# Selective Beat Averaging to Evaluate Ventricular Repolarization Adaptation to Deconditioning after 5 Days of Head-Down Bed Rest

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## Abstract

*The study of QT/RR relationship is important for the clinical evaluation of possible risk of ventricular tachyarrhythmia. Our aim was to assess the effects of 5-days of head-down (-6 degrees) bed-rest (HDBR) on ventricular repolarization. High fidelity 12-leads Holter ECG was acquired before (PRE), the last day of HDBR (HDT5), and five days after its conclusion (POST). X,Y,Z leads were derived (inverse Dower matrix) and vectorcardiogram computed. Selective beat averaging applied to the night period resulted in averages preceded by the same stable heart rate (for each 10 msec bin amplitude, in the range 900-1200 msec). For each template (i.e., one for each bin), T-wave maximum amplitude (Tmax), T wave area, R-Tapex and R-Tend were computed. Results (in 8 male volunteers) showed that, compared to PRE, at HDT5 both R-Tapex and R-Tend resulted significantly shortened (-5% and -3%, respectively), together with a decrease in T-wave area (-7%), while Tmax was unchanged. At POST, duration parameters showed a trend towards their control values (-1.5% and -3%, respectively) while amplitude parameters resulted restored. Despite the short-term BR, cardiac adaptation to deconditioning affected ventricular repolarization during the night period.*

## 1. Introduction

The study of QT/RR relationship is important for the clinical evaluation of possible risk of acquired or congenital ventricular tachyarrhythmia, predisposing to life-threatening arrhythmias. In this context, episodes of post-spaceflight orthostatic intolerance and decreased exercise capacity are usually present in about 50% of astronauts at re-entry from sub-orbital missions, so it is known that microgravity leads to cardiovascular deconditioning. As regards cardiac electrophysiology, several episodes of dysrhythmias and conduction disorders have been repeatedly observed during spaceflight over the years [1]. In particular, long duration space flight was found to prolong QTc interval, corrected by the Bazett's formula, thus increasing potentially arrhythmia susceptibility [2]. Also in short-term exposure to microgravity, induced by parabolic flight, it has been shown that QT interval is prolonged, even though not to pathological levels, during the 0Gz phase of the parabola, while it is shortened during the hypergravity phase [3].

Besides the potential interest in understanding potential changes in cardiac repolarization induced by weightlessness exposure, no systematic study has been conducted, and all observations are only based on data retrospective analysis. Ground-based studies represent an invaluable perspective to investigate human physiology during simulated microgravity conditions. Among them, the model of 6◦ Head-Down Tilt 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 induce changes in the repolarization mechanisms, and thus in the QT/RR relationship, with potential effects on increasing the risk of arrhythmia susceptibility in astronauts. Accordingly, the aim of this study was to use the 5-days strict HDBR manoeuvre to test if it induces alterations on the dynamics of QT/RR intervals, by applying selective beat averaging methods.

## 2. Methods

### 2.1. Subjects

Twelve healthy men aged 33±7 (range, 21 to 41 years; body mass index, 23.7±2.1 kg/m$^2$, maximal oxygen uptake 39±6 ml*kg-1*min-1) were selected for this study. Each subject provided their voluntary written, informed consent to participate in protocols approved by the Institutional Review Board of the "Comité de Protection des Personnes Sud Ouest et Outre Mer I" and by the French Drug Agency (Agence Française de Sécurité Sanitaire pour le Produits de Santé).

## 2.2. Study design

Strict bed rest was performed at -6° head-down tilt position for a total of 5 days. Subjects were housed in the Institut de Médecine et de Physiologie Spatiales (MEDES) facility at the University Hospital of Rangueil, Toulouse, France.

As part of the European Space Agency HDBR strategy, subjects were enrolled in a cross-over design with a wash out period of about 1.5 months between two consecutive campaigns, with one control (CTRL) and two treatment groups applied each day during BR: AG1, with AG for 30' continuously, and AG2, with AG for 30' intermittently (6 periods of 5' each), both obtained with a short-arm centrifuge producing a 1g gravity level at the level of the heart. Before the beginning and after the end of each 5-days HDBR, subjects were evaluated during 5 days of ambulatory period, during which lying in bed during the day was prohibited.

## 2.3. ECG data acquisition

The ECG signals analyzed in this study were acquired using a 12-lead Holter 24-hours high fidelity (1000 Hz) digital recorder (H12+, Mortara Instrument Inc., Milwaukee, WI) with beginning of the acquisition 6 days before the start of the HDBR (BCD-6), the fifth day of HDBR (HDT5) and five days after the end of HDBR (R+4).

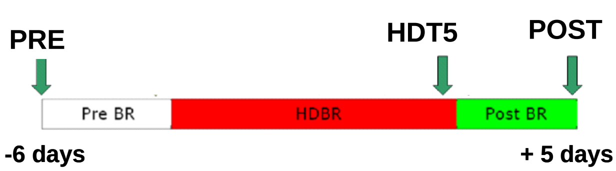


Figure 1. Schematization of the different phases of a bed rest (BR) campaign. Arrows indicate the epochs in which Holter 24-hours acquisitions were performed.

## 2.4. ECG signal processing

Only the RR values classified as in sinusal rhythm (H-scribe and SuperECG software, Mortara Instrument Inc.) were included in the following analysis. First, the RR intervals were classified as day-time (from 6:30 to 23:00) and night-time (from 23:00 to 06:30), to apply the next steps to the analysis of the night period only, to avoid misinterpretation due to daily movements or subject's involvement.

From the 12-leads, inverse Dower matrix transformation [4] was applied to obtain the orthogonal leads X, Y, Z, from which the vectorcardiogram was computed. Then, selective beat averaging [5] was used to obtain averages of P-QRS-T complexes preceded by the same stable heart rate in the range from 900 to 1200 msec: 1) a RR duration histogram with 10 msec bin amplitude was computed; 2) for each bin n, the beats with the corresponding RR duration were located on the vectorcardiogram, and the following beat was extracted and assigned to the C(n) class. After beats realignment according to the R wave peak [5], filtering with a low pass FIR filter (15 Hz), a simple averaging operation was applied, thus obtaining a mean template M(n), representative of all the beats owing to the class C(n), from which the isoelectric line (defined by a stationary point between S and T waves and by a relative minimum after 800 msec) was subtracted (Figure 2).

For each template M(n), a procedure for the automated detection of some fiducial points, such as Tapex (defined as the maximum of the parabolic interpolation between up-slope and down-slope points [6]), Tend (defined as the point with maximum distance from the line that joints the T apex and an adjusted point, dependent on beat length, after the T-wave [7]), Tstart (defined as the point where the product of the first and second derivative falls below the 10% of a threshold defined as the product of the last maximum first and second derivatives [5]) has been applied (Figure 2).

Basing on these points, RTapex and RTend interval durations, T wave maximum and T wave area have been computed for each M(n) (Figure 3).

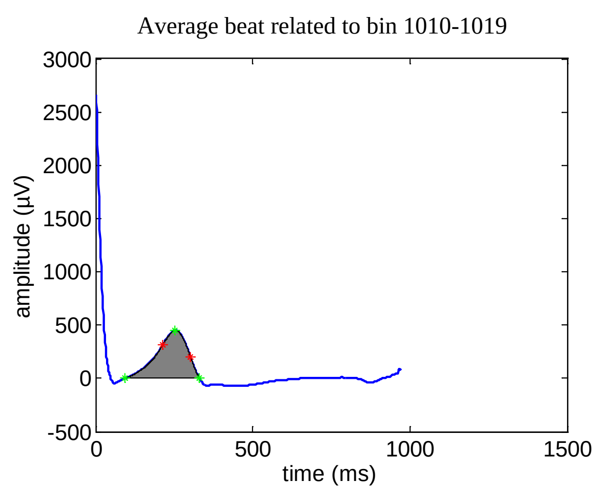


Figure 2. Example of averaged beat M(n) computed from all beats on the vectorcardiogram preceded by an heart cycle with duration in the range 1010-1019 msec. Maximum amplitude, T end and T start are evidenced in green, while maximum up-slope and down-slope in red.

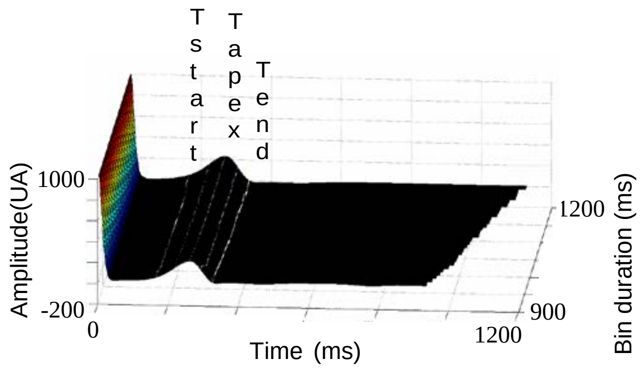


Figure 3. Example of averaged beats relevant to all considered bins obtained in one subject, with detected T start, T apex, and T end on evidence

## 3. Results

Results (see Table 1), obtained in 8 of the 12 subjects enrolled in the control group, are presented as median values of the results, computed over each bin, for each data epoch (i.e., PRE, HDT5, POST), together with the relevant boxplot computed over the considered RR duration range. Non-parametric Friedman test has been applied to evaluate the effect of HDBR on the computed ventricular repolarization parameters.

Table 1. Changes in QT parameters induced by 5-days head-down-bed-rest. Results are reported as median (25th; 75th percentiles)

| | **PRE** | **HDT5** | **POST** |
|---|---|---|---|
| **T-apex (µV)** | 407 (383;442) | 392 (375;423) | 489*# (473;505) |
| **T-area (µV*ms)** | 44227 (40010;46514) | 39585* (37076; 42714) | 45969*# (43705; 47068) |
| **RT-apex (ms)** | 282 (277;285) | 263* (260;267) | 278*# (269;283) |
| **RT-end (ms)** | 353 (350;355) | 342* (335;347) | 344* (334;350) |

*: p < .05 vs PRE, #: p < .05 HDT5 vs POST

As regards temporal parameters, compared to PRE, at HDT5 both RT-apex and RT-end were shortened (-5% and -3%, respectively), while at POST they still were reduced (-3%), but with RT-apex trending towards its control values (Figure 4).

As regards amplitude parameters, compared to PRE, at HDT5 a decrease in T-area (-7%) was found, but this was not present in T-apex. At POST, both T-apex (+14%) and T-area (+9%) were larger than PRE and HDT5 (Figure 5).

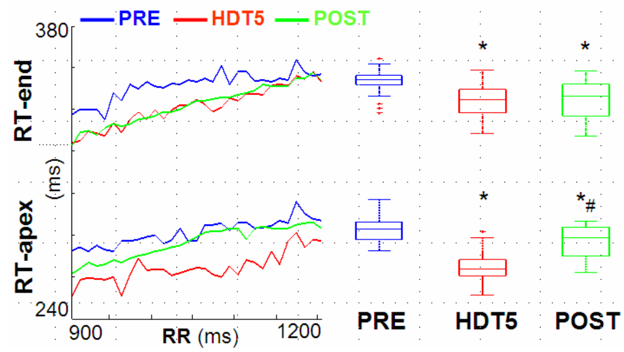


Figure 4. Relationship between RR duration and RT-apex and RTend computed on 8 subjects. *: p < 0.05 vs PRE, #: p <0 .05 HDT5 vs POST, +: outlier.

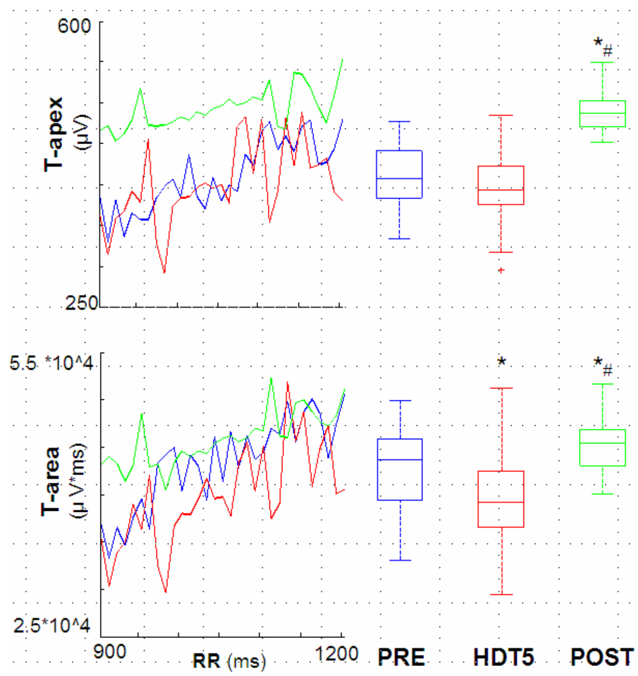


Figure 5. Relationship between RR duration and T-apex (top) and T-Area (bottom) computed on 8 subjects. *: p < 0.05 vs PRE, #: p <0 .05 HDT5 vs POST, +: outlier.

## 4. Discussion and conclusions

Automated analysis of QT interval from Holter recordings represents a difficult task. The proposed procedure of selected beat averaging appeared able to overcome some of the limitations connected with previous averaging methods, revealing to be effective in the improvement of the SNR, due to the high number of beats included in each of the 10 msec duration classes, while not affecting the T wave original morphology. This allowed the automatic detection of fiducial points (T wave start, apex and end) for the calculation of repolarization parameters from each template to be fast and reliable.

By eliminating the head-to-foot hydrostatic gradient, the HDBR position leads to an initial increase in diastolic filling and forward stroke volume. Short-term activation of volume regulatory mechanisms by this central fluid shift results in loss of plasma volume and establishment of a new hemodynamic steady state within 24 to 48 hours [8] that could affect not only the cardiac mechanics, but also its electrical counterpart.

In a previous study, on the same group of subject, by comparing the adaptation of QT to abrupt changes in heart rate induced by tilt test before and after HDBR, 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 [9]. In this study, more focused on detecting more stationary changes in the QT/RR relationship over the night period, we detected changes both in QT temporal and amplitude parameters showing that, despite the short duration HDBR, it introduces some alterations in the cardiac electrophysiology. Moreover, the use of the vectorcardiogram should have avoided the dependence of the observed results from one particular projection.

Interestingly, the observed changes in T wave amplitude showed opposite results compared to what we observed during the 0Gz phase in parabolic flight, where an increase in this parameter was observed (unpublished data). This could be explained by the different mechanisms at the origin of these changes: in parabolic flight, due to abrupt venous return, cardiac dilation and increased conductibility in the thorax; with HDBR, related to loss of fluids and hypovolemia, with shrinking of the heart cavities. This possible explanation is also confirmed by the fact that, after HDBR, with cardiac volume loading restored, amplitude and area parameters returned to their control values.

As regards shortening in RT-apex and RT-end intervals, observed with HDBR, the phenomenon seems to persist even 5 days after its end, thus being probably connected with cardiac deconditioning at the level of autonomic nervous system, requiring more time to be restored to control values. However, as a prolongation of ventricular repolarization interval is usually considered as a sign of increased risk of possible tachyarrhythmias, but our results showed a shortening, based on this data we cannot confirm our starting hypothesis that microgravity exposure induce changes in the QT/RR relationship with potential effects on increasing the risk of arrhythmia susceptibility in astronauts.

However, the observed changes should be taken into account in the clinical settings in patients with cardiovascular diseases, when immobilized in bed, to proper adjust the pharmacological therapy in order to avoid further complications.


## Acknowledgements

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