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Microgravity effects on ventricular response to heart rate changes

Juan Bolea[1], Enrico G. Caiani[2], Esther Pueyo[3], Pablo Laguna[1] and Rute Almeida[4]

Abstract— **The effect of simulated microgravity on ventricular repolarization (VR) has been evaluated on healthy volunteers by a 5-day Head Down ($-6°$) Bed Rest (HDBR) maneuver. QT to RR and QT_p (measured until the peak of the T wave) to RR hystereses have been measured during a tilt table test, and differences between them have been studied to better understand possible changes in the final part of the repolarization. To characterize the hystereses, two indices have been computed: M_{90}, quantifying adaptation lag in beats, and α evaluating the slope of parabolic regression fitting. Significant differences between QT and QT_p were found before, but not after HDBR. Specifically, before HDBR was considerable lower for QT_p than for QT, while α was significantly higher. After HDBR, M_{90} and α took essentially the same values for QT and QT_p. This fact evidenced the different effect of HDBR on QT to RR and QT_p to RR adaptations, and suggest HDBR could lead to an impairment in ventricular repolarization dispersion.**

I. INTRODUCTION

Head down ($-6°$) bed rest (HDBR) is one of the maneuvers commonly utilized to simulate microgravity conditions on the human body. Long term exposure to microgravity leads to body deconditioning: decrease of muscle mass, plasma volume reduced by 10-15% or cardiac deconditioning leading to orthostatic intolerance once returning to Earth in cases of space flights, among others. Also, some episodic modifications in cardiac conduction during space flight have been reported, altogether leading to the hypothesis that microgravity could increase the risk of developing arrhythmias [1]. During the last decades, some electrocardiogram (ECG)-based arrhythmic risk-markers have been proposed based on ventricular repolarization (VR) or on its dispersion (VRD) [2], [3].

In particular, the duration of VR, as assessed by the QT interval (measured from QRS onset to T end), and its dependency on heart rate (HR) have been proposed as pro-arrhythmic risk indices [4], [5]. In a previous work [6], the adaptation of the interval from Q wave to T apex (QT_p) with respect to HR changes provoked by a tilt table test (TTT) was evaluated. It was found a different behaviour, depending on if the subject did support the TTT for a period longer than 7 and a half minutes or not.

The QT interval represents the time period when it occurs depolarization and repolarization of all ventricular cells, whereas QT_p is an incomplete measure this time period. As a matter of fact, the differences between QT and QT_p measured by the T_{pe} (T peak to T end) interval has been proposed as an index for evaluation of VRD and restitution dispersion [7] .

With this in mind, this study aimed at investigating the QT to RR and QT_p to RR hystereses during TTT in healthy volunteers before and after exposure to 5 days HDBR, to evaluate its effects on VR and the susceptibility to a potential increase in the arrhythmic risk. Our hypothesis was that, if HDBR deconditions the myocardium, this will be expressed as a decrease in the repolarization adaptation capability to follow abrupt changes in HR, which will lead to a prolonged QT hysteresis lag after RR changes. We want to evaluate if this modifies VR hysteresis lag after HR changes and if it affects the later part of the T wave (T_{pe}), resulting in different dependency of QT and QT_p with respect to HR.

II. METHODS

Population. 22 male subjects (age range 21-43 years) were enrolled with a cross-over design in two 5-days HDBR experiments, conducted at MEDES (Toulouse, France) and DLR (Koln, Germany) as part of the European Space Agency bed rest studies. High fidelity (1000 Hz) 12-lead ECGs (Mortara Instrument) were acquired during at least 15' of stable conditions followed by 30' TTT at 80 degrees, performed before (PRE) and at the conclusion of HDBR (R+0). The test was interrupted once one stop criterion was reached: very low blood pressure, extreme tachycardia or clinical symptoms. All subjects had no previous history of cardiovascular disease, and had undergone a comprehensive medical

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[1]J. Bolea and P. Laguna are with Communications Technology Group (GTC), Aragón Institute of Engineering Research (I3A), IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain and with CIBER - Bioingeniería, Biomateriales y Nanomedicina, Zaragoza, Spain jbolea, laguna at unizar.es

[2]E.G. Caiani is with the Biomedical Eng. Dpt., Politecnico di Milano, Milan, Italy enrico.caiani at biomed.polimi.it

[3]E. Pueyo is with CIBER - Bioingeniería, Biomateriales y Nanomedicina, Zaragoza, Spain and with Communications Technology Group (GTC), Aragón Institute of Engineering Research (I3A), IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain epueyo at unizar.es

[4]R. Almeida is with the CIBER - Bioingeniería, Biomateriales y Nanomedicina, Zaragoza, Spain, and with Communications Technology Group (GTC), Aragón Institute of Engineering Research (I3A), IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain and with Centro de Matemática Aplicada da Universidade do Porto (CMUP), Univ. do Porto, Porto, Portugal rbalmeid at unizar.es

examination during the selection process. Each subject provided written, informed consent to participate in the study, which was approved in advance by the respective Ethical Committee for Human Research at the hosting institutions.

Signal preprocessing. For *RR*, *QT*, QT_p and T_{pe} beat-to-beat measurements, eight independent ECG leads (I, II, V1-V6 standard leads) were considered. Each lead was delineated using an automatic system and the eight sets of marks were combined using post processing rules [8]. T peak was measured as the median value from the eight single lead based T peak locations while T wave end was taken as the latest single mark among the eight candidates, when at least 3 neighbor marks were within a 12 ms interval. The beat-to-beat series were extracted from those global marks, where anomalous values of *RR*, *QT*, QT_p and T_{pe} series were treated as outliers and excluded. Series were interpolated at 1 Hz, and the resampled series were denoted by $x_{\mathrm{RR}}(n)$, $y_{\mathrm{QT}}(n)$, $y_{\mathrm{QTp}}(n)$ and $y_{\mathrm{Tpe}}(n)$ respectively, where n is the sample index.

Segments presenting downward abrupt changes in RR (initial part of TTT) were manually identified and visually checked (see Fig. 1), and selected for being processed with the following methods. Subjects with unreliable *QT* or QT_p delineation, or too short (<4') orthostatic tolerance time (OTT) were excluded from the analysis. Subjects with OTT >4' were arbitrarily divided into two groups: OTT between 4' and 7'30" at R+0(G_{Short}), and OTT>7'30" (G_{Long}) at PRE and R+0, resulting in 5 subjects in G_{Short} and 12 in G_{Long} groups, respectively.

Measurement of QT to RR and QT_p to RR hystereses. *QT* (or QT_p) interval adaptation to *RR* changes was modeled using a system composed of a FIR filter, with impulse response $\mathbf{h} = \begin{bmatrix} h(1) & \dots & h(N) \end{bmatrix}^T$, followed by a biparametric regression function $g_k(\cdot, \mathbf{a})$, dependent on a parameter vector $\mathbf{a} = \begin{bmatrix} a(0) & a(1) \end{bmatrix}^T$ (see Fig. 2). Noise $v(n)$ was included to account for modeling and delineation errors [5]. The FIR filter describes the influence of a history of previous RR intervals on each *QT* measurement, while the regression function $g_k(\cdot, \mathbf{a})$ represents the relationship between the *QT* and *RR* intervals once the *QT* memory lag has been compensated for. The estimated output of the system was computed as: $\widehat{y}_{\mathrm{QT}}(n) = g(z_{\overline{\mathrm{RR}}}(n), \mathbf{a})$, where $z_{\overline{\mathrm{RR}}}(n) = \mathbf{h}^T \mathbf{x}_{\mathrm{RR}}(n)$, $\mathbf{x}_{\mathrm{RR}}(n) = \begin{bmatrix} x_{\mathrm{RR}}(n) & \dots & x_{\mathrm{RR}}(n-N+1) \end{bmatrix}^T$. The length N of the FIR filter was set to 150 samples, which corresponds to 150 seconds. A set of biparametric regression functions, spanning from a linear to a hyperbolic model, were considered for $g_k(\cdot, \mathbf{a})$, $k = 1, \dots, 10$, [6].

System identification was performed by minimizing the difference between the estimated output $\widehat{y}_{\mathrm{QT}}(n)$ and the *QT* series $y_{\mathrm{QT}}(n)$. Specifically, a regularized least square estimator was used to solve the optimization problem

$$\{\mathbf{h}^*, \mathbf{a}^*, k^*\} = \arg\{\min_{\mathbf{h},\mathbf{a},k}\} \left(\|\mathbf{y}_{\mathrm{QT}} - \widehat{\mathbf{y}}_{\mathrm{QT}}\|^2 + \|\mathbf{D}\mathbf{h}\|^2 \right)$$

subject to two constraints: $\sum_{i=1}^{N} h(i) = 1$ to be able to interpret this as a running mean RR and $h(i) \geq 0, i = 1, \dots, N$ since negative values will have no physiological sense. [7]. In the above equation, $\mathbf{D}$ is a regularization matrix that penalizes the fact that $\mathbf{h}$ deviates from having an exponential decay, as acknowledged in previous studies [5] and $\mathbf{y}_{\mathrm{QT}}$ and $\widehat{\mathbf{y}}_{\mathrm{QT}}$ are the signals expressed in vector notation.

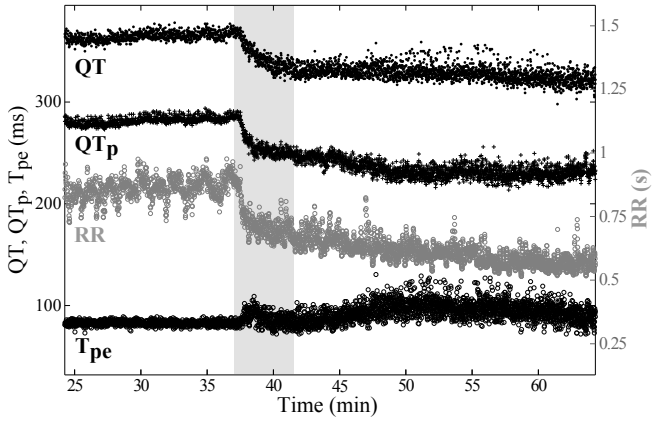

Fig. 1. Example of *QT*, QT_p and T_{pe} changes produced by an abrupt change in *RR* during the beginning of a TTT before HDBR, for a particular subject of the study. On the left, the temporal scale for *QT*, QT_p and T_{pe} series is shown in black, while on the right, the temporal scale for *RR* series is shown in gray. Gray band indicates the initial part of TTT selected for the analysis.

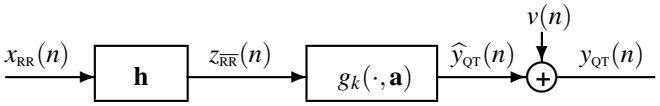

Fig. 2. Block diagram of the system used to model *QT* (or QT_p) to *RR* relationship.

To quantify how fast the *QT* interval responds to a change in HR, the parameter M_{90} was measured, representing the number of beats required for the *QT* to reach 90% of its adaptation (Fig. 3(a)). Parabolic log/log regression function ($g_3(\cdot, \mathbf{a})$) was fitting again (see Fig. 3(b)) to all cases but now considering the $\mathbf{h}$ identified for the optimum model ($\mathbf{h_{opt}}$ of the model with minimum regression residuum), independently of which was the optimal biparametric regression function:

$$\widehat{y}_{\mathrm{QT}}(n) = g_3(z_{\overline{\mathrm{RR}}}, \begin{bmatrix} a(0) & a(1) \end{bmatrix}^T) = a(0) z_{\overline{\mathrm{RR}}}(n)^{a(1)} \qquad (1)$$

where now $z_{\overline{\mathrm{RR}}}|_{\mathbf{h}=\mathbf{h}_{opt}}$ and $a(1)$ is further denoted as α representing the slope of the regression between *QT* and *RR* (in log terms).

III. Results

Figures 4 and 5 present the distribution of the indices M_{90} and α over the study population and the significance levels of the comparisons PRE versus R+0 and *QT* versus QT_p.

Comparing PRE versus R+0, in all subjects group together (G_{Short}+G_{Long}), a significant reduction in M_{90} was found using *QT* and in α using QT_p. Looking to the OTT duration based groups separately, using any of *QT* or QT_p, no

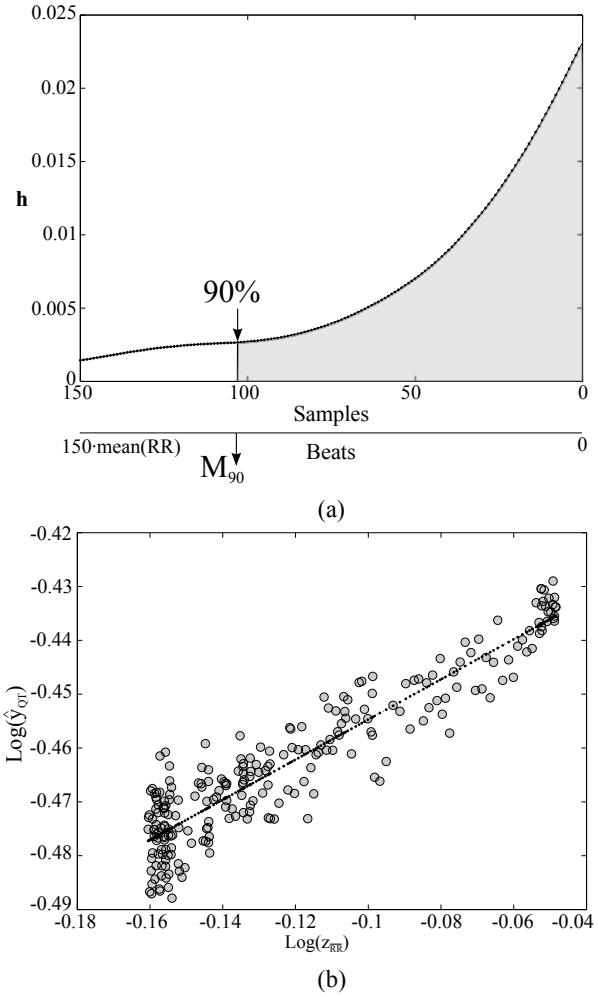

Fig. 3. Example of data analysis for the same subject whose series are shown in Fig. 1. (a) Impulse response **h** of the FIR filter, provides the weight distribution for QT memory on RR. M_{90} indicates number of beats for reaching 90% of the adaptation (gray area). (b) Dispersion graph for $z_{\overline{RR}}$ (after memory compensation) and QT, computed before HDBR. To compute α, a parabolic log/log regression function was used Eq. (1).

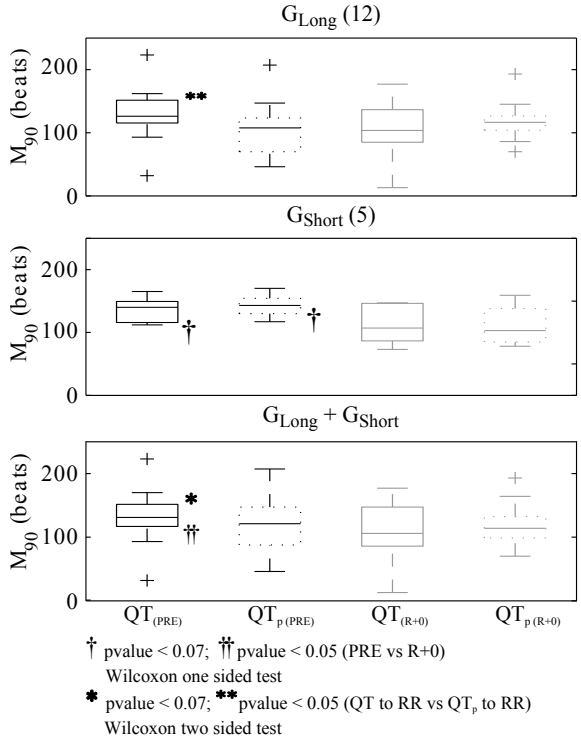

Fig. 4. Values of M_{90} in baseline recordings before and after HDBR for QT and QT_p adaptation to HR changes. () Indicates number of subjects in each group.

significant change in M_{90} was observed in G_{Long} while in G_{Short} a reduction in M_{90} was found (pvalue = 0.0625). For α, a very significant decrease was found in G_{Long} for QT_p to RR adaptation, but not for QT to RR, with no changes in G_{Short}. This could indicate different repolarization adaptation, affected in a different manner by the HDBR, according to the OTT duration. These results highlight the cardiac deconditioning produced by HDBR. Moreover they indicate that the final part of the repolarization (T_{pe} interval) is affected differently from the initial part, as QT and QT_p present different effects.

Comparing QT versus QT_p at PRE, significant differences in time lags were observed, being M_{90} shorter and $alpha$ higher for QT_p as compared to QT (Fig. 4 and 5), both for G_{Long} and for all subjects (G_{Short}+G_{Long}). At R+0, no differences were found in M_{90}, while for α differences were visible only in the G_{Short} group.

These results confirm the differences in QT and QT_p dependencies on HR, as affected by HDBR. As mentioned in Section I., QT interval contains all the electrical information of the ventricles, whereas QT_p is an incomplete measure of VR. Differences between them highlight variations in the T_{pe} interval, which are affected by HDBR, as illustrated in Fig. 6. Nevertheless, T wave morphology and duration may be affected by postural change provoked by TTT, producing a variation in the electrical heart vector (EHV). As T wave peak was computed using the median value of single lead delineation marks, an EHV change could affect T wave peak measurements. We additionally considered T wave peak location based on the derived vectorcardiogram (VCG), in order to compensate for EHV changes. The VCG was obtained using the inverse Dower transform and the T wave peak was detected as the time instant of the maximum of the T wave loop. We found out that the T_{pe} interval measured using this strategy behaves in the same way than using the median location. Thus, we can assume that the observed differences between QT and QT_p reflect a physiological variation in their HR dependencies attributable to the fact that QT contains VRD information not present in QT_p.

IV. Conclusions

Orthostatic intolerance is sometimes manifested with a presyncope producing a decompensation in the baroreflex system, which could interfere with the analysis performed in the present study. For that reason, we excluded all cases with OTT <4' and analyzed separately the subjects presenting short and long OTT. Our results indicate differences in the repolarization adaptation between groups, possibly related

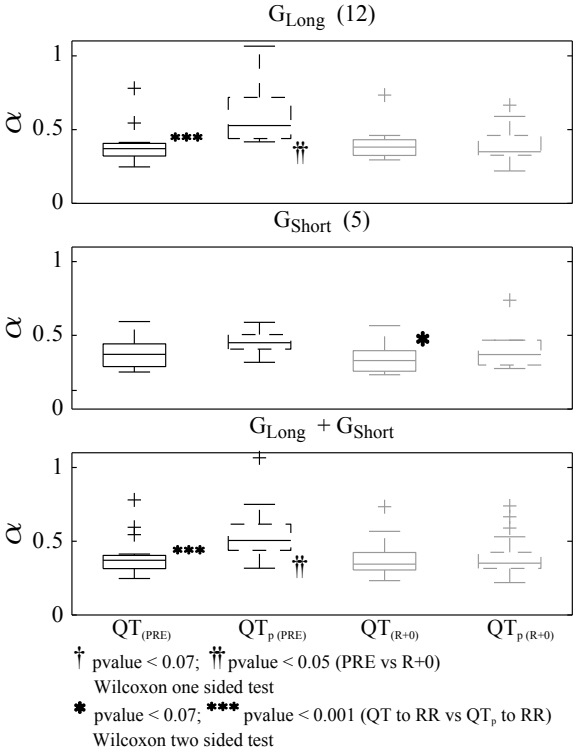

Fig. 5. Values of α in baseline recordings before and after HDBR for QT and QT_p adaptation to HR changes. () Indicates number of subjects in each group.

with inter-individual differences.

Considering all subjects together ($G_{Short} + G_{Long}$), both indices, M_{90} meaning the VR adaptation time, and α meaning the regression slope of VR to HR, showed differences between the two VR measures considered in the study, i.e. QT and QT_p at control conditions (PRE). However, those indices became indistinguishable after HDBR. We can summarize it as: $QT \not\Leftrightarrow QT_p$ at PRE, and $QT \Leftrightarrow QT_p$ at R+0.

VRD is related to heterogeneities in the action potential duration (APD) of the ventricular tissue. Pueyo et al. [9] reported that APD adapts to abrupt HR changes in two phases: a fast initial phase <30 seconds related with L-type calcium and potassium currents, followed by a slow phase >2 minutes produced mainly by intracellular sodium concentration dynamics among others. These two phases are observed in Fig. 1 for the QT and QT_p series measured in a subject performing TTT before HDBR. Once the subject has experimented HDBR for 5 days, the initial fast phase of adaptation seems to disappear, or at least is less pronounced, as illustrated in Fig. 6.

Sympathovagal response has been reported to be impaired after simulated microgravity by HDBR [10]. We hypothesize that this deconditioning in the autonomic nervous system could affect autonomic modulation of L-type calcium and potassium currents, and could lead to a decrease in the initial phase of APD adaptation to an abrupt HR acceleration. Those changes could in turn translate into alterations in the QT and QT_p adaptations, as observed in the recordings analyzed in the present study.

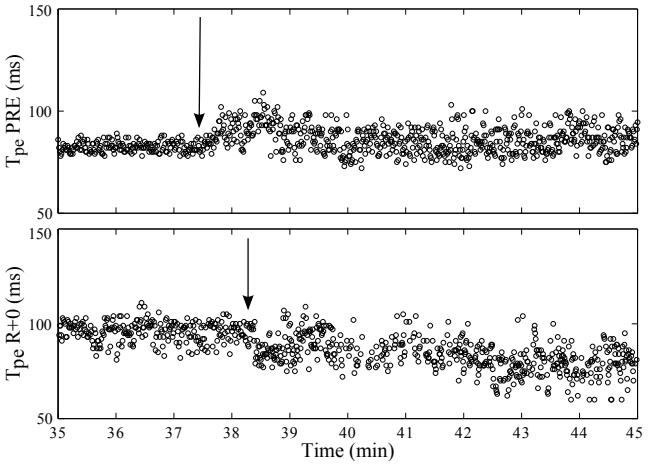

Fig. 6. T_{pe} series computed for the same subject illustrated in Fig. 1 and 3. Top panel: T_{pe} series before HDBR. Bottom panel: T_{pe} series after HDBR; TTT start point is marked with an arrow.

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