Microgravity Exposure Alters Sympathetic Modulation of Ventricular Repolarization Quantified From the ECG via Periodic Repolarization Dynamics

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Abstract

Prolonged microgravity exposure induces cardiovascular deconditioning, including orthostatic intolerance due to dysregulation of autonomic modulation of the cardiovascular system. Recent studies suggest that sympathetic modulation of ventricular repolarization can be assessed by measuring the index of Periodic Repolarization Dynamics (PRD), which quantifies low-frequency oscillations in ECG T-waves. In this study PRD was analyzed in ECGs from 22 volunteers at rest and during orthostatic Tilt-Table Test (TTT) performed before and after 60-day Head-Down (-6°) Bed Rest (HDBR) experiments to simulate microgravity effects. A very notable increase was found in resting PRD values measured at POST-HDBR with respect to PRE-HDBR: 2.70[3.21] deg^2 vs 2.05[1.18] deg^2 (median[IQR]). When PRD was evaluated during TTT, an even more remarkable increase was found in POST-HDBR with respect to PRE-HDBR: 4.25[6.46] deg^2 vs 2.39[3.32] deg^2. A jump-based countermeasure was only able to counteract microgravity-induced effects in response to TTT but not at baseline. In conclusion, prolonged exposure to simulated microgravity induces changes in ventricular repolarization that are measurable by PRD and are more manifested when assessed following sympathetic provocation. A jump-based countermeasure is only partially effective in counteracting such effects.

1. Introduction

Microgravity exposure induces a number of effects on the human body, including muscular, cardiac and bone-related [1]. Orthostatic intolerance is one of the most relevant cardiovascular issues experienced by astronauts upon return to the Earth following a space mission due to cardiac deconditioning, with some astronauts not even being able to remain standing upright after landing. Both the sympathetic and parasympathetic branches of the autonomic nervous system are involved in orthostatic regulation [2]. The orthostatic Tilt-Table Test (TTT) is a procedure commonly utilized to assess autonomic function.

The index of Periodic Repolarization Dynamics (PRD) has been recently proposed to assess sympathetically-modulated ventricular repolarization by measuring low-frequency ($\leq$ 0.1 Hz) oscillations in the T-wave of the body-surface electrocardiogram (ECG) [3]. Studies assessing microgravity effects on the heart's electrical activity are limited, with major findings indicating prolonged cardiac conduction and repolarization [4] in association with long duration spaceflight. Head-down bed rest (HDBR) is one of the ground-based models utilized to simulate microgravity effects on the human body [5]. ECG signals recorded under such model are analyzed in this study to evaluate microgravity effects on ventricular repolarization, which remain, to a high extent, unknown [6]. Specifically, our aim is to quantify the PRD index before and after microgravity exposure, both at baseline and following sympathetic provocation induced by TTT.

2. Methods

2.1. Study population

22 male volunteers (29$\pm$6 years, 181$\pm$5 cm, 77$\pm$7 kg) were enrolled in a 60-day $-6°$ HDBR experiment conducted in the :envihab facility of the Institute of Aerospace Medicine at the German Aerospace Center-DLR (Cologne, Germany) as part of the European Space Agency (ESA) bed rest studies. The volunteers were randomly distributed into two groups: a countermeasure group (JUMP), who exercised on a sledge jump system [7] during the HDBR time period; a control group (CTRL), not performing any exercise. All subjects underwent a prior comprehensive

 ISSN: 2325-887X DOI: 10.22489/CinC.2018.358

medical examination during the selection process and provided written, informed consent to participate in the study, which was approved by the Ethical Committee for Human Research at the host institution.

The whole campaign consisted of 15 days of pre-bed rest (BDC-15 to BDC-1), 60 days of HDBR (HDT1 to HDT60) and 15 days of post-bed rest recovery (R+0 to R+14), as illustrated in Figure 1. Each volunteer underwent two TTT: the first one, two days before the start of the HDBR period (BCD-2); the second one, just after completing HDBR (R+0). Each TTT had a maximal duration of 15 minutes with the subject tilted head-up to an angle of 80°.

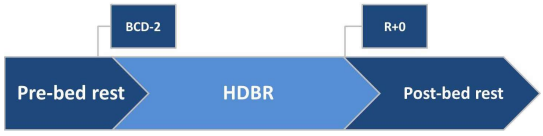

Figure 1. Phases of the long-term microgravity campaign, with indication of the days when volunteers underwent TTT.

12-lead ECG signals acquired with a sampling frequency of 1000 Hz (Mortara Instrument, Inc., Milwaukee, WI, USA) were available for this study. A 5-minute interval prior to TTT as well as the first 5 minutes at the beginning and the last 5 minutes at the end of TTT were analyzed. In very few cases, TTT duration was less than 5 minutes and, in those cases, the whole TTT interval was analyzed.

2.2. Signal Preprocessing

Noise and artifacts were removed by using a 50 Hz notch filter, a 40 Hz Finite Impulse Response filter and cubic splines interpolation. The filtered signals were input to a wavelet-based single-lead automatic system for QRS detection and ECG wave delineation, whose outputs were combined with rules to obtain multi-lead delineation [8].

2.3. Periodic Repolarization Dynamics

The PRD index was calculated following these steps [3]:
1. The 12-lead ECG was converted into 3 orthogonal leads X, Y, Z by using the inverse Dower matrix.
2. T-wave onsets and ends were identified as described in 2.2. In some beats the T-wave onset (T_{on}) could not be identified. For each of those beats, T_{on} was calculated based on T_{on} locations with respect to QRS calculated for adjacent beats. Specifically, T_{on} was located at the time point distanced from the QRS fiducial point as much as the median interval between the QRS and T_{on} marks of 30 beats around it.
3. The Cartesian coordinates (X, Y, Z) were converted into time series of spherical coordinates. Specifically, for each time point t, the corresponding XYZ vector was transformed into the elevation and azimut angles (θ_t, ϕ_t) and the vector magnitude (r_t).
4. Two angles were defined to describe the weight-averaged direction of repolarization. These angles were called weight-averaged azimuth (WAA) and weight-averaged elevation (WAE) and were calculated as follows:

$$WAA = \frac{\sum_{t=T_{on}}^{T_{end}} (r_t \cdot \phi_t)}{\sum_{t=T_{on}}^{T_{end}} r_t} \quad (1)$$

$$WAE = \frac{\sum_{t=T_{on}}^{T_{end}} (r_t \cdot \theta_t)}{\sum_{t=T_{on}}^{T_{end}} r_t} \quad (2)$$

where T_{on} and T_{end} denote the T-wave onset and end, respectively.
5. The angle dT° between successive repolarization vectors was calculated using the dot product, as follows:

$$\begin{aligned} dT^\circ = \text{acos}[&\sin(WAE_1) \times \cos(WAA_1) \times \sin(WAE_2) \times \cos(WAA_2) \\ &+ \cos(WAE_1) \times \cos(WAE_2) \\ &+ \sin(WAE_1) \times \sin(WAA_1) \times \sin(WAE_2) \times \sin(WAA_2)] \end{aligned} \quad (3)$$

where subindexes 1 and 2 refer to consecutive T-waves.
6. The dT° time series was filtered by using a 10th-order median filter to attenuate abrupt variations.
7. Linear interpolation at 2 Hz and 30-sample moving average were applied to remove artifacts.
8. Continuous wavelet transformation using a 4th-order Gaussian wavelet was used to quantify the periodic components of dT°. Coefficients for each scale at each time point were obtained and an average wavelet coefficient was computed for each scale.
9. Scales (a) were converted to pseudo-frequencies (F_a) according to the following equation:

$$F_a = \frac{F_c}{a \cdot \Delta} \quad (4)$$

where F_c is the center frequency of the mother wavelet and Δ denotes the sampling period.
10. PRD was defined as the average wavelet coefficient in the frequency range between 0.025 and 0.1 Hz.

2.4. Statistical analysis

The Mann-Whitney U test (or Wilcoxon rank-sum test) was used for comparison of independent samples, as when comparing JUMP vs CTRL subgroups. Wilcoxon signed-rank test was used for comparison of paired samples, as when comparing changes induced by HDBR or by TTT in a given group of subjects. For all tests, the null hypothesis was rejected if $p \leq 0.05$.

3. Results and Discussion

3.1. PRD reflects periodic variations in ventricular repolarization

Figure 2 presents the time series of dT° (left panel) and frequency spectra (right panel, represented in terms of wavelet coefficients) corresponding to two different volunteers shown in blue and red (one at PRE-HDBR and the other one at POST-HDBR), respectively. As can be observed from the figure, the case shown in blue corresponds to an ECG recording with low-frequency dT° oscillations, which translates into a low value of the PRD index. On the other hand, the case shown in red presents larger low-frequency oscillations in dT° and has an associated PRD index of considerably higher value. In [3] PRD was shown to be tightly regulated by the sympathetic nervous system. The examples shown in Figure 2 would, thus, correspond to cases of weak and strong sympathetically-modulated ventricular repolarization.

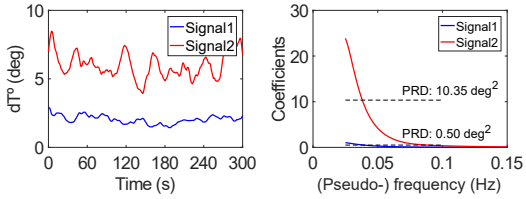

Figure 2. Examples of dT° (left panel) and frequency spectra (right panel) for two volunteers of the study, one at PRE and the other at POST, presenting notably different magnitudes of low-frequency periodic oscillations in ventricular repolarization. Their associated PRD values are indicated in the right panel.

3.2. Effect on PRD because of tilt test

For each volunteer, baseline (prior to TTT) as well as the beginning and end of the TTT were analyzed, for both before HDBR (PRE) and after HDBR (POST). Changes in cardiac autonomic modulation induced by TTT led to general increases in PRD, both as measured at PRE (Figure 3, left panel) and at POST (Figure 3, right panel). As shown in the figure, the change in PRD was more marked when evaluated at the beginning than at the end of the TTT. The observed increases in PRD associated with TTT, particularly during the first part of this test, are in line with the fact that PRD is enhanced in response to sympathetic stimulus [3]. An increase in low-frequency oscillations of ventricular repolarization duration has additionally been shown to occur in response to sympathetic activation and mechanisms underlying such oscillations have been postulated, all of which would serve to support the results found in this study [9, 10].

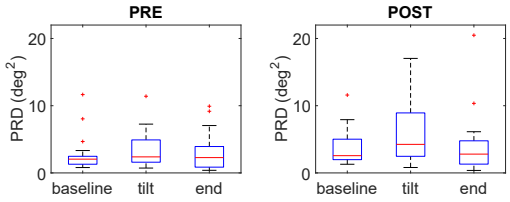

Figure 3. Boxplots of PRD values at PRE (left panel) and POST (right panel) HDBR, evaluated at baseline and during the beginning and end of TTT.

3.3. Effect on PRD due to microgravity

The effect of microgravity exposure on ventricular repolarization was evaluated at each of the baseline and beginning and end of TTT phases. At baseline conditions, PRD was remarkably increased at POST with respect to PRE for most of the subjects in the study, as can be observed in Figure 4, left panel. In the overall population, PRD changed from 2.05 [1.18] deg^2 (median[IQR]) at PRE to 2.70 [3.21] deg^2 at POST. Similarly, PRD was notably augmented at POST with respect to PRE both when evaluated at the beginning and at the end of TTT (Figure 4, middle and right panels), with such augmentation being even more manifested than in the case of baseline conditions. Specifically PRD changed from 2.39 [3.32] deg^2 at PRE to 4.25 [6.46] deg^2 at POST when evaluated at the beginning of TTT and from 2.28 [3.07] deg^2 at PRE to 2.80 [3.47] deg^2 at POST at the end of TTT. All these presented results confirm that microgravity induces relevant alterations in the cardiovascular system in general, and in ventricular repolarization in particular [5,6], with such alterations being magnified if evaluated under conditions enhancing sympathetic nervous system activity.

3.4. Effect due to countermeasure

The effectiveness of the jump-based countermeasure was evaluated by comparing PRD values at PRE and POST in each of the CTRL and JUMP subgroups. PRD increased, even if not significantly, at POST with respect to PRE in both subgroups (2.41 [3.77] deg^2 vs 1.99 [2.02] deg^2 for CTRL and 2.83 [2.63] deg^2 vs 1.93 [1.16] deg^2 for JUMP) when evaluated at baseline conditions (Figure 5). When PRD was measured at the end of the tilt test, significantly higher PRD values were observed at POST for the CTRL subgroup,(3.90 [3.11] deg^2 vs 1.80 [2.57] deg^2) while a decrease to baseline values was observed in the JUMP subgroup. Consequently, the applied countermeasure was only able to partially reverse the microgravity-induced effects on ventricular repolarization, as it atten-

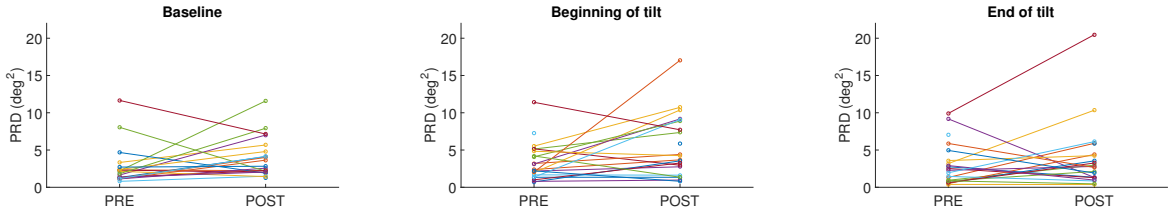

Figure 4. Individual PRD responses to HDBR evaluated at baseline (left panel) and at the beginning (middle panel) and end (right panel) of TTT.

uated its effects in response to TTT but was not able to counteract them at baseline. This is in agreement with previous studies that have assessed the impact of this countermeasure on other cardiovascular indices [7]. This type of exercise-based countermeasure might be more efficient if combined with other countermeasures, like for instance those based on dietary supplements, and altogether might reduce adverse cardiac microgravity-induced effects.

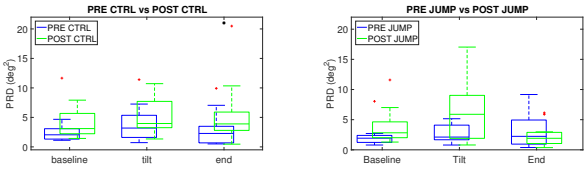

Figure 5. PRD values (median $\pm$ IQR) at PRE and POST separately measured for CTRL subgroup (left panel) and JUMP subgroup (right panel) at baseline, beginning of TTT and end of TTT.

4. Conclusions

The major findings of this study are: (a) The PRD algorithm is robust enough to measure repolarization variations in response to autonomic provocation; even during a long exposure microgravity; b) Microgravity exposure alters autonomic modulation of ventricular repolarization, as quantified from the PRD index; c) TTT induces notable increases in PRD both before and after simulated microgravity; and d) A jump-based countermeasure is not able to completely prevent changes in ventricular repolarization due to long-term microgravity exposure simulation.

Acknowledgements

This work was supported by projects ERC-2014-StG 638284 (ERC), DPI2016-75458-R (MINECO), European Social Fund (EU) and Aragón Government through BSICoS group (T39_17R). We also acknowledge the support of the Italian Space Agency (project QT-Bed, PI and recipient EG Caiani).

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