Computational Analysis of Head-Down Bed Rest Effects on Cardiac Action Potential Duration

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Abstract

Several episodes of ventricular arrhythmias have been reported during spaceflights, and cardiovascular deconditioning induced by microgravity exposure has already been assessed.

Strict Head-Down Bed Rest (HDBR) can be used to simulate microgravity effects on the cardiovascular system. Therefore, it represents an invaluable opportunity to study and analyse this phenomenon.

The aim of this work has been to evaluate the possible effect of blood electrolyte changes induced by 21 days of HDBR on the electrical activity of the heart, by using a computational model of human ventricular myocyte.

Simulation results point out a biphasic course of action potential duration, which shortened during HDBR and recovered after the end of it, accordingly with RT interval measurements from ECG data analysis.

1. Introduction

It is well known that microgravity affects the cardiovascular system: indeed, there are many effects associated with spaceflights, e.g. reduction in plasma volume, decrease in left ventricular mass and modifications of the autonomic nervous system. Moreover, several episodes of cardiac arrhythmias and conduction disorders have been reported during space missions, such as Gemini and Apollo [1,2], and aboard space stations [3,4].

However, the specific causes leading to this suggested increased risk of arrhythmias have not been entirely understood. To further explore this phenomenon, ground-based experiments, such as strict Head Down Bed Rest (HDBR), represent a great opportunity to analyse simulated microgravity effects on cardiovascular system, by monitoring ECG signal and different physiological parameters over time [5].

In this context, computational modeling constitutes a useful tool as well: in fact, changes observed experimentally may be tested *in silico* in order to evaluate their possible impact on cardiac electrical activity.

The aim of this work has been to verify if the blood electrolyte variations occurring during 21 days of HDBR can be directly linked to the corresponding changes observed in cardiac repolarization phase, by using a computational model of human ventricular action potential (AP) and comparing simulation results with ECG data analysis.

2. Methods

2.1. Bed-rest protocol

Experimental data were recorded during a mid-term (21 days) strict -6º Head-Down Bed-Rest (HDBR) campaign held at the German Aerospace Center (DLR, Koln, Germany) by the European Space Agency (ESA) from September 2011 to April 2012. Ten healthy subjects (aged 23-42 years) were enrolled for this study in a cross-over design, including a control and a countermeasure (CM) group, with a washout period of about 1.5 months between the two HDBR sessions. Subjects in the CM group received a daily supplementation of whey protein (0.6 g/kg body weight) and potassium bicarbonate ($KHCO_3$, 90 mmol).

In this study, our attention will be focused on the CM group only. Each subject underwent a comprehensive medical examination during the selection process and provided written informed consent to participate in this study, approved by the independent ethics committee Aerztekammer Nordrhein, Duesseldorf, Germany.

2.2. Experimental data acquisition

ECG signals have been acquired using a 24-h high resolution (sampling frequency: 1000 Hz) 12-lead Holter digital recorder (H12+, Mortara Instrument Inc,

Milwaukee, WI, USA). Acquisitions were performed 8 days before the beginning of the test (PRE), after 5, 16 and 21 days of Head-Down Tilt (HDT_5, HDT_{16} and HDT_{21} respectively) and 4 days after the end (POST).

The RR values classified as "sinusal rhythm" (H-scribe and SuperECG software, Mortara Instrument Inc, Milwaukee, WI, USA) have been considered and the night period only (from 23:00 to 6:30) has been taken into account, in order to avoid possible noise due to subject daily movement. Selective beat averaging technique [5,6] was used to obtain averages of P-QRS-T complexes preceded by the same stable heart rate (cycle length from 900 to 1200 ms, 10 ms RR bins). Repolarization phase has been evaluated considering the time distance from the QRS peak and the T-wave end (RT interval).

Blood samples have been collected 7 days before the beginning of the test (PRE), at HDT_{10} and 5 days after the end (POST). Electrolyte concentrations ($[Na^+]$, $[K^+]$, $[Cl^-]$ and total $[Ca^{2+}]$) were measured, together with many other physiological parameters (e.g. cell volume, glucose, pH, etc.) which will not be considered in this study.

A schedule of the considered HDBR phases and data acquisitions is represented in Figure 1.

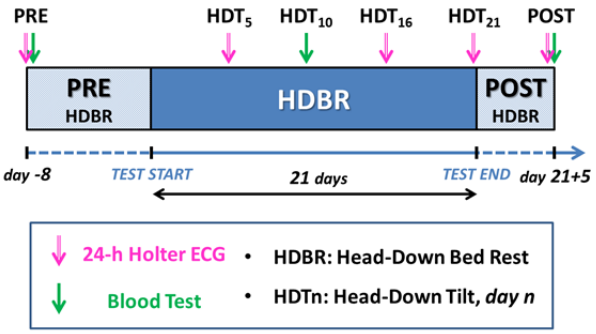

Figure 1. Time schedule of the 21 days Head-Down Bed Rest (HDBR) campaign. Arrows indicate the epochs in which 24-h Holter acquisition and blood analysis have been performed.

2.3. Computational modeling

The most recent human ventricular mathematical model (O'Hara-Rudy, [7]) has been used as basis for simulations. However, the original model is not able to reproduce properly the effects of extracellular Ca^{2+} variations on action potential duration (APD). Therefore, as similarly done for previous models [8,9], specific modifications were needed in order to reproduce the inverse relationship between extracellular $[Ca^{2+}]$ and APD. The original L-type Ca^{2+} current formulation has been replaced by a new Markov model and Ca^{2+}-dependent inactivation has been strengthened. Other minor changes were need to preserve the physiological properties of the whole cell [10].

Extracellular electrolyte concentrations were considered in equilibrium with blood and used as model inputs to simulate PRE, HDT_{10} and POST conditions, as similarly done in a previous work for haemodialysis patients [11].

Single cell simulations. Model differential equations were implemented in Matlab (Mathworks Inc., Natick, MA, USA) and solved with a variable order solver (ode15s), based on numerical differentiation formulas [12]. Pacing at 1 Hz was maintained until a steady state AP was reached and APD was measured as the interval between AP upstroke and the 90% repolarization level (APD_{90}).

Multicellular simulations. One dimensional fiber (2 cm length) composed by 100 endo- and 100 epi-cardial cells has been considered. Model equations have been translated into cellML language using COR environment [13] and monodomain equations have been solved with Chaste Software [14,15]. Pseudo-ECG signal has been computed as described by Gima-Rudy [16]; RT interval has been evaluated considering a slope inferior to 1e-4 V/s as T wave end.

3. Results

3.1. Experimental data analysis

Experimental data presented below refer to only 8 subjects out of 10, since one participant left during the test and another one had some ECG recording problems. PRE and POST data have been compared to the ones acquired during HDBR test, i.e. HDT_{16} for ECG and HDT_{10} for electrolyte concentrations.

ECG analysis provided evidence of a biphasic trend in repolarization for each considered RR bin: RT interval considerably shortened at HDT_{16}, and then completely recovered at POST, reaching values even higher than in PRE (Figure 2).

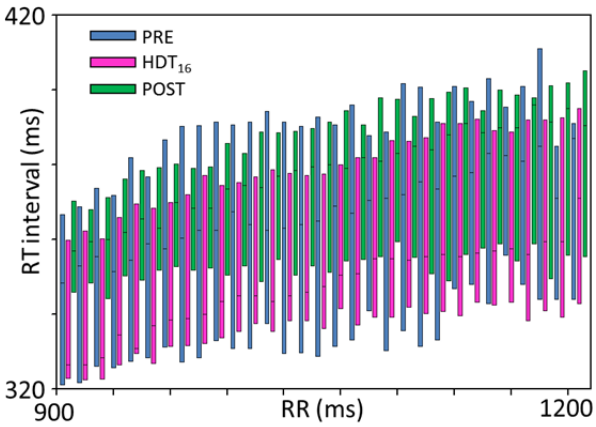

Figure 2. Relationship between RR and RT interval. Whisker plots represent median and 25-75th percentiles for each RR bin in PRE, HDT_{16} and POST conditions.

Non parametric Friedman and Wilcoxon tests were applied and significant differences ($p<0.001$) were found for the three considered groups: PRE, HDT_{16} and POST.

As for electrolyte concentrations, $[Ca^{2+}]$ increased during HDBR and then recovered at POST. Non parametric Wilcoxon test was applied and differences resulted significant in HDT_{10}vsPRE and POSTvsHDT_{10} ($p<0.05$). Relevant and sometime contrasting variations were found in extracellular $[K^+]$ as well, while changes in $[Na^+]$ and $[Cl^-]$ were almost negligible. A summary of experimental data results is reported in Table 1.

Table 1. Experimental data in PRE, HDT and POST conditions. Since computational simulations have been performed at 1Hz pacing, only the RT interval corresponding to the 905-1005 ms RR bin has been shown. Data are presented as Median(25^{th}-75^{th}).

	RT interval (ms)	***changes (ms)***
PRE	362.5(337.0-382.5)	-
HDT_{16}	343.5(335.3-373.3)	-19 ms vs PRE
POST	373.5(351.5-385.3)	+30 ms vs HDT_{16}
	total $[Ca^{2+}]$(mM)	***% changes***
PRE	2.33(2.28-2.39)	-
HDT_{10}	2.36(2.33-2.44)	+1.29% vs PRE
POST	2.31(2.27-2.35)	-2.12% vs HDT_{10}
	$[K^+]$ (mM)	***% changes***
PRE	4.25(4.08-4.39)	-
HDT_{10}	4.40(4.24-4.59)	+3.53% vs PRE
POST	4.33(4.18-4.46)	-1.59% vs HDT_{10}

3.2. Computational results

Single cell simulations were run for each subject considering the corresponding electrolyte concentrations in PRE, HDT_{10} and POST conditions.

Consistently with RT interval, APD decreased during HDBR and recovered at POST. Indeed, median variations were relatively small (-3.7 ms HDT_{10} vs PRE, +1.4 ms POST vs HDT_{10}), but when considering individual subjects with larger electrolyte variations, there were many cases where concurrent changes of $[Ca^{2+}]$ and $[K^+]$ produced greater effects, as shown in Table 2.

Multicellular simulations have been performed once considering median electrolyte variations as inputs.

Pseudo-ECG was computed and the simulated RT interval varied in accordance both to single cell APD and measured RT interval (-4.6 ms HDT_{10} vs PRE, +2.0 ms POST vs HDT_{10}).

Pseudo-ECG was simulated also considering the subject with the greater electrolytes and APD variations (i.e. #3): here, changes of RT interval were significantly larger (-35.5 ms HDT_{10} vs PRE, +13.8 ms POST vs HDT_{10}). His pseudo-ECG traces and T wave in PRE, HDT_{10} and POST conditions are shown in Figure 3.

Table 2. Simulation results in terms of APD for each subject during PRE, HDT_{10} and POST conditions. Notable changes are marked in bold.

HDT_{10} vs PRE			
Subject	***% $\Delta[Ca^{2+}]$***	***% $\Delta[K^+]$***	***ΔAPD_{90} (ms)***
#1	+1.7%	+3.9%	-3.0
#2	+0.4%	+2.7%	-3.2
#3	**+3.6%**	**+38.4%**	**-20.0**
#4	+1.8%	+2.0%	-4.8
#5	+2.7%	**+3.2%**	-5.7
#6	-1.3%	+1.8%	-4.1
#7	**+5.2%**	-2.8%	-3.2
#8	+2.2%	+2.6%	-2.5
POST vs HDT_{10}			
Subject	***% $\Delta[Ca^{2+}]$***	***% $\Delta[K^+]$***	***ΔAPD_{90} (ms)***
#1	**-6.9%**	**+6.7%**	+2.0
#2	-0.9%	+2.4%	-0.7
#3	**-4.3%**	**-15.8%**	**+18.0**
#4	-0.4%	- 2.8%	0.8
#5	-0.4%	+0.4%	- 0.4
#6	**-4.7%**	**-12.6%**	**+10.1**
#7	-0.8%	+0.5%	-1.5
#8	**-22.0%**	**- 4.9%**	**+14.8**

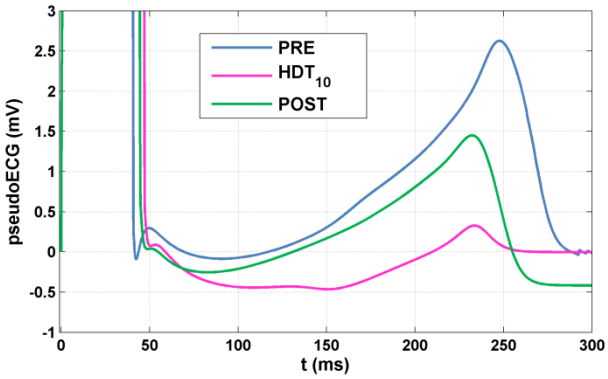

Figure 3. Pseudo-ECG for subject #3. Repolarization phase varied considerably in the three considered conditions: simulated RT interval highly decreased during HDBR (-35.5 ms HDT_{10} vs PRE) and only partially recovered at the end of it (+13.8 ms POST vs HDT_{10}).

4. Discussion and conclusions

Experimental data acquired from 8 subjects during 21 days of HDBR have been presented and analysed, in order to assess the effects of simulated microgravity on the cardiovascular system, and possibly clarify the underline mechanisms involved.

ECG recording showed a significant decreased of RT interval during HDBR with respect to PRE and POST conditions. Blood test provided the extent of extracellular electrolytes variations, especially Ca^{2+} and K^+.

A computational model of human ventricular myocyte has been used to simulate subject conditions PRE, POST and during HDBR, considering the corresponding electrolyte concentrations as inputs. Simulations results showed small but consistent changes in APD and simulated RT interval.

These findings support the hypothesis that electrolyte imbalances occurring during HDBR may be linked to the electrical changes observed experimentally.

However, several additional mechanisms are affected by microgravity. Therefore, for a more comprehensive computational analysis, other factors should be considered in simulations.

5. Limitations and future developments

Simulations have been performed using electrolyte data acquired on HDT_{10}, and compared with ECG analysis from HDT_{16}: 24-h Holter and blood samples collected at the same day could lead to a more precise comparison. Moreover, ionized Ca^{2+} concentration has been estimated as half total Ca^{2+}, since no direct measurements were available.

A new mid-term HDBR campaign, involving one control and two CM groups, has been recently completed by ESA. Experimental data, including ionized Ca^{2+} concentration, will be available for further investigations in the near future.

Acknowledgements

We are extremely grateful to all the personnel of ESA and DLR involved in the study for the support to the realization of our experiment, as well as to the experimental subjects for their dedicated collaboration. The research “Evaluation of changes in ventricular repolarization and its relationship with heart rate during bed-rest experiment” has been performed thanks to the contribution of the Italian Space Agency (Contracts no. I/047/10/0 and 2013-033-R.0, recipient Dr. EG Caiani).

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