Heart rate and ventricular repolarization variabilities interactions modification by microgravity simulation during head-down bed rest test

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Abstract

It is known that the cardiac function is affected by head down bed rest microgravity simulation. Nevertheless its consequences for the health both during the bed-rest and at recovery are still a matter of research. In particular the effects over ventricular repolarization (VR) are not well known. Ventricular repolarization dysfunctions could lead to cardiac arrhythmias and eventually to sudden cardiac death. Interactions of VR variability with heart rate variability (HRV) was used as pro-arrythmic marker. In this study, three VR beat-to-beat indexes extracted from ECG signals as QT, QT_p (QRS onset to T wave peak) and T_{pe} (peak to end of T wave) were measured and their variabilities studied. ARARX modeling was the tool used to estimate the VR variability fraction driven by HRV at different time periods: PRE, during head down bed rest and POST.

We found significant differences (p-values < 0.05) comparing the VR variability content driven by heart rate in all VR series at PRE versus during BR microgravity conditions by multiple comparisons statistical analysis. Head down bed rest test increases the amount of linear dependency of VR variability and HRV. Furthermore, in a pairwise comparison between PRE and POST conditions, significant differences for T_{pe} variability contents were also found. The results evidence a reduced recovery capacity for the T_{pe} repolarization variability to restore its linear dependency values to HR in the first moments at the end of BR.

1. Introduction

The Head Down (-6 degrees) Bed Rest (HDBR) experiments are commonly used as an Earth-based analogue study to simulate the microgravity (weightlessness) condition experienced during space flight. Cardiovascular system is affected by weightlessness [12]. The longer the period of time the subject is in this condition, the many and more notable changes are produced in the system by cardiac deconditioning [3], lead to the generation of arrhythmic episodes, both during the flight and on return to Earth's gravity [4].

It is well known that heart rate variability (HRV) is related to variations in the parasympathetic and sympathetic activity. In some way, ventricular repolarization (VR) beat-to-beat indexes and their variability have certain dependency with HR and with its variability respectively. Parasympathetic or sympathetic changes produced by a perturbation on the autonomic nervous system could modify the relationship between VR and HRV. These variations were possibly related with the high incidence of sudden death, reported in heart failure [7]. With this in mind, we utilized several VR beat-to-beat series (QT, QT_p (measured from QRS onset to T wave peak) and T_{pe} (time interval between peak-to-end T wave)) extracted from ECG signals, as it is shown in Fig. 1 for the evaluation of the effect of HDBR over the linear contribution of HRV interactions on VR indexes variability.

2. Database

22 male subjects (age range 21-43 years) were enrolled within a -6 degree 5-days HDBR experiment, conducted at MEDES (Toulouse, France) and DLR (Koln, Germany) as part of the European Space Agency bed rest studies. No countermeasure on subjects was carried out during the HDBR time period. The analyzed 12-lead ECGs Holter recordings (Mortara Instrument) were acquired at 1000 Hz

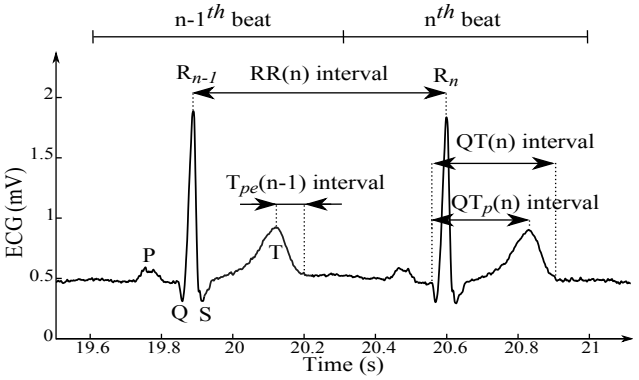

Figure 1. Schematic representation of relevant information in a cardiac beat related with the main waves in an ECG recording. Each time intervals along the beats represents one sample of the series used in the study.

at PRE (two days before the beginning of the 5-days bed rest), during BR (last day of HDBR) and at POST BR (the day they stood) conditions. All subjects had no previous history of cardiovascular disease, and had undergone a comprehensive medical examination during the selection process. Each subject provided written, informed consent to participate in the study, which was approved in advance by the respective Ethical Committee for Human Research at the hosting institutions.

3. Preprocessing

Eight independent ECG leads (II, III, V1-V6 standard leads) were considered from the Holter recordings. Each lead was delineated using an automatic system and the eight sets of marks were combined using post processing rules described elsewhere [8]. In particular, R and T peaks were obtained as the median mark from the eight single lead based R or T peak locations, while QRS onset and T wave end were taken as the first and the latest, respectively, single mark among the eight candidates, for which at least 3 neighbor marks were within a 12 ms interval. RR , QT, QT_p and T_{pe} beat-to-beat intervals were defined as reported in the Fig. 1, and the series were extracted from those global marks. Values greater than 3 standard deviations of these series were treated as outliers and excluded and finally interpolated at 1 Hz.

4. Method

The methodology used in this paper was previosly considered to quantify the HRV influence on RTapex (measured between R and T wave peaks) [10] and QT beat-to-beat variations [1]. The model is schematically presented in Fig. 2, where series $w_{RR}(n)$ and $w_{\xi}(n)$ are uncorrelated stationary zero mean white noises and ξ represents any of the VR beat-to-beat series. The variability of the series is assumed to result from two uncorrelated sources, one of them driven by HR ($\xi V_{|RR}$). This model is known as ARARX, where $A_{11}(z)$, $A_{12}(z)$, $A_{22}(z)$ and $D(z)$ are polynomials whose orders are selected by AIC automatic criteria and define the memory of the system. The same order q is used for the two branches of repolarization model while a possibly different order p is used in the AR model for RR part. Model residuals are considered to be uncorrelated white noises if their normalized autocorrelations and cross-correlation are not different from zero according to 5% significance bilateral tests. Pole-zero decomposition is used to compute the variability contribution on each typical spectral band [9]. Finally, only valid models producing valid spectral measures are accepted. For further details see the work published by Almeida et al [1].

Time segments used (of 3.5 minutes duration) were selected in resting conditions with subjects awake. Mean and variance in subsegments of 30 seconds of the VR series and RR were evaluated. If the mean or the variance were greater than 0.1 percent respect the first subsegment then the total segment is discarded, as clearly non stationary. Otherwise the segments were considered to be approximately stationary and adequate for parametric spectral analysis.

Normality of the data distribution was previously evaluated by Lilliefors test obtaining negative results in several cases. Therefore, the statistical analysis (performed on R statistical free software) of the results was carried out using multiple comparisons procedure between PRE, BR and POST conditions by a Friedman's ANOVA (non parametric) test. A post-hoc Wilcoxon test was used for pairwise comparisons with the adjusment method of Bonferroni in order to counteract the problem of multiple comparisons. P-values less than 0.05 were considered as significant.

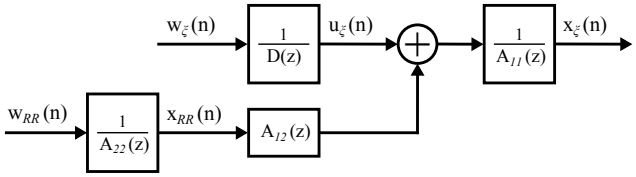

Figure 2. Diagram for ξ variability and HRV interactions. Where ξ represents any beat-to-beat VR series.

Table 1. Median | interquartile range of studied series.

	PRE	BR	POST
RR [s]	0.99 | 0.26	0.89 | 0.22	0.89 | 0.26
QT [ms]	385 | 26	385 | 36	380 | 27
QT_p [ms]	300 | 33	295 | 33	290 | 36
T_{pe} [ms]	84 | 12	87 | 14	85 | 13

5. Results

As we can see in Table 1, median values of each series were found in usual range corresponding to a resting conditions. In this case, the effect of HDBR on these series did not show any significant difference between any of the three conditions.

Table 2 shows the ARARX spectral analysis results, including both HRV parametric analysis considering the typical frequency bands [9] and VR series variability analysis.

PRE versus BR.

HF content in HRV was found as significantly different, decreasing from PRE to BR, while LF content did not change in a significant level. On the other hand, the VR variability and the fraction driven by HR ($\xi V_{|RR} + \xi V_{|\xi}$ and $\xi V_{|RR}$) shown a significant increase, for all VR series considered, where $\xi \in \{QT, QT_p, T_{pe}\}$.

BR versus POST.

LF content was remarkable decrease from BR to POST HDBR in HRV. Regarding VR variability, only the fraction of QT_p variability driven by HR was significantly different.

PRE versus POST.

Both of them, LF and HF content were still found significantly lower at POST for HRV.

The effect of HDBR just after BR exposition, was different for VR series. Only $T_{pe}V_{|RR}$ and $(T_{pe}V_{|RR} + T_{pe}V_{|T_{pe}})$ were still significantly increased caused only by HDBR strict condition, due to in both time periods the subjects were lying down at zero degrees whereas at BR the subjects were at -6 degrees head down.

6. Discussion and conclusions

In this work, HR and VR beat-to-beat indexes variabilities were measured and their linear dependency was evaluated in a ground-base study of simulated microgravity by a HDBR. Before, during and post HDBR time periods were compared. An ARARX autoregressive random process was used for modelling the linear dependency of the variabilities. The results consist of HRV measures (splitted in typical frequency bands [9]) and the fraction of VR variability linearly driven by HRV.

In HRV analysis, LF and HF content had different behaviors due to the effect of HDBR. Firstly, LF shown an increase from PRE to BR and afterwards a significant decrease from BR to POST conditions. Values, at POST time period, inmediately at the conclusion of BR, were found significantly lower than PRE values. On the other hand, we observed a HF content reduction along the three time moments, presenting still significant differences between PRE to POST. Those changes, reflect lower variability content at POST HDBR, can be interpreted of autonomic origin. These results are in agreement with results published by R. Hughson et al [5] and K. Iwasaki et al [6]. R. Hughson and co-workers report a reduction in the *RR*-interval and a significant reduction in HF as an index of parasympathetic activity with a nonsignificant increase in a sympathetic indicator after a 28d HDBR. Besides, K. Iwasaki team has found a significant reduction in HF content in the control group in 14-days bed resting.

All VR beat-to-beat series considered were affected by HDBR. The linear interaction between VR variability with the HRV has shown significant differences before (PRE) and the last day of 5-day bed rest test (BR), with an increasing dependency on HRV. A recovery towards to PRE levels is noticed for all VR series with the exception of T_{pe} variability that carried on with significant differences between PRE to POST conditions. That suggests an increase in the linear dependency of VR series with HRV produced by HDBR at resting awakening subject conditions, that leads to an increment of the global VR variability. Also it seems that it could affect differently the second part of the T wave, which does not recover as fast as the initial part of the QT interval.

The multiple comparison statistical analysis was carried out assuming comparability of the three studied situations: PRE, Bed Rest and POST. However actually PRE and POST time periods were absolutely analogue in terms of position of the subjects (all subjects were lying down in the stretcher at horizontal position) while during BR a -6 degrees position was sustained. It is known that the body position could affect the T wave morphology, causing changes in the T peak position more than in the T wave end due to the movement of the electric heart vector over the leads [11]. However, those changes should not affect the current measures because this study is focused on the variability of VR series not on the time events themselves. That limitation does not apply to PRE versus POST comparison and therefore changes reported are entirely due to HDBR effect.

As it is mentioned above, the variability content, in terms of median of total power of the VR series driven by HR was increased respect the basal condition (PRE) for all series. Thus, the linear dependencies of their variabilities on the HRV were also increased suggesting that BR conditions altered the linear dependency making it stronger. The more

Table 2. Spectral indexes values of *RR* beat-to-beat series (HRV) and VR series variability fraction (in 0-0.4 Hz) driven and undriven by HR and the sum of both expressed as median | interquartile range.

		PRE		BR		POST	
HRV	VLF (0 - 0.04 Hz) [ms^2]	0.0018	0.0048	0.0010	0.0015	0.0021	0.0047
	LF (0.04 - 0.15 Hz) [ms^2]	837	1013	1063	1035 ††	425	303 †††
	LFn (%)	0.78	0.29	0.82	0.28	0.75	0.53
	HF (0.15 - 0.4 Hz) [ms^2]	358	406 †	190	277	140	156 †††
	HFn (%)	0.17	0.23	0.18	0.24	0.14	0.21
	LF/HF	4.12	4.24	4.49	12.70	3.64	6.41
	TP [ms^2]	1634	1887	1341	787	694	857
VR Variability	$QTV_{\|RR}$ [ms^2]	3.86	5.51 †	13.85	20.45	5.47	14.21
	$QTV_{\|QT}$ [ms^2]	0.90	2.19	1.17	2.30	1.97	2.42
	$QTV_{\|RR} + QTV_{\|QT}$ [ms^2]	6.36	5.91 †	17.21	21.15	7.35	15.71
	$QT_pV_{\|RR}$ [ms^2]	1.78	2.93 †	11.54	16.99 ††	5.13	5.97
	$QT_pV_{\|QT_p}$ [ms^2]	0.85	1.22	0.76	2.47	1.15	2.53
	$QT_pV_{\|RR} + QT_pV_{\|QT_p}$ [ms^2]	0.62	1.68 †	13.09	19.34	7.13	16.10
	$T_{pe}V_{\|RR}$ [ms^2]	2.50	3.56 †	14.43	16.46	5.67	5.10 †††
	$T_{pe}V_{\|T_{pe}}$ [ms^2]	0.53	0.79	0.60	1.54	0.84	1.57
	$T_{pe}V_{\|RR} + T_{pe}V_{\|T_{pe}}$ [ms^2]	3.15	4.59 †	15.20	17.36	7.42	7.67 †††

†: $p < 0.05$ PRE vs BR; ††: $p < 0.05$ BR vs POST; †††: $p < 0.05$ PRE vs POST;

strength linear dependency they have, the more similar behavior they must experiment. In the hypothetical case of having a QT series extremely linearly dependent on HR, QT beat-to-beat series would experiment the same behavior than HR, and also their variability due to these results. And on the contrary case, if both series are totally independent, changes in HR would not affect the behavior of QT series.

In a previous work [2], we studied in the same patients the VR adaptation (as arrhythmic marker) to abrupt changes in the HR by using a set of non linear regression functions. We observed a significant decrease for the time adaptation of QT series but not of the QT_p when comparing PRE versus POST conditions during an orthostatic Tilt test perfomed immediatly following the time periods studied in this current work. The effect of -6 degrees head down bed rest was evaluated and indirectly concluded that transmural dispersion is affected by HDBR. Those results and the obtained in this paper give strength to the hypothesis of not only VR (through their indexes) is affected by HDBR but the VR variability as well, showing a slow capacity to restore its linear dependecy values at first moments at the end of HDBR.

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