Effect of Simulated Microgravity by Head-Down Bed Rest on T Wave Alternans

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Abstract

Reports of ventricular arrhythmias during spaceflights raise the question of whether microgravity increases sudden cardiac death risk. Our aim in this work was to study changes in T-wave alternans (TWA) during VO_2max stress tests before and after five days of -6° head-down bed rest (HDBR) simulating exposure to microgravity. Two HDBR campaigns were organized by the European Space Agency in MEDES (Toulouse, France) and DLR (Koln, Germany). High-resolution ECG signal was recorded in 19 male volunteers during VO_2max tests by bicycle exercise stress, the day before the beginning of HDBR (pre) and within 26 hours after the end of HDBR (post). ECG was analyzed for multilead TWA detection. In the MEDES campaign, 4 subjects at pre while 6 at post-HDBR presented TWA. In the DLR campaign, TWA was detected in all subjects both in pre and post-HDBR. Various TWA features were compared, but only the heart rate at the onset of TWA episodes from the beginning of the VO_2max test resulted in significant differences between pre and post, being always higher than 110 beats/min.

1. Introduction

It is well known that microgravity leads to cardiovascular deconditioning, as evidenced by post-spaceflight orthostatic intolerance and decreased exercise capacity. Several episodes of cardiac arrhythmias and conduction disorders during spaceflight have been reported in the literature, such us in Gemini and Apollo missions [1, 2]. In more recent studies, it was reported that long duration spaceflights lead to the prolongation of the QTc interval, thus increasing potential arrhythmia susceptibility [3]. For this reason, changes in ventricular repolarization during exposure to microgravity are considered of great interest. However, while there is some evidence suggesting that spaceflight may be associated with an increased susceptibility to ventricular arrhythmias, the cause/effect of this phenomenon has not yet been clarified.

T-wave alternans (TWA) is a consistent beat-to-beat alternation in the amplitude or morphology of the ST segment and/or the T wave, that reflects temporal and spatial heterogeneity of repolarization. It is presently regarded as a noninvasive risk marker for predicting sudden cardiac death and ventricular vulnerability [4].

Ground-based studies represent an invaluable perspective to investigate human physiology during simulated microgravity conditions. The Head-Down Bed Rest (HDBR) test represents an opportunity for inducing and studying the effects on the cardiovascular system of prolonged exposure to simulated microgravity.

Our hypothesis in this work was that simulated microgravity induces changes in electrical repolarization which may increase the susceptibility to arrhythmias and therefore may be manifested by an increase in TWA. The main goal of this study was to measure and analyze changes in TWA during VO_2max stress test in a group of 19 healthy volunteers undergoing five-day -6° HDBR simulating exposure of the cardiovascular system to microgravity.

2. Materials

2.1. HDBR experimental protocol

Two short-term HDBR campaigns were organized by the European Space Agency (ESA) at the Institute of Space Medicine and Physiology (MEDES) in Toulouse, France, and at the German Aerospace Center (DLR) in Koln, Germany. During each campaign, subjects were placed on a bed with a 6° negative tilt (HDBR) for a continuous period of five days. The process was repeated three times for each subject in a cross-over design. Two countermeasures (exercise and centrifuge) were applied in two cases and no countermeasure was applied in one case (control case). Each test included 5 days of pre-bed rest (BCD-5, ..., BCD-1), 5 days of -6° HDBR (HDT1, ... , HDT5) and 5 days of post-bed rest recovery (R+0, ... , R+4), as illustrated in Figure 1.

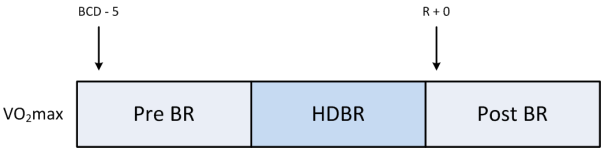

Figure 1. Head-Down Bed Rest protocol acquisition for VO_2max recordings. BCD−5 indicates the acquisition of pre-HDBR recordings and R+0 the same for post-recordings, going from 5–6 hours after the end of the HDBR in MEDES up to 26h in DLR.

2.2. ECG data

Only signals corresponding to control cases were selected for the study. That is, from each subject we selected the pair of pre-HDBR and post-HDBR signals with no counter-measures. Therefore, the study dataset consisted of a total of 38 ECG signals from 19 healthy subjects (11 at MEDES and 8 at DLR). All volunteers (age range 21–43 years) had undergone a comprehensive medical examination during the selection process and provided written informed consent to participate in the study, approved by the respective Ethical Committee for Human Research at the hosting institutions.

ECG signals were acquired using a high-resolution (sampling frequency of 1000 Hz) 12-lead 24-hours Holter digital recorder (H12+, Mortara Instrument Inc., Milwaukee, WI) during VO_2max test by bicycle exercise stress, at the BCD-5 day and at R+0 (within 5 – 6 hours after the end of HDBR in MEDES and within 26 hours in DLR).

Based on max VO_2 quantified during recruitment, the protocol for the VO_2max test was defined. After 5 minutes of baseline conditions, workload was increased to 25% of the maximum workload, and it was increased by 25% after each 5 min. After 15 min, additional 25 W/min was applied up to exhaustion. The test ended with a 5-min recovery stage.

3. Methods

Preprocessing of ECG recordings included QRS detection and labeling using a wavelet-based ECG delineator that combines the set of marks obtained after delineating each ECG lead and produces an unique set of marks for all leads using post processing rules [5]. Baseline wander was removed in each lead with a cubic splines interpolation technique. The frequency content of TWA is located below 15 Hz, so the ECG signal was low-pass filtered (cut-off frequency of 15 Hz) and downsampled to a new sampling frequency, Fs = 30 Hz, to remove offband noise.

Subsequently, we used Periodic Component Analysis (πCA, see next section for a description) in two different stages. First, πCA analysis with a period of 1 beat was used to remove non-periodic components in the PQRS complex (πCA-1). Then, a multilead method based on applying πCA with a period of 2 beats was combined with the Laplacian Likelihood Ratio method (LLRM) for TWA analysis, as we proposed in [6]. These πCA-based stages were applied to a linearly independent set of 8 leads (standard lead V1-V6, I and II), using a sliding 64-beat signal window. The multilead TWA method provides detection of TWA episodes as well as amplitude estimation in the original lead set. Figure 2 shows an scheme of the analysis performed in this work.

Signal transformation with πCA. The πCA technique searches for the optimal linear combination of the available leads in the ECG signal, arranged as columns of the matrix signal $\mathbf{X}$, which maximizes the desired periodicity in the combined lead. For TWA analysis, we are interested in combining the leads in such a way that the 2-beat periodicity (TWA periodicity) is maximized in the resulting signal, $\mathbf{y} = \mathbf{w^T X}$. The desired transformation must minimize the following residual measure of periodicity (m beats period):

$$\epsilon(\mathbf{w}, m) = \frac{\sum_{k=0}^{K-1} \|\mathbf{y}_{k+m} - \mathbf{y}_k\|^2}{\sum_{k=0}^{K-1} \|\mathbf{y}_k\|^2} \quad (1)$$

As it has been shown in [7], the optimal combination is given by solving a generalized eigenvalue problem of the matrix pair ($\mathbf{A_X}(m)$,$\mathbf{R_X}$), where $\mathbf{R_X}$ is the spatial correlation matrix of $\mathbf{X}$, defined as:

$$\mathbf{R_X} = \frac{1}{(K-1)N} \mathbf{X X^T} \quad (2)$$

with K the number of beats in the analysis window and N the number of samples of each learning segment.

In the same way, we defined $\mathbf{A_X}(m)$, the analogous spatial correlation matrix of the non-periodic components ($\mathbf{X}^{(m)} - \mathbf{X}$), where ($\mathbf{X}^{(m)}$ is the equivalent of $\mathbf{X}$) after sliding the analysis window m beats forward.

The weight $\mathbf{w}$ that minimizes (1) is given by the generalized eigenvector corresponding to the smallest generalized eigenvalue. In this way, the transformation $\mathbf{Y} = \mathbf{\Psi^T X}$, (matrix $\mathbf{\Psi}$ chosen as the generalized eigenvector matrix of ($\mathbf{A_X}(m)$,$\mathbf{R_X}$)), projects the most periodic component into the first row of $\mathbf{Y}$. Note that the optimal combination was computed for each segment of $K = 64$ beats, as it depends on how the alternant components and noise are distributed within the ECG leads.

Filtering of non-periodic components (πCA-1): In each beat, an interval of 200 ms, corresponding to the P-wave together with the QRS complex, was selected. Prior to the πCA analysis for TWA detection in the ST-T complex, another πCA analysis (πCA-1), with weight estimated in the P-wave together with the QRS complex and applied to the whole beat, was carried out in order to remove components which are not beat-to-beat periodic in the P-QRS segment of the ECG, since they can interfere

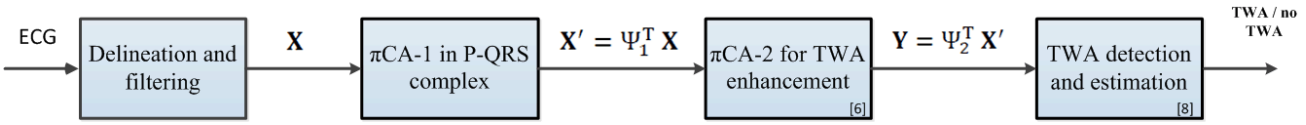

Figure 2. Scheme of the multilead TWA analysis combining πCA and the Laplacian Likelihood Ratio method.

with posterior TWA detection in the ST-T complex, especially if this noise has some 2-beat periodic components, making TWA analysis unreliable. Considering all generalized eigenvectors of this problem, we defined a linear transformation from the 8 original leads (V1-V6, I, II) to 8 transformed leads (T'1 ... T'8) which maximizes the 1-beat periodicity in the combined lead. Non-periodic components, if present, are mostly projected into the last transformed lead. That is why only the first 7th transformed leads are introduced in the second πCA analysis (πCA-2) for detecting the TWA in the ST-T segment as in [6].

πCA-2 transformation: After non-periodic components have been filtered, an interval of 320 ms from the fiducial point of the QRS complex was selected in each beat, corresponding to the ST-T segment. In this case we defined another optimal linear transformation based on πCA from the 7 transformed leads (T'1 ... T'7) to 7 new transformed leads (T1 ... T7) where the 2-beat periodicity was maximized. In this case, TWA, if present, is mostly projected into the first transformed lead T1.

TWA detection and estimation. It has been previously shown that the analysis of the πCA-transformed leads allows the detection of TWA episodes embedded in noise, which remain undetectable when they are analyzed in the original leads [6]. After πCA transformation, the LLRM [8] was applied to detect and estimate TWA in each transformed lead.

TWA was considered to be present in the analyzed segment if the generalized likelihood ratio test (GRLT) passed a threshold in any of the transformed leads. The detection threshold γ was set so that the probability of false alarm (P_{FA}) was 0.05 (to do so, γ was set as the 95% of the GLRT values of all MEDES' volunteers during the 5 minutes previous to the start of the VO_2max test in pre-HDBR records, which was considered to be a TWA-free control period). To avoid spurious detections, detected episodes with a duration shorter than 32 beats were not considered as reliable, and thus were discarded.

In segments where TWA was detected, the TWA-waveform (that is, the median difference between even and odd beats) was estimated using the maximum likelihood estimator for Laplacian noise [8]. The multilead TWA amplitude was defined as the RMS value of the estimated waveform. When no TWA was detected, the amplitude was considered to be zero.

4. Results

In a first analysis, TWA was detected in all volunteers from DLR campaign (in both, pre- and post-HDBR recordings) with an onset heart rate of 150 beats/min. Such consistency in the onset heart rate suggested the influence of external factors, possibly of a mechanical nature, such as the pedaling cadence. Examining the VO_2max test protocol, we could check that in DLR subjects were asked to keep a cadence of 75 rpm, which corresponds to the TWA frequency at a heart rate of 150 bpm, and it was possibly causing an interference in the ECG signal. In the MEDES campaign, the pedaling frequency was set to be > 70 rpm.

To avoid those interferences of the pedaling cadence with the TWA frequency, the analysis was limited to heart rates between 90 beats/min and the 95% of twice the minimum pedaling cadence (133 beats/min in MEDES and 142.5 beats/min in DLR).

In this second analysis, TWA episodes were detected in 4 out of 11 subjects at BCD-5 in MEDES (36.3%) while this number increased up to 6 in post-HDBR records (45%). No subject at DLR campaign presented TWA at the analyzed heart rates. Different TWA features between pre- and post- recordings were compared (see Table 1), but only the heart rate at the onset of TWA episodes resulted in statistically significant differences. Onset time of episodes, maximum TWA amplitude and duration of TWA episodes did not show any significant change after the HDBR. Results are shown in Table 1.

5. Discussion and conclusions

In this work, we have studied the prevalence and changes in TWA between before and after five-day -6° HDBR, performing TWA analysis and comparing several TWA features. In the DLR campaign, results indicated that there was a clear interference with the pedaling cadence (75rpm), and mechanical alternant components were induced at the heart rate of 150 beats/min, making physiological TWA detection unreliable at those heart rates.

For this work, we used the VO_2max tests performed before and after the HDBR. The protocols of these tests were not specific to detect TWA, and the pedaling rates during the test limited the range of heart rates where TWA could be reliably measured. As in [9, 10], this cadence interference can be avoided by asking the patients to change the pedaling cadence depending on the heart rate.

Subject	onset (min)		HR onset (beats/min)		max amplitude (μV)		duration (sec)	
ID	BCD-5	R+0	BCD-5	R+0	BCD-5	R+0	BCD-5	R+0
A	7.4	8.4	133	129	57.1	80.3	10.2	83.0
B	12.4	11.5	126	125	110.0	36.6	162.0	16.3
C	-	4.6	-	120	0	34.7	0	76.7
D	-	4.7	-	94	0	13.5	0	62.0
E	10.0	8.8	126	121	37.5	43.2	21.8	62.2
F	11.3	7.1	126	121	65.4	125.9	37.3	149.4
*	10.4	7.5	127.4	118.4	45.0	56.0	38.6	75.0
**	10.4	8.9	127.4	124.1 †	67.5	72.0	57.8	77.7

Table 1. Comparison of TWA features of pre- and post-HDBR tests for positive-TWA subjects in MEDES campaign.* Average values considering all subjects. ** Average values considering only the 4 positive-TWA subjects in both pre and post recordings. († paired t-test, p-value < 0.05)

In the MEDES campaign, results indicate that HDBR decreased the onset heart rate of TWA episodes (127.4 $\pm$ 3.6 beats/min before HDBR and 124.1 $\pm$ 3.6 beats/min after HDBR, p-value=0.048). On the other hand, in the DLR campaign no subject presented TWA at the analyzed heart rates. This lack of significant changes in DLR could be explained by the fact that the VO_2max test was made 26 hours after the end of the five-day period, whereas in MEDES it took place more immediately, within 5–6 hours after the HDBR.

The absence of significant changes between pre- and post-HDBR in TWA parameters suggests that five-day exposure to microgravity is not enough to induce significant changes in myocardial substrate. The only previous study during bed rest [11] that found an increase in TWA comparing before and after BR, was based on a 9–16 days bed rest. Also in [12] authors concluded that at least 9 days of spaceflight are needed to observe repolarization changes in the ECG. Nevertheless, a reduction in the TWA onset HR was found, which might be indicative of initial alterations in the repolarization phase. Therefore, it would be interesting to repeat the analysis on longer (> 9 days) HDBR experiments, where the effects of microgravity on TWA phenomenon, if any, would appear more clearly.

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