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Identification of vascular responses to exercise and orthostatic stress in bed rest-induced cardiovascular deconditioning

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***Abstract*—In this paper, the effects of bed rest-induced cardiovascular deconditioning were investigated by means of a previously developed multivariate model for the assessment of arterial control of circulation. The vascular response to exercise and tilt, before and after a 14-day head down tilt bed rest, was identified and disentangled from the main mechanisms due to global, neural control of circulation. Results of the decomposition of diastolic pressure and pulse pressure beat-by-beat series and the relevant spectral analysis suggested that the autoregulation-related response is not affected by prolonged exposition to microgravity. As to the complex regulation of arterial blood pressure, a maintained responsiveness to sympathetic stimuli was found, even in presence of indications of the cardiovascular deconditioning, such as tachycardia, reset of baroreflex, cardiopulmonary unloading. These preliminary results emphasized the necessity for more complex analyses of the main alterations and compensatory mechanisms elicited by microgravity-induced-cardiovascular deconditioning, in order to develop more effective long term strategies to prevent it.**

I. Introduction

CARDIOVASCULAR (CV) deconditioning occurring under actual or simulated microgravity has been extensively studied, but several issues still need to be addressed in order to achieve a deeper characterization of the main alterations that affect the regulatory mechanisms of the CV function. Although the reset of the baroreflex, the tachycardiac response to compensate for the reduction of stroke volume, the diminished blood volume, the decreased peripheral vascular resistances [1] and the reduction of the sympathetic mediated vasoconstrictive response [2] are among the most relevant experimental findings that defined the paradigm of CV deconditioning, there are open questions as to the compensation to the blunting of the global control. In particular, the role of vascular responses in the systemic regulation is a marginally addressed problem in the field of CV variability (CVV). Still, the assessment of the systemic effects of peripheral mechanisms should assume great importance when the global regulation is blunted or impaired. Nevertheless, CV deconditioning due to microgravity is characterized by edema phenomena that can perturb local responses and their capability of modulating peripheral resistances [3].

In this paper, CV variables from a bed rest protocol will be analyzed by means of a previously published model [4], in order to separate the vascular components of arterial blood pressure (ABP) variability from other sources of beat-by-beat ABP regulation and discuss their altered responsiveness to microgravity-induced CV deconditioning.

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II. Methods

A. Experimental Protocol

Seven young, healthy subjects (age 24 years ± 3.5; weight 78 kg ± 7.7; height 182 cm ± 5.6), all non-smokers, were enrolled in a 14 days head down tilt (-6°) bed rest (HDTBR) campaign, for which they signed the informed consent. The study was approved by the ethical committee of the School of Medicine of the University of Udine, Udine, Italy. Each subject had abstained from caffeine for 24h before the beginning of the HDTBR and no caffeine was allowed during HDTBR period. Two different types of experiments were carried out before and after the HDTBR period; both of them were characterized by a major sympathetic stimulus:

- before the beginning and one day after the end of HDTBR, a tilt test was performed.
- before and after bed rest, two identical protocols of exercise took place. They consisted of a habituation epoch at rest (Rest) and two epochs of exercise on a cycle-ergometer (Monark 839E, Sweden).) at 50 W (Exe1) and 100 W (Exe2), each of them followed by a period of recovery at rest (respectively Rec1, Rec2). During the whole duration of the exercise protocol, the subjects were sitting on the cycle-ergometer.

During both experiments, ABP (Portapress; TPD Biomedical Instrumentation, Amsterdam, The Netherlands) and ECG (ECG 100C, BioPac systems Inc., Santa Barbara,

CA) were continuously recorded; for the exercise protocol, respiration (Tuba; GHG, Switzerland) was acquired as well. Sampling frequency of the recordings was 100 Hz.

B. Pre-processing of the signals, model of CV interactions

Artifact free, stationary segments approximately 3 minutes long were picked for each epoch of the protocols and beat-by-beat series of RR intervals, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), respiration, were identified on the signals. Pulse pressure (PP) series was obtained as difference between SAP and DAP in each beat.

A multivariate (MV) parametric model (Fig. 1) [4] for the investigation of CV dynamics was applied to data. This model describes the relationship between measured CV variables, such as respiration, heart rate (HR), or equivalently heart period (HP), SAP, DAP, PP in order to derive a black-box estimation of the physiological mechanisms characterizing their closed-loop interactions.

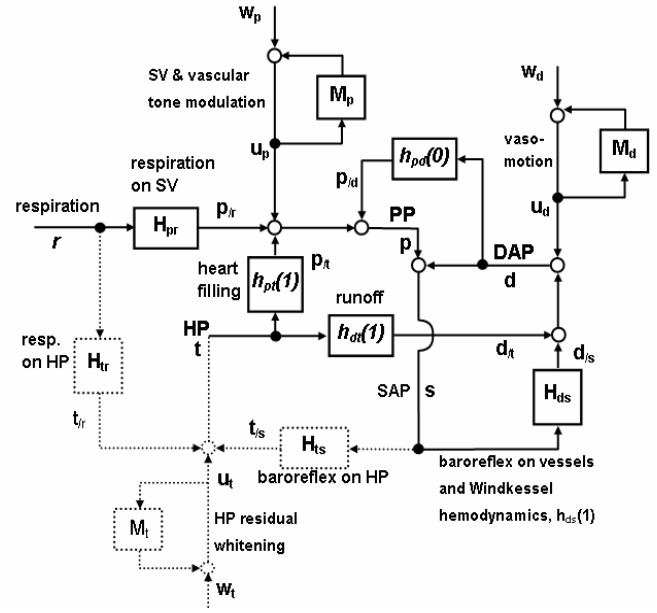

Fig. 1: Multivariate parametric model of diastolic pressure (DAP) {*d(i)*} and pulse pressure (PP) {*p(i)*} prediction from heart period (HP) {*t(i)*}, respiration {*r(i)*}, and systolic pressure (SAP) {*s(i)*}. HP prediction (dotted blocks and arrows) is also included for the MV joint process assessment (from [4]).

The model belongs to the ARXAR (autoregressive with exogenous input) class. Causal blocks are all-zero FIR filters fed by an exogenous input (X components of the model); all residuals u_i are autoregressive (AR) uncorrelated processes, fed by white noises w_i. The exogenous inputs are respiration and the three residuals of the loops of DAP, PP and HP.

For the purposes of this paper, we focused on the closed-loop models for the prediction of DAP and PP, whose separation into components allows to disentangle the complex interactions between global, neural control of vascular resistances, heart period duration, cardio-respiratory modulations, vascular autoregulation [4].

As to the tilt tests, since no measurement of respiration was available, the analysis was limited to DAP prediction.

The AR model of DAP consists of three components as shown in the following equation:

$$DAP(i) = \sum_{j=1}^{n} h_{ds}(j)\cdot s(i-j) + h_{dt}(1)\cdot t(i-1) + u_d(i) = DAP_{/SAP} + DAP_{/HP} + u_d \quad (1)$$

The three components are respectively representative of:

- $DAP_{/SAP}$: global control of vascular resistance, such as arterial baroreflex on vessels;
- $DAP_{/HP}$: effect of HP variability on diastolic interval and decay;
- u_d: unmeasured sources of vascular resistance modulations, i.e. peripheral autoregulation;

As regards the prediction of PP, it is similarly decomposed into four components:

$$PP(i) = \sum_{j=0}^{n} h_{pr}(j)\cdot r(i-j) + h_{pt}(1)\cdot t(i-1) + h_{pd}(0)\cdot d(i) + u_d(i) = PP_{/RESP}(i) + PP_{/HP}(i) + PP_{/DAP} + u_p(i) \quad (2)$$

- $PP_{/RESP}$: cardiopulmonary (i.e., respiratory, cardio-pulmonary baroreflex) modulations of venous return, preload;
- $PP_{/HP}$: effect of HP variability on systolic duration;
- $PP_{/DAP}$: afterload;
- u_p: other modulations of cardiac ejection;

C. Data analysis

The optimal order of the model filters was assessed according to the minimum of Akaike Information Criterion (AIC) figure of merit, verifying the residual whiteness and estimating the model parameters by the generalized least squares. Whiteness and uncorrelation of residuals w_d, w_p, w_t, and w_r were tested via Anderson's test (p<0.05).

AR spectral analysis of the original beat-by-beat series and of the signals derived from model decomposition was performed. Classical CV spectral bands were considered and powers in the very low frequency (VLF, 0.003-0.04Hz), low frequency (LF, 0.04-0.15Hz) and high frequency (HF, 0.15-0.4Hz) bands were computed.

Statistical analysis to compare baseline recordings before and after HDTBR was carried out by means of paired t-test, both for the exercise protocol (where the t-test was applied to compare the Rest epochs) and for the tilt tests.

III. Results

A. Effects of bed rest on CV variables

The bed rest-induced cardiovascular deconditioning was first of all evaluated observing the alterations in the mean values of HR and ABP. The baseline recordings before and after bed rest were compared in order to verify the changes induced by the restoration of the orthostatic stress, with the subjects in upright position.

Consistently with literature on bed rest, HR was significantly higher (from 77±4 bpm to 93±2 bpm, P-value<0.05) and mean arterial pressure (MAP) was lower (from 94.3±3.5 to 83.2±2.2 mmHg, P-value<0.05) in

baseline (Rest) after HDTBR. Significant reductions (P-value<0.05) were found also in SAP (from 139.9±5.9 to 120.8±3.6 mmHg), DAP (from 71.5±2.8 to 64.3±2.0 mmHg) and PP (from 68.4±4.4 to 56.5±3.0 mmHg).

During exercise and recovery, the patterns of pressures (DAP, SAP, PP, MAP) all tended to respond to exercise attaining the same values displayed before HDTBR, so that no significant change was found comparing the exercise and recovery epochs before and after HDTBR.

B. Spectral analysis of ABP components

Fig. 2 shows the total power of DAP and components during the exercise protocols, before and after HDTBR.

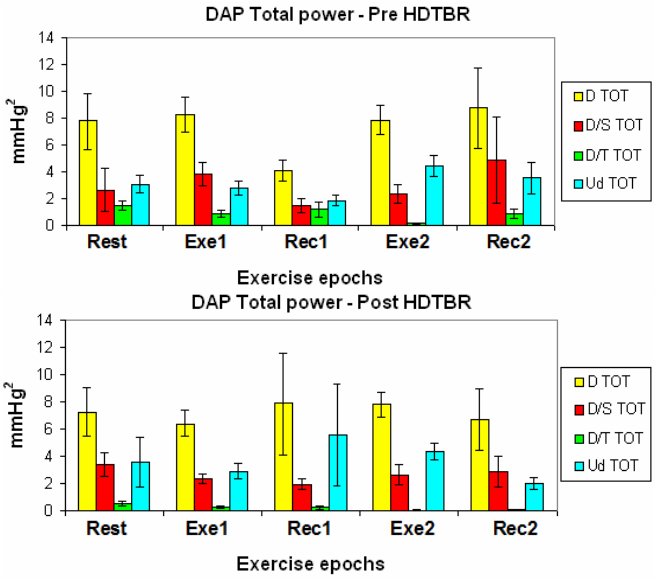

Fig. 2: Total power of DAP, $DAP_{/SAP}$, $DAP_{/HP}$, u_d before (top) and after (bottom) bed rest, across the epochs of the exercise protocol.

Most of DAP power was mediated by its systolic-dependent component ($DAP_{/SAP}$) and by the residual u_d. Although no significant differences were revealed by statistical analyses, an increasing trend of the weight of the residual and a decreasing trend of the weight of $DAP_{/SAP}$ component in explaining DAP variability were observed.

The effect of HP became negligible after bed rest.

The power of the residual was predominant in the VLF band, both before and after HDTBR, as expected.

The spectral decomposition of PP (fig. 3) showed an expected decrease of the HP dependent modulations after bed rest and, more interestingly, a considerably diminished role of the respiration. The role of DAP in the DAP to PP loop seemed to be unaffected by the bed rest.

In the tilt experiments, the power of the residual u_d was mainly concentrated in the VLF band and did not vary significantly with the tilting maneuver or after bed rest.

DAP power in the VLF did not change significantly with tilt, potentially as a result of the unaltered peripheral responses after bed rest. The LF power of DAP increased with the tilting after bed rest, whereas the trend was not significant before. The LF power of both DAP and DAP/SAP were increased in response to tilt (see Table I).

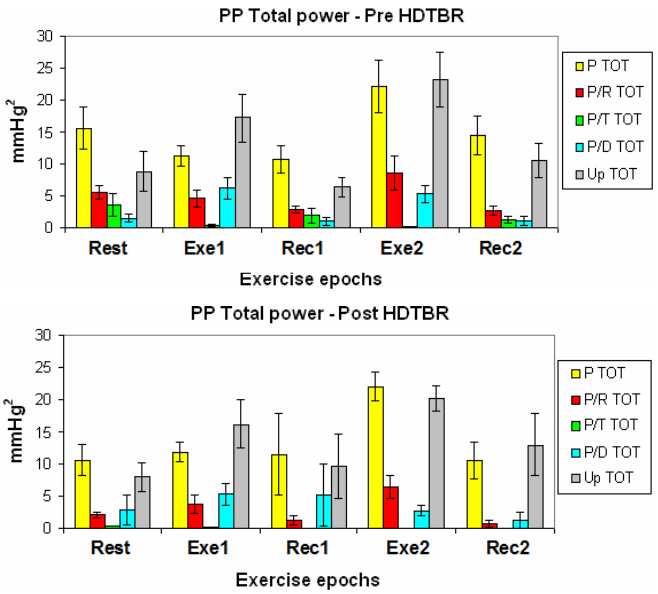

Fig. 3: Total power of PP, $PP_{/RESP}$, $PP_{/HP}$, $PP_{/DAP}$ u_p before (top) and after (bottom) bed rest, across the epochs of the exercise protocol.

The power of PP in both the LF (significant only before bed rest) and the HF (significant only after bed rest) band showed an increasing tendency with tilt.

In addition, for the tilt protocol the cardiac baroreceptor reflex sensitivity (BRS) was assessed by cross-spectrum analysis, i.e. as the average gain of the transfer function between SAP and RR in the range where the coherence is high (≥0.5) in either LF (α_{LF}) and HF band (α_{HF}) [5]. As table I shows, the α_{HF} at upright position displayed a significant reduction *after HDTBR* with respect to the values obtained before the bed rest p (P-value<0.05).

IV. Discussion

The tachycardiac response is meant to compensate for the reduced stroke volume and myocardial contractility caused by bed rest, so that cardiac output can be maintained unaltered [1]. The increased HR produced an expected and remarkable decrease in the power of the component of DAP dependent on HP series.

The diminished MAP was likely due to the decrease in total peripheral resistance (TPR). This suggested a blunted vasomotor tone, which could depend on the reset of the baroreflex and be also consistent with the inhibited sympathetic discharge [2]. These observations were supported by spectral analysis. In particular, DAP showed a lower total power and LF power after HDTBR.

Although no significant reductions were found in the $DAP_{/SAP}$ component, the combined effect of a reduced effect of both HP variability and sympathetic activity, coupled withan impaired baroreflex sensitivity, could explain the decrease of the overall variability of DAP.

As to the diastolic residual u_d it was previously [4] proposed as an index of the role of autoregulation in

TABLE I
Values of LF and HF spectral components assessed on DAP, PP and the estimated DAP/SAP signals (avg±std).Spectral indices of PP and DAP are in $mmHg^2$. The P-values refer to the comparisons between the rest and tilt condition.

	PRE bed rest			POST bed rest		
	rest	**tilt**	**P-value**	**rest**	**tilt**	**P-value**
$\mathbf{LF_{DAP}}$	573.083± 642.006	1407.233±1027.745	0.08	302.335±148.172	1380.568±1441.799	0.06
$\mathbf{LF_{DAP/SAP}}$	226.367±336.964	528.048±431.716	0.07	86.165± 65.206	733.998±830.158	0.04
$\mathbf{LF_{PP}}$	837.635± 754.395	1558.785±1113.941	0.06	613.422± 384.821	1631.926±1784.464	0.12
$\mathbf{HF_{PP}}$	489.397± 428.411	600.987± 381.501	0.56	167.795± 89.539	524.434± 258.293	0.01
BRS $\boldsymbol{\alpha_{LF}}$	9.465±2.964	6.471±1.918	0.05	6.742±4.555	5.791±1.731	0.63
BRS $\boldsymbol{\alpha_{HF}}$	13.561±5.876	6.352±3.397	0.03	10.554±3.536	3.693±1.198	0.01

mediating systemic ABP oscillations. Its preponderant power content in the VLF band, was consistent with the typically slow rhythms of vascular phenomena supported by spectral analysis. In particular, DAP showed a lower total power and LF power after HDTBR.

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As to the diastolic residual u_d it was previously [4] proposed as an index of the role of autoregulation in mediating systemic ABP oscillations. Its preponderant power content in the VLF band, was consistent with the typically slow rhythms of vascular phenomena.

The trends of pressures during exercise and in response to tilt appeared maintained after bed rest and did not show any significant difference. Such findings suggested that, although the CV deconditioning could take place and affect the sympathetic activity [2] and produce a general reset of the baroreflex and other reflexes, the responsiveness of the regulatory systems to typical sympathetic and orthostatic stimuli may be not inhibited by prolonged bed rest.

As regards the responses to exercise as a countermeasure, the high power of the residual after bed rest can suggest that: 1) autoregulation mechanisms and responses are not affected by the suppression of gravitational stimuli and could potentially emerge with more relevance in compensating the blunting of systemic, neural control; 2) other mechanisms could appear when global control is blunted and play a bigger role, whereas they are normally unimportant and screened by the strong role of major controllers.

With respect to the results of the tilt tests performed before and after the HDTBR, it may be hypothesized that the impaired sympathetic nerve activity which has been reported after bed rest [2] potentially blunts the normal sympathetic vasomotor tone control, without losing its responsiveness to the insurgence of a strong sympathetic stimulus, such as tilt. This was confirmed by the increased LF of DAP, $DAP_{/SAP}$ and PP. Interestingly, the raise in both LF and HF of SAP that was observed in [6] in response to tilt was here separated into the DAP and PP responses: it appeared that DAP is responsive to the sympathetic stimulus, both before and after bed rest (thus hinting at an unaltered responsiveness of pressure regulation to sympathetic stimuli), whereas PP is mostly associated to cardiopulmonary modulations. This could be related to phenomena of cardiopulmonary unloading that may occur in response to bed rest and that need to be better addressed.

V. Conclusion

This paper took into consideration two different experimental protocols, both characterized by a sympathetic stimulus before and after a 14-day HDTBR and proposed a novel approach to the quantitative characterization of CV deconditioning, based on a previous model of the interactions between CV variables. The potential advantage of this approach is represented by the capability of estimating indices inherent to the vascular dynamics, thus integrating the information relevant to the global control. From a physiological point of view, the role of autoregulation in responding to CV deconditioning and compensating for the reset of global controls, as well as the partially maintained responsiveness of regulation systems, deserve further attention, following in the path of this preliminary analysis.

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