Accelerations and Decelerations in Heart Rhythm Differentiate Vasovagal Sensitive Humans

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Abstract

The double exponential function which approximates the distributions of accelerations and decelerations in heart rate can be used in assessing vasovagal pathophysiology evoked by the head-up tilt test. We test how the coefficients of the exponential decay depend on the bin size used in the numerical construction of distributions. These coefficients turn out to be stable in a wide range of bin sizes, which justifies our proposition of indices of autonomic activation in assessing the dynamic interplay among physiological processes altered by tilting.

1. Introduction

Nearly complete or complete loss of consciousness, called syncope, can occur if a person rapidly changes position from supine to upright [1, 2]. Syncope occurs because of the failure of compensatory adjustments which are responsible for maintaining the cerebral blood volume. In addition, in susceptible persons, an inappropriate set of neural reflex responses appears to be triggered, namely vasodilation and severe bradycardia [2–4]. The head-up tilt test has become a widely accepted diagnostic tool for evaluation of neuromediated syncope, as it provides a diagnosis for about 35% of patients [4, 5].

Although the precise basis for all reflex responses remains speculative [2, 4], we have found that distributions of increments between successive RR-intervals could be a powerful source of information about the functioning of the autonomic nervous system provoked by the head-up tilt table test [6]. However, the results obtained in [6] were based on the properties of probability density functions of accelerations and decelerations obtained with a fixed bin size used in numerical procedures. In the following, we discuss how these results depend on the details of the numerical methods used, especially on the size of bin applied.

2. Methods

2.1. Data acquisition

Signals from two hundred people were analyzed. Fifty signals represented healthy individuals, with no history of fainting, and one hundred and fifty were from vasovagal sensitive patients who experienced vasovagal syncope in everyday life. Our study complied with the Declaration of Helsinki and was approved by the Bioethics Committee of the Medical University of Gdansk.

The head-up tilt tests were performed under a paced breathing protocol, which is considered to standardize the impact of breathing on the heart rate [7]. Each subject remained in the supine position for 20 minutes and followed a recorded voice instruction to breathe in and out at a frequency of 0.25 Hz. Then the table was tilted to 60 degrees. The subjects stayed in the upright position for the next 20 minutes, or until syncope occurred — the *passive part* of the test. In the event of no syncope, the *active part* was performed with the administration of 400 micrograms of nitroglycerine (aerosol, sublingually). The active test lasted 10 minutes or until syncope occurred. A typical recording is shown in Figure 1.

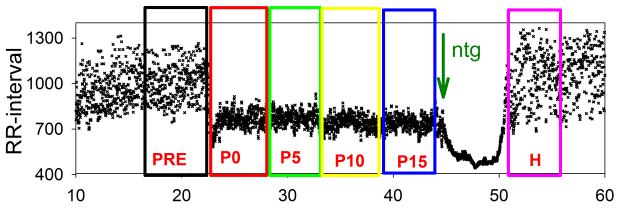

Figure 1. A typical signal of RR intervals recorded from a person who fainted during the head-up tilt test. Each signal was divided into successive five-minute time windows: PRE, P0, P5, P10, P15 and H, which are denoted by coloured rectangles. PRE stands for the supine interval prior to tilting, P0-P15 for the time during tilting and H for the final period in the supine position.

The results of the head-up tilt test were interpreted according to the modified VASIS classification [8]: *negative* if no syncope occurred, *positive of VVS1 type* if so-called mixed syncope occurred, and *positive of VVS2 type* in the case of cardiodepressive syncope. We did not differentiate between syncope occurring in the passive or active parts of the test.

According to the results of the head-up tilt test and the history of syncope, the signals were divided into four groups as follows:
CG – control group of 34 healthy people who did not faint;
NEG – 50 vasovagal patients who did not faint;
VVS1 – 74 vasovagal patients who fainted of VVS1-type;
VVS2 – 26 vasovagal patients who fainted of VVS2-type.
Signals of 16 healthy people who fainted in the active part of the test were excluded from further analysis.

A total of 24 groups of signals: four groups of subjects in the six time windows, will be referred to as follows:
If P denotes a patient group, and T is a five-minute window, then a group $\mathbf{G}$ denotes a pair (P, T), where

$$\begin{aligned} P &\in \{\text{CG, NEG, VVS1, VVS2}\} \\ T &\in \{\text{PRE, P0, P5, P10, P15, H}\}. \end{aligned}$$

2.2. Signal processing

Let $\mathbf{RR} = \{RR_0, RR_1, \ldots, RR_N\}$ be a time sequence of RR-intervals. We say that the heart *decelerates* at time i if $RR_i > RR_{i-1}$, and *accelerates* if $RR_i < RR_{i-1}$. A *no-change event* takes place if $RR_i = RR_{i-1}$. Thus, if $\Delta RR_i = RR_i - RR_{i-1}$, then $\Delta RR_i > 0$ corresponds to a deceleration, $\Delta RR_i < 0$ to an acceleration, and $\Delta RR_i = 0$ to a no-change event.

Our recordings had a resolution of 1 ms. Therefore, we could build distributions of increments in $\mathbf{RR}$ signals with a large range of bin sizes. Here, we present results obtained when the distribution constructions were performed with bin sizes of 3, 5, 7, 11 and 21 ms. Because of the binning, the set of values $\{\Delta RR_i\}$ consists of the finite number of multiplies of the bin size: $\Delta^{bin} RR_i = 0, \pm bin, \pm 2bin, \ldots,$ ms, which will be referred to as:

$$\Delta_J^{bin} \in \{-\Delta_K^{bin}, \ldots, 0, \ldots, \Delta_K^{bin}\},$$

$$\text{where } \Delta_K^{bin} = \max\{|\Delta^{bin} RR_i|\}.$$

For each individual five-minute recording, the probability distribution of increments $\{p(\Delta_J^{bin})\}$ was calculated.

As an example, Figure 2 shows the distributions of probabilities obtained from signals of healthy people in the supine position (CG, PRE). They were obtained for different bin sizes. The plots are drawn as log-plots to validate their approximation by a double exponential distribution for $|\Delta_J^{bin}| < 100$ ms.

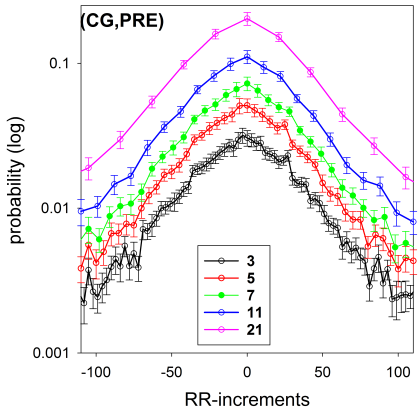

Figure 2. The mean values (with std err) of distribution functions obtained for the group (CG, PRE) of signals (log plots) for different bin sizes: 3, 5, 7, 11, 21 ms.

We performed linear fits to log-values with weights provided by the inverse of variations with the help of Mathematica 10.0 (Wolfram Research Inc.). The linear fit parameters were found at P-value $P \ll 0.001$ resulting from the t-test. The squared Pearson coefficients were $R^2 > 0.95$. In the following, we validate the values of these linear fit coefficients by their 95% confidence intervals (95% CI). If two 95% CI of the two coefficients are separated, these coefficients are statistically different in the t-test at a significance level of P=5% [9].

By α_{dece}^G we denote an exponential coefficient of the deceleration decay for a group G, and by α_{acce}^G an exponential coefficient of the acceleration decay.

3. Results

The double exponential approximations of the distributions of RR-increments: accelerations and decelerations, were obtained with high accuracy for all the groups considered. In Figure 3, we show the values of the exponential coefficients α_{acce}^G and α_{dece}^G, together with their 95% CI for all groups and bin sizes considered.

We see that these coefficients change in the same way for all groups independently of the bin size:
— the absolute values of the coefficients α_{acce}^G and α_{dece}^G are bigger when the subject is tilted;
— for the same groups $\mathbf{G}$, coefficients $\alpha_{acce}^G \neq \alpha_{dece}^G$.
Moreover, the results obtained for different bins are almost indistinguishable. However, when the bin size increases, the 95% CI also increases. Therefore, the values α_{acce}^G and α_{dece}^G can be considered to describe the total effect of activation of reflexes caused by tilting.

Interestingly, during tilting the coefficients of the exponential decay of the distribution function in the group of healthy subjects CG are significantly lower than in the

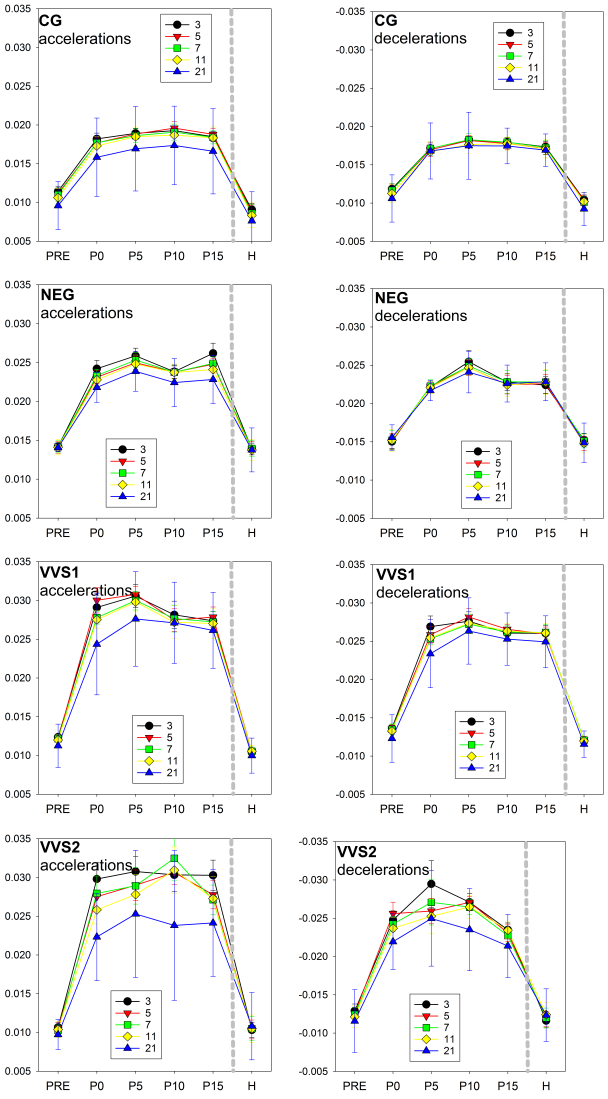

Figure 3. Coefficients of the exponential decay of pdf of accelerations and pdf of decelerations if the data are analyzed with bin sizes equal to $3, 5, 7, 11, 21$ ms. The grey dashed lines indicate the time break in recordings between windows P15 and H.

other groups studied. Thus, the homeostasis state in vasovagal sensitive people is maintained by changes in RR-interval of a smaller size than changes evoked by head-up tilt in healthy subjects. Moreover, it is also worth noting that the coefficients of vasovagal patients who did not faint in the test (NEG) are substantially lower than the coefficients found for groups of people who fainted (VVS1, VVS2). These two observation together indicate that the reason for the lack of proper cerebral blood perfusion in vasovagal patients could be related to a slow reaction to the circumstances.

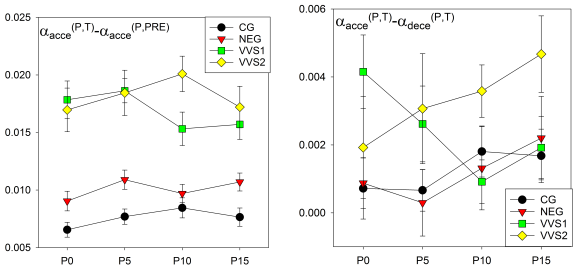

Figure 4. Activation of response reflexes by difference between exponential coefficients obtained after titling and at rest $\alpha_{acce}^{(P,T)} - \alpha_{acce}^{(P,PRE)}$ (left). Difference in activation of accelerating and decelerating forces by $\alpha_{acce}^{(P,T)} - \alpha_{dece}^{(P,T)}$ for T=P0, P5, P10, P15 (right).

In Figure 4, the differences between $\alpha_{acce}^{(P,T)} - \alpha_{acce}^{(P,PRE)}$ and $\alpha_{acce}^{(P,T)} - \alpha_{dece}^{(P,T)}$ are plotted for $bin = 5$ ms. We see that the groups of people who fainted, VVS1 and VVS2, provide significantly different plots from the groups of people who did not faint in the test, CG and NEG.

In order to measure the total impact of the tilting on the autonomic nervous system, we propose using the maximal difference observed in the accelerations coefficients:

$$\mathbf{A}^P := \max_{T \in \{P0, P5, P10, P15\}} \alpha_{acce}^{(P,T)} - \alpha_{acce}^{(P,PRE)}. \quad (1)$$

Moreover, to measure the balance in sympathovagal reflexes evoked by the tilt test, we propose using the maximal difference between the acceleration and deceleration coefficients in the same time window:

$$\mathbf{B}^P := \max_{T \in \{P0, P5, P10, P15\}} (\alpha_{acce}^{(P,T)} - \alpha_{dece}^{(P,T)}). \quad (2)$$

In Table 1, we provide values for $\mathbf{A}^P$ and $\mathbf{B}^P$. Similar estimates hold for all $bin < 10$ ms.

Note that the values of $\mathbf{A}^P$ and $\mathbf{B}^P$ for groups CG and NEG, hence for the groups consisting of people who did not faint in the head-up tilt test, are about half the values obtained for the groups of vasovagal patients who fainted during the test, VVS1 and VVS2.

Moreover, for vasovagal sensitive people the maximal activation of the autonomic regulation measured by $\mathbf{A}^P$ occurs at a different time after tilting. Namely, in the vasovagal patient groups NEG and VVS1 it happens earlier than in the healthy group CG. So comparing the vasovagal sensitive people to the healthy people, we see that not only is the activation of reflexes stronger in vasovagal patients but it also introduces disorder in the balance between sympathetic and vagal regulations.

The discrepancy between α_{acce} and α_{dece} may suggest that the homeostatic state is maintained by many small size accelerations interrupted by rarer, though larger, decelerations. The highest discrepancy between accelerations and

Table 1. Indexes $\mathbf{A}$ and $\mathbf{B}$ ($\pm$95% CI) for the groups studied in the case of $bin = 5$ ms and time windows at which the maximal difference is observed.

P	$\mathbf{A}^P$		$\mathbf{B}^P$	
CG	p10	0.0085±0.0004	p10	0.0018±0.0004
NEG	p5	0.0109±0.0003	p15	0.0022±0.0004
VVS1	p5	0.0186±0.0003	p0	0.0042±0.0006
VVS2	p10	0.0201±0.0007	p15	0.0049±0.0007

decelerations occurs in the groups of patients who fainted in the test, VVS1 and VVS2. In the case of the healthy people, this maximal discrepancy accompanies the state of maximal activation, while this is not true in the case of vasovagal sensitive people.

4. Discussion and Conclusions

Accelerations, driven by the sympathetic branch of the autonomic nervous system, and decelerations maintained by vagal activity, recorded during a head-up tilt test, provide information about the complex interplay between sympathetic and vagal responses to a rapid, though controlled, deregulation of homeostasis. We show that exponential functions with coefficients α_{dece} and α_{acce} approximate very accurately the distributions of RR-increments for $|\Delta RR| < 100$ in positions both at rest and when tilting. This approximation is numerically stable. Therefore the proposed indices: $\mathbf{A}$ for autonomic activation, and $\mathbf{B}$ for sympatho-vagal balance, provide a way to assess the dynamic interplay between physiological processes evoked by tilting.

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