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Effectiveness of high-intensity jump training countermeasure on mitral and aortic flow after 58-days head-down bed-rest assessed by phase-contrast MRI

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Abstract

Aims. Prolonged immobilization generates cardiac deconditioning, a possible risk factor: efficient countermeasures (CM) are needed to prevent it. We aimed at assessing the effectiveness of high-intensity jump training CM on aortic and mitral flow by Phase-Contrast (PC) MRI during 60 days head-down (-6°) bed-rest (BR). Methods. 23 males (29±6 y, 181±6 cm, 77±7 kg) were enrolled at :envihab research facility in Cologne as part of the European Space Agency BR studies. Participants were randomly allocated to the jump training (JUMP, n = 12) or the control (CTRL, n = 11) groups. Training consisted of 4x10 countermovement jumps and 2x10 hops in a horizontal sledge jump system, with 5-6 sessions/week. PC-MRI images (3T Biograph mMR, Siemens) with interleaved three-directional velocity encoding (VENC: x and y: 80 cm/s; z: 150 cm/s) were obtained (spatial resolution 1.4 x 1.4 mm²) at the level of the aortic root, and of the mitral plane, before (BCD-4), after 21d (HDT21) and 58d (HDT58), and on the fifth day after BR conclusion (R+4). Velocity images were analysed to compute among others: cardiac output (CO), stroke volume (SV), max blood flow rate (Qpeak), systolic and heart beat duration (RR), rapid filling (Ewave) and early filling peak flow rate (Ef). Results. In CTRL, compared to BCD-4, at HDT58 a significant RR (14%) and systolic (10%) shortening, with a decrease in SV (22%), Qpeak (12%), Ewave (26%), Ef (26%) were observed. In CM, only RR was shortened (8%), together with a decrease in SV (12%), Qpeak (7.5%), Ewave (11%), Ef (15%). Interestingly, at R+4, compared to BCD-4, RR was still decreased by 10% in CTRL, while Ef increased by 18% and by 15%, respectively in CTRL and CM, where also CO (+19%) and SV (+8%) were increased. Conclusions. In this first study addressing aortic and mitral flow using PC-MRI during BR, cardiac deconditioning affected both flows. The applied CM was effective in partially opposing this phenomenon, inducing reduced changes at HDT58.

Keywords: head-down bed rest, cardiac magnetic resonance imaging, transvalvular flow, countermeasures

Acronyms/Abbreviations

Bed-rest (BR)
Countermeasure (CM)
Left ventricular (LV)
End-diastolic volume (EDV)
Stroke volume (SV)
Magnetic resonance imaging (MRI)
Phase-contrast (PC)
Jump training group (JUMP)
Control group (CTRL)
Velocity encoding (VENC)
Head-down tilt (HDT)
Cardiac output (CO)
Max blood flow rate (Qpeak)
Ejection phase duration (Syst)
Mean velocity at Qpeak (vQ)
Heart beat duration (RR)
Rapid filling (Ewave)
Atrial contraction filling (Awave)
Early filling peak flow rate (Ef)
Atrial contraction peak flow rate (Af)
Time-to-peak E (Ttp)
Deceleration time (DT)

1. Introduction

Ground-based studies allow observing human physiology during simulated microgravity conditions. Among them, the 6° head-down tilt BR, consisting in a model of chronic circulatory unloading, represents a unique opportunity to simulate sustained exposure to microgravity for studying the effects of prolonged space flight on the cardiovascular system, and to evaluate the

effectiveness of applied CM in reducing the undesired changes.

BR causes a fluid shift from the legs to the chest, thus leading to an increase in LV transmural pressure, EDV, and SV [1, 2]. These changes activate short-term volume regulatory mechanisms that result in plasma volume loss, with the achievement of a new hemodynamic steady state within 48 h characterized by decreased volume loading of the heart similar to what reported during space-flight [3,4]. This new steady state leads to LV remodelling, with a reduction in LV mass and EDV together with reduced cardiac distensibility and SV, potentially contributing to orthostatic hypotension when the gravitational gradients are restored [4, 5]. In previous (5 days÷5 weeks) BR studies, slowed ventricular relaxation and decreased diastolic suction have been reported [4, 6-11], mainly using Doppler echocardiography.

We hypothesized that prolonged immobilization (60 days) induced by BR could lead to even larger changes to the heart function. To image the heart, MRI is considered the gold standard, for its non-invasiveness and ability to provide high-quality images in any anatomical orientation, with less operator variability than ultrasound imaging. In addition, 2D PC-MRI is able to provide blood flow in-vivo assessment in a specific cross-sectional plane by the acquisition of MRI magnitude complemented by three modulated gradients inducing phase offsets between $\pm \pi$ to moving protons [12]. Their motion is then encoded into velocity data along three orthogonal directions, thus generating a full 4D velocity-map (3D spatial + 1D time) of the specific anatomical cross-section of interest.

Accordingly, our hypothesis was to accurately study using PC-MRI the changes in aortic and mitral flow induced by 60-days BR, and to evaluate the effectiveness of a novel sledge jump system CM.

The paper is organized as follows: in Section 2 a description of the BR, of the CM protocol, and of the imaging performed are presented. Section 3 reports the image processing applied to PC-MRI images to extract clinically useful parameters, while Section 4 describes the obtained results. In Section 5, a discussion of them is provided, followed by conclusions.

2. Material and methods

This paragraph provides details about the implemented BR study (more information can be found in [13]), as well as the performed imaging acquisition.

2.1 Study design

This BR study was conducted in the: envihab facility of the Institute of Aerospace Medicine at the German Aerospace Center (DLR) in Cologne, Germany. Two campaigns with initially 12 participants each were performed (the first started in August 2015, the second in January 2016), in which 6 subjects were randomly allocated to CTRL and 6 subjects to the exercise CM (JUMP) group. Each campaign consisted of 15 days of baseline data collection (BDC-15 through BDC-1), 60 days of HDT bed rest (HDT1 through HDT60) and 15 days of recovery (R+0 through R+14).

2.2 Subject population

Basic inclusion criteria were: male, age between 20 and 45 years, body mass index between 20–26 kg/m^2, non-smoking, no medication, no competitive athlete, and no history of bone fractures. One subject discontinued the study on BDC-4 for medical reasons unrelated to the study, thus resulting in 12 subjects in the JUMP group (age 30±7 years, height 181±7 cm and body mass 77±7 kg) and 11 subjects in the CTRL (age 28±6 years, height 181±5 cm and weight 76±8 kg).

The study was approved by the ethics committee of the Northern Rhine Medical Association (Ärztekammer Nordrhein) in Duesseldorf, Germany, as well as the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz), and all participants gave written informed consent to the experimental procedures.

2.3 JUMP Countermeasure training protocol

The applied CM consisted of a sledge jump system (Novotec Medical GmbH, Pforzheim, Germany), in which the participant is attached to the sledge via two straps around the shoulders, allowing movement in a natural manner [14], and a force pulling the sledge towards the force plates is generated by four low-pressure cylinders (range 0÷1800 N).

The CM group underwent the sledge jump protocol in 48 out of 60 days; each session consisted of a varying number of countermovement jumps and repetitive hops, preceded by a warm-up (i.e., familiarization) and three maximal countermovement jumps at 80% body weight (for additional details refer to [13]).

2.4 Imaging protocol

MRI acquisitions were performed 4 days before the start of BR (BCD-4), during the 21° and the 58° day of BR (HDT21 and HDT58, respectively) and 5 days after its end (R+4).

The subject was placed inside the MRI machine (Biograph mMR 3-Tesla scanner, Siemens, Erlangen, Germany) and positioned at 0° directly from his bed. Several sequences were applied to study cardiac chambers anatomy and function, using a phased array cardiac coil. In particular, 2D PC-MRI images (30 frames/cardiac cycle, spatial resolution 1.4 x 1.4 x 5 mm^3) during spontaneous breathing and pulse pressure gating were obtained transecting the aorta at four different levels with interleaved three-directional velocity encoding (VENC: x and y: 80 cm/s; z: 150 cm/s, 12 bit), and at the level of the mitral valve plane

with one-directional velocity encoding (VENC: z: 100 cm/s) (Figure 1).

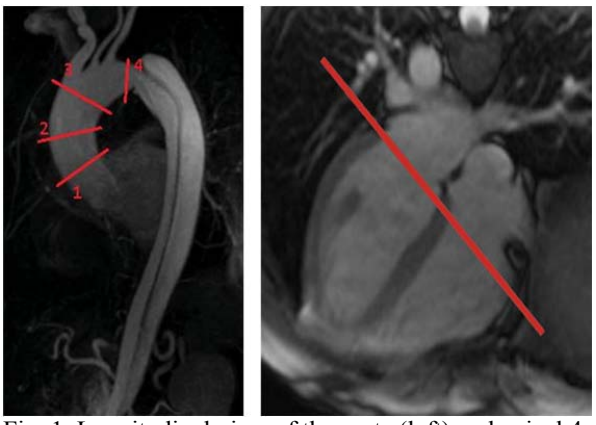

Fig. 1. Longitudinal view of the aorta (left) and apical 4-chamber view of the heart (right), in which the acquired planes for PC-MRI are depicted in red

3. Theory and calculation

This paragraph provides details about the implemented image processing and data analysis.

3.1 Image processing

PC-MRI images were analyzed with a custom-developed tool, completely implemented in Matlab (The MathWorks Inc., Natick, MA, USA), in which cartesian velocity components (vx, vy, vz) from delta phase images along the three orthogonal directions (x, y, z) were extracted based on the corresponding VENC value according to the formula:

$$v(i,j)_d = \frac{I(i,j)_d - (2^{n-1}-1)}{(2^n-1)-(2^{n-1}-1)} * VENC_d \qquad (1)$$

where I_d represents the acquired image videointensity with d referring to each of the three cartesian components x, y, z, and (i,j) indicates the pixel coordinates inside the image, with n the number of bits in the quantization process (n=12) [15]. Then, once the three velocity components were available, velocity magnitude images were obtained:

$$\overline{v(i,j)} = \sqrt{v(i,j)_x^2 + v(i,j)_y^2 + v(i,j)_z^2} \qquad (2)$$

After manual initialization in one frame of a region of interest (ROI) corresponding to the valvular section to be analysed, in all the remaining frames the ROI was automatically adapted to the changing valvular morphology by cross-correlating for each pixel the videointensity in a 5 frames-wide sliding window with the averaged videointensity in the whole ROI.

If the cross-correlation was less than an empirically derived threshold value of 0.85, the pixel was classified as background, otherwise as part of the ROI for that frame.

After this step, the area of the valvular lumen computed as the area inside the ROI was used to derive the area of each pixel A_p and to calculate the blood flow rate Q as:

$$Q = A_p * \Sigma_{k=1}^{N} \overline{v(k)} \qquad (3)$$

with N the number of pixels, and k indicating each pixel in the ROI.

This procedure was repeated for each frame in the cardiac cycle, thus obtaining corresponding time curves (Figure 2).

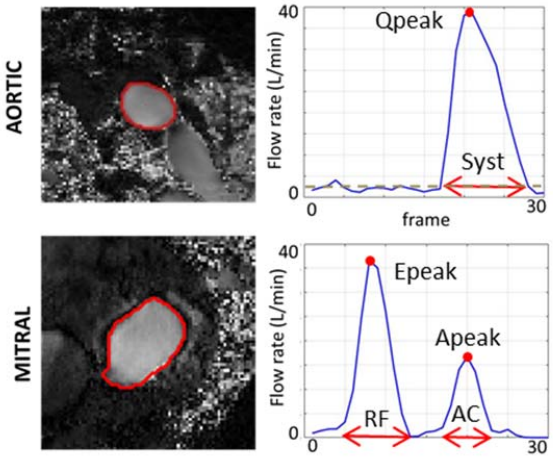

Fig. 2. Left: examples of the detected lumen (red contours) from the aortic and mitral valve planes. Right: Corresponding quantification along the cardiac cycle of transvalvular flow rate, with indication of the extracted fiducial points. RF: rapid filling, AC: atrial contraction.

From these curves, the following parameters were computed: for the aortic valve, max blood flow rate (Qpeak, l/min), stroke volume (SV, ml) as integral of flow rate in the systolic ejection period, cardiac output (CO, l/min), mean velocity at Qpeak (v_O, cm/s), systolic ejection period duration (Syst, ms), cardiac cycle duration (RR, ms).

For the mitral valve, total LV filling (TF, ml) and its rapid (Ewave, ml) and atrial contraction (Awave, ml) components, early filling peak flow rate (Ef, l/min), atrial peak flow rate (Af, l/min), time-to-peakE (ms), deceleration time of the Ewave (DT, ms).

3.2 Data analysis

Data are expressed as mean±SD, unless otherwise specified. Separately for the CTRL and JUMP groups, a one-way ANOVA with repeated measures was applied to test the null hypothesis that BR did not induce any change over time. In addition, to test the null hypothesis

that during recovery all values went back to their original level, a paired t-test ($p<.05$) was applied between BCD-4 and R+4.

4. Results

Two of the 23 subjects that completed the study (one CTRL, one JUMP) were re-ambulated after respectively 49 and 50 instead of 60 days of HDT due to medical reasons that did not affect their ability to complete the study further nominally (i.e., they were reambulated sooner, but completed the recovery phase with all the scheduled measurements). For those two subjects, MRI examination was performed the day before re-ambulation, and results were considered together the other subjects.

4.1 Aortic flow

In Table 1 and 2, the parameters obtained from the PC-MRI images relevant to the aortic outflow (i.e., measured from plane 1 in Figure 1), for the CTRL and CM groups, respectively, are reported.

In the CTRL group, BR-induced changes included (see Table 1):
- a shortening of systolic duration (10%), already significant at HDT21, and a progressive shortening of RR, significant at HDT58 (14%);
- a trend of decrease in CO (8%), hence not significant ($p=.14$)
- a progressive and significant decrease in SV (22%), already visible at HDT21 (14%);
- progressive decreases in Qpeak (12%) and in v_Q (8%), both significant at HDT58.

During the recovery phase, at R+4 RR was still shortened (10%) compared to baseline while all other parameters returned to baseline level.

Table 1. Results of aortic outflow parameters obtained in the control group.

	BCD-4	HDT21	HDT58	R+4
RR (msec)	988±114	945±119	846±113*	893±141#
CO (l/min)	7.0±1.2	6.4±1.1	6.4±.8	7.8±1.2
SV (ml)	115±18	99±11*$	90±9*	114±14
Qpeak (l/min)	33±4.4	32±3.8$	29±2.5*	32±3.9
Syst (msec)	390±31	348±29*	352±47*	400±66
v_O (cm/s)	83±14	85±13$	76±11*	84±13

CO: cardiac output; SV: stroke volume; Syst: ejection phase duration; v_Q: mean velocity at Qpeak

*:p<.05 vs BCD-4; $:p<.05 HDT21 vs HDT58
#: p<.05 BCD-4 vs R+4 (paired t-test);

Table 2. Results of aortic outflow parameters obtained in the countermeasure group.

	BCD-4	HDT21	HDT58	R+4
RR (ms)	988±137	914±110	905±105	892±136
CO (l/min)	6.5±.8	6.5±6	6.1±1	7.7±1.2#
SV (ml)	105±7	99±11	92±16*	113±14#
Qpeak (l/min)	31±1.9	31±3.8	29±4	33±4.1
Syst (ms)	367±26	348±25	352±36	386±48
v_Q (cm/s)	78±10	80±12	75±10	84±14

CO: cardiac output; SV: stroke volume; Syst: ejection phase duration; v_Q: mean velocity at Qpeak

*:p<.05 vs BCD-4
#: p<.05 BCD-4 vs R+4 (paired t-test);

In the CM group, BR-induced changes included (see Table 2) were visible only in a significant decrease in SV (12%) at HDT58. During the recovery phase, at R+4 all parameters were similar to baseline, except for CO (+19%) and SV (+8%).

4.2 Mitral flow

In Table 3 and 4, the parameters obtained from the PC-MRI images relevant to the mitral inflow, for the CTRL and CM groups, respectively, are reported.

In the CTRL group, BR-induced changes of diastolic flow included (see Table 3):
- a reduction in TF (24%), already significant at HDT21 (16%), due to a reduction in rapid filling (26%, 16% at HDT21), while LV filling due to atrial contraction was not affected;
- a progressive reduction in Ef (14% at HDT21, 26% at HDT58).
- a trend of decrease in deceleration time, hence not significant.

During the recovery phase, at R+4 TF and its components returned to baseline level, while Ef and Af resulted increased by 18% and 10%, respectively. Interestingly, DT was shortened by 19% compared to baseline.

In the CM group, BR-induced changes of diastolic phase included (see Table 3):
- a reduction in TF (14%), already significant at HDT21 (11%), due to both a reduction in rapid filling (11%) and atrial contraction filling components at HDT21 (23%);
- a progressive reduction in Ef (5% at HDT21, 15% at HDT58)

During the recovery phase, at R+4 TF and its components returned to baseline level, except Ef that

resulted increased by 18%. Interestingly, DT was shortened by 19% compared to baseline.

Table 3. Results of mitral inflow parameters obtained in the control group.

	BCD-4	HDT21	HDT58	R+4
TF (ml)	112±14	94±14*	86±11*	113±14
E wave (ml)	82±13	69±11*	61±10*	84±10
A wave (ml)	27±6	23±4	25±8	27±5
Ef (l/min)	31.4±5	26.9±4*	23.1±3*	37.2±3#
Af (l/min)	12.1±3	10.9±2	12.6±3	13.4±3#
Ttp (ms)	143±26	140±24	142±31	131±18
DT (ms)	193±45	188±25	163±38	156±28#

TF: total filling; Ef: early filling peak flow rate; Af: atrial peak flow rate; Ttp: time-to-peak E; DT: deceleration time

*:p<.05 vs BCD-4;
#: p<.05 BCD-4 vs R+4 (paired t-test);

Table 4. Results of mitral inflow parameters obtained in the countermeasure group.

	BCD-4	HDT21	HDT58	R+4
TF (ml)	113±14	111±14*	97±16*	116±18
Ewave(ml)	78±13	74±14	69±17*	84±19
Awave(ml)	31±6	24±7*	26±3	31±8
Ef (l/min)	31.4±4	29.9±6$	26.7±5*	36.2±7#
Af (l/min)	13.7±3	11.2±2*	11.9±2	14±5
Ttp (ms)	143±24	141±27	148±30	137±30
DT (ms)	188±34	173±36	176±39	161±35#

TF: total filling; Ef: early filling peak flow rate; Af: atrial peak flow rate; Ttp: time-to-peak E; DT: deceleration time

*:p<.05 vs BCD-4; $:p<.05 HDT21 vs HDT58
#: p<.05 BCD-4 vs R+4 (paired t-test);

Table 5. Comparison between the CTRL and the countermeasure groups of significant % of decrease observed in aortic outflow parameters.

	RR	CO	SV	Qpeak	Syst	v_Q
CTRL	14%	n.s.	22%	12%	10%	8%
CM	n.s	n.s.	12%	n.s.	n.s.	n.s.

Table 6. Comparison between the CTRL and the countermeasure groups of significant % of decrease observed in mitral inflow parameters.

	TF	E wave	A wave	Ef	Af	Ttp	DT
CTRL	24%	26%	n.s.	26%	n.s.	n.s.	n.s.
CM	n.s	n.s.	23%	15%	18%	n.s.	n.s.

In Table 5 and 6, a comparison of significant % of decrease observed during BR in respect to baseline, for the CTRL and JUMP CM group are reported, respectively for aortic outflow and mitral inflow parameters.

It is straightforward observing the reduced changes that were measured in the CM groups, and the different effects induced on the pattern of LV filling. This is further highlighted by Figure 3, which shows in a paired way the changes induced by BR in SV, in the two groups.

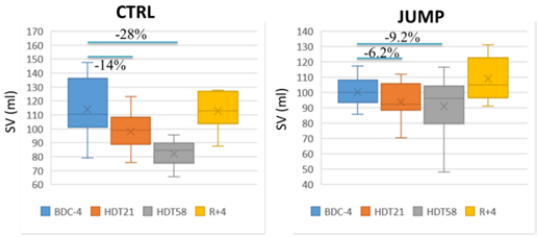

Fig. 3. Comparison of the changes induced by BR in stroke volume (SV), in the control (CTRL) and countermeasure (JUMP) groups.

5. Discussion

To our knowledge, this is the first study in which PC-MRI has been applied to evaluate aortic and mitral transvalvular flows in subjects undergoing a 60-days BR study.

The main findings of this study are 1) long-term BR had a major impact on both aortic outflow and mitral inflow (i.e., reduction in SV; decrease in flow rate during early filling as well as a decrease in aortic flow velocities associated with shortened LV ejection time), presumably secondary to decreased physiological loading and dehydration, both resulting in reduced plasma and blood volume; 2) all changes appeared reversed 5 days after the conclusion of BR; and 3) JUMP applied as a CM during BR seemed able to prevent or reduce these changes.

As expected, BR resulted in a reduction in plasma (13%) and blood (13%) volume [13] that was reflected in alterations in both preload and afterload. Changes in LV outflow and inflow were interrelated and completely reversible after BR, confirming the hypothesis of Carrick-Ranson et al. [17] that a reduction in LA pressure rather than changes in intrinsic ventricular function is likely to explain the effects of BR on Doppler measures of LV filling.

Compared to other similar investigations, in the CTRL group the progressive decrease in SV is in line with what we previously observed: in a 21-days BR, Doppler echocardiographic examination performed at HDT17 resulted in a reduction of 14% in SV, and a reduction of 11% in early diastolic filling peak E velocity [16], while peak A velocity did not change. Larger changes were instead observed in a 5-days BR study [11], probably still as a result of the acute changes

induced by head-down bed rest. Perhonen et al. [9] showed in five subjects using cine-MRI a decrease of approximately 24% in LV SV after 6 wk of supine bed rest that was already noted after 2 wk. Also our group, using cine-MRI, reported a decrease of 22% in SV after 21 days of BR [17]. Interestingly, comparing results of different BR campaigns at HDT21, SV measures derived from cine-MRI appear larger than those observed using Doppler or PC-MRI.

5.1 Effectiveness of JUMP as countermeasure

The applied training with JUMP was well tolerated by the subjects (see [13] for details). with a relatively low number of reported training-attributed discomforts. By this short (about 3 min/session) but intensive jump training program protocol applied in 48 out of 60 days, the participants of the CM group were able to preserve lean body mass, maintain high peak forces and even increase jump height and power output throughout the 60 days of bed rest [13].

As already observed for resting heart rate [13], the CM group and the CTRL group showed different heart rates even during the PC-MRI acquisition, with the CTRL group's heart rate significantly increased at HDT58, in agreement with results from previous BR studies [18, 19], resulting still increased compared to baseline at R+4. The CM group, however, showed no significant changes during HDT or at R+4.

It was previously reported [20] that an elevated heart rate during or after BR is associated with decreased SV (i.e., in agreement with what we observed), decreased cardiac vagal tone, increased sympathetic catecholamine secretion, and greater cardiac beta-receptor sensitivity and an overall decrease in maximal cardiac output. As exercise is able to influence these interconnected variables [21], it is possible that the applied CM positively influenced several of them, thus counteracting the cardiac deconditioning effects observed in the CTRL group, as we observed in aortic outflow and mitral inflow parameters.

In addition, while at R+4 early filling and atrial peak flow rates

It is worth noting that the observed difference between groups cannot be explained by changes in plasma volume, which was similar in both groups and comparable to the volume losses reported in earlier studies [22, 23].

The positive effect of exercise on E wave is in agreement with [6], where no changes were observed after 21-days BR with daily rowing ergometry and biweekly strength training.

Interestingly, we observed a different effect on the filling pattern, with a larger reduction of atrial contribution to filling and atrial peak flow rate in the CM group. As plasma volume was reduced, and thus filling pressure was the same in the two groups, this could be explained in a more preserved ventricular (but not atrial) contractility in the CM group.

6. Conclusions

This is the first study in which PC-MRI imaging was used to study aortic and mitral transvalvular flows during 60-days BR. Obtained results demonstrate how BR is impacting on both aortic outflow and mitral inflow, with changes that appear reversed 5 days after the conclusion of BR, presumably secondary to decreased physiological loading and dehydration.

The applied JUMP countermeasure seemed able to prevent or reduce these changes.

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References

[1] S.M. Fortney, V.S. Schneider, J.E. Greenleaf. The physiology of bed rest, in: Handbook of Physiology. Environmental Physiology. Bethesda, 1996, pp. 889–939.

[2] A. Pavy-Le Traon, M. Heer, M.V. Narici, J. Rittweger, J. Vernikos. From space to Earth: advances in human physiology from 20 years of bed rest studies (1986 –2006). Eur. J. Appl. Physiol. 101 (2007) 143–194.

[3] P. Arbeille, G. Fomina, J. Roumy, I. Alferova, N. Tobal, S. Herault. Adaptation of the left heart, cerebral and femoral arteries, and jugular and femoral veins during short- and long-term head-down tilt and spaceflights. Eur. J. Appl. Physiol. 86 (2001) 157–168.

[4] B.D. Levine, J.H. Zuckerman, J.A. Pawelczyk. Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance. Circulation 96 (1997) 517–525.

[5] M.A. Perhonen, J.H. Zuckerman, B.D. Levine. Deterioration of left ventricular chamber performance after bed rest: "cardiovascular deconditioning" or hypovolemia? Circulation 103 (2001) 1851–1857.

[6] G. Carrick-Ranson, J.L. Hastings, P.S Bhella, S. Shibata, B.D. Levine. The effect of exercise training

on left ventricular relaxation and diastolic suction at rest and during orthostatic stress after bed rest. Exp. Physiol. 98 (2013) 501–513.

[7] T.A. Dorfman, B.D. Rosen, M.A. Perhonen, T. Tillery, R. McColl, R.M. Peshock, B.D. Levine. Diastolic suction is impaired by bed rest: MRI tagging studies of diastolic untwisting. J. Appl. Physiol. 104 (2008) 1037–1044.

[8] J.L. Hastings, F. Krainski, P.G. Snell, E.L. Pacini, M. Jain, P.S Bhella, S. Shibata, Q. Fu, M.D. Palmer, B.D. Levine. Effect of rowing ergometry and oral volume loading on cardiovascular structure and function during bed rest. J. Appl. Physiol. 112 (2012) 1735–1743.

[9] M.A. Perhonen, F. Franco, L.D. Lane, J.C. Buckey, C.G. Blomqvist, J.E. Zerwekh, R.M. Peshock, P.T. Weatherall, B.D. Levine. Cardiac atrophy after bed rest and spaceflight. J. Appl. Physiol. 91 (2001) 645–653.

[10] S. Shibata, M. Perhonen, B.D. Levine. Supine cycling plus volume loading prevent cardiovascular deconditioning during bed rest. J. Appl. Physiol. 108 (2010) 1177–1186.

[11] E.G. Caiani, P. Massabuau, L. Weinert, P. Vaïda, R.M. Lang. Effects of 5 days of head-down bed rest, with and without short-arm centrifugation as countermeasure, on cardiac function in males (BRAG1 study). J. Appl. Physiol. 117 (2014) 624–632.

[12] M.A. Bernstein, K.F. King, X.J. Zhou. Handbook of MRI Pulse Sequences, first ed., Academic Press, Cambridge, MA, 2004.

[13] A. Kramer, J. Kümmel, E. Mulder, A. Gollhofer, P. Frings-Meuthen, M. Gruber. High-intensity jump training is tolerated during 60 days of bed rest and is very effective in preserving leg power and lean body mass: an overview of the Cologne RSL study. PLoS ONE 12 (2017) e0169793

[14] A. Kramer, R. Ritzmann, A. Gollhofer, D. Gehring, M Gruber. A new sledge jump system that allows almost natural reactive jumps. J. Biomechanics 43 (2010) 2672–7.

[15] S. Pirola, F. Piatti, F. Sturla, E. Votta, I. Nesteruk, M. Lombardi, A. Della Corte, M. Bissell, A. Redaelli, E. Caiani. Phase Contrast MRI: development of a user-friendly platform for fast-automated segmentation and fluid-dynamic post-processing, pp. 717-720, 42th Computing in Cardiology Conference, Nice, France, 2015 6-9 September.

[16] E.G. Caiani, P. Arbeille, P. Massabuau, F. Colombo, G. Ferri, C. Kasswat, D. Meme, R.M. Lang, P. Vaida. Cardiac adaptation to deconditioning after 21-days of head-down bed-rest: an echocardiographic study. Eur. Heart J. – Cardiovasc. Imaging 16 Suppl 2 (2015) S156-S182 (https://doi.org/10.1093/ehjci/jev276).

[17] E.G. Caiani, A. Pellegrini, M.C: Carminati, R.M: Lang, A. Auricchio, P. Vaida. Cardiac adaptation to deconditioning after 21-days of head-down bed-rest: an MRI study. Eur. Heart J. – Cardiovasc. Imaging 14 Suppl 2 (2013) ii176.

[18] H.Z. Shi, Y.Z. Li, Z.Z. Tang, C.F. Zhong, Q.C. Fan, J.Y. Gao, J.L. Liu, T. Mi, S. Zhao, Y.H. Li. Impact of 60 days of 6 degrees head down bed rest on cardiopulmonary function, and the effects of Taikong Yangxin prescription as a countermeasure. Chinese J. Integrative Med 20 (2014) 654–60.

[19] J. Spaak, S. Montmerle, P. Sundblad, D. Linnarsson. Long-term bed rest-induced reductions in stroke volume during rest and exercise: cardiac dysfunction vs. volume depletion. J. Appl. Physiol. 98 (2005) 648–54.

[20] V.A. Convertino. Cardiovascular consequences of bed rest: effect on maximal oxygen uptake. Med. Science Sports Exe 29 (1997) 191–6.

[21] C.J. Lavie, R. Arena, D.L. Swift, N.M. Johannsen, X. Sui, D.C. Lee, C.P. Earnest, T.S. Church, J.H. O'Keefe, R.V. Milani, S.N. Blair. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ. Res. 117 (2015) 207–19.

[22] E. Mulder, P. Frings-Meuthen, M. von der Wiesche, G. Clement, D. Linnarsson, W.H. Paloski, F.L. Wuyts, J. Zange, J. Rittweger. Study protocol, implementation, and verification of a short versatile upright exercise regime during 5 days of bed rest. J. Musculoskeletal & Neuronal Interactions. 14 (2014) 111–23.

[23] A. Pavy-Le Traon, M. Heer, M.V. Narici, J. Rittweger, J. Vernikos. From space to Earth: advances in human physiology from 20 years of bed rest studies (1986–2006). Eur. J. Appl. Physiol. 101 (2007) 143–94.