Influence of Simulated Microgravity by Head-Down-Bed-Resting on QT/RR Dynamics

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Abstract

There are evidences suggesting that spaceflight may be associated with increased susceptibility to ventricular dysrhythmias. To explore this hypothesis, five days -6° head-down bed rest (HDBR) was performed with the aim at testing the changes in QT/RR dynamics. Electrocardiogram signals (ECG) was acquired in 22 males during tilt-tests performed before and after HDBR. The dynamics of QT interval adaptation in response to upward and downward heart rate (HR) changes during the tilt test was evaluated modeling QT dependence on a history of previous RR intervals. The adaptation time of QT to abrupt changes in RR (t_{90}) was found reduced after HDBR, with no changes in the optimum regression residuum (r_{opt}) of the QT/RR dynamics. However, a dependence of the results to the width of the memory window considered was found. HDBR seems to induce variations in the phenomena by shortening the memory lag in QT/RR dependecy.

1. Introduction

It is well known that microgravity leads to cardiovascular deconditioning, manifested by post-spaceflight orthostatic intolerance and decreased exercise capacity. In addition, several episodes of dysrhythmias and conduction disorders have been repeatedly observed during space flight over the years [1]. Retrospective analysis of ECG data obtained in microgravity environment showed significant differences in cardiac conduction and repolarization between short- and long-duration space flights. Long duration space flight was found to prolong QTc interval, corrected by the Bazett's formula, thus increasing potentially arrhythmia susceptibility [2]. Several studies have demonstrated that the modulation of the autonomic nervous system (ANS) is different during microgravity and hypergravity periods in parabolic flight [3–5]. Due to those changes, not only the RR interval is expected to be altered, but also the beat-to-beat relationship between the QT and the RR interval, which is, to a great extent, under the control of the ANS. In a recently published report [6], it has been shown that QT interval is prolonged, even though not to pathological levels, during parabolic microgravity and, on the other hand, it is shortened during parabolic hypergravity.

An in-depth assessment of the cardiac adaptation to weightlessness is crucial for a better understanding of both cardiac physiology in space and appropriate design and testing of specific countermeasures. Nevertheless, few studies were performed to investigate the possible increased risk of cardiac dysrhythmias during spaceflight and no prospective studies on this matter have been conducted in the simulated microgravity environment. Ground-based studies represent an invaluable perspective to investigate human physiology during simulated microgravity conditions. Among them, the model of 6° Head-Down Bed Rest (HDBR) represents a unique opportunity for inducing and studying the effects of simulated prolonged exposure to microgravity on the cardiovascular system and for testing potential countermeasures.

We hypothesised that microgravity exposure could affect repolarization mechanisms, thus increasing the risk of arrhythmia susceptibility in astronauts. Accordingly, the aim of this study was to use the HDBR manouver to test if it induces alterations on the dynamics of QT/RR intervals, characterizing the QT interval adaptation lag to abrupt RR interval changes, by analyzing the ECG signal acquired during tilt test performed before and after a 5-day HDBR.

2. HDBR experimental protocol

Two short-term (5 days) bed rest campaigns were organized by the European Space Agency at the Institute of Space Medicine and Physiology (MEDES) in Toulouse, France, and at the German Aerospace Center (DLR) in Koln, Germany. In each campaign, subjects were enrolled in a cross-over design that involved a three times repetition of the HDBR, with enrollement in a control group or in a specific countermeasure group. Each repetition included 5 days of pre-bed rest (BCD-5, ..., BCD-1) for acclimatation into the facility, 5 days at -6 degrees HDBR (HDT0, ..., HDT5) and 5 days of post-bed rest recovery (R+0, ..., R+4) as illustrated in figure 1.

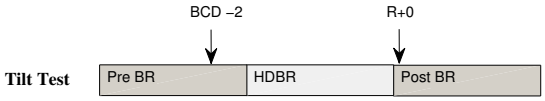

Figure 1. Head Down Bed Rest protocol acquisition for Tilt Tests recordings.

2.1. ECG data acquisition

The ECG signals analyzed in this study were acquired using a 12-lead Holter 24 hour high fidelity (1000 Hz sampling rate) digital recorder (H12+, Mortara Instrument Inc., Milwaukee, WI) during a Head-up Tilt with Low Body Negative Pressure orthostatic tolerance test (TILT/LBNP) performed at BCD-2 and R+0. Specifically, the TILT/LBNP protocol included an initial period of at least 15 minutes to reach stable conditions, followed by the head-up tilt at 80 degrees for 30 minutes. Then, an increasing LBNP was applied (additional 10 mmHg every 3 min). The test was interrupted once one of the stop criteria was reached (very low blood pressure, extreme tachycardia or clinical symptoms).

2.2. Population

A total of 22 male subjects were studied: 12 at MEDES mean age (32.6 $\pm$ 7), and 10 at DLR mean age (29.4 $\pm$ 5.9). All subjects had no previous history of cardiovascular disease, and had undergone a comprehensive medical 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. The ECG data analyzed in this study refers to repetition of the bed rest when each subject was included into the control group.

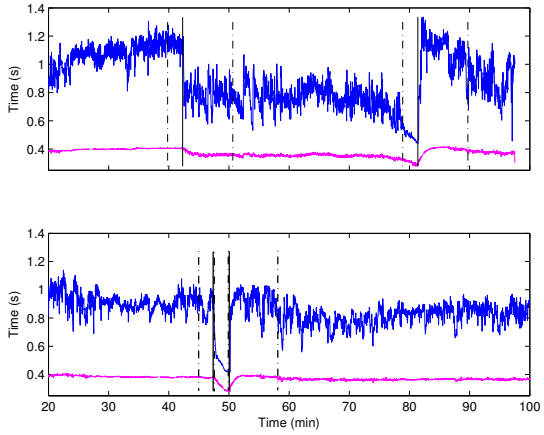

Figure 2. Example of the RR (in blue) and QT (in magenta) beat-to-beat series centered in the tilt test. Upper panel refers to BCD-2, while lower panel refers to R+0.

3. Methods

For RR and QT beat-to-beat measurements, 8 uncorrelated ECG leads (I, II, V1-V6 standard leads) were considered. Each lead was delineated using an automatic system and the 8 sets of marks were combined using post processing rules [7]. The beat-to-beat RR and QT series were extracted from those global marks and anomalous values of QT series were treated as outliers and excluded. Both series were interpolated at 1 Hz, and the resampled series were denoted by $x_{\text{RR}}(n)$ and $y_{\text{QT}}(n)$, respectively, where n is the sample index. Segments presenting upward and downward abrupt RR changes were identified manually and were visually checked during the tilt test protocol, see figure 2.

QT interval adaptation to RR changes was modeled using a system composed of a FIR filter, with impulse response $\mathbf{h} = \begin{bmatrix} h(1) & \dots & h(N) \end{bmatrix}^{\mathbf{T}}$, followed by a nonlinear biparametric regression function $g_k(\cdot, \mathbf{a})$, dependent on parameter vector $\mathbf{a} = \begin{bmatrix} a(0) & a(1) \end{bmatrix}^{\mathbf{T}}$ (see figure 3). Noise v(n) was included to account for modeling and delineation errors [8]. 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: $\widehat{y}_{\text{QT}}(n) = g(z_{\overline{\text{RR}}}(n), \mathbf{a})$, where $z_{\overline{\text{RR}}}(n) = \mathbf{h}^{\mathbf{T}} \mathbf{x}_{\text{RR}}(\mathbf{n})$, $\mathbf{x}_{\text{RR}}(\mathbf{n}) = \begin{bmatrix} x_{\text{RR}}(n) & \dots & x_{\text{RR}}(n-N+1) \end{bmatrix}^{\mathbf{T}}$. The length N of the FIR filter was set either to 300 or 150 samples, which corresponds to 300 or 150 seconds, respectively. These two approaches were applied due to the shorter length of the Tilt tests in R+0 recordings, which precludes

the analysis of 300 second filter windows for some of the recordings. Ten different biparametric regression functions, spanning from a linear to a hyperbolic model, were considered for $g_k(\cdot, \mathbf{a})$, $k = 1, \ldots, 10$.

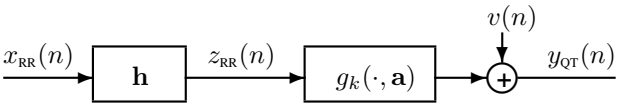

Figure 3. Block diagram of the system used to model the relationship between QT and RR, composed of a FIR filter followed by a nonlinear regression function.

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

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

subject to two constraints: $\sum_{i=1}^{N} h(i) = 1$ and $h(i) \geq 0, i = 1, \ldots, N$ [9]. In the above equation, $\mathbf{D}$ is a regularization matrix that penalizes the fact that $\mathbf{h}$ deviates from having an exponential decay, β is the regularization parameter set to 1 in this study, and $\mathbf{y}_{QT}$ and $\widehat{\mathbf{y}}_{QT}$ are the signals expressed in vector notation [10].

The time required for QT to complete 90% of its rate adaptation, denoted by t_{90}, was computed as:

$$t_{90} = \frac{1}{f_s} \arg\max_n (c(n) > 0.1), \text{ where } c(n) = \sum_{i=n}^{N} h(i).$$

Additionally, a measure of the optimum regression residuum, denoted by r_{opt}, was computed as the root mean square of the vector difference $\mathbf{y}_{QT} - \widehat{\mathbf{y}}_{QT}$.

4. Results

Data at BCD-2 and R+0 when the volunteers were assigned to the control group were available in all participating subjects. The analysis of the QT/RR dynamics with the described methodology was feasible in everyone. Table 1 shows the results of the t_{90} parameter, computed separately for the downward and upward RR changes of the tilt test, at BCD-2 and R+0 calculated using both a 150 and a 300 maximum memory beats, see figure 4. Interestingly, for both abrupt shortening and lengthening of the RR, t_{90}^{150} showed a significant decrease at R+0, compared to BCD-2. On the contrary, t_{90}^{300} did not evidence any significant change potentially induced by the HDBR condition.

Table 2 shows the corresponding results of the r_{opt} parameter. The observed values were small, thus demonstrating the goodness of the performed identification and fitting process but no significant change was observed between BCD-2 and R+0, both with 150 and 300 maximum memory beats.

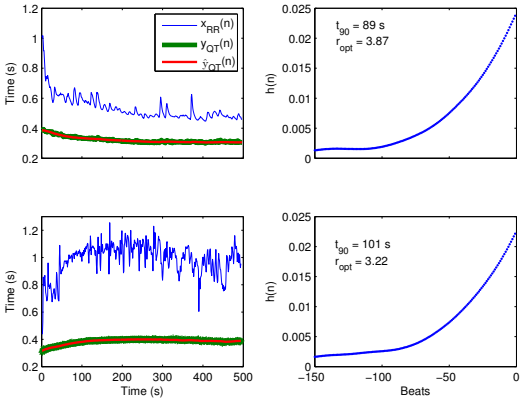

Figure 4. (Left) Example of QT modeling (red) overprint with original QT series (green) (Upper panel in downwards RR change and lower panel in upwards RR change). (Right) Correspondent $h(n)$ in each case.

Table 1. Adaptation time (in seconds) of the QT to RR interval for up and down sudden RR changes for different filter lengths N = 150 and N = 300

RR change	t_{90}^{150} BCD-2	t_{90}^{150} R+0	t_{90}^{300} BCD-2	t_{90}^{300} R+0
Down	93 ± 24	$72^{\dagger} \pm 16$	99 ± 34	85 ± 24
Up	96 ± 27	$85^{\dagger} \pm 24$	102 ± 34	93 ± 36

† p<0.05 BCD-2 vs R+0 (paired t-test)

5. Discussion and conclusions

By comparing the adaptation of QT to abrupt changes in heart rate induced by tilt test we found that bed rest seems to induce changes in this adaptation phenomenon, in the direction of shortening the time window in which the past RR are found to contribute to the actual QT value. This was observed both with the increase in heart rate when the head-up tilt at 80 degrees position was reached, and when the heart rate was decreased in association with the termination of the test.

However, a dependence of these results from the setting of the memory beats considered in the FIR filter was ob-

Table 2. r_{opt} of the QT/RR adaptation model for up and down sudden RR changes for different filter lengths N = 150 and N = 300.

RR change	r_{opt}^{150} BCD-2	r_{opt}^{150} R+0	r_{opt}^{300} BCD-2	r_{opt}^{300} R+0
Down	4.6 ± 1	6 ± 4	4.6 ± 1	6 ± 4
Up	4.9 ± 2	4.8 ± 2	4.9 ± 2	4.7 ± 1

served. Possible explanations are related to the fact that the applied protocol includes activation of LBNP (-10 mmHg steps every 3 min) at 30 min of head-up tilt at 80 degrees position. This situation has been often associated with the BCD-2 test. In these cases, the utilization of a 300 beats of maximum memory leads to include in the memory window with respect to RR increasing period, a decreasing RR period, with different LBNP steps, just before the abrupt increase in RR. Conversely, at R+0 the tilt test duration is considerably reduced, thus not including LBNP activation. With this experimental setting, we concluded that the 150 memory beats maximum width could allow a better comparison of the physiologic response of each subject, independently of the shortening in the tilt-test duration induced by the cardiac deconditioning associated with the HDBR.

The range of results we found for t_{90}^{150} are similar to those observed in [10], in which QT adaptation in normal volunteers was studied during postural changes (t_{90}^{300} found between 35-65 sec); also, our findings are in agreement with [10] where we concluded that larger changes in RR could provoke longer QT adaptation time. Conversely, when survivors of acute myocardial infarction were studied [8], a mean of t_{90}^{300} equal to 156 sec was found, with higher values found in the amiodarone than the placebo group and associated to increased arrhythmia risk, conversely to what we found here, assuming the HDBR induce risk. Also, r_{opt} was found as the strongest index to separate survivors (lower values) from victims (higher values) in the amiodarone groups. However, in both studies the analysis was conducted based on changes in heart rate of lesser amplitude compared to that provoked by tilt, so that a direct comparison of the results with those obtained in this study is not adequate. Further observations on larger HDBR study population, or by comparing the results before and after longer HDBR (21 days), would allow to better highlight the effect provoked by simulated microgravity on the adaptation of QT, thus delineating if those are related to a potential increase or decrease of risk of arrhythmia.

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