The Linear Dependence of Ventricular Repolarization Variability on Heart Rate Variability in Head-Down Bed Rest Studies

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Abstract

Head down bed rest as Earth-based study for simulating microgravity affects cardiovascular system. However the consequences for the health of this experiment during and at recovery are still under research and in particular ventricular repolarization (VR) effects are not well known. VR dysfunctions could lead to cardiac arrhythmias and eventually to sudden cardiac death. Interactions of VR variability with heart rate variability (HRV) was used as proarrhythmic marker. In this study, three VR beat-to-beat indices 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 (5-day & 21-day periods) and POST.

We found significant differences (p-values < 0.01) comparing the repolarization variability content driven by heart rate in all VR series at PRE versus during BR microgravity conditions and after in both cases of study. Head down bed rest test increases the amount of linear dependency of VR variability and HRV. Results tend to evidence a slow recovery capacity for all VR variability after simulated microgravity exposition, being more notable for 21-day HDBR.

1. Introduction

The most commonly Earth-based study to simulate microgravity is the Head Down (-6 degrees) Bed Rest (HDBR) experimental condition. Cardiovascular system is affected by weightlessness [1] and prolonged exposition time produced notable changes in the system [2]. Some of them could lead to arrhythmic episodes during space flight [3].

Heart rate (HR) variability (HRV) is related to variations in the parasympathetic and sympathetic activity. Ventricular repolarization (VR) beat-to-beat indexes and their variability have 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. Furthermore, these variations in the interaction between VR and HR variability were possibly related with the high incidence of sudden death, reported in heart failure [4]. With this in mind, our aim was to evaluate the effect of different HDBR durations (5-days and 21-days) over the linear contribution of HRV interactions on ventricular repolarization indexes variability (VRV). To carry out this study, 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, were used. They were extracted from ECG recorded before (PRE), during (BR) and after (POST) one HDBR campaign of 5-days (short-term, ST) and one of 21-days duration (mid-term, MT).

2. Methods

2.1. Data acquisition

Two groups of male subjects (age range 21-43 years) were enrolled in a cross-over design with use of different countermeasures: one group of 12 subjects underwent a 5-day HDBR conducted at MEDES (Toulouse, France), while a second group of 10 subjects underwent a 21-day HDBR at DLR (Koln, Germany) were part of the European Space Agency bed rest studies. Data used in this study refer only to the control group, with no countermeasure applied during HDBR. Holter 12-lead ECGs (Mortara Instrument) were acquired at 1000 Hz a few days before (PRE), at the 5^{th} day of both 5-day and 21-day HDBR (BR) and (POST) after the end of 5- or 21- days of HDBR.

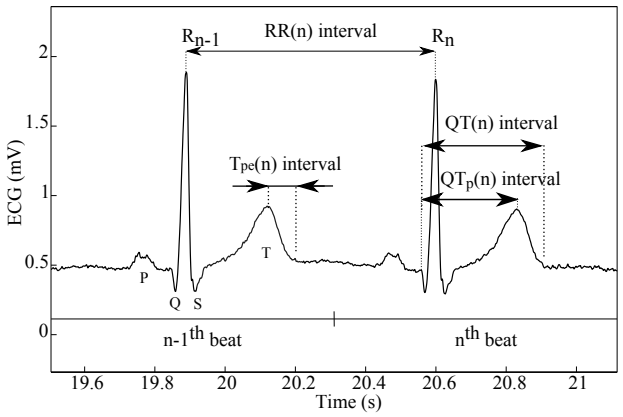

Figure 1. Schematic representation of relevant information in a cardiac beat related with the main waves in an ECG recording. Each time interval along the beats represents one of series used in the study.

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.

2.2. Preprocessing

Eight independent ECG leads (II, III, V1-V6 standard leads) were considered. Each lead was delineated using an automatic system [5] and the eight sets of obtained marks were combined using post-processing rules. In particular, T peak was obtained as the median mark from the eight single leads based T peak locations while QRS onset and T wave end were taken as the earlies and the latest, respectively, single marks among the eight candidates, for which at least 3 neighbour marks were within a 12 ms interval. *RR* , *QT*, QT_p and T_{pe} beat-to-beat series were extracted from those global marks. Values of these series greater than 3 standard deviations were treated as outliers and excluded to finally interpolate them at 1 Hz.

3. ARARX model

The methodology here applied was previously proposed to quantify the HRV influence on RTapex (measured between R and T wave peaks) [6] and *QT* beat-to-beat variations [7]. The model is schematically presented in Fig. 2, where series $w_{RR}(n)$ and $w_{\xi}(n)$ are uncorrelated stationary zero mean white noises. Heart rate beat-to-beat duration, x_{RR} is modeled by an autoregressive process and x_{ξ} represents one of the VR beat-to-beat series under examination. The variability of each VR series, ξV, is assumed to result into two uncorrelated sources, the former driven by the HR ($\xi V_{|RR}$), and the latter independent from the HR ($\xi V_{|\xi}$). This model is known as ARARX, where $A_{11}(z)$,$A_{12}(z)$,$A_{22}(z)$ and $D(z)$ are polynomials whose orders 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 was used in the AR model for the RR part. These orders were selected automatically by Akaike information criterion. Model residuals were considered to be uncorrelated white noises if their normalized autocorrelations and cross-correlation were not different from zero according to 5% significance bilateral tests. For VRV, the total power was computed from pole-zero decomposition and for HRV the contribution on each spectral band was obtained [8]. Finally, only valid models producing valid spectral measures were accepted. For further details see the work published by Almeida et al [7].

The time segments analyzed (of 3.5 minutes duration) were selected in resting conditions with the subjects waked. Mean and variance of the relevant VR and *RR* beat-to-beat series were verified, not allowing changes greater than 10 percent.

Statistical analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago IL). For the sake of comparison, normality of the data distribution was evaluated by Lilliefors test obtaining negative results in several cases. Wilcoxon rank sum test was applied for the following pairwise comparisons: PRE vs. BR (all subjects); PRE vs. POST (5-day HDBR subjects) and PRE vs. POST (21-day HDBR subjects). P-values less than 0.05 were considered as significant.

4. Results

Table 1 shows the results in terms of median|interquartile range. First, the HRV was estimated for each typical frequency band, and then linear dependencies of VRV with the HRV were estimated.

PRE versus BR (at 5-day HDBR, all 22 subjects): The high-frequency (HF, 0.15-0.4 Hz) content in the spectral

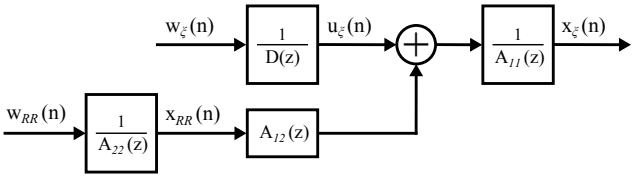

Figure 2. Diagram for ξ variability and HR variability interactions. Where ξ is representing any beat-to-beat VR series.

Table 1. Spectral indexes values of *RR* beat-to-beat series (HRV) and total power of VR series variability fraction driven and undriven by HR and the sum of both expressed as median | interquartile range.

		PRE			BR (5d)	POST	
		ST	MT	ST+MT	ST+MT	ST (5d)	MT (21d)
HR Variability	VLF [ms^2]	0.002|0.005	0.001|0.001	0.002|0.003	0.001|0.001	0.002|0.005	0.001|0.001
	LF [ms^2]	837|1013	763|695	762|873	974|1050	425|303††	653|548
	LFn (%)	0.78|0.29	0.81|0.17	0.81|0.25	0.83|0.25	0.75|0.53	0.77|0.25
	HF [ms^2]	358|406	264|217	278|387	173|287*	140|156††	140|160
	HFn (%)	0.17|0.23	0.17|0.16	0.17|0.18	0.17|0.23	0.14|0.21	0.20|0.16
	LF/HF	4.12|4.24	4.66|4.60	4.49|4.33	4.87|11.96*	3.64|6.41	3.87|4.65
	TP [ms^2]	1634|1887	1110|881	1488|1333	1287|943	694|857†	849|1365
VR Variability [ms^2]	$QTV_{\|RR}$	3.86|5.51	5.31|5.26	4.50|5.59	9.33|13.03**	5.47|14.21†	9.46|7.90$^{\diamond\diamond}$
	$QTV_{\|QT}$	0.90|2.19	1.25|1.60	1.22|1.95	1.20|1.49	1.97|2.42	1.11|2.04
	QTV	6.36|5.91	8.09|6.62	6.41|6.42	11.28|13.49*	7.35|15.71†	10.34|10.26$^{\diamond\diamond}$
	$QT_pV_{\|RR}$	1.78|2.93	3.53|3.83	2.70|3.42	6.01|10.43**	5.13|5.97	5.44|6.08$^{\diamond\diamond}$
	$QT_pV_{\|QT_p}$	0.62|1.68	0.50|1.40	0.56|1.68	0.75|1.50	1.15|2.53	0.43|0.87
	QT_pV	3.16|3.39	4.35|2.69	3.71|3.62	6.73|10.84**	7.13|16.10†	5.79|8.45$^{\diamond\diamond}$
	$T_{pe}V_{\|RR}$	2.50|3.56	4.69|3.07	3.86|4.04	9.04|13.91**	5.67|5.10††	7.89|9.67$^{\diamond\diamond}$
	$T_{pe}V_{\|T_{pe}}$	0.53|0.79	0.45|0.39	0.46|0.69	0.65|1.19	0.84|1.57	0.90|2.18
	$T_{pe}V$	3.15|4.59	5.14|3.55	4.37|4.28	9.35|14.53**	7.42|7.67††	10.30|10.45$^{\diamond\diamond}$

*: p $<$ 0.05 PRE_{ST+MT} vs. BR_{ST+MT}; †: p $<$ 0.05 PRE_{ST} vs. $POST_{ST}$; $^{\diamond}$: p $<$ 0.05 PRE_{MT} vs. $POST_{MT}$;
**: p $<$ 0.01 PRE_{ST+MT} vs. BR_{ST+MT}; ††: p $<$ 0.01 PRE_{ST} vs. $POST_{ST}$; $^{\diamond\diamond}$: p $<$ 0.01 PRE_{MT} vs. $POST_{MT}$;

analysis of HRV was found significantly decreasing after 5^{th} day of HDBR. This could suggest either a decrease or a shift of variability from HF to low-frequency (LF, 0.05-0.15 Hz) band. Differences were found in the sympatho-vagal balance as a consequence of the decrease of HF with no differences in LF values. From this analysis, we could conclude that 5-day HDBR produces an unbalance in the autonomic nervous system.

Total power of VRV in all VR series, in particular, for the fraction driven by HR, showed significant differences. Comparing PRE versus BR, the content of the fraction driven by HRV was increased at BR for all VR series, thus indicating a higher level of linear dependency.

PRE versus POST (5-day HDBR, 12 subjects): For the *RR*, significant differences were found both in LF and HF bands, that were decreased in respect to PRE and, as a consequence, the total power was decreased as well.

The effect of HDBR at POST was different for the VR series. All VR series showed a significant increase in the total power variability, ξV. However, T_{pe} variability driven by HR, $T_{pe}V_{|RR}$ and its total power, $T_{pe}V$, showed higher changes, with a p-value < 0.01, than the other VR series.

PRE versus POST (21-day HDBR, 10 subjects): In this case, the HRV analysis revealed no significant differences between these time periods in every parameter. However, the effect of the 21-days of HDBR was more noticeable in the VRV. The linear dependency of the VRV driven by the heart rate showed higher significant differences in respect to the same results obtained after the 5-day HDBR campaign. The total power of the three VRV series at POST was greater than at PRE pointing out an increase of the linear dependency between both variabilities. In the previous two comparisons, PRE vs. POST (5-days or 21-days), main differences might be caused only by HDBR, because in both time periods the subjects were lying down at zero degrees whereas at BR the subjects were at -6 degrees.

5. Discussion and conclusions

In this work, the variability of ventricular repolarization beat-to-beat indexes was studied, together with their linear interaction with the HR variability. The process was modeled by ARARX autoregressive random model. The linear relationship between VRV and the HRV show significant differences between baseline (PRE) and the 5^{th} day of bed rest test, as well as between PRE and POST for both 5-days and 21-days HDBR. All ventricular repolarization beat-to-beat series were affected by HDBR. For the 5-days HDBR, at POST the measured parameters trended back, with some lag, to the initial values. However, for the 21-days HDBR,

at POST the effect of the simulated weightlessness was still present. These facts suggest an increase in the linear dependency of VR series with HR variability induced by HDBR, for both 5- and 21-days with more prolonged time exposition to simulated microgravity producing more alterations in the cardiovascular system, and in particular a stronger linear dependency of VRV driven by HR.

The effect of the time exposition to bed resting was noticeable where the slower ability at POST to restore the PRE linear dependency values was extended from only $T_{pe}V$ for 5-days HDBR to all the VR series for 21-days HDBR. In our previous work [9], we found that VR after 5-days of HDBR was characterized by the time adaptation (as an arrhythmic marker) to abrupt changes in the heart rate considering a set of non-linear regression functions. We showed a significant decrease for the time adaptation of QT series but not for the QT_p lag when comparing PRE versus POST conditions after 5-days HDBR. This finding could be related to the increased dependency of QT and T_{pe} on RR found in this study, while no significant change was noticed for QT_p dependency on RR. Those results give strength to the hypothesis that HDBR affects not only ventricular repolarization mean temporal and amplitude values [10] but also ventricular repolarization variability and transmural dispersion variability, expressed as $T_{pe}V$. The effects produced by 21-days HDBR exposition needed a longer time to be reverted than those produced by 5-days HDBR. Thus, for a better evaluation of the time of recovery, an analysis later in time (a few days after the HDBR ending) should be required.

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