VENTRICULAR REPOLARIZATION CHANGES DRIVEN BY DECONDITIONING AFTER 21-DAYS OF HEAD-DOWN BED-REST

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ABSTRACT

Our aim was to assess the effects of 21-days head-down (-6º) bed-rest (BR) on ventricular repolarization (VR) by advanced ECG processing. 22 healthy men (20÷42 years old) were investigated (MEP and MXP, ESA BR studies). 24-h Holter ECG was acquired before (PRE), the last day of BR (HDT21), and five days after BR conclusion (POST), and the night period (23:00-06:30) analyzed by vectorcardiogram computation and selective beat averaging approach. Compared to PRE, at HDT21 both RTapex and RTend resulted unchanged, with a 22% decrease in T-wave amplitude and area. The R/T amplitude ratio increased by 27% and ventricular gradient (VG) was diminished by 17%. At POST, all parameters restored to their control values. In conclusion, BR affected VR.

1. INTRODUCTION

Microgravity is known to lead to cardiovascular deconditioning, accompanied by post-spaceflight orthostatic intolerance and decreased exercise capacity. Also, heart rhythm disturbances have been reported among astronauts [1-2]. Known and well-defined changes in the cardiovascular system occur with space flight, such as a reduction in plasma volume, decrease in left ventricular (LV) mass, and adaptation of the autonomic nervous system to the new environment. The combination of these physiologic adaptations suggests that modifications in the cardiac structure due to the weightlessness condition, together with adrenalin/neurohormonal changes and stress related to space flight, could also alter electrical conduction [3]. Besides the single episodes reported along several space programs, the evidence supporting this hypothesis is based on QTc interval prolongation found in a small number of astronauts after long-duration (but not short-duration) space flight [4]. However, the question on whether space flight alters the cardiac structure and function sufficiently to increase the risk of arrhythmias remains opened.

Head-down (6º) bed-rest (HDBR) represents an experimental model of circulatory unloading, useful to induce and study the effects of exposure to simulated microgravity on the cardiovascular system. In previous studies, the effects of HDBR on ventricular repolarization were investigated:

- Sakovski et al [5] found in 20 healthy subjects (14 men and 6 women) that sedentary, long-duration (90 days) HDBR reversibly increases ECG repolarization heterogeneity and by inference ventricular arrhythmic risk;
- Caiani et al [6], in 22 healthy men undergoing sedentary, short-duration (5 days) HDBR, found changes in T-wave amplitude, together with a loss in strength of its linear relation with heart beat duration (RR interval), and ventricular repolarization heterogeneity, that could evidence an increased risk for life-threatening arrhythmias.

Based on these observations, we hypothesised that microgravity exposure could induce changes in the repolarization mechanisms, and thus in the QT/RR relationship and repolarization heterogeneity, with potential effects on increasing the risk of arrhythmia susceptibility. Accordingly, our aim was to test if even a mid-term 21-day strict 6◦ HDBR manoeuvre could induce alterations on the QT/RR relationship and repolarization heterogeneity.

2. METHODS

As part of the European Space Agency HDBR strategy, subjects were enrolled in a cross-over design with a wash out period of at least 3 months between two consecutive campaigns, with one control and one or two countermeasure groups (Fig. 1). Strict bed rest was performed at -6º head-down tilt position for a total of 21 days. Subjects were housed in the Institut de Médecine et de Physiologie Spatiales (MEDES) facility at the University hospital CHU Rangueil, Toulouse, France, or at the German Aerospace Center (DLR), Koln, Germany, as part of the European Space Agency HDBR strategy (MXP and MEP studies, respectively). Before the beginning and after the end of each 21-days HDBR, subjects were evaluated during 7 days of ambulatory

period, during which lying in bed during the day was prohibited.
Twenty-two healthy men aged 32±7 (range, 20 to 42 years) were recruited for this study. Each subject provided their voluntary written, informed consent to participate in protocols approved by the corresponding Institutional Review Boards. In this paper, our attention will be focused on the subjects in the control group only.

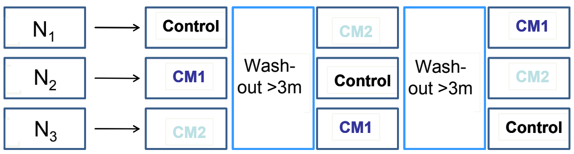

Figure 1. Schematization of the cross-over protocol utilized in MXP and MEP study.

2.1. Data acquisition

ECG signals were acquired using a high-resolution (sampling rate 1000 Hz) 12-lead 24-hours Holter digital recorder (H12+, Mortara Instrument Inc., Milwaukee, WI) with acquisitions before the start of the HDBR (PRE), the last day of HDBR (HDT21) and six days after the end of HDBR (R+5, POST).
From blood samples, Calcium serum content (mmol/l) measurements were available at PRE (at BCD-7 for DLR and at BCD-5 for MEDES), during bed rest (at HDT10 for DLR or at HDT13 for MEDES), and at POST, at R+5 for DLR or at R+6 for MEDES (Fig. 2).

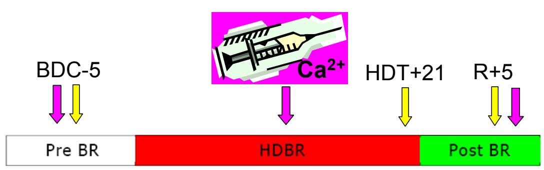

Figure 2. Schematization of the data acquisition: in yellow the Holter ECG, in pink the blood sampling from Calcium was derived.

2.2. ECG signal processing

To avoid potential interactions induced by other experiments conducted during the day, the nocturnal ECG (23:00-6:30) was analyzed as described in [6]. Briefly, from the 12-leads, inverse Dower matrix transformation [7] was applied to obtain the orthogonal leads X, Y, Z, from which the vectorcardiogram was computed. Only the RR values classified as in sinusal rhythm (H-scribe and SuperECG software, Mortara Instrument Inc.) were included in the following analysis.
Selective beat averaging [8] 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 (10 msec bin amplitude). After beats realignment according to the R wave peak and filtering with a low-pass FIR filter (15 Hz), a simple averaging operation was applied, thus obtaining a mean template for each bin, from which the isoelectric line (defined by a stationary point between S- and T-waves and by a relative minimum after 800 ms) was subtracted.
From each averaged waveform, a procedure for the automated detection of some fiducial points, such as Rapex, 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), Tapex and 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), was applied.
From these points, several parameters were automatically computed: RTapex and RTend duration, Tapex, Tarea, R/T waves amplitude ratio, ventricular gradient amplitude (VG) [9] and spatial QRS-T angle [10].
Statistical analysis was performed by Friedman test, followed by Wilcoxon Signed Rank test with Bonferroni correction, to test for differences among timepoints (PRE, HDT21 and POST).

3. RESULTS

Results are presented as median (25^{th};75^{th} percentile), unless otherwise specified, obtained over 18/22 subjects that completed the experiment.
In Tab. 1, parameters extracted from the ECG nocturnal Holters for the different epochs are reported.

Table 1. Median values (25^{th};75^{th} percentile)of the computed parameters over the range of 900-1200 ms heart rate duration.

	Bed rest measurements		
	PRE	***HDT21***	***POST***
RTapex (msec)	273 (269;284)	271 (261;284)	275 (268 ;293)
RTend (msec)	377 (366;390)	371 (356;382)	381 (365;394)
Tmax (µV)	758 (602;897)	595 (481;668)*	771 (612;926)
Tarea (mV*msec)	93 (69;107)	72 (54;80)*	87 (77;111)
R/T (a.u.)	2.2 (2.1;2.7)	2.8 (2.7;3.1)*	2.2 (2.1;2.7)
VG (mV*msec)	125 (87;157)	101(84;132)*	146 (112;162)*
QRS-T (º)	34 (16;58)	38 (18;59)	24 (20;44)

*: p<0.05 vs PRE

Compared to PRE, at HDT21 both RTapex and RTend resulted unchanged, together with a 22% decrease in T-wave amplitude (Fig. 3) and area.

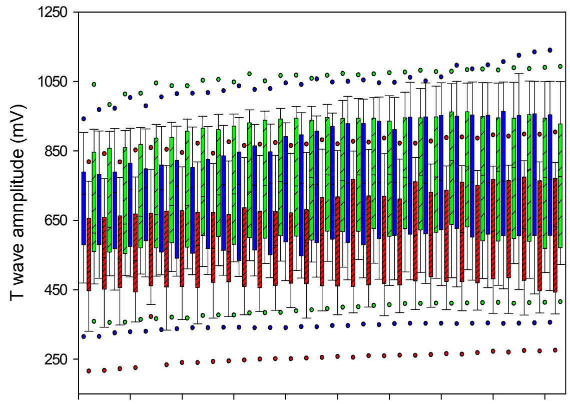

Figure 3. Results of T wave amplitude for each 10 msec RR bin duration, from 900 to 1200 msec. PRE in blue, HDT21 in red, POST in green.

The R/T amplitude ration increased by 27%, with no changes in R peak amplitude.VG was diminished by 17%, while QRST angle showed only a trend in increase. At POST, all ECG parameters were restored to their control values, except a significant increase of 8% in VG and a trend of decrease in QRST angle.
Calcium content (Fig. 4) resulted increased by 3% during HDBR (PRE: 2.40 (2.32;2.43), HDT10-13: 2.43 (2.36;2.52)).

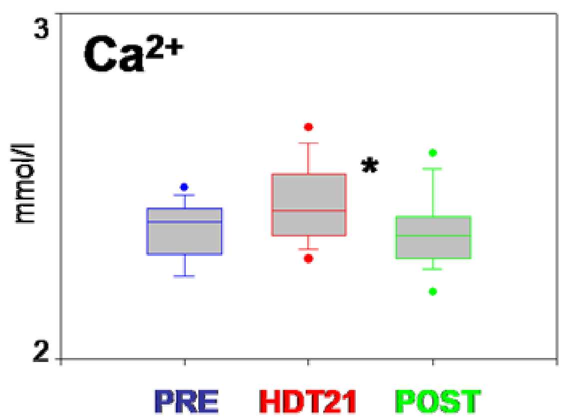

*Figure 4. Results of serum Calcium content. *: p<.05*

4. DISCUSSION

Sustained reduced gravitational stimulus and immobilization affected ventricular repolarization during the night period.
In particular, changes in both T amplitude, ventricular gradient and QRS-T angle parameters were found, showing that mid-duration 21-days HDBR introduces alterations in the cardiac electrophysiology.
The observed decrease in T wave amplitude could probably be related to loss of fluid and hypovolemia, as well as to shrinking of left ventricular dimensions [11], even if R wave amplitude appeared not affected.
A different explanation could be related to an increase in sympathetic tone, even if this should be accompanied by changes in RT intervals, that we did not found.
Also, the increase in Calcium content seen during HDBR could explain both the reduction in T-wave amplitude and the increase in R/T ratio [12].
The observed decrease in VG, together with a trend of increase in QRS-T angle found at HDT21 underlines augmented repolarization heterogeneity with HDBR. This has been associated with risk of life-threatening arrhythmias in patients, as it is functionally linked to dispersion of refractoriness, which facilitates ventricular tachycardia [13].
However, none of the subjects developed VG and spatial QRS-T angles > 130º, that is considered a limit of normality in males when inverse Dower matrix transformation is used [14].

Table 2. Comparison of the results relevant to ventricular repolarization and HDBR obtained in different studies investigating different HDBR durations. Arrows show differences versus PRE (green, p<.05; yellow, p<.1)

	5d HDBR [Caiani et al 2013]	21d HDBR	90d HDBR [Sakovski et al 2011]
QT duration	↓ (green)	↓ (yellow)	↓ (green)
Twave amplitude	↓ (green)	↓ (green)	↓ (green)
SVG	↓ (green)	↓ (green)	↓ (green)
QRST	↑ (green)	↑ (yellow)	↑ (green)
Ca^{2++}	n.a.	↓ (green)	n.a.

As shown in Table 2, results found in this study confirmed the directions of variations in several QT parameters, compared to PRE values, observed in both shorter [5] and longer [6] HDBR.
In conclusion, 21-days of sedentary HDBR is associated with changes in temporal and spatial repolarization heterogeneity that completely reversed during the week after resumption of ambulation.
These observations should be taken into account in the evaluation of potential countermeasures for long-term exposure to microgravity, as well as in patients with cardiovascular diseases, when immobilized in bed, to proper adjust the pharmacological therapy in order to avoid further complications.

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6. REFERENCES

1. Charles, J.B., Bungo, B.A. & Fortner, G.W. (1994). *Cardiopulmonary Function*, in Space Physiology and Medicine, A.E. Nicogossian, C.L. Huntoon, S.L. Pool (Eds), Philadelpia: Lea & Febiger.

2. Fritsch-Yelle, J.M., Leuenberger, U.A., D'Aunno, D.S., Rossum, A.C., Brown, T.E., Wood, M.L., Josephson, M.E. & Goldberger, A.L. (1998). An Episode of Ventricular Tachycardia during Long-duration Spaceflight. *Am. J. Cardiol.* **81**, 1391-2

3. Bacharova, L., Estes, H., Bang, L., Rowlandson, I., Schillaci, G., Verdecchia, P. & Macfarlane, P.W. (2010). The First Statement of the Working Group on Electrocardiographic Diagnosis of Left Ventricular Hypertrophy. *J. Electrocardiol.* **43**(3), 197-9.

4. D'Aunno, D.S., Dougherty, A.H., DeBlock, H.F. & Meck, J.V. (2003). Effect of Short- and Long-duration Spaceflight on QTc Intervals in Healthy Astronauts. *Am. J. Cardiol.* **91**, 494–497.

5. Sakowski, C., Starc, V., Smith, S.M. & Schlegel, T.T. (2011). Sedentary Long-duration Head-down Bed Rest and ECG Repolarization Heterogeneity. *Aviat. Space Environ. Med.* **82**, 416-23.

6. Caiani, E.G., Pellegrini, A., Bolea, J., Sotaquira, M., Almeida, R. & Vaïda, P. (2013). Impaired T-wave Amplitude Adaptation to Heart-rate Induced by Cardiac Deconditioning after 5-Days of Head-down Bed-rest. *Acta Astronautica* **91**, 166–172.

7. Dower, G.E. (1968). A Lead Synthesizer for the Frank System to Simulate the Standard 12-lead Electrocardiogram. *J. Electrocardiol.* **1**, 101-116.

8. Badilini, F., Maison-Blanche, P., Childers, R. & Coumel, P. (1999). QT interval analysis on ambulatory electrocardiogram recordings: a selective beat averaging approach. *Med. Biol. Eng. Comput.* **37**, 71-9.

9. Burger, H.C. (1957). A Theoretical Elucidation of the Notion Ventricular Gradient. *Am. Heart J.* **53**, 240-246,

10. Scherptong, R.W.C., Henkens, I.R., Man, S.-C., Le Cessie, S., Vliegen, H.W., Draisma, H.H.M., Maan, A.C., Schalij, M.J. & Swenne, C.A. (2008). Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. *J. Electrocardiol.* **41**, 648-655.

11. Feldman, T., Childers, R.W., Borow, K.M., Lang, R.M. & Neumann, A. (1985). Change in Ventricular Cavity Size: Differential Effects on QRS and T Wave Amplitude. *Circulation* **72**, 495-501.

12. Passini, E., Pellegrini, A., Caiani E., Severi, S. (2013). Computational Analysis of Head-Down Bed Rest Effects on Cardiac Action Potential Duration. *Computing in Cardiology* **40**, 357-360.

13. Saltin, B., Blomqvist, G., Mitchell, J.H., et al. (1968). Response to Exercise After Bed Rest and after Training. *Circulation* **38**, VII1-78.

14. Scherptong, R.W.C., Henkens, I.R., Man, S.-C., Le Cessie, S., Vliegen, H.W., Draisma, H.H.M., Maan, A.C., Schalij, M.J. & Swenne C.A. (2008). Normal Limits of the Spatial QRS-T Angle and Ventricular Gradient in 12-lead Electrocardiograms of Young Adults: Dependence on Sex and Heart Rate. *J. Electrocardiol.* **41**, 648-655.