· *ORIGINAL RESEARCH* ·

Cardiovascular Control Mechanism during Head-down Bed Rest Using Nonlinear Techniques

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Abstract: **Objective** To investigate the influence of −6 ° head-down bed rest (HDBR) on the cardiovascular control mechanism and effects of Chinese herbal medicine (CHM) as a countermeasure. **Methods** Fourteen Chinese healthy men were randomly allocated to a control group and a CHM group. Heart rate and blood pressure variability (HRV & BPV) were assessed before, during and after 60 d HDBR with a focus on nonlinear techniques to quantify scaling behaviour, chaotic behaviour and complexity. **Results** There was no change in heart rate till the 21st day of HDBR, but increased significantly from the 41st day, without any recovery afterwards. DFA α1 was significantly higher on the 2nd day of HDBR compared with baseline and remained so high until even 12 d after HDBR. The chaos level was drastically lower during HDBR compared with the period before HDBR. Over all time sessions, heart rate, HRV 1/f slope and the BPV parameters SDNN, LF/HF, DFA α1 and 1/f were significantly higher in the control group compared with CHM group although HRV DFA α2 and BPV HF showed significantly lower values. **Conclusion** It confirmed the reduced vagal modulation and higher sympathovagal balance at the end of HDBR. Moreover, a change in nonlinear heart rate and blood pressure dynamics during HDBR was still present after 1 week of recovery. It demonstrates that CHM has restricted some influences of HDBR on the cardiovascular regulation, only partially functions as a countermeasure.
Key words: head-down bed rest; heart rate variability; autonomic nervous system; Chinese herbal medicine; nonlinear dynamics

利用非线性方法研究头低位卧床对心血管调控机制的影响. Steven Vandeputa, 刘杰昕, 李勇枝, 陈善广, 谢 琼, 陈章煌, 盖宇清, 高建义, Sabine Van Huffela, Andre E Aubertb. 航天医学与医学工程, 2010, 23(6): 391 ~ 396
摘要: **目的** 本研究旨在用非线性分析方法, 探讨 −6° 头低位卧床试验对心血管调控机制的影响, 并将对照组和中药组进行比较。**方法** 14 名男性健康志愿者随机分入对照组和中药组, 进行 60 d 的头低位卧床试验。在试验前、中、后, 运用非线性分析技术对心率变异、血压变异进行测试。**结果** 志愿者心率水平在卧床开始后的前 21 d 保持稳定, 但从卧床试验的第 41 天起显著升高, 且在卧床结束后亦未恢复至正常; 趋向波动指数(DFAα1)于卧床试验开始后的第 2 天出现明显升高, 且维持升高状态至试验结束后的第 12 天; 混沌指数(chaos)在卧床过程中明显下降。卧床试验过程中组间对比发现: 对照组心率变异的 1/f 以及血压变异的 SDNN、LF/HF、DFAα1 和 1/f 明显高于中药组, 并且心率变异的 DFAα2 和血压变异的 HF 明显降低。**结论** 在卧床试验后期机体出现迷走神经张力下降, 迷走交感平衡升高; 而中药可以减轻模拟失重对心血管系统的影响。
关键词: 头低位卧床试验; 心率变异性; 自主神经系统; 中药; 非线性动力学
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During space missions, the lack of gravitational stress is associated with adaptation in cardiovascular structure and neurohumoral control passage ways[1-2]. Head-down bed rest (HDBR) is often applied as an alternative to investigate physiological adaptation to microgravity.

How the autonomic nervous system (ANS) is deconditioned or influenced by microgravity remains an open question. As the ANS modulates directly the heart rate and indirectly blood pressure, heart

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rate variability (HRV) and blood pressure variability (BPV), analysis can be used to study the autonomic modulation mechanism under microgravity conditions. Most studies reported a decrease in total HRV and in high frequency power (HF) reflecting parasympathetic influence at rest. However, no univocity exists when this decrease takes place. While the majority of those studies adopted linear techniques, only a little was studied with the nonlinear dynamics of this physiological system[3-6].

Most studies in the past were limited to the linear parameters or even to the pure hemodynamic signals. However, in agreement with Lefebvre *et al.*[7] and Yamamoto & Hughson[8], it seemes likely that the cardiovascular system is followed by some nonlinear dynamics which needs exploring further.

The main goal of this study is to investigate the mechanism of autonomic modulation changes during HDBR. We hypothesize that HDBR would decrease some nonlinear HRV and BPV characteristics. As a previous animal microgravity simulation study showed the possibility of CHM as a countermeasure[9], additionally the hypothesis that CHM will improve orthostatic function after HDBR is investigated.

1 Methods

1.1 Subjects and data collection

Fourteen Chinese healthy men took part in this 60 d HDBR. While 7 were randomly allocated to a control group, the other 7 took Chinese herbal medicine (CHM). The full study protocol was explained by Liu *et al.*[10] and was approved in advance by the Medical Committee of CARTC.

ECG and blood pressure were non-invasively measured before (day -10), during (day 2, 7, 21, 41, 56) and after (day R + 6, R + 12) HDBR. Subjects were monitored for 10 min while resting quietly in the supine position with comfortable uncontrolled respiration. Detailed information about the data acquisition and the pre-processing was described by Liu *et al.*[10].

Tai Kong Yang Xin Prescription, a Chinese herb formulae composed of 21 Chinese herbs was used in this study as a countermeasure.

1.2 HRV & BPV analysis

Linear HRV parameters were obtained according to the standards of measurement, proposed by the Task Force committee[11]. Mean and standard deviation (SD) of the tachogram, the square root of the mean of the sum of the squares of differences between consecutive RR intervals (rMSSD) and the percentage of intervals that varied more than 50 ms from the previous interval (pNN50) were calculated in the time domain. After re-sampling the tachogram at 2 Hz, the power spectral density (PSD) was computed with the Welch method. In the frequency domain, low frequency power (LF: 0.04 ~ 0.15 Hz), high frequency power (HF: 0.16 ~ 0.40 Hz) and total power (0.01 ~ 1.00 Hz), as well as the ratio of low over high frequency power (LF/HF), were calculated. In addition, the power could be expressed in absolute values (ms^2) or in normalized units (n.u.).

Nonlinear parameters did not describe the amount of modulation as such, but were able to describe the scaling, complexity and chaotic properties of the signal. Parameters used to study the scaling of the system were 1/f slope[12], fractal dimension (FD)[13] and de-trended fluctuation analysis (DFA 1 & 2)[14] while the complexity was addressed via sample entropy (Samp En)[15]. Also a chaotic signature was calculated by means of the recently developed numerical noise titration technique (NLmean and NLdr)[16]. These nonlinear techniques were applied in exactly the same way for RRI and BP time series.

1.3 Statistical analysis

Statistical analysis was performed with Matlab R2008a (The Math Works Inc., Natick, MA, USA). To investigate the evolution over time and the difference between both groups, a 2-way ANOVA analysis was performed on all HRV and BPV parameters with the time sessions (before, during and after HDBR) as within subject factor and the experimental conditions (control group vs. CHM group) as between subject factor. To compare, for each HRV and BPV parameter, pairwise the different time moments with the baseline value, a post hoc analysis was obtained taking into account the multiple testing problem. Similarly, the nonparametric Mann-Whitney U test was used to evaluate group differences at each time moment. $P < 0.05$ were considered statistically significant.

2 Results

All subjects completed the whole study. There were no significant differences in baseline characteristics.

2.1 Cardiac control

Fig. 1 showed the changes in HR and several HRV parameters before, during and after HDBR in the control and CHM group respectively. The output of the 2-way ANOVA test statistic revealed that, for

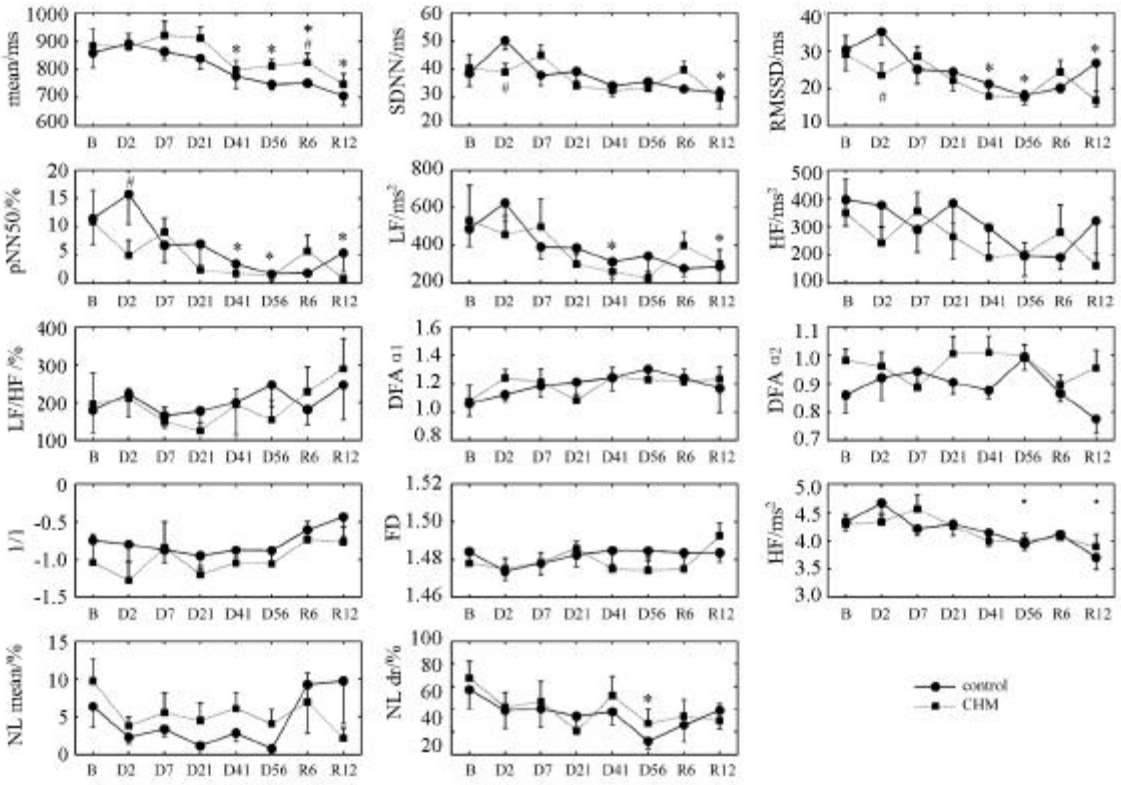


Fig. 1　Evolution of all described HRV characteristics in CHM and control group before (B), during (D) and after (R) HDBR

* $P<0.05$, as compared with before bed rest; #$P<0.05$ between groups

all parameters, the effects of within subject factor time and between subject factor groups were not additive, meaning that there was no interaction between time and group. Therefore, the results of the F-test for each factor were correct and could be interpreted now.

The results between subject factor groups (control vs. CHM) were statistically significant for mean RR ($P=0.025$), DFA 2 ($P=0.007$) and 1/f ($P=0.043$). In general (over all time sessions), heart rate and 1/f slope were higher in the control group than those in CHM group, whereas while DFA 2 showed lower values. Looking to each time moment, especially on the 2nd day of HDBR CHM group had completely different values for SDNN, RMSSD and pNN50 compared with the control group (see # in figure). Opposite to increase of these HRV parameters in control group shortly after starting bed rest compared to the baseline, the CHM group showed decrease in values.

With respect to the change in time (over all 14 subjects), the within subject factor was statistically significant for mean RR ($P=3.16\ E-5$), SDNN ($P=0.006$), pNN50 ($P=0.008$), LF ($P=0.025$) and SampEn ($P=0.001$). Mean RR remained approximately the same till the 21st day of HDBR, but dropped significantly from day 41 of HDBR. Even after HDBR, no change in the initial baseline values could be observed. This increased heart rate was more expressed in the control group compared to the CHM group. SDNN (total cardiac variability), LF (mainly sympathetic modulation) and SampEn reflected all the same time evolution, namely there was an increase at the 2nd day of HDBR followed by a gradual decrease till the 56th day of HDBR. Six days after HDBR, those parameters increased, although did not reach the baseline level. However, we could not call it a recovery since they decreased again on the 12th day after HDBR. Vagal modulation (RMSSD, pNN50 and HF, although less pronounced) did not change for the initial days of HDBR, but declined monotonously from the 7th day of HDBR till the end of HDBR, which was significantly lower than the corresponding baseline value from the 14th day of HDBR on. After HDBR, a slow increase started, but even after 12 d, the values were still significantly lower than those obtained before HDBR. DFA 1, reflecting short term correla-

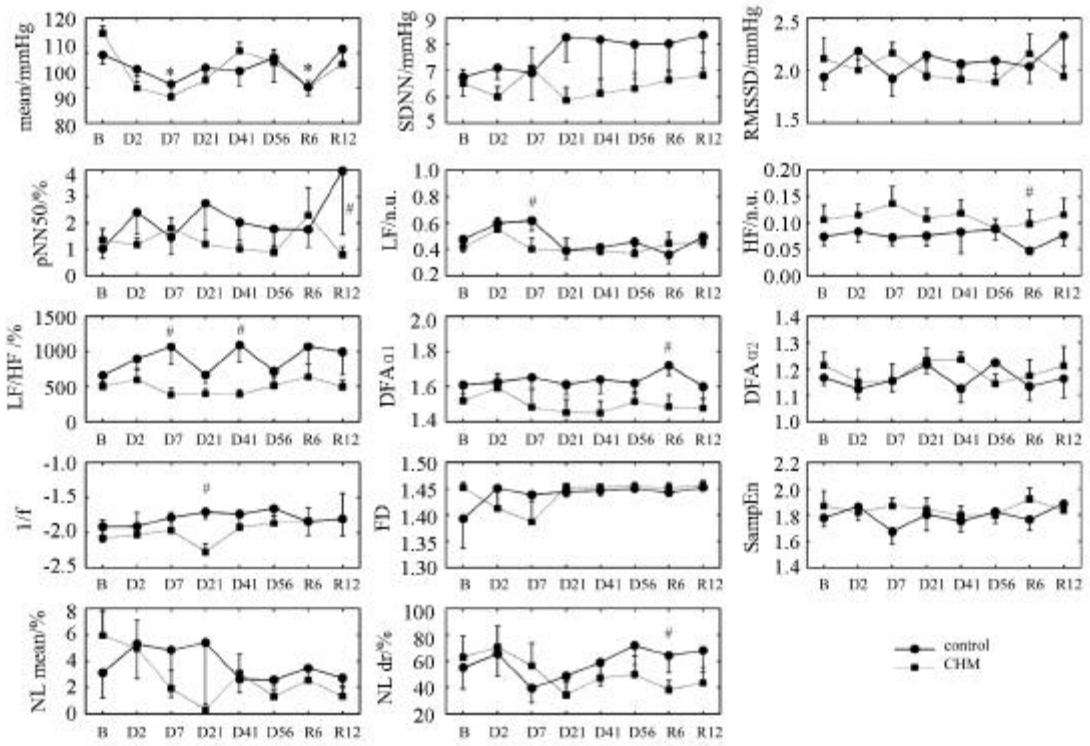


Fig. 2 Evolution of all described BPV characteristics in CHM and control group before (B), during (D) and after (R) HDBR

* $P<0.05$, as compared with before bed rest; # $P<0.05$ between groups

tion, was significantly higher at the 2nd day of HDBR compared with baseline and remained so high until even 12 d after HDBR. Finally, NLmean and NLdr, both giving information about chaotic behaviour of HR modulation, were drastically lower during HDBR compared with the period before HDBR. whereas NLmean increased quickly after HDBR to the initial values, NLdr remained low.

2.2 Blood pressure variability

The evolution in time of BP and several BPV parameters before, during and after HDBR were shown in Fig. 2, respectively for the control and CHM group. Analogously to the HRV results above, no interaction between the within subject factor time and the between subject factor group was found. Again, the result of the F-test for each factor could be interpreted now.

Between subject factor group (control vs. CHM), there was statistically significant for SDNN ($P=0.005$), HF ($P=0.003$), LF/HF ($P=3.80$ E-5) and DFA 1 ($P=6.73$ E-5). pNN5 ($P=0.053$) and 1/f ($P=0.101$) had a nearly significant factor group. In general (over all time sessions), all these parameters, except HF, were higher in the control group compared to the CHM subjects. Some group differences were also found at a specific time moment. Concerning the change in time (over all 14 participants), within subject factor there was only statistically significant for mean SAP ($P=0.001$). Systolic arterial pressure decreased significantly when HDBR started ($P=0.02$). From the 21st day on, SAP increased slightly, not anymore significantly lower than baseline level at the end. After HDBR, SAP first decreased but it increased again to the baseline level. In contrast to many HRV parameters, BPV parameters did not show a clear time evolution, but fluctuated more or less around the values before HDBR.

3 Discussion

In this study, heart rate and blood pressure modulation were examined in 14 Chinese healthy men before, during and after HDBR. We also verified how CHM acted as a countermeasure. Our main findings were twofold. Firstly, administering Chinese herbs during HDBR did not really change the time evolution of any HRV or BPV parameter, which limited its function as a countermeasure. However, it influenced some of the parameters statistically compared with the control group. Secondly, signifi-

cant changes were found over time as a consequence of HDBR.

3.1 Effect of HDBR on linear cardiovascular control

This study found that there was no remarkable change in HR during the first 3 weeks of HDBR. From the 41st day of HDBR on, HR became significantly higher. Other studies reported that there was no change or an increase depending on the different HDBR duration. Therefore, HR seemed only to be affected by long-duration HDBR (> 20 d) and remained high even after more than 12 d of recovery. This phenomenon was probably related to the hemodynamic changes in the second phase of HDBR, in which plasma volume was reduced and central blood volume had been restored to the baseline level. The significant increase in urine output after the 30th ~ 45th day of HDBR, reported by Liu *et al.* [10], confirmed this. A decreased total cardiac variability (SDNN) during HDBR was also reported by Fortrat *et al.* [4]. Thanks to the frequent measurement times, we remarked that vagal modulation (pNN50, RMSSD, HF) did not decrease in the first week of HDBR and resulted in a stable sympathovagal balance, but it declined slightly afterwards. According to the literature, this decreases in total HRV and parasympathetic indices were evident in chronic adaptation to HDBR after 2 weeks[17], 4 weeks[6] and 6 weeks[18].

The specific evolution of SAP during HDBR, namely a gradual decrease during the first week of HDBR, followed by a slight increase to baseline level, was not reported elsewhere. Reduced SAP might be induced by damaged adaptability of the body to the external environment, possibly causing cardiovascular deconditioning.

3.2 Effect of HDBR on nonlinear cardiovascular control

This study focused more on the nonlinear HRV and BPV characteristics being not investigated often, though expected to give extra information[7-8]. The actions and continuous interactions of sympathetic and parasympathetic control mechanisms were nonlinear[19]. Therefore its applicability of techniques based solely on linear models such as spectral analysis was limited. When physiological systems became less complex, they were less adaptable and less able to cope with the demands of changing status. It was why a reduced nonlinearity during HDBR was hypothesized. Goldberger *et al*[5]. conducted the first preliminary study using approximate entropy (ApEn) during 13 d HDBR in healthy young women, observed only a decrease in HRV ApEn at peak levels of applied lower body negative pressure. Probably, the duration of HDBR was not long enough to induce changes in nonlinear dynamics. Hughson *et al.* [6] have shown changes in HRV fractal noise during 28 d HDBR. Here, HRV SampEn[15], a better version of ApEn, decreased during HDBR as well as the parameters related to chaotic behaviour which confirmed our hypothesis. The changes in nonlinear dynamics of HRV and BPV seemed to be independent in amplitude and behaviour, despite the links between heart rate and blood pressure. However, this was in correspondence with the observation of Butler *et al.* [20] that HRV and BPV fractal components were independent. Several studies described a link between HRV fractal alteration during HDBR and the baroreflex, mainly vagally mediated[6, 18]. As baroreflex sensitivity quickly recovered after HDBR and nonlinear HRV and BPV parameters were either still influenced after HDBR or showed another trend, a change in baroreflex could not fully explain the change in cardiovascular dynamics. Other factors seemed to be involved such as vagal modulation for nonlinear HRV which we mentioned earlier. Regarding nonlinear BPV, peripheral resistance of the vessels probably played an important role since it changed during HDBR.

3.3 Limitations

The number of subjects available in HDBR studies was very limited. Although standardization of experimental procedures was imposed, there would always be some differences compared with other HDBR studies. The duration of the HDBR was another important factor. Also the fact that all subjects were Chinese men had to be taken into account as there were some indications that autonomic cardiovascular control was different between European astronauts and Chinese astronauts. No women were included which could be regarded as another limitation.

4 Conclusion

The influence of HDBR on autonomic cardiovascular control was confirmed in this study. In particular, we proved a change in nonlinear heart rate and blood pressure dynamics during HDBR, still present after a week of recovery. Those nonlinear HRV and BPV parameters will not replace linear analysis, but yield extra information about a specific aspect of scaling behaviour, chaotic behaviour or complexity. Chinese herbal medicine (Tai Kong Yang Xin Prescription) seems to restrict the influences of microgravity environment during HDBR on

the cardiovascular regulation, though only partially functions as a countermeasure.

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