Changes in ventricular repolarization and cardiac function induced by head-down bed rest

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Abstract— **Reports of ventricular arrhythmias during spaceflights raise the question of whether microgravity increases sudden cardiac death risk. To test if changes in cardiac structure and neurohumoral environment during space flight could alter electrical conduction, we studied both changes in ventricular repolarization (VR) and cardiac echocardiographic parameters in 12 males before and after five days of head-down (-6º) sedentary bed-rest (HDBR), simulating exposure to microgravity. Increased heterogeneity in VR was found, but not related to cardiac atrophy. In fact, changes in LV morphology were restored 3 days after HDBR. Longer HDBR studies are needed to better elucidate the phenomenon.**

I. 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. Hence, the evidence supporting this hypothesis consists mostly of minor changes in QT interval in a small number of astronauts after long-duration space flight [3]. 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. We hypothesized that simulated microgravity could induce changes in cardiac function and structure that could explain possible changes in ventricular repolarization. Accordingly, our aim was to test if even short 5-days strict 6◦ HDBR maneuver could induce alterations in LV volumes and mass, as well as on ventricular repolarization.

II. MATERIALS AND METHODS

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 recruited. 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). Sedentary bed rest was performed at -6º head-down tilt position for a total of 5 days at 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 (BRAG1). The experiment included 5 days of pre-bed rest hospitalization (PRE), 5 days of HDBR and 5 days of post-bed rest recovery (POST).

ECG signals were acquired using a high-resolution (fs=1000 Hz) 12-lead 24-hours Holter digital recorder (H12+, Mortara Instrument Inc., Milwaukee, WI) with beginning of the acquisition 6 days before the start of the HDBR (PRE), the fifth day of HDBR (HDT5) and five days after the end of HDBR (POST). To avoid potential interactions induced by other experiments conducted during the day, the nocturnal ECG (23:00-6:30) was analyzed as described in [4]. Briefly, inverse Dower matrix transformation [5] was applied to obtain the orthogonal leads X, Y, Z, from which the vectorcardiogram was computed. Selective beat averaging [6] 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). From them, several parameters were computed: RTapex and RTend duration, also with Bazett correction ($RTend_c$), Tapex, Tarea, R/T amplitude ratio, ventricular gradient (VG) [7] and spatial QRS-T angle [8].

Plasma and blood volumes were measured two days before (PRE) and during in the last day (HDT5) of HDBR, using the optimized CO-rebreathing method (SpiCO®, Blood tec GbR, Bayreuth, Germany).

Transthoracic echocardiographic acquisitions were performed five days before (PRE), within 3 hours from the conclusion of HDBR (HDT5), and three days later (POST), with the subject in supine left decubitus position, by a single expert operator using a iE33 ultrasound equipment (Philips Medical System). All participants underwent standard 2D, Doppler, and tissue Doppler echocardiography (S5 phased array). In addition, real-time 3D echocardiography (RT3DE) was performed (X3-1 matrix array) using wide-angled acquisitions with particular care to include the entire left atrium and ventricle within the pyramidal 3D scan volume.

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TABLE I. ECG ANALYSIS

	Bed rest measurements		
	PRE	***HDT5***	***POST***
RTapex (msec)	278 (262;282)	265 (256;275)*	279 (267;286)
RTend (msec)	366 (354;377)	360 (351;368)*	371 (360;376)
$RTend_C$(msec)	357 (345;369)	351 (343;361)*	362 (349;367)
Tmax (mV)	674 (538;753)	616 (464;724)	734 (572;876)*
Tarea (mV*msec)	80 (68;92)	73 (54;86)*	93 (63;104)*
R/T (a.u.)	3.14 (2.9;3.5)	3.63 (2.8;4.2)	3.06 (2.3;3.4)*
VG (mV*msec)	125 (91;134)	113(80;130)*	133 (92;154)
QRS-T (º)	50 (43;59)	63 (48;73)*	48 (42;53)

*: p<.05 vs PRE

Data are expressed as median (25^{th};75^{th} percentile), unless otherwise specified. Friedman test for repeated measures was applied to test for differences among timepoints (PRE, HDT5 and POST).

III. RESULTS

Results are presented relevant to 10/12 subjects studied, in which both ECG and echo data were available during sedentary bed rest. In Table 1, parameters extracted from the ECG nocturnal Holter are reported. All measurements of duration of the combined timing of ventricular depolarization and repolarization waves (RTapex, RTend, $RTend_C$) showed a significant, hence reduced, shortening at HDT5 (4%, 2%, 2%, respectively). Tmax showed a trend of reduction (7%), while the T-wave area was reduced by 8%. The VG was reduced by 7%, while the QRS-T angle increased by 32%. In Table II, results of echo analysis are presented. At HDT5, compared to PRE, LV mass was found decreased by 16%, while LV end-diastolic (EDV), end-systolic (ESV) and stroke (SV) volumes diminished by 19%, 26%, and 17%, respectively. Ejection fraction (EF) did not change. Global longitudinal strain (GLS) from apical 4-chamber view was depressed by 6%.

TABLE II. ECHO ANALYSIS

	Bed rest measurements		
	PRE	***HDT5***	***POST***
LV mass (g)	137 (129;145)	110 (93;123)*	156 (123;163)
LV EDV (ml)	142 (130;165)	114 (102;124)*	135 (110;160)
LV ESV (ml)	56 (51;67)	49 (36;51)*	47 (37;56)*
LV SV (ml)	85 (77;99)	71(64;74)*	88 (71;93)
LV EF (%)	60 (57;62)	63 (59;65)	66 (62;67)
GLS (%)	-22 (-23;-21)	-21(-21;-20)*	-22 (-23;-22)
Peak E (cm/s)	87 (80;102)	63 (59;73)*	89 (76;105)
Plasma volume (l)	3.7 (3.3;3.8)	3.1 (3.0;3.4)*	-
Blood volume (l)	6.0 (5.5;6.2)	5.4 (5.2;5.8)*	-

*: p<.05 vs PRE

Doppler peak mitral early velocity (E) was diminished by 20%, while plasma and blood volume were reduced by 16% and 12%, respectively. At POST, all ECG parameters were restored, or higher than control values. Also echo measurements were back to their reference PRE values, except ESV.

IV. DISCUSSION AND CONCLUSION

Changes in ECG ventricular repolarization parameters, as well as LV function and morphological parameters, were found with the short-term HDBR. Despite the shortening of RT interval, the decrease in VG together with the increase in QRS-T angle found at HDT5 could underline augmented repolarization heterogeneity. This was previously associated with risk of life-threatening arrhythmias, as it is functionally linked to dispersion of refractoriness, facilitating ventricular tachycardia [9]. However, these changes should not be related to cardiac atrophy but to decreased physiological loading and dehydration [10]. In fact, despite the reduced LV mass at HDT5 but completely reversed three days later, it is unlikely that the cardiac muscle can remodel to such an extent in such a short period of time. Changes in plasma and blood volumes were consistent with the reduced preload and shrinking of the LV. Interestingly, a decrease in contractility as showed by longitudinal strain was found, probably as a result of the Frank-Starling law. In conclusion, increased heterogeneity in ventricular repolarization was found, but apparently not related to cardiac atrophy. Longer HDBR studies are needed to better elucidate the phenomenon.

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