) were allowed. The aim is to assess the status of the ANS just before the VPC. HRV is usually assessed on 5-min segments, however this would lead to very few valid VPC tachograms. Table 1 shows the HRT and HRV indices used in this work.

3. Partial Least Squares - Path Modeling

In this work, we propose to model the HRT (quantified by TS and TO) as a result of the modulation of the ANS, in turn, driven by the sympathetic and vagal activities, and the local conditions of the VPC-tachogram (SCL, CP, CI). These (HRT, ANS, sympathetic, vagal and VPC-tachogram conditions) are unobservable variables, i.e., latent variables (LV). On the other hand, we have several manifest variables (MV), i.e., directly measured variables (HRT and HRV indices in Table 1), that are somehow related to each LV. In this way, LVs represent abstract concepts that are combinations of the observable variables, i.e., MVs. We propose to use PLS-PM, which is an alternative method to covariance-based estimation for structural equation models (SEM) [11, 12], to build a relational model that allows to create LV from MV in a linear way.

PLS-PM is an iterative algorithm that estimates the relationship between MVs and LVs by the weights of multiple and simple regressions. PLS-PM allows to also obtain linear relationship between LVs ([11, 12]). A full path model is comprised of two submodels: (1) measurement model, which establishes the relationship between each LV and its own MVs; (2) structure model, which considers the relationship between LVs ([12, 13]):

- *LV–Sympathetic*: We associated several indices which, in the scientific literature, are related to the sympathetic activity, namely, from HRV analysis: P_{lf}, $SDNN$, even though there is some controversy about its association to sympathetic and vagal branches ([14–17]). However, PLS-PM allows us to measure the adequacy of belonging to each LV and therefore allowing the convenience of changing membership to another LV.
- *LV–Vagal*: The MVs associated with this LV are, from HRV analysis, P_{hf}, $pNN50$, $RMSSD$, $SDSD$, $SD1$. The evidence from scientific literature supports the relationship between these indices and the Vagal activity ([3, 14, 16]).
- *LV–ANS*: The MVs associated with this LV is, from HRV analysis, the sympatho-vagal balance: LF/HF. ([14,18]).
- *LV–VPC-measurements*: This LV represents the local conditions for each VPC as quantified by MVs SCL, CI, CP and $AVNN$.
- *LV–HRT*: This LV represents the response after a VPC of the subjects, measured by MVs TS and TO.

Regarding the structural model, it was assumed that the *ANS* directly depends on the *Sympathetic* and *Vagal* LVs, while the *HRT* LV depends directly on *ANS* and *VPC-measurements*. The complete scheme of the structural and the measurement model can be seen in Figure 1.

The model was designed, such as MVs are considered to be caused by the latent variables, i.e., reflective indicators, except for *VPC-measurements*. This assumption imposes a restriction since all the MVs are measuring the same LVs. Therefore, all MVs have to be highly correlated ([13]). Consequently, some of the MVs had to change their sign to follow along with the remaining MVs. The structure model is statistically represented by two linear regression models: (1) ANS as a function of Sympathetic and Vagal activity, and (2) HRT as a function of the ANS and VPC-measurements. The path coefficients (β) were obtained as classical weights in linear regression, i.e., using a least-square approach ([19]). The overall fit of the final model was assessed by the goodness-of-fit ([20]).

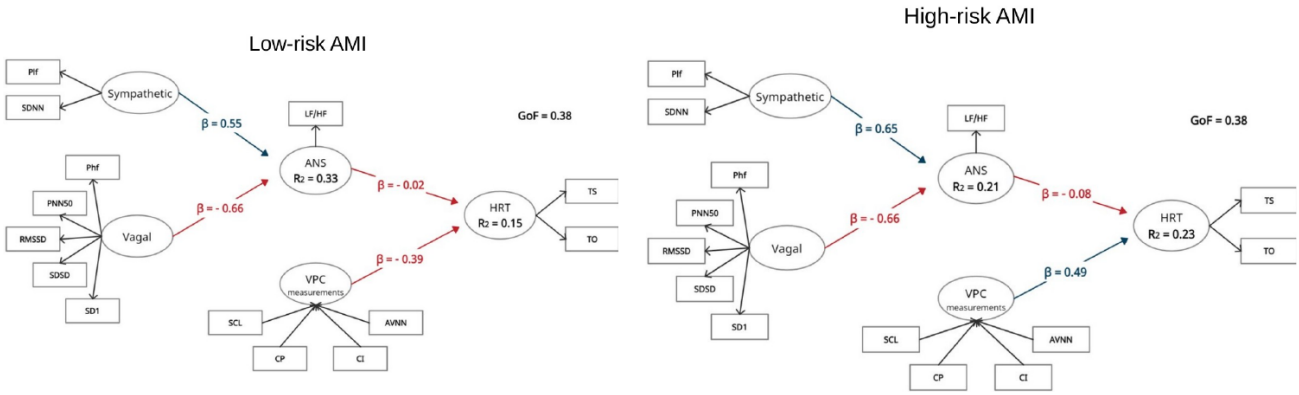

Figure 1. PLS-PM model fitted to AMI data set, low (top) and high risk (bottom). Red values correspond to negative coefficients, while blue values correspond to positive coefficients of the latent model.

4. Data Sets and Preprocessing

We compared the proposed approach on three different data sets which comprise 481 holter recordings from different cardiac pathologies, namely: acute myocardial infarction (AMI 93 patients; age: 59.10 ± 14.98; 23 females), coronary artery disease (CAD 271 patients; age: 59.06 ± 10.68; 48 females) and end-stage renal disease (ESRD 51 patients; age: 59.89 ± 12.10; 21 females); from The telemetric and Holter ECG Warehouse [21].

Each data set was split into two different subsets, namely, a **low risk** subset including patients with $T_S \geq 2.5$ ms/RR and $TO \leq 0$ %, and a **high risk** subset with $TS < 2.5$ ms/RR and $TO > 0$ %. These T_S and T_O cutoff values are commonly used in most clinical studies, where $T_S > 2.5$ ms/RR and $T_O < 0$ % are normal [2].

Isolated VPC-tachograms were filtered according to usual HRT procedures [2]. In this work, HRV indices were computing on 3-min segments before each individual VPC tachogram, with more than 90% of sinusal beats.

5. Results

Figure 1 shows the fitted PLS-PM model for AMI data set, low (top) and high risk (bottom) subsets. The figure shows the beta coefficients of the latent model, the R^2 coefficient and the Goodness-of-Fit (GoF) index to evaluate the global performance of the model.

The LVs *Sympathetic* and *Vagal* have the same behaviour and contributes in the same way to build the new LV *ANS* in the three data sets (AMI, CAD, ESDR). *Sympathetic* is positively correlated with ANS, whereas *Vagal* is negatively correlated. This behavior is the same for each data set and each subgroup (low-risk and high-risk). However, the contributions of the LVs *ANS* and *VPC-measurements* to build the LV *HRT* is different for each data set. In AMI, both are negatively correlated for low-risk patients, whereas for high-risk patients, *ANS* is negatively correlated and *VPC-measurements* is positively correlated, and higher regression coefficient (more important linear relationship). In CAD data set, both for low-risk and high-risk patients, *ANS* and *VPC-measurements* are negatively correlated, always the latter more important. Finally, for ESDR data set, for low-risk patients, *ANS* is positively correlated and *VPC-measurement* is negatively correlated, whereas for high-risk patients the behavior is the opposite.

For every data set, $SDNN$, LF, TS and TO where the most significant variables to explain the whole model. The global performance of the models range from $GoF = 0.29$ up to $GoF = 0.44$, which is a reasonable good value given the complexity of the problem.

6. Conclusions

In this work, we propose to use PLS-PM to model the relationship between HRT (TS, TO) and VPC-measurements SCL, CI, CP, and several HRV time and frequency domain indices. HRV was assessed on 3-min NN interval segments just before every VPC. The model was fitted using data from three different data sets with different heart conditions, AMI, CAD and ESDR. Data sets were split into two different groups, namely, low risk and high risk groups according to T_S and T_O cut-off values reported in the literature.

Our results suggested that the influence of the ANS status and the local conditions (VPC-measurement) on HRT is different for each cardiac condition and also depends on whether the patient is low or high risk. For every data set, $SDNN$, LF, TS and TO where the most significant variables to explain the whole model. The global performance of the models range from $GoF = 0.29$ up to $GoF = 0.44$,

which is a reasonable good value given the complexity of the mechanisms involve in the problem. Further work should be aimed to incorporate information available, such as gender and age of the patients. Also, having a control group (a non-disease group) would allow to compare results properly, as well as to improve the model to account for nonlinear relationships.

Acknowledgements

This work has been partially supported by Ministerio de Ciencia e Innovación PID2019-105032GB-I00.

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