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BREATHING MODULATION OF CARDIOPULMONARY COUPLING – A POTENTIAL WAY OUT OF AUTONOMIC DECONDITIONING AFTER PROLONGED MICROGRAVITY EXPOSURE

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Abstract: Microgravity causes a specific consequence on cardiovascular system – an orthostatic intolerance experienced by astronauts after long space flights. The major reason for this phenomenon is deconditioning of the cardiovascular autonomic regulation due to microgravity environment. Sympathetic withdrawal is the consequence of cephalad shift of blood and body fluids which is considered as a primary cause of several neurophysiologic disturbances during the space flight and postflight recovery (postural hypotension, sleep disturbances, low stress coping abilities). Cardiopulmonary coupling is the issue that potentially offers the possibility of the autonomic conditioning before and during the spaceflight. In humans, as opposed to cardiac rhythm, breathing can undergo volitional control. Paced 0.1 Hz breathing rhythm is characteristic, resonant frequency of many autonomic and cortical circuits, which amplifies heart rate modulation on one side, and recruits central cortical and subcortical circuits resulting in increased sleep propensity and relaxed attentive consciousness. We applied a battery of coefficients estimating the change of self-similarity and irregularity of heart rate and respiratory rate in four different states: supination, standing, supination with 0.1 Hz breathing and standing with 0.1 Hz breathing (Matić et al. 2020). Additionally, we analysed the posture and breathing regime dependence of quotient of pulse per respiration (Qpr), the number of heartbeats in each respiratory cycle. Chosen parameters are of importance for evaluation of cardiopulmonary adaptability and plasticity. Our results (Matić et al. 2020) and state dependent Qpr relation vs. breathing

rate support the evidence that cardiorespiratory coupling and cardiorespiratory variability are posture and breathing regime dependent, with the state of combined standing with 0.1 Hz breathing identified as the state with maximal conditioning effect on heart rate, respiratory rate, and cardiorespiratory coupling. We propose this manoeuvre as the autonomic conditioning strategy for the crew before long space flights.

Keywords: microgravity, autonomic nervous system, cardiopulmonary coupling, space flight, autonomic conditioning strategy

1. INTRODUCTION

Autonomic nervous system (ANS) is a functional division of the nervous system, with structural parts in both the central nervous system and the peripheral nervous system, controlling the glands and all the internal organs (viscera) including cardiovascular system. In general, ANS has great ability to adjust physiological functions to respond to internal and external demands, with respect to changes of internal natural rhythms, changing states of activity (standing, sitting, laying, sleeping, running etc.), geophysical conditions and environmental rhythms. Gravity is one of the most important and constantly present factors that ANS accounts while regulating the blood pressure and heart rate (Levy & Martin 1996). Human ANS has evolved to use both homeostatic and homeodynamic regulation patterns in Earth gravitational field of 1 g (Patel 2020, Ernst 2014, Matić et al. 2020).

During sojourn in space stations astronauts are exposed to entirely different conditions due to presence of strong cosmic radiation and almost complete absence of gravity (these two factors might even produce negative synergetic influence on health (Patel 2020)). Even though astronauts float in space stations, the force of gravity there is not zero, rather it is very attenuated. Therefore, it is called microgravity (μg) (Nassef et al. 2020). Acceleration of gravity on Earth is well known g=9.78-9.83 m/s^2 (Faller et al. 2020); and so far, measured acceleration of microgravity varies in broad range: $g=10^{-6}$-10^{-4} m/s^2 (Dong et al. 2019). Without μg space stations would be unable to orbit the Earth. However, according to astromedical research μg turns out to be very inhospitable and pathogenic condition for human organism (Patel 2020, Antonutto & Prampero 2003, Demontis et al. 2017). For the relevance of astromedicine μg is characterized as "mechanically unloaded condition" (Wuest et al. 2018). Since g of Earth has been almost unchanged during life and human evolution, "there is little or no genetic memory in organisms on how to respond" (Nassef et al. 2020) to shift from g to μg. Therefore, it has been estimated that one week of presence in μg environment decreases size and weight of the heart for about 25% (Hill & Olson 2008). This is equal to atrophy of heart muscle that happens after six weeks of bed immobility (Hill & Olson 2008, Hargens & Vico 2016, Payne et al. 2007). Staying in μg causes similar reductive changes to other structures like skeletal muscles (Trappe et al. 2009) and bones (Holick 2000). In addition to these adverse effects, μg induces a typical consequence on cardiovascular system – an orthostatic intolerance

experienced by astronauts after a long space flight (Antonutto & Prampero 2003, Xu et al. 2020, Gaffney 1987), which might be followed by hypotension and syncope episodes (Eckberg et al. 2016).

Orthostatic intolerance is defined as incapacity of the cardiovascular system to maintain required arterial blood pressure in central circulation in orthostatic body position (Goldstein 2001). Orthostatic intolerance can be induced in terrestrial conditions by genetic predisposition, prolonged laying down in bed or infection, while the major reason for orthostatic intolerance in space is deconditioning of the cardiovascular autonomic regulation due to microgravity environment (Goldstein 2001) (Figure 1.).

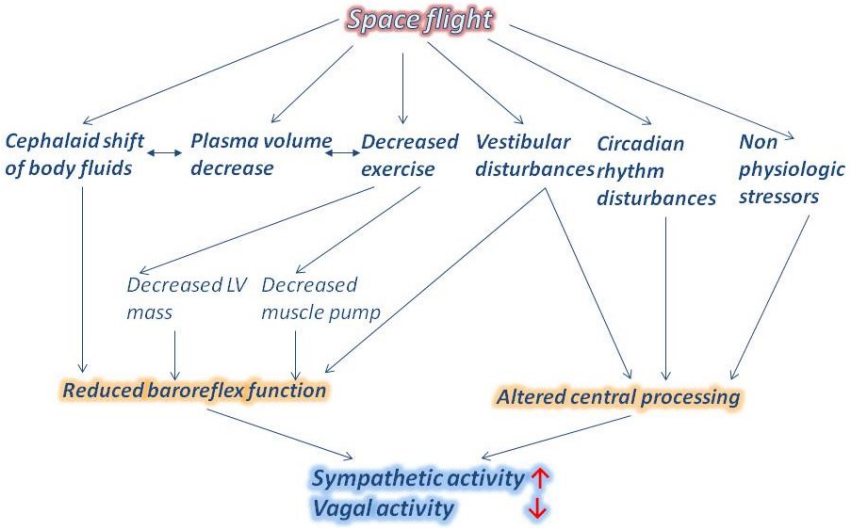

Figure 1: Major physiological disturbances affecting autonomic cardiovascular control during space flight (adapted from Mandsager et al. (2015)).

Cardiopulmonary coupling, an intriguing reciprocal interface of heart period and respiratory signal oscillations, represents the physiological solution for energetic efficiency of oxygen transport (Feldman & Ellenberger 1988) and organism adaptability to external and internal challenges (Porges 2007). Beside eye blinking (Ren et al. 2019), breathing in humans is a rare function that might be shifted from automatic and autonomic control to volitional (paced) performance (Negro et al. 2018). As such, paced breathing, through cardiopulmonary coupling (Migeotte et al. 2003, Xu et al. 2013), is a potential possibility for autonomic conditioning related to microgravity challenge before and during spaceflights.

The physiological terrestrial conditions, important for our paradigm, are:

- Orthostasis: gravity challenge for autonomic cardiovascular regulation, characterized by the highest sympathetic modulation of heart period in physiologic quiescence (Levy & Martin 1996), and
- Paced 0.1 Hz breathing: characterized by resonant frequency of many autonomic and cortical circuits which amplifies respiratory,

parasympathetic heart rate modulation (Matić et al. 2020, Migeotte et al. 2003) on one side, and recruits central cortical and subcortical circuits resulting in increased sleep propensity and relaxed attentive consciousness (Noble & Hochman 2019) on the other side. It is characterized by the highest respiratory mediated vagal modulation of heart period, in physiologic quiescence (Cooke et al. 1998).

The aim of our research was to investigate individual and joint effect of these conditions on cardiorespiratory coupling in nonlinear and linear domains, defining in this way potentially the most beneficial behavioural pattern for cardiorespiratory conditioning before and during the spaceflight. Special focus is put on state dependent changes in quotient of pulse per respiration (Qpr), a bidimensional autonomic parameter closely correlated to ventilation/perfusion relation, and state dependent Qpr vs. BR relations. Paced 0.1 Hz breathing, by optimization of blood oxygenation and together with arterial pressure conditioning (Karavaev et al. 2009), could be an important behavioural strategy for coping with autonomic outburst such as orthostatic hypotension. In this paper we will analyse the cardiorespiratory features of spontaneous and paced 0.1 Hz breathing in supine and standing position, focusing on respiratory rate - heart period interrelation, to compare experimental Qpr with simulated data results (Scholkmann & Wolf 2019).

2. METHODS

Electrocardiogram (ECG) and respiration signal acquisition was done by means of Biopac MP100 system (Biopac System, Inc, Santa Barbara, CA, USA; AcqKnowledge 3.91 software). For details, see Matić et al. (2020).

We investigated in terrestrial conditions 20 healthy human subjects for changes using ECG RR interval (RRI) and respiratory signal (Resp) measures of detrended fluctuation analysis (DFA) (Peng et al. 1995a, Peng et al. 1995b, Peng et al. 2002, Fadel et al. 2004, Ivanov et al. 1999, Gierałtowski et al. 2013, Kristoufek 2014, Barbieri et al. 2017) (α_{1RRI}, α_{2RRI}, α_{1Resp}, α_{2Resp}); multiscale entropy (Costa et al. 2003, Silva et al. 2017a, Silva et al. 2017b, Silva et al. 2016) (MSE_{RRI1-4}, $MSE_{RRI5-10}$, $MSE_{Resp1-4}$, $MSE_{Resp5-10}$); methods of nonlinear cardiorespiratory coupling, cross DFA (Kristoufek 2014, Podobnik & Stanley 2008, Horvatic et al. 2011, Podobnik et al. 2011, Zebende 2011, Kwapień et al. 2015) (ρ_1 and ρ_2), cross MSE (Richman & Moorman 2000, Costa et al. 2005) (X_{MSE1-4} and $X_{MSE5-10}$) and linear cardiorespiratory coupling, spectral coherence (Daoud et al. 2018) ($Coh_{RRI-Resp}$) and pulse/respiration quotient (Scholkmann & Wolf 2019, Hildebrandt 1954, Scholkmann et al. 2019) (Qpr), in four physiological conditions:

- supine position with spontaneous breathing (supin),
- standing with spontaneous breathing (stand),
- supine position with 0.1Hz breathing (supin01) and
- standing with 0.1 Hz breathing (stand01). (Matić et al. 2020)

In the same conditions we analysed the relation of Qpr vs breathing rate (BR, 1/min) to evaluate on experimental data a hyperbolic relation of Qpr vs. BR, previously reported on simulated data (Scholkmann & Wolf 2019).

2.1. DATA PROCESSING

Data processing for DFA, MSE, ρ_1, ρ_2, X_{MSE} and $Coh_{RRI–Resp}$ are explained in (Matić et al. 2020) in detail; R peaks and the beginnings of breathing cycles (B nadirs) were detected within the ECG and respiration signal using Pick Peak tool of Origin software (Microcal, Northampton, MA, USA) (Figure 2.).

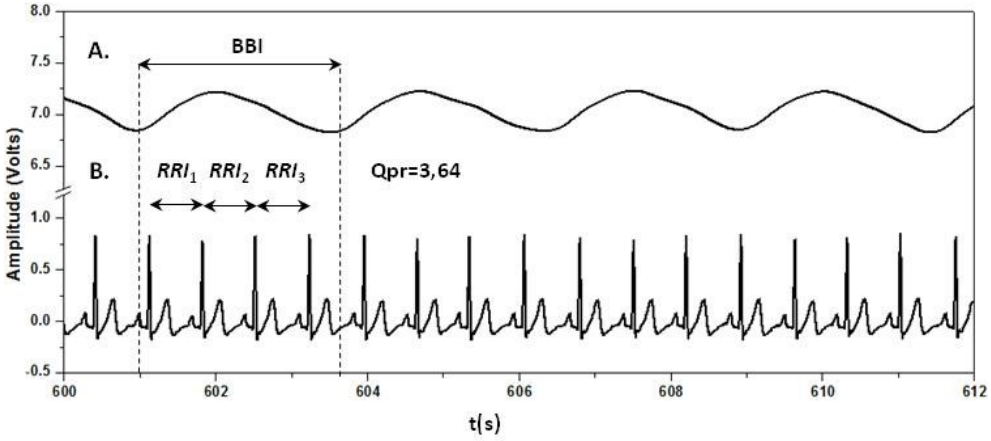

Figure 2: Segment of respiratory signal (A.) and ECG signal (B.) in one subject, recorded simultaneously, in a supine state with spontaneous respiration, for 12s selected from a total of 1200 s registered in this condition. *RRI* -time interval between two adjacent R peaks of ECG, *BBI* -breath-to-breath interval, Qpr -quotient of pulse per respiration, number of heart beat intervals in each breath-to-breath interval.

Then, BB and RR intervals were calculated as differences between successive x coordinates of R peaks and B peaks:

X(i)=col(Pkx)[i+1]-col(Pkx)[i] (1)

col(Pkx)[i] – column of x (time) coordinates of detected signal peaks

col(Pkx)[i+1] – column of x (time) coordinates of subsequently detected signal peaks

X(i) - *RRI*(i) or *BBI*(i), with respect to the type of signal (ECG or breathing)

Qpr was calculated according to the following procedure (explained for the first breathing interval as an example). Suppose that respiratory and R peaks were arranged in the following order (i.e., – points in time when inspiration and expiration started, respectively, r – occurrence of an ECG R peak):

Respiration e.....i1.....e.....i2.....

R peaks r0.....r1...r2 .....r3....r4...r5....r6

Number of intervals 1 2 3 4

First, we counted integer number of whole r…r intervals that fell between i1 and i2. In this case there were three of them: r2 - r1, r3 - r2 and r4 - r3. Then parts of the boundary r…r intervals that belong to (i1, i2) breathing interval, as non-integer parts of the Qpr, were added:

$$b1(i1,i2) = (r1-i1) / (r1-r0), \quad \text{and} \quad b2(i1,i2) = (i2-r4) / (r5-r4). \tag{2}$$

Finally, total (integer and decimal) value of Qpr belonging to (i1, i2) breathing interval was calculated as

$$Qpr(i1,i2) = 3 + b1(i1,i2) + b2(i1,i2). \tag{3}$$

3. RESULTS

To investigate the relation of Qpr with breathing rate (BR) we plotted Qpr values vs. BR (Figure 3.)

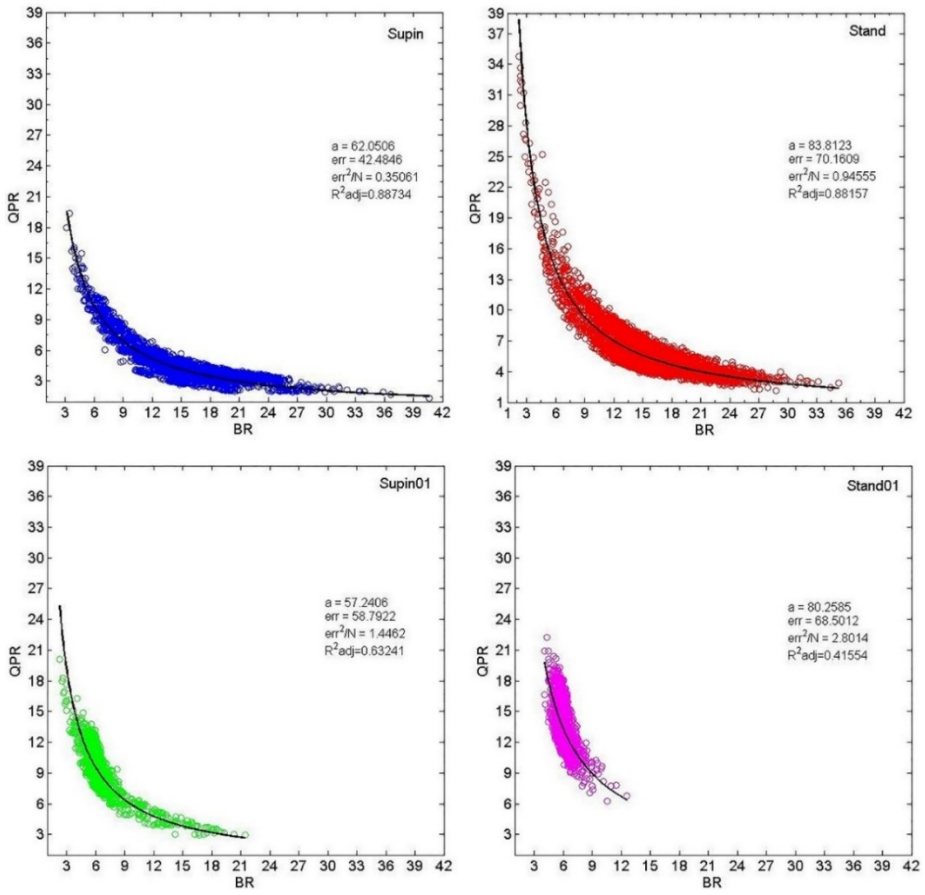

Figure 3: The state-specific correlation pattern between pulse respiration coefficient (Qpr) and breathing rate (BR, 1/min) for 20 healthy subjects. supin-supine position with spontaneous breathing; stand – standing; supine01-supine position with paced 0.1Hz breathing; stand01 - standing with paced 0.1 Hz breathing.

Table 1: Linear and nonlinear parameters (mean ± SD) of 20 healthy subjects (adopted from Matić et al., 2020 and completed by Qpr data for comprehensive analysis). Supin-supine position with spontaneous breathing; stand - standing; supin01-supine position with paced 0.1Hz breathing; stand01 - standing with paced 0.1 Hz breathing; RRI - interval between two adjacent R peaks of ECG, i.e. heart period; mRRI - mean value of RRI signal; sdRRI - standard deviation of RRI signal; α_{1RRI} - short term fractal scaling exponent of RRI signal; α_{2RRI} - long term fractal scaling exponent of RRI signal; θ_{RRI} – inter-fractal angle of RRI signal; MSE_{RRI1-4} - short term multi scaling entropy of RRI signal (for 1-4th sample); $MSE_{RRI5-10}$ - long term multi scaling entropy of RRI signal (for 5-10th sample); mResp - mean value of respiration signal; sdResp - standard deviation of respiration signal; α_{1Resp} - short term fractal scaling exponent of respiration signal; α_{2Resp} - long term fractal scaling exponent of respiration signal; θ_{Resp} – inter-fractal angle of respiration signal; $MSE_{Resp1-4}$ - short term multi scaling entropy of respiration signal (for 1-4th sample); $MSE_{Resp5-10}$ - long term multi scaling entropy of respiration signal (for 5-10th sample); $Coh_{RRI-Resp}$ - RRI-respiration spectral coherence; Qpr – quotient of pulse per respiration; $\rho_{DCCARRI-Resp}$ - RRI-respiration detrended cross correlation coefficient; ρ_1 - short term scaling RRI-respiration detrended cross correlation coefficient; ρ_2 - long term scaling RRI-respiration detrended cross correlation coefficient; X_{MSE1-4} - short term RRI-respiration cross multi scaling entropy; $X_{MSE5-10}$ - long term RRI-respiration cross multi scaling entropy.

group	parameter	Supin	Stand	Supin01	Stand01
Cardiac parameters	mRRI [s]	0.9937 ± 0.1377	0.7263 ± 0.1021	1.0592 ± 0.1257	0.7480 ± 0.0867
	sdRRI [s]	0.0621 ± 0.0237	0.0465 ± 0.0175	0.0905 ± 0.0347	0.0702 ± 0.0225
	α_{1RRI}	0.8975 ± 0.1925	1.3114 ± 0.1379	1.0342 ± 0.1421	1.3408 ± 0.1005
	α_{2RRI}	0.8232 ± 0.1244	0.7874 ± 0.1249	0.6922 ± 0.1647	0.5545 ± 0.1463
	θ_{RRI} [^{0}]	2.2 ± 8.3	14.5 ± 5.6	11.5 ± 8.7	24.6 ± 6.7
	MSE_{RRI1-4}	1.7936 ± 0.1783	1.5583 ± 0.2974	1.6713 ± 0.2463	1.4715 ± 0.1784
	MSE_{RR5-10}	1.7706 ± 0.2138	1.8951 ± 0.2391	1.4991 ± 0.1848	1.9123 ± 0.1732
Respiratory parameters	mResp [s]	4.55 ± 1.45	4.56 ± 1.78	10.0605 ± 0.1942	9.9676 ± 0.1466
	sdResp	0.89 ± 0.61	1.09 ± 1.35	1.4235 ± 0.9437	1.0313 ± 0.4060
	α_{1Resp}	0.3679 ± 0.2603	0.4975 ± 0.2728	0.9268 ± 0.3133	1.1387 ± 0.2357
	α_{2Resp}	0.5848 ± 0.2319	0.6119 ± 0.2132	0.4850 ± 0.2003	0.3759 ± 0.1028
	θ_{Resp} [^{0}]	-10.3 ± 18.8	-5.5 ± 18.5	16 ± 16.1	27.5 ± 7.2
	$MSE_{Resp1-4}$	1.4456 ± 0.2631	1.3185 ± 0.4117	1.3772 ± 0.3074	1.0995 ± 0.2837
	$MSE_{Resp5-10}$	1.1396 ± 0.2532	1.0423 ± 0.3523	1.3040 ± 0.3065	1.3382 ± 0.3132
Cardio-pulmonary coupling	$Coh_{RRI-Resp}$	0.8983 ± 0.0563	0.7397 ± 0.1986	0.8703 ± 0.1137	0.8663 ± 0.1363
	Qpr	4.8118 ± 1.6659	6.3854 ± 2.4308	9.4144 ± 1.2062	13.4761 ± 1.6591
	ρ_1	-0.2419 ± 0.1905	-0.2002 ± 0. 1916	-0.0096 ± 0. 2665	-0.0697 ± 0.2787
	ρ_2	-0.1346 ± 0. 1314	-0.0190 ± 0.1234	-0.0232 ± 0.2471	0.0097 ± 0.2429
	X_{MSE1-4}	2.2733 ± 0.20298	2.2719 ± 0.40199	2.1490 ± 0.24829	1.9344 ± 0.21773
	$X_{MSE5-10}$	2.1765 ± 0.21385	2.1253 ± 0.27514	2.3176 ± 0.15034	2.4292 ± 0.46726

Table 2: Change of linear and nonlinear cardiorespiratory parameters in different conditions (p-value of Wilcoxon signed-rank test for 20 healthy subjects (adopted from Matić et al., 2020 and completed by Qpr data for comprehensive analysis); ↓-decrease of the change; ↑-increase of the change). supin-stand – supine position (with spontaneous breathing) vs. standing position (with spontaneous breathing); supin-supin01 – supine position (with spontaneous breathing) vs. supine position with paced 0.1 Hz breathing; supin-stand01 – supine position (with spontaneous breathing) vs. standing with paced 0.1 Hz breathing; bolded numbers - results with statistical significance ($p<0.05$); RRI - interval between two adjacent R peaks of ECG, i.e. heart period; mRRI - mean value of RRI signal; sdRRI - standard deviation of RRI signal; α_{1RRI} - short term fractal scaling exponent of RRI signal; α_{1Resp} - short term fractal scaling exponent of respiration signal; α_{2RRI} - long term fractal scaling exponent of RRI signal; α_{2Resp} - long term fractal scaling exponent of respiration signal; MSE_{RRI1-4} - short term multi scaling entropy of RRI signal (for 1-4th sample); $MSE_{RRI5-10}$ - long term multi scaling entropy of RRI signal (for 5-10th sample); $MSE_{Resp1-4}$ - short term multi scaling entropy of respiration signal (for 1-4th sample); $MSE_{Resp5-10}$ - long term multi scaling entropy of respiration signal (for 5-10th sample); $Coh_{RRI-Resp}$ - RRI-respiration spectral coherence; Qpr- quotient of pulse per respiration; ρ_1 – short term scaling RRI-respiration detrended cross correlation coefficient; ρ_2 – long term scaling RRI-respiration detrended cross correlation coefficient X_{MSE1-4} – short term RRI-respiration cross multi scaling entropy, $X_{MSE5-10}$ – long term RRI-respiration cross multi scaling entropy.

group	parameter	supin-stand	supin-supin01	supin-stand01
Cardiac parameters	mRRI	**0.000**↓	0.306	**0.000**↓
	sdRRI	**0.072**↓	**0.021**↑	0.831
	α_{1RRI}^{*}	**0.000**↑	**0.030**↑	**0.000**↑
	α_{2RRI}^{*}	1.065	**0.027**↓	**0.000**↓
	θ_{RRI} [^{0}]	**0.000**↑	**0.006**↑	**0.000**↑
	MSE_{RRI1-4}	**0.015**↓	0.471	**0.000**↓
	$MSE_{RRI5-10}$	0.120	**0.000**↓	0.063↑
Respiratory parameters	mResp	1.805	-	-
	sdResp	2.968	-	-
	α_{1Resp}^{*}	0.273	**0.000**↑	**0.000**↑
	α_{2Resp}^{*}	2.775	0.273	**0.000**↓
	θ_{Resp} [^{0}]	0.942	**0.000**↑	**0.000**↑
	$MSE_{Resp1-4}$	1.335	1.485	**0.000**↓
	$MSE_{Resp5-10}$	1.149	0.258	**0.054**↑
Cardio-pulmonary coupling	$Coh_{RRI-Resp}$	**0.018**↓	2.703	2.712
	Qpr	**0.000**↑	**0.000**↑	**0.000**↑
	ρ_1	1.194	**0.003**↑	**0.072**↑
	ρ_2	0.015	0.228	0.105
	X_{MSE1-4}	2.397	0.402	**0.000**↓
	$X_{MSE5-10}$	0.981	0.189	**0.051**↑

4. DISCUSSION AND CONCLUSION

Our results show that cardiopulmonary coupling exhibits state specific characteristics in both linear and nonlinear domain. Standing with slow 0.1 Hz breathing (stand01), the physiologic condition characterized by the highest capacity for cardiopulmonary adaptation (Tables 1. and 2., nonlinear cardiopulmonary coupling) resulted with the highest mean values and the lowest standard deviation of Qpr.

This speaks in favour of the hypothesis that development of adaptive capacity and sympatho-vagal responsiveness (Eckberg et al. 2016, Malik et al. 2019) of the organism to external demands (parameters of nonlinear cardiorespiratory variability) occurs during highly regular relation of HR vs. BR (Qpr). Regarding the Qpr vs. BR relation, states with spontaneous breathing (supin and stand) are characterized by specific hyperbolic correlation, with high standard deviation. These conditions characterized by typical cardiovascular patterns (dominant vagal vs. dominant sympathetic HR modulation, respectively) form two distinct hyperbolic distributions analogue to the "family" of different, parallel hyperbolas, as it was reported in Scholkmann & Wolf (2019). The results of hyperbolic Qpr vs. BR dependence were, until now, reported only on simulated signals, in spontaneous breathing regime (Scholkmann & Wolf 2019). Our data, for the first time, confirm this relation on experimental signals.

Breathing rate, as a *modifiable variable* both in healthy and diseased subjects, invokes special interest for its impact on cardiovascular variables and cardiopulmonary coupling. In our results it was shown for the first time that BR restricts the deviation of Qpr values to BR range specific for our study (6.1±1.4/min), without changing the "y level" of respective posture specific Qpr vs. BR hyperbola. This relative Qpr constancy, specific for paced 0.1 Hz breathing could be of particular importance for memory and learning process of cardiorespiratory networks in physiologic conditions requiring greater adaptive capacities of cardiorespiratory system (specific pattern of nonlinear RRI and Resp variability, Table 1. and Table 2.). In general terms, terrestrial respiratory pacing (i.e., "tuning") of desired Qpr could be the strategy of cardiorespiratory autonomic networks training for the optimal ventilation/perfusion efficiency of cardiorespiratory system in accordance with behavioural demands and the duration of planned spaceflight. Additional, extra terrestrially applied respiratory training protocol, in the conditions of artificial gravity could be preparation of ventilation/perfusion adaptive efficiency for the return into gravity conditions. To confirm these hypotheses, additional necessary studies are needed, regarding, in specific, the scale of long-term learning of cardiorespiratory networks (i.e., days, weeks or months). In parallel with space physiology, the practice of BR and postural manoeuvres could also have significant medical benefits as the ICU interventions beneficial for re-training of cardiorespiratory autonomic networks of artificially ventilated patients and their preparation for artificial respiration weaning (Matić et al. 2020, Papaioannou et al. 2011, Welsh et al 2020).

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