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Generalised heart rate statistics reveal neurally mediated homeostasis transients

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Abstract – Distributions of accelerations and decelerations, obtained from increments of heart rate recorded during a head-up tilt table (HUTT) test provide short-term characterization of the complex cardiovascular response to a rapid controlled dysregulation of homeostasis. A generalised statistic is proposed for evaluating the neural reflexes responsible for restoring the homeostatic dynamics. An evaluation of the effects on heart rate of the neural regulation involved in achieving homeostasis indicates a distinction between vasovagal patients and healthy subjects who are not susceptible to spontaneous fainting. A healthy cardiovascular response to the HUTT test is identified in the sympathetic tone appropriately punctuated by vagal activity.

Introduction. – Modern physics faces the challenge of understanding systems of biological origin, with one such example being the physiological cardiac regulatory system. Numerous studies have been reported on the complex dynamics of the neurophysiological control of the human cardiac system in both health and disease. Few works have, however, addressed syncope —a transient loss of consciousness, as a consequence of inadequate cerebral nutrient delivery resulting most often from transient hypotension [1,2]. Recurrent syncope has a serious impact on patients' quality of life, comparable with chronic illnesses. Vasovagal syncope (VVS) is a reflex syncope in which an inappropriate reaction of the autonomic nervous system (ANS) plays a key role in pathophysiology.

The head-up tilt table (HUTT) test is a simple and non-invasive method for provoking vasovagal events [3,4]. Patients, initially placed in a supine position on a special tilting table, are raised to the upright position. The upright posture induces the downward displacement of about 500 to 1000 ml of blood. The major part of this redistribution occurs in the first ten seconds after verticalisation. In the next ten minutes, an additional 700 ml of fluid relocates within the interstitial space. To compensate for the transfer of fluids, two processes are evoked: i) an increase in the heart rate and ii) the constriction of small arteries and arterioles [3]. These processes are mediated by the ANS —by both its vagal and sympathetic branches. It has been shown that vagal influences dominate over sympathetic ones in heart rate regulation [5], but homeostatic blood supply to the organs is preserved due to the cascade of complex feedback loops in which both ANS branches simultaneously participate [6].

Complexity of the cardiovascular regulation during various parts of the HUTT test provides an opportunity to exploit new methods developed for the time series analysis of stochastic complex systems. Hitherto, the

assessment of the HUTT test results [7–9] and their modelling [10] have been challenging. Although widely used in the diagnosis of VVS, the HUTT test is known to have many limitations [11]. The standard characteristics of heart rate variability (HRV), especially low-frequency (LF) and high-frequency (HF) components of the spectral analysis, manifest changes depending on the cardiovascular system reaction. However, their reliability is poor and contradictory results have often been observed [11–14].

Interbeat time series do not exhibit reversal time symmetry [15], which suggests that asymmetric time patterns characterize the underlying dynamics [16]. Establishing this link would help in translating complex system concepts into a reliable quantification of the pathological dynamics provoked by the HUTT test, and is the main purpose of this letter. If the RR-interval denotes a time interval between two consecutive heartbeats, the probability distribution functions (pdfs) of heart accelerations and decelerations, formed from time increments ΔRR between two consecutive RR-intervals, describe the short-term response of the cardiovascular system to actual bodily demands. In the following, we investigate how the changes in pdfs of accelerations and decelerations explain neural reflexes activated in the HUTT test.

The statistics of ΔRR increments have been widely used in the characterisation of cardiac signals [17–20]. Both the increments' magnitudes $|\Delta RR|$ and signs show long-range dependencies which discriminate healthy heart dynamics from that of heart failure patients [18]. They also allow the quantification of sleep stages [19]. The scaling properties of $|\Delta RR|$ have also been shown to be age independent in healthy aging [20].

The asymmetry between accelerations and decelerations has been proposed as a measure of sympathetic activity [16,21]. In particular, the Porta Index (PI) quantifies this asymmetry by the ratio of the total number of accelerations to the total number of all non-zero changes in RR-interval values [16]. In pdf representation, this is

$$PI = \frac{\sum_{\Delta RR<0}\ p(\Delta RR)}{\sum_{\Delta RR\neq 0}\ p(\Delta RR)}, \qquad (1)$$

with $p(\Delta RR)$ denoting the probability of a given RR-increment. Since decelerations occur in shorter runs than accelerations do, especially when sympathetic activity is high, $PI > 0.5$ is expected [16,21,22]. The index PI has been measured in various conditions, in humans at rest [21,22] and during the HUTT test [16,23]. The results reveal a tendency to be larger than 50%, in accordance with increased sympathetic activity, however often with unsatisfactory statistics [16].

Equation (1) can be generalized for any real number q as

$$GPI(q) := \frac{\sum_{\Delta RR<0}\ p^q(\Delta RR)}{\sum_{\Delta RR\neq 0}\ p^q(\Delta RR)}. \qquad (2)$$

$GPI(q)$ will be referred to as the "Generalized Porta Index" (GPI). For any q, $GPI(q)$ takes values in the interval $[0,1]$, which lend themselves to straightforward interpretation. By varying q, we consider parts of the pdf corresponding to large decelerations separately from parts describing small accelerations, which gives insight into how large decelerations can be compensated for by short accelerations.

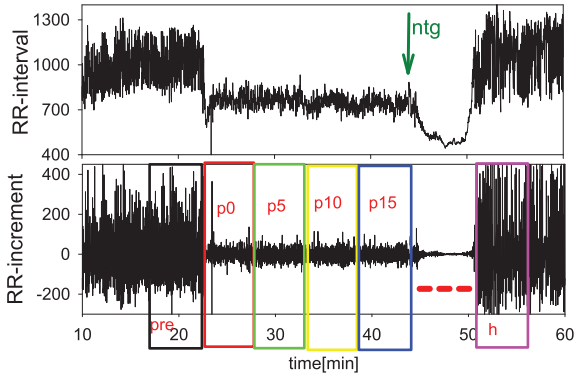

Fig. 1: (Colour on-line) A typical recording of RR-intervals obtained in the HUTT test for a subject who fainted after nitroglycerine (ntg) administration. Altering the position from supine to upright and back to supine results in marked changes of RR-intervals. The recording is divided into five-minute windows indicated by coloured rectangles. The red dashed line denotes a break in the recording during the active part of the test.

Data acquisition and preprocessing. – Included in the study were fifty healthy individuals with no history of fainting, and one hundred and fifty VVS patients who experienced vasovagal syncope. The study complied with the Declaration of Helsinki and was approved by the Bioethics Committee of the Medical University of Gdańsk. The HUTT tests were performed under paced breathing protocol, standardising the impact of breathing on the heart rate [24]. 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* with administration of 400 micrograms of nitroglycerine (aerosol, sublingually) was performed. The active test lasted 10 minutes or until syncope occurred.

In fig. 1, a recording is shown of RR-intervals and the corresponding RR-increments, obtained from a subject who fainted in the active part of the HUTT test. In order to study dynamical changes in pdfs, each signal is divided into five-minute windows. The first window (named *pre*) contains recordings just before tilting, when the subject was still in the supine position. Then, when the table was tilted, the next 20 minutes is covered by four consecutive five-minute windows named: $p0$, $p5$, $p10$, and $p15$. Finally, when the subject was returned to the supine position, the last five-minute window h succeeds. The results were interpreted according to the modified VASIS

Table 1: Description of the groups of signals considered.

Group name	Number of subjects	History of syncope	Syncope during HUTT	Type of VVS reaction
CG	36	no	no	–
NEG	50	yes	no	–
VVS1	74	yes	yes	VVS1
VVS2	26	yes	yes	VVS2

classification [25]. The result of the HUTT test was assumed to be positive, *i.e.*, a patient's state was classified as a faint of type:

- VVS1: if blood pressure fell, followed by an increase in RR-intervals to less than 1.5 s, or if they increased to more than 1.5 s, this increase lasted less than 10 s;
- VVS2: if RR-intervals increased to an asystole of more than 3 s, or RR-intervals of a size greater than 1.5 s lasted longer than 10 s, together with or before the drop in blood pressure.

Among a hundred patients who fainted because of the HUTT test, only eight had vasovagal syncope during the passive test (6 were of type VVS1 and 2 were of type VVS2). All the other patients fainted in the active test. 68 faints were classified as type VVS1, and 24 as type VVS2. Surprisingly, 14 healthy people also fainted during the active test. The signals of healthy people with a positive HUTT test were excluded from further analysis.

According to the results of the HUTT test and the history of syncope, we divided the signals studied into four groups described in table 1. Taking into account the six time windows, we obtain 24 groups of signals to consider. We identify them as follows. If P denotes the patient group, and T is the five-minute window, then a group $\mathbf{G}$ indicates a pair (P, T), where

$$P \in \{\mathrm{CG}, \mathrm{NEG}, \mathrm{VVS1}, \mathrm{VVS2}\},$$
$$T \in \{pre, p0, p5, p10, p15, h\}.$$

In table 2, we show basic HRV indices obtained from individual signals pooled into the groups considered. Data from most of the groups did not pass the normality tests. Therefore the central tendency of each group is represented by the median, and the data dispersion as the first and third quartiles.

Our recordings had a resolution of 1 ms. However, all the signals were binned with the bin size of 5 ms. Such binning provides pdfs with satisfactory smoothness and acceptable values of std errors. Moreover, such pdfs preserve the variability of events.

Let $\mathbf{RR} = \{RR_0, RR_1, \ldots, RR_N\}$ be a time sequence of RR-intervals. We say that the heart beat *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 with a deceleration, $\Delta RR_i < 0$ with an acceleration, and $\Delta RR_i = 0$ with a no-change event. Because of the binning, the set of values $\{\Delta RR_i\}$ consists of the finite number of multiplies of 5 ms: $0, \pm 5, \pm 10, \ldots$ ms, which will be referred to as $\Delta_J \in \{-\Delta_K, \ldots, 0, \ldots, \Delta_K\}$, where $\Delta_K = \max\{|\Delta RR_i|\}$.

Table 2: Standard indices of HRV for the groups studied —the median together with its lower and upper quartiles. All indices were estimated by Kubios HRV 2.0 [26] at the software default settings. RR (ms), SDNN (ms): the mean, and standard deviation of normal-to-normal RR-intervals, respectively; RMSSD (ms): square root of the mean squared differences between successive RR-intervals; pNN50 (%) rate of the successive RR-intervals which differ more than 50 ms; LF (%), HF (%): relative power of LF, HF, respectively, to the total power.

Group	CG	NEG	VVS1	VVS2
		RR (ms)		
pre	843 [792, 995]	822 [764, 950]	852 [790, 930]	901 [871, 977]
*p*0	718 [684, 804]	728 [682, 828]	712 [663, 767]	771 [742, 831]
*p*5	720 [682, 820]	723 [677, 811]	693 [644, 757]	749 [717, 816]
*p*10	742 [685, 833]	730 [661, 792]	685 [646, 767]	744 [696, 803]
*p*15	731 [684, 814]	719 [662, 783]	689 [640, 748]	733 [690, 799]
h	915 [844, 1075]	868 [794, 991]	876 [802, 984]	979 [869, 1036]
		SDNN (ms)		
pre	58 [48, 86]	60 [43, 77]	63 [49, 82]	62 [50, 84]
*p*0	62 [45, 71]	45 [35, 63]	48 [38, 59]	49 [42, 62]
*p*5	56 [42, 67]	38 [31, 55]	39 [31, 48]	44 [34, 51]
*p*10	56 [45, 73]	40 [31, 57]	43 [32, 52]	47 [38, 56]
*p*15	61 [50, 73]	42 [29, 62]	44 [34, 52]	52 [41, 63]
h	80 [56, 125]	72 [50, 94]	94 [69, 117]	105 [76, 129]
		RMSSD(ms)		
pre	51 [34, 80]	37 [22, 67]	45 [27, 57]	48 [37, 58]
*p*0	32 [25, 43]	25 [17, 30]	21 [15, 29]	24 [20, 29]
*p*5	29 [21, 42]	21 [14, 26]	20 [14, 24]	21 [18, 27]
*p*10	32 [21, 43]	22 [14, 30]	20 [14, 24]	21 [18, 29]
*p*15	32 [23, 44]	20 [14, 31]	20 [15, 25]	23 [18, 29]
h	72 [38, 128]	41 [24, 84]	63 [38, 84]	60 [40, 85]
		pNN50 (%)		
pre	28 [11, 43]	14 [2, 36]	23 [6, 34]	21 [15, 35]
*p*0	11 [5, 18]	5 [1, 8]	3 [1, 8]	5 [1, 8]
*p*5	8 [3, 19]	2 [0, 6]	2 [0, 4]	2 [1, 6]
*p*10	7 [3, 21]	3 [0, 8]	2 [1, 4]	3 [1, 7]
*p*15	9 [4, 20]	2 [0, 7]	2 [0, 5]	3 [1, 7]
h	38 [17, 59]	16 [3, 38]	28 [13, 43]	31 [10, 48]
		LF (%)		
pre	34 [20, 39]	26 [21, 34]	25 [19, 40]	28 [20, 37]
*p*0	37 [27, 49]	36 [29, 46]	35 [24, 47]	42 [28, 47]
*p*5	42 [32, 54]	33 [24, 50]	39 [29, 50]	35 [31, 38]
*p*10	48 [32, 58]	37 [29, 52]	38 [31, 50]	39 [31, 44]
*p*15	47 [39, 53]	39 [28, 53]	39 [31, 50]	43 [32, 55]
h	27 [16, 39]	28 [22, 35]	25 [17, 32]	20 [13, 26]
		HF (%)		
pre	35 [28, 48]	20 [10, 35]	25 [13, 36]	23 [13, 35]
*p*0	13 [9, 22]	10 [6, 19]	8 [4, 17]	9 [7, 11]
*p*5	16 [9, 23]	9 [5, 21]	11 [5, 17]	11 [7, 18]
*p*10	14 [10, 21]	10 [7, 16]	9 [6, 14]	9 [7, 13]
*p*15	14 [10, 20]	11 [6, 16]	9 [6, 14]	9 [7, 12]
h	33 [20, 49]	21 [10, 33]	20 [11, 33]	15 [9, 35]

Methods. – For each individual five-minute recording, the pdf of increments $p(\Delta_J)$ was calculated. Then the results were pooled into the groups $\mathbf{G}$. Finally, for each group $\mathbf{G} = (P, T)$ the mean probability $p_{\mathbf{G}}(\Delta_J)$ that a given increment Δ_J occurred in a signal of the group (P, T) was calculated.

In fig. 2, we show pairs of pdfs obtained for the particularly important groups. The top row shows pdfs representing records from the *pre* window of people who did not faint in the test —groups CG and NEG. The bottom row summarises the results obtained from the groups of VVS patients who did not faint (NEG) and those who fainted (VVS1) in the $p5$ window when displacement of body fluids is maximal. The pdfs are shown as log-plots to validate their approximation by a double-exponential distribution for $|\Delta_J| < 100$ ms. The numerical approximations (linear fit to log-values with weights provided by the inverse of variations) and their validity were found by Mathematica

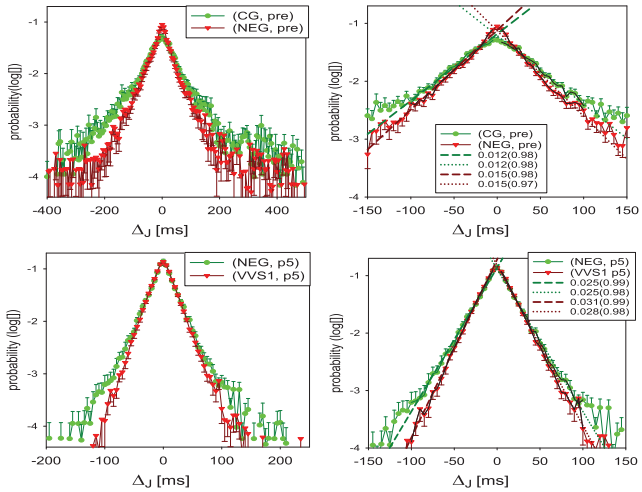

Fig. 2: (Colour on-line) The mean pdfs obtained for the selected groups of signals (log-plots). The top row presents $p_{(\mathrm{CG},pre)}$ *vs.* $p_{(\mathrm{NEG},pre)}$, while $p_{(\mathrm{NEG},p5)}$ and $p_{(\mathrm{VVS1},p5)}$ are compared in the bottom row. The right column figures illustrate the quality of the regression coefficients for accelerations: $-100 < \Delta_J < 0\,\mathrm{ms}$ and for decelerations $0 < \Delta_J < 100\,\mathrm{ms}$. Values of these coefficients, together with the squared Pearson coefficients of the approximation, are given next to the curve labels.

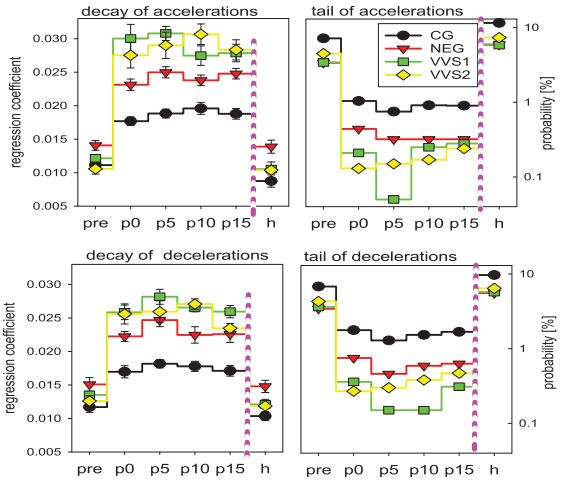

Fig. 3: (Colour on-line) Coefficients of the exponential decay (with 95% CI) (left column), and probabilities of the acce- and dece-tails (right column) of pdfs for the groups considered. Pink dotted lines represent a break in time between $p15$ and h.

9.0 (Wolfram Research Inc.). All linear-fit parameters were estimated at P-value $P \ll 0.001$ resulting from the t-test and with squared Pearson coefficient $R^2 > 0.95$. The statistical validation for the values of the linear-fit coefficients are represented by a 95% confidence interval (CI).

The probability of RR-increments such that $\Delta_J < -100\,\mathrm{ms}$ (henceforth referred to as acce-tail) and $\Delta_J > 100\,\mathrm{ms}$ (henceforth referred to as dece-tail) were calculated to ensure the importance of the Δ_J interval where the double-exponential approximation holds.

The least probable events from the tails are often accidental events, which may represent artefacts or abnormal beats, usually not typical of the group considered. Such events strongly influence the GPI value if q is negative. In accordance with the properties of the acce- and dece-tails shown in fig. 2, we limited the sums in (2) to Δ_J containing at least 99% accelerations and 99% decelerations in the upright position, and at least 95% events in the supine position. Thus, in the case of groups *pre* and h, we assumed $|\Delta_J| < 200\,\mathrm{ms}$, and for the remaining groups $|\Delta_J| < 100\,\mathrm{ms}$. For each signal, the value of $GPI(q)$ was calculated separately for $q = -5.0, \ldots, 5.0$ with step $\delta q = 0.1$. The results obtained for each q were pooled into the groups considered. The limits described do not influence the $GPI(q)$ value when $q \geq 0$, but they strongly stabilize $GPI(q)$ properties if $q < 0$.

If both side slopes of the pdfs are symmetrical with respect to the no-change event, then $GPI(q)$ varies at about 0.5 for any q value. The more probable events are gradually enhanced by $GPI(q)$ when q departs from 1 to larger q values. In our case, small accelerations and small decelerations are the most probable events, hence the presence of these events is magnified. A GPI value significantly greater than 0.5 implies domination of accelerations over decelerations.

Large changes in the RR-intervals are the least probable events. Therefore, GPI for negative q provides information about rare events. Here, a GPI smaller than 0.5 indicates the prevailing of large accelerations over large decelerations. In order to collect properties from a relatively wide pool of events, we restrict our estimates to $-1.5 < q < 2.5$. To emphasize the details of these properties, we concentrate on the following values of q : $q = 1$ (the Porta Index), $q = 2$ and $q = -1$.

Results. – We obtained double-exponential approximations of the pdfs of RR-increments with high accuracy for all the groups considered, see fig. 3. Furthermore, the acce- and dece-tails contain less than 1% of the events in the upright position ($\sim 2\%$ for the CG) and no more than 10% in the case of the supine position. These two facts strongly support the view that the decay coefficients are valuable indices in assessing the ANS couplings evoked by the HUTT test.

Let us denote as $\alpha^{(G,P)}_{dece}$ a coefficient of the deceleration decay for a group (G, P), and as $\alpha^{(G,P)}_{acce}$ a coefficient of the acceleration decay. These coefficients change systematically for all groups —all pdf slopes fall more sharply when the subject is tilted. Hence, this property reflects the total effect of activation of reflexes caused by tilting. Moreover, in the group of healthy subjects CG, the coefficients of pdf slopes are significantly lower than in the other groups studied. Thus, the neural reflexes in VVS patients evoke changes in the RR-interval of a smaller size than the changes evoked in healthy subjects. Surprisingly, also the slope coefficients of VVS patients with no syncope during the test (NEG) differ from the slope coefficients found for

Table 3: Indexes of activation of reflexes $\mathbf{A}$ and of sympathovagal balance $\mathbf{B}$ for the groups studied (time window: difference $\pm$ 95% CI).

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

groups of people who fainted (VVS1, VVS2). The relation is similar to the difference between healthy and syncope subjects described above: RR-intervals change in steps with smaller Δ_J.

Additionally, a discrepancy between the slopes of accelerations and decelerations observed for the groups consisting of people who fainted suggests that this difference between α_{acce} and α_{dece} could be a measure of the imbalance in ANS regulation.

To summarise, we propose to measure the ANS coupling evoked by the HUTT test, for a given group of subjects P as

$$\mathbf{A}^P := \max_{T\in\{p0,p5,p10,p15\}} \alpha_{acce}^{(P,T)} - \alpha_{acce}^{(P,pre)}, \qquad (3)$$

and to estimate the balance in sympathovagal reflexes as

$$\mathbf{B}^P := \max_{T\in\{p0,p5,p10,p15\}} (\alpha_{acce}^{(P,T)} - \alpha_{dece}^{(P,T)}). \qquad (4)$$

In table 3, we give values for $\mathbf{A}^P$ and $\mathbf{B}^P$. In general, these results depend on the bin size used when the signals were preprocessed. Note that their values for groups CG and NEG of people who did not faint in the HUTT test are about a half smaller than the values for groups VVS1 and VVS2. Therefore, they provide a qualitative description for the total effect of reflexes evoked by the HUTT test.

Exponential functions with coefficients α_{dece} and α_{acce} approximate the pdfs. However, using GPI, we obtain complete insight into the actual proportions between accelerations and decelerations in the heart RR-increment dynamics. Figure 4 shows GPI dependence on q in a way which emphasizes changes in asymmetry over time in particular groups.

The fastest increase in the GPI value for $q > 0$ is observed in the $p15$ windows in all groups. Moreover, in healthy people this growth is the biggest. This could indicate that the prolonged stimulation of the sympathetic nervous system aggregates over time, leading to an increasing number of small accelerations, and in the case of VVS patients, this accumulated increase is smaller than in healthy people. Considering the asymmetry in large accelerations, *i.e.* in the case $q < 0$, we see that in healthy people large changes are maintained in a similar way in all the time windows, whereas in the case of VVS patients, we observe the dependence of the GPI value on the time window.

In particular, the Porta Index $PI = GPI(1)$, see fig. 5, left, attains the highest value in the h time window.

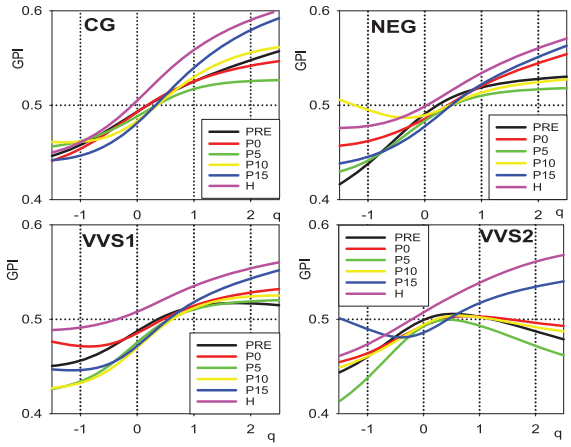

Fig. 4: (Colour on-line) GPI dependence on q obtained from $GPI(q)$ values pooled in the groups calculated for each signal separately.

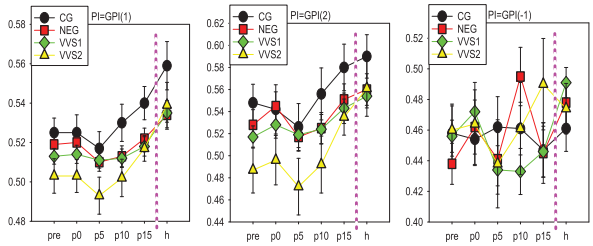

Fig. 5: (Colour on-line) GPI values (mean $\pm$ std err) for $q = 1$ (left), $q = 2$ (middle) and $q = -1$ (right) for all the groups considered. By t-test, the following differences are statistically significant with $P < 0.05$: case $GPI(1)$: CG *vs.* VVS2 in *pre*, and $p10$, and CG *vs.* VVS1 in $p15$; case $GPI(2)$: CG *vs.* VVS2 in *pre*, and NEG *vs.* VVS2 in $p0$; case $GPI(-1)$: NEG *vs.* VVS1 in $p10$.

This apparently results either from the preceding administration of nitroglycerine or from fainting in the passive test. Moreover, the highest PI in each time window is reached for the CG group. This observation may suggest that a slight dominance of accelerations is a fingerprint of appropriate, balanced ANS activity. However, in each group studied, the lowest values of PI occur in the $p5$ window. This window covers the time period when the maximal volume of fluids is redistributed downwards, and therefore can be thought of as quantifying the quality of ANS afferents.

The values of $GPI(2)$ enhance PI observations but they are characterised by larger errors, see fig. 5, middle. In the *pre* window, they clearly separate healthy people from people sensitive to vasovagal events, *i.e.*, VVS patients[1]. $GPI(2)$ also seems to be efficient in

[1]Note that two groups of patients attain similar values: NEG and VVS1. The VVS2 group is different because the syncope in these patients is of a different origin. Here an RR-interval increase precedes the blood pressure drop and asystole or bradycardia emerges. Hence, effects other than the baroreflex (the basic reflex commonly assumed to be responsible for maintaining pressure and heart rate homeostatic states) must be responsible for the changes observed in these cases.

quantification processes activated by the HUTT test. For all the groups, the $GPI(2)$ value changes in time windows with a similar pattern: a small increase is followed by a decrease in the first ten minutes, after which, in the next ten minutes, a steady increase is observed, supporting the idea of prolonged sympathetic activation. The highest dominance of small accelerations over small decelerations is found for the CG group in the $p15$ time window. It can be interpreted that the way of restoring a homeostatic state goes via many small accelerations balanced by rarer but larger decelerations[2]. To conclude, $GPI(2)$ identifies groups similar from the clinical point of view.

Although rare events, as described by $GPI(-1)$, see fig. 5, right, have the largest errors, the difference between NEG and VVS1 in $p10$ is significant. This property could suggest that a loss of minor domination of large accelerations over decelerations in NEG allows the maintenance of the proper blood distribution, and avoids fainting.

Conclusions. – Although the precise understanding of all the reflex responses involved in the compensatory adjustments to the upright position remains speculative [1,2], in this letter we have shown that the distribution of the RR-increments, is a powerful source of information about the strength of couplings between the cardiovascular system and other organs which are driven by the ANS provoked by the HUTT test.

The properties of accelerations expressed by **A** and accelerations *vs.* decelerations measured by **B** allow the differentiation between healthy subjects who are not sensitive to the HUTT test and other subjects. The greater their values are, the greater the probability is of fainting in the passive test. Therefore we can see them as predictors of the results of the active part of the HUTT test in subjects who did not faint in the passive test.

An ideal diagnostic method should identify patients with VVS without the need of performing the HUTT test, preferably on the basis of the analysis of short fragments of electrocardiograms. In our opinion $GPI(q)$ satisfies these requirements. For each patient, this function can be estimated. Then based on the set of $GPI(q)$ markers, which could be, *e.g.*, $GPI(1)$, $GPI(2)$ and $GPI(-1)$, we should be able to separate healthy people from VVS patients based on signals before the HUTT test. We believe that the methodological insights obtained will contribute to the development of future diagnostic methods for dysfunctions of the complex cardiac regulatory system —a prominent example of physiological complexity.

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[2]Only the VVS2 group shows a small predominance of decelerations over accelerations in *pre* and during the first half of the HUTT test. Again, this fact points to potentially different mechanisms involved in the syncope.

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