Quantification of Different Regulatory Pathways Contributing to Heartbeat Dynamics during Multiple Stimuli: a Proof of the Concept

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Abstract— **The dynamical interplay between brain and heart is mediated by several feedback mechanisms including the central autonomic network and baroreflex loop at a peripheral level, also for a short-term regulation. State of the art focused on the characterization of each regulatory pathway through a single stressor elicitation. However, no studies targeted the actual quantification of different mediating routes leading to the generation of heartbeat dynamics, particularly in case of combined exogenous stimuli. In this study, we propose a new approach based on computational modeling to quantify the contribution of multiple concurrent stimuli in modulating cardiovascular dynamics. In this preliminary attempt, the model estimates the high-frequency power of heartbeat dynamics, and derives disentangling coefficients quantifying the effect of multiple elicitations. Model evaluation is performed on healthy rate variability (HRV) series from fourteen healthy subjects undergoing physical (tilt-table) and mental stressors (aritmetics), as well as their combined administration. Results indicate that, at a group-wise level, in base of concurrent physical and mental elicitations, the physical stressor contributes for the 85% of the resulting heartbeat dynamics. These findings are in agreement with the current knowledge on heartbeat regulatory systems, providing valuable perspectives on the quantification of underlying generative mechanisms of HRV.**

I. INTRODUCTION

The interaction between the sympathetic and parasympathetic outflows constitutes the neural control of autonomic functions for the regulation of heartbeat dynamics and blood pressure modulation [1]. This interaction occurs through multiple control mechanisms, resulting in nonlinear and complex physiological dynamics [2].

In case of exogenous stimuli, several mechanisms act for a proper regulation of heartbeat dynamics. An integral component of such control mechanisms is the Central Autonomic Network (CAN), which comprises a number of structures including, at the forebrain level, the amygdala, insular cortex and anterior cingulate cortex regions [3], [4]. Recently, there has been an increasing interest in identifying specific pathways acting on the neural autonomic control to the heart [5]. Exemplarily, it has been demonstrated that the CAN output and the sinoatrial node are connected through the stellate ganglia and the vagus nerve [3]. Another important homeostatic mechanism is the baroreflex, which is a negative feedback loop sensing blood pressure variations through baroreceptors and adjusting the heart rate to keep the blood pressure at a constant level. Several studies aimed to characterize baroreflex regulatory systems through analysis of heartbeat dynamics [6].

The aforementioned physiological regulatory mechanisms can be investigated through the analysis of cardiovascular variability series while specific stressors are administered, maybe in different laboratory settings. According to the specific stimuli (physical, pscychological, mental) and their delivery modes, different autonomic responses maybe activated [7]–[9]. Although previous endeavours investigated heartbeat modulation in the occurrence of one specific stressor, a few studies focused on the quantitative assessment of heartbeat dynamics during multiple concurrent elicitations provided by two or more stressors delivered simultaneously. These studies aimed to the assessment of baroreflex regulation on to the heart [10], the investigation of alternations in heartbeat spectral parameters [11], and the comparison of time-varying autonomic outflow between physical and mental stress [7].

However, under the hypothesis that each stressor provides a specific contribution to the generation of heartbeat dynamics, an actual quantification of how such contribution can be measured has not yet been addressed. In this perspective, by exploiting combined elicitation tasks, we aim to quantifying the contribution of two separate regulatory pathways that are deemed as responsible for the generation of heart rate variability (HRV) series. We assume that during multiple stimuli different regulatory autonomic pathways contribute to the generation of HRV, and propose an analytical approach to evaluate the role of separate routes. In this preliminary endeavour, we evaluated the proposed approach by estimating the high-frequency power of HRV that maybe associated with vagal autonomic outflow from 14 subjects, who were exposed to postural changes and mental stress, either separately or through their combined administration.

II. MATERIALS AND METHODS

A. Proposed model for the quantification of heartbeat regulatory mechanisms

In this section, we describe the proposed model to disentangle the activation of two pathways for the generation of HRV. We define the variables $[C_{Stressor1}, C_{Stressor2}, C_{Stressor1+Stressor2}]$ as the estimates we obtain by the quantification of the HRV series during the separate activation of the two pathways $(C_{Stressor1}, C_{Stressor2})$ and their combined activation $(C_{Stressor1+Stressor2})$.

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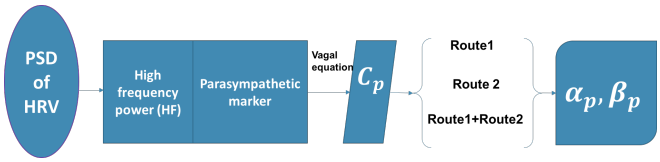

Fig. 1. The procedure for the derivation of contribution of each regulatory route in the simultaneous activation of both pathways. From the power spectral density of HRV series, C_p (input variable for the parasympathetic equation) is calculated which results in the output $[\alpha_p\ ,\ \beta_p]$.

The model aims to find the relationship between $C_{Stressor1+Stressor2}$ as the function of $C_{Stressor1}$ and $C_{Stressor2}$ (Equation 1).

$$C_{Stressor1+Stressor2} = f(C_{Stressor1}, C_{Stressor2}) \quad (1)$$

The two sets of equations that aim to model this relationship are defined as:

$$C_{Stressor1+Stressor2} = \beta C^2_{Stressor2} - \alpha C^2_{Stressor1}, \quad \alpha + \beta = 1 \quad if C^2_{Stressor1} > C_{Stressor1+Stressor2} \quad (2)$$

$$C_{Stressor1+Stressor2} = \frac{C^4_{Stressor1}}{\beta C^2_{Stressor2} - \alpha C^2_{Stressor1}}, \quad \alpha + \beta = 1 \quad if C^2_{Stressor1} < C_{Stressor1+Stressor2} \quad (3)$$

We aim to estimate the variables defined in the model to the level of parasympathetic activity, and rely on the conventional parasympathetic correlate from the spectral analysis of HRV, i.e. the power in the high frequency band [9]. Thus, the variables $[C_{Stressor1}, C_{Stressor2}, C_{Stressor1+Stressor2}]$ are estimated from the spectral analysis of the time series of the RR intervals measured from the ECG. Specifically, the variables $[C_{Stressor1}, C_{Stressor2}, C_{Stressor1+Stressor2}]$ are replaced with $[HF_{Stressor1}, HF_{Stressor2}, HF_{Stressor1+Stressor2}]$ for the assessment of vagal dynamic activity. Feeding the model with the $[HF_{Stressor1}, HF_{Stressor2}, HF_{Stressor1+Stressor2}]$ in equations 2 and 3 results into a set of outputs $[\alpha_p\ ,\ \beta_p]$ which are defined as follows:

$[\alpha_p\ ,\ \beta_p]$: The percentage of the contribution of parasympathetic (vagal) outflow during the stimulation of Stressor 1 (α_p) or Stressor 2 (β_p) in the generation of heartbeat dynamics. In Figure 1 the complete procedure for the derivation of $[\alpha_p\ ,\ \beta_p]$ calculated through frequency analysis of HRV is depicted.

B. Experimental protocol and data acquisition

We exploited an experimental protocol to investigate the proposed model on actual cardiovascular data. The dataset was collected through the acquisition of the ECG signals from 14 healthy subjects. The protocol comprised four phases each lasting for 12 minutes. The experiment foresaw 4 phases according to the following tasks:

- 1) Resting state in supine position
- 2) Mental arithmetics (MA)
- 3) Head up tilt (HUT)
- 4) MA plus HUT

The MA was used to evoke mental stress in the supine position. During this task random 3-digit numbers were displayed in the computer screen repeatedly and the participants were asked to sum up the three digits. In case of obtaining 2 digit number as the output they were asked to sum up again. Eventually, participants had to indicate if the output was odd or even. There was no notification to show the correctness of the result. The task had to be done as rapidly and precisely as possible. The HUT test aimed to elicit mild orthostatic stress by tilting the subjects to 45 degree using a motor-driven tilt table. The subjects signed their informed consent in the beginning of the experiment. The ethical committee of Jessenius Faculty of Medicine, Comenius University approved the study. The RR time series were extracted from the ECG signal. In each phase, sequences of 500 beats measured starting 60 second after phase change were considered for the analysis. More details on the experimental protocol can be found in [10].

C. Model Setup and Statistics

According to the experimental protocol, HRV series are calculated from the acquired ECG signal at each experimental phase, and are fed as an input to a linear point-process model [12]. A parametric estimation of the power spectral density is then performed instantaneously, resulting in $[HF_{Stressor1}, HF_{Stressor2}, HF_{Stressor1+Stressor2}]$ values to be averaged over time. In this preliminary study we condensed the time varying dynamics of the resulting indices through the median value calculated along the whole duration of each phase.

Feeding the averaged HF estimates to Equation 2 and Equation 3 denoted as $[C_{Stressor1}, C_{Stressor2}, C_{Stressor1+Stressor2}]$, a set of percentages $[\alpha_p\ ,\ \beta_p]$ are calculated as the output of the model.

Taking into account the Non-Gaussian distribution of some data samples, the table values are expressed as Median$\pm 1.4826\text{MAD}(X)/\sqrt{n}$, where $\text{MAD}(X) = \text{Median}(|X - \text{Median}(X)|)$, with X as the defined index and n is the number of subjects in group. Note that, in case of Gaussian distribution, $\sigma(X) = 1.4826\text{MAD}(X)$ with σ as the sample standard deviation.

III. EXPERIMENTAL RESULTS

Results are shown in terms of percentage of heartbeat dynamics contribution associated with the physical stressor phase (tilt-table) and the mental stressor phase (mental arithmetics), referring to the experimental phase in which both stimuli were concurrently administered. Results, reported in Table I, indicate a group-wise contribution to heartbeat dynamics from the postural change of 85%, whereas the

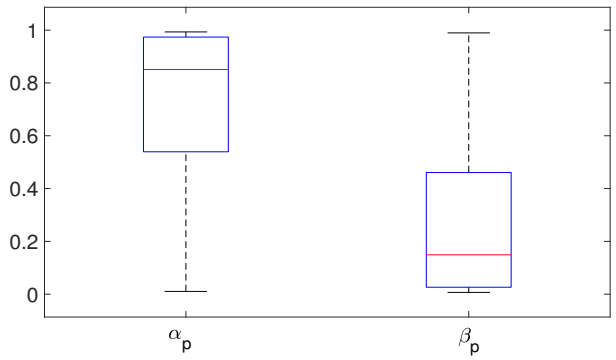

Fig. 2. Boxplots of the contribution of separate routes on cardiovascular dynamics resulted from the output of the model. Refer to section II.A for definitions of α_p and β_p.

contribution from the mental arithmetics was quantified in a 15%. Box-plot statistics are shown in Figure 2.

TABLE I

CONTRIBUTION OF SEPARATE ROUTES ON CARDIOVASCULAR DYNAMICS

Index	Percentages (%)
α_p	85 ± 14
β_p	15 ± 14

α_p (β_p) indicates the contribution of postual change (mental arithmetics) stimulus in heartbeat dynamics generation during concurrent tilt-table and mental arithmetics tasks.

A. Model Evaluation

The model evaluation is based on the comparison of results obtained in three different scenarios. Similar to the estimates obtained from HRV spectral analysis during the phase with physical stressor ($C_{Stressor1}$) and the phase with mental stressor ($C_{Stressor2}$), we perform the same analysis considering heartbeat dynamics from a resting phase, therefore leading to indices defined as C_{Rest}. To perform the evaluation, we replace C_{Rest} with either the $C_{Stressor1}$ or $C_{Stressor2}$ in the original model, obtaining the following scenarios:

- Case 1) The original model: $C_{Stressor1+Stressor2} = f(C_{Stressor1}, C_{Stressor2})$ resulting in [α_p , β_p]
- Case 2) Mental phase ($C_{Stressor2}$) replacement : $C_{Stressor1+Stressor2} = f(C_{Rest}, C_{Stressor1})$ resulting in [α'_p , β'_p]
- Case 3) Physical phase ($C_{Stressor1}$) replacement : $C_{Stressor1+Stressor2} = f(C_{Stressor2}, C_{Rest})$ resulting in [α''_p , β''_p]

We expect that removing the contribution of one stimulus ($C_{Stressor1}$ or $C_{Stressor2}$) and replacing it with a resting phase would result in an increase in the contribution of the other stimuli($C_{Stressor2}$ or $C_{Stressor1}$). This originates from the fact that in Case 2 or Case 3 only one stimulus (either mental or physical) with a phase without any stimuli (resting phase) are contributing to the generation of heartbeat dynamics whereas in Case 1 both stimuli (mental and physical) are contributing. Accordingly, the following inequalities should be satisfied.

- Condition 1) $\alpha'_p > \alpha_p$
- Condition 2) $\beta''_p > \beta_p$

A graphical explanation of the defined evaluation in one exemplary randomization of the experimental protocol is shown in Figure 3.

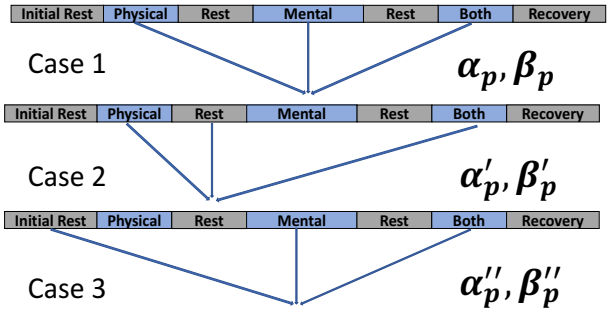

Fig. 3. Schematic logic for the evaluation of the model during one exemplary randomization of the experimental protocol. Case 1 is the original model having the both phase as a function of physical and mental phases. Case 2 is the replacement of the resting phase with the physical phase. Case 3 is the replacement of the resting phase with the mental phase.

Table II shows the results of the evaluation performance on our dataset. For each condition, the trend as well as the calculated p-values using the Wilcoxon non-parametric tests of paired data for the comparison of the two variables are shown. Related boxplots are depicted in Figure 4.

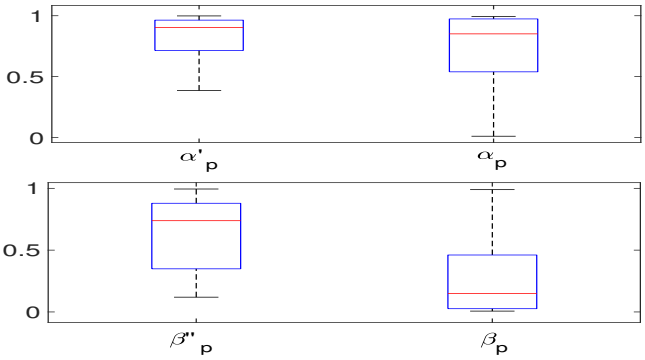

Fig. 4. Boxplot of the variables obtained from performing the validation method. Refer to Sections II.A and III.A for the definition of the variables.

TABLE II

RESULTS FROM THE MODEL EVALUATION

	Condition	Trend	P-value
1	$\alpha'_p > \alpha_p$	True	0.32
2	$\beta''_p > \beta_p$	True	0.001

Trends of the quantifying variables are in agreement with the evaluation hypothesis. A significant p-value below 0.001

was also associated with the comparison between β_p'' and β_p, which are related to the contribution of mental arithmetics task in heartbeat dynamics generation during concurrent tilt-table and mental arithmetics stimuli.

IV. DISCUSSION AND CONCLUSION

In this preliminary study, we propose a novel methodology to quantify the contribution of multiple concurrent elicitations in the modulation of heartbeat dynamics. These stimuli are likely to be associated with different regulatory mechanisms of vagal, and/or sympatho-vagal autonomic outflow, considering the administration of physical and mental stressors. The quantification of the contribution on heartbeat dynamics was performed on heartbeat series gathered during the simultaneous presence of the stimuli, also by feeding the model with exemplary data where each stimulus was administered separately.

The simple non-trivial model expressed in Equation 2 and Equation 3 was chosen after several attempts for the function in Equation 1. The conditional structure of the model confirms its generalization and is mainly done due to our assumption for the constraint. We chose the proposed quadratic formulation due to the presence of the condition and the constraint. The nonlinear relationship (Equation 3) is obtained as a complimentary formula to satisfy the cases when the second inequality is true among the estimates. As a future endeavour we aim to propose another formulation by adding a third term to the core model architecture that accounts also other physiological dynamics.

In this prelimanry study we quantified the autonomic response at the vagal level through spectral analysis of HRV series, particularly referring to the power in the high-frequency band. However, in the future we aim to expand our results at a sympathetic level as well. Our previous studies proposed two different approach for this quantification. A new sympathetic activation marker was used using the spectral measures of electrodermal activity signal in [13], while the study in [14] proposes a new identification of the sympathetic and parasympathetic measures associated with a proper combination of Laguerre base functions. Another option is using the formulation based on the modulation of the sinus oscillator by the sympathetic and parasympathetic oscillators in the generative model of heartbeat known as integral pulse modulation. [15]. The coupling constants defined in their paper reflect the levels of sympathetic and parasympathetic modulation which can be used as a quantifier of each separate branch.

The choice of a point process model for the power spectral calculation is due to major methodological advantages for obtaining instantaneous heartbeat estimates with any time resolution, as well as metrics of goodness of fit. In the future, we aim to derive time-varying estimates from the model, therefore achieving a quantitative dynamic tracking of the partial contributions of each regulatory mechanism along in time. To best of our knowledge. this is the first study aiming to disentangle and quantify the activation of probably different regulatory mechanisms on heartbeat dynamics. Therefore, there is no validated ground truth for the validation of the proposed model and results obtained from it. By exploring both trends and statistics of the defined inequalities in the evaluation section (Table II), results show expected trends in both conditions together with a statistical significance reached for the second condition.

Besides the mentioned limitations this study provides a mathematical insight into a physiological phenomenon involving various regulatory systems on to cardiovascular dynamics. Designing an experimental protocol by considering the physiological basis of the cardiovascular and neural system will also lead us to an imrpoved quantification of model from actual data. The idea behind the model opens a new horizon in the cardiovascular, neural and psychological fields of research for a novel exploration of the underlying physiological state of a human subject.

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