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ORIGINAL ARTICLE

Effects of exercise countermeasure on myocardial contractility measured by 4D speckle tracking during a 21-day head-down bed rest

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Abstract

Objective To evaluate functional myocardial contractility after 21 days of head-down bed rest (HDBR) in sedentary control (CON) or with a resistive vibration exercise (RVE) countermeasure (CM) applied, by using 4D echocardiographic (4D echo) imaging and speckle tracking strain quantification.

Methods Twelve volunteers were enrolled in a crossover HDBR design, and 4D echo was performed in supine position (REST) at BDC-2 and at R + 2, and in − 6° HDT at day 18, and during the first and the last minute of the 80° head-up step of tilt test performed at both BDC-2 and R + 2. Radial (Rad-Str), longitudinal (Lg-Str) and twist (Tw-Str) strains were measured by 4D speckle tracking, as well as left ventricle diastolic volume (LVDV) and mass (LVmass).

Results *On HDT 18:* in the CON group, LVDV and LVmass were reduced ($p < 0.05$), the Rad-Str decreased ($p < 0.05$) and Tw-Str showed a tendency to increase ($p < 0.11$), with no changes in Lg-Str. In RVE group, LVDV and LV mass, as well as all the strain parameters remained unchanged. *On R + 2:* in the CON group, LVDV and LVmass were not recovered in all subjects compared to pre-HDBR ($p < 0.08$) and Rad-Str was still decreased ($p < 0.05$), while Tw-Str tended to increase ($p < 0.09$). These parameters remained unchanged in the RVE group. *Tilt 80°:* Rad-Str and Lg-Str values at 80° tilt were similar post-HDT in both groups.

Conclusion The 4D echo and speckle tracking analysis showed that in the CON group, Rad-Str decreased concomitant with LVmass and LVDV with HDBR, but this observation did not allow concluding if HDBR induced a real remodeling or a muscle atrophy. RVE was able to preserve LVmass, LVDV and contractility during HDBR, thus proving its effectiveness to this aim. Nevertheless, the significant HDBR-induced changes observed in the CON group had only a limited effect on the cardiac contractile response as observed during post-HDBR tilt test. The level of contractility at 80° Tilt position was not affected either by HDBR or by RVE CM.

Keywords Echocardiography · Head-down tilt bed rest · Resistive exercise · Cardiac contractility · Cardiac strain · Speckle tracking · Ultrasound

Introduction

Head-down bed rest (HDBR) represents an experimental model commonly used to simulate the effect of microgravity on Earth. This model is considered as an effective microgravity simulation for most physiological effects of spaceflight such as muscular, metabolic and cardiovascular changes (Demontis et al. 2017). For the cardiovascular aspect, it leads to fluid shift from the legs to the chest, causing an increase in left ventricular transmural pressure, end-diastolic volume (LVDV), and stroke volume (Fortney et al., 1996) that activate short-term volume regulatory mechanisms resulting in plasma volume loss, with the achievement of a new hemodynamic steady state within

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48 h characterized by decreased volume loading of the heart similar to that reported during space flight (Arbeille et al. 2001) (Levine et al. 1997).

Echocardiography is an imaging technique that has been performed since the beginning of manned spaceflight, thus allowing to observe a reduction in left ventricular (LVDV) volume accompanied by a reduction in plasma volume due to space flight (Martin et al. 2003). This cardiac adaptation persisted throughout both short-duration and long-duration spaceflight missions, and HDBR studies, due to insufficient or inadequate effectiveness of applied exercise countermeasures performed at that time (Arbeille et al. 1987; Bungo and Charles 1985; Dorfman et al. 2007).

To compensate or minimize the effects of cardiac deconditioning, additional countermeasures (CM) have since been developed and studied, with the specific aim of maintaining or restoring cardiac volume and mass during both real and simulated microgravity exposure. These CM have included pharmaceuticals, short-arm centrifugation (ground only), lower-body negative pressure, nutritional supplementations and, as in the focus of the current study, aerobic and resistive exercise. The majority of these CM have been shown to be at least partially effective (Ferrando et al. 1997; Arbeille et al. 2008; Hargens and Richardson 2009; Ploutz-Snyder et al. 2014; Caiani et al. 2014).

In the field of muscle–skeletal deconditioning, skeletal muscle atrophy has been associated with a reduced protein synthesis rate and redistribution of muscle fiber types: both issues can be mitigated by an approach that combines amino acid supplementation and resistive exercise. However, in contrast to what is known about skeletal muscle, little is known regarding potential changes to myocardial tissue structure or changes to myocyte metabolism (Bennet et al. 1989; Kumar et al. 2009).

Methodological limitations in directly detecting changes in cardiac contractility in a non-invasive way have produced a yearly paradox in the literature: the cardiac mass is known to decrease due to spaceflight, but with no concomitant changes observed in contractility (Negishi et al. 2017 Unpublished ICV, 6 month ISS flight data). Indeed, measurements of contractility (strain) were indirectly performed using 2D tissue doppler imaging (DTI), which measures the contractile performance only along parallel directions to the ultrasound beam, thus allowing measurement of longitudinal strain only, but the sensitivity of this parameter was insufficient to detect significant changes associated with space flight. As with any one-dimensional Doppler technique, DTI is angle dependent, and regional velocity estimates can be influenced by overall heart motion, cardiac rotation, and contraction in adjacent segments. In addition, it is sensitive only along parallel directions to the ultrasound beam, thus allowing measurement of longitudinal strain only.

As the cardiac motion is intrinsically 3D, other imaging techniques are needed to fully investigate strain along other directions (i.e., radially or due to twist), to test for possible changes induced by microgravity.

Four-dimensional echocardiographic (4D echo) imaging is a relatively new technique that allows acquisition of a 3D volume of the whole heart over an entire cardiac cycle, with time representing the fourth dimension. The cardiac structures can be visualized in 3D in real time, or as any 2D cut-plane selected within the 3D volume. By 4D speckle tracking processing, it is possible to achieve improved assessments of contractility along various axes (Perez de Isla et al. 2010, 2011; Seo et al. 2011; Arbeille et al. 2013). This overcomes the limitations of the traditional DTI method, thus giving 4D echo datasets and speckle tracking a clear advantage.

Our hypothesis was that changes in contractility do indeed accompany the previously documented changes in left ventricular mass occurring with spaceflight and HDBR (in non-countermeasure groups). Using an improved echocardiographic imaging technique (4D speckle tracking), the previous limitations of 2D imaging could be overcome, thus allowing demonstrating for the first time the expected changes in strain outcome associated with the observed decrease in cardiac mass.

Accordingly, the aim of this study was to assess the effects of mid-duration (21 days) HDBR on the left ventricular volume, mass, and myocardial contractility along three components (i.e., radial, longitudinal, and ventricular twist) of 4D echo and speckle tracking, and evaluate the effectiveness of resistive exercise in acting as a countermeasure on these outcomes.

Methods

Subjects

Twelve healthy male volunteers participated in this study. All were non-smokers with no pre-existing medical conditions, were taking no medications and had all parameters, for hematology, blood chemistry and standard clinical examinations, in the respective range of normality defined by clinical practice and relevant guidelines. All participants gave informed, written consent to participate in the study. This experiment was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and approved by the local institutional ethics committee (CPP Sud-Ouest Outre-Mer I) as well as by the Government of France Health Authority. The study was performed at the Institute for Space Medicine and Physiology (MEDES-IMPS) in Toulouse, France.

General protocol

Subjects were enrolled in a crossover design with a washout period of 4 months between two consecutive campaigns, with one sedentary control (CON) group and two countermeasure (CM) interventions, either resistive vibration exercise group (RVE), or RVE plus nutrition supplementation (NEX). The order of inclusion in CON, RVE or NEX group was randomly assigned to each subject at the beginning of the bed rest, with four subjects assigned to each group in each campaign. All subjects adhered to a strict 6° head-down tilt bed rest for 21 days (HDBR) for each campaign. Subjects were acclimated to the bed rest unit for 7 days before initiating uninterrupted bed rest, monitored 24 h a day, and provided with strictly controlled diet aimed at preventing body weight changes. The daily cycle started each day at 7:00 AM and ended at 11:00 PM, with no napping allowed during the day. After completing the 21 days of bed rest, subjects remained in the facility for an additional 7 days for further testing. In the ambulatory periods preceding and following HDBR, lying in bed during the day was not allowed. In this way, each campaign spanned 35 days in clinic.

All exercise training was performed on an integrated training device supplied by Novotec Medical (Pforzheim, Germany). The vibration platform (Galileo® Fitness, Novotec, Germany) was combined with a system designed to allow exercise training in −6° head-down position. RVE sessions were performed away from meals two times per week with 3–4 day intervals, starting at HDT 2.

In the NEX group, this training was complemented with daily high protein intake (1.2 g/kg body weight/day plus 0.6 g/kg body weight/day whey protein) with alkaline salts (90 mmol potassium bicarbonate/day).

At BDC-2 and R + 2, participant underwent progressive head-up tilt test consisting of three steps (20°, 45°, 80°) of 3 min duration each (Fig. 5a).

During the bed rest campaigns, four subjects in the NEX group withdrew for personal reasons from the study. In addition, for technical problems, we were not able to acquire good-quality data in pre-HDBR, HDT, or post-HDBR in the other three subjects of the same group, thus precluding paired analysis between a NEX gr of 5 subjects and the other group of 11 and 12 subjects, respectively. For this reason, we are not reporting results relevant to the NEX countermeasure, but only results relevant to the CON and RVE groups.

Echocardiographic imaging protocol

Echocardiographic imaging using an ARTIDA (Toshiba Medical, Amsterdam NL) equipment was performed in supine position (REST) at BDC-2 and at R + 2, and in −6° HDT at day18. In addition, image acquisition was also performed during the first and the last minute of the 80° head-up step of the tilt test, at both BDC-2 and R + 2 (Fig. 5). For each session, three 4D volume scans (3D over time) of the left ventricle, each representing a cardiac cycle, were acquired. In particular, the first 4D capture was stored as raw data to be processed off-line by 4D speckle tracking analysis. The same device settings (i.e. gain, depth, resolution) were used on a given volunteer across all his acquisition sessions.

Echocardiographic measurements

Left ventricular diastolic volume (LVDV) and mass (LVmass) were also calculated both by 3D (by automatic contouring) and 2D method (Simpson biplane).

Cardiac contractility was quantified by measuring radial strain (Rad-Str), longitudinal strain (Lg-Str), and twist strain (Tw-Str), using speckle tracking processing of the 4D scan of the left ventricle. The 4D speckle tracking echocardiographic mode allows simultaneous visualization of left ventricular myocardial strain changes in real time, on both apical four- and two-chamber views, as well as on three transverse views of the left ventricle at the apical, middle, and submitral level. The software uses conventional gray-scale B-mode recordings to automatically detect the internal and external contours of the left ventricle and tracks myocardial speckles, which serve as natural acoustic markers. In case of poor echogenicity resulting in a sub-optimal view, background noise may interfere with the automated detection of the endocardium. In this case, the left ventricle internal contour was manually corrected. At each point of the myocardium on these five cut-planes, the computed strain value is displayed using a parametric color scale (from yellow the highest, to blue the lowest), and all this information is projected on a polar view of the left ventricle divided into 17 segments (Fig. 1), according to the AHA model (Cerqueira et al. 2002). The percent displacement of each speckle in three directions (longitudinal, radial and twist strain) was used to quantify the strain value for each of the 17 segment. This percent value represents the contractility of each segment in each direction (Perez de Isla et al. 2010), the 4D strain being the evolution of these (3D) strain values over time.

To evaluate changes in myocardium contractility between pre-HDBR and HDT18, and between the CON and RVE groups, we defined total strain as the sum of the % values in all segments, and mean strain as their average, and decided to use arbitrary units (a.u) to represent them, to differentiate from the original strain values. The total strain represents an index of the whole contractility of the heart, while the mean strain gives a qualitative evaluation of such contractility. Accordingly, mean and total radial strain (Rad-Str), longitudinal strain (Lg-Str), and twist (Tw-Str) strain were computed and presented in the results (Fig. 1, 3, 4).

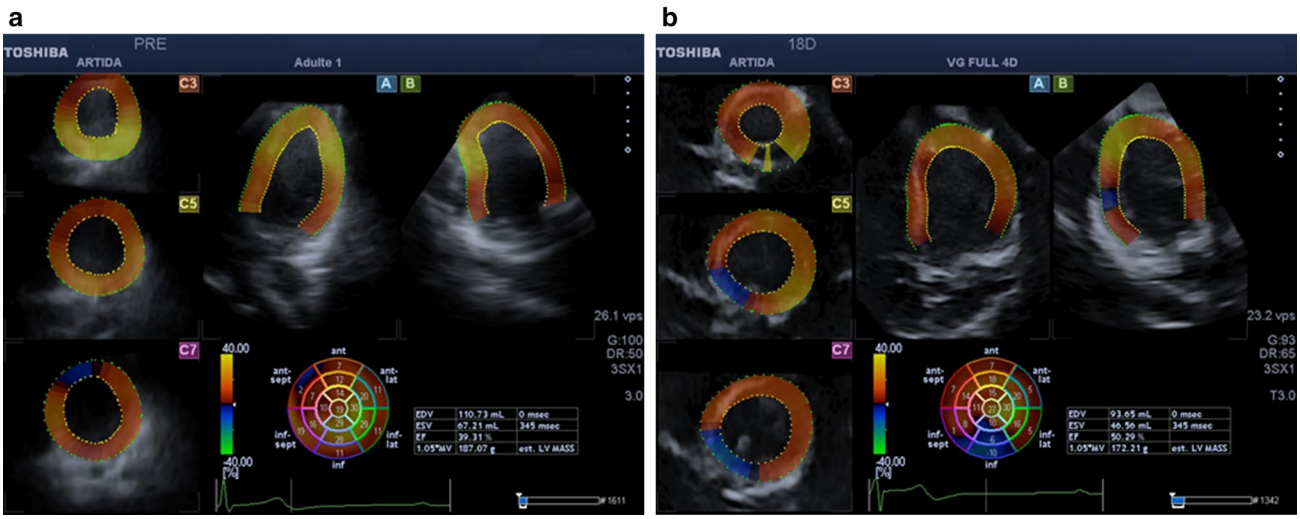


Fig. 1 Example of speckle tracking analysis performed off-line on the acquired 4D volumetric echo in one subject before HDBR in supine position (**a**) and at HDT18 at −6° head-down (**b**). Apical long-axis 4- and 2-chamber views, as well as 3 transverse short-axis views of the left ventricle are visualized, each with the myocardial contour identified, and the corresponding color-coded strain computed. The 17 cardiac segments polar map summarizes the strain value (radial strain in this screenshot) in % for each segment in which the left ventricle was automatically sub-divided. By comparing pre-HDBR and HDT18 images, it is possible to evidence a reduction in yellow areas (higher values) with bed rest. This resulted in decrease in total strain from 275 a.u. (19 + 14 + 30 + 29 + 10 + 12 + 20 + 29 + 28 + 16 + 7+7 + 11 + 11 + 11 + 19 + 2) at pre to 178 a.u. (27 + 15 + 30 + 10 + 11 + 18 + 20 + 16 − 6 + 8+14 + 7+5 + 5 − 10 + 1+7) at HDT18

Statistical analysis

The effects of HDBR and the exercise countermeasure on cardiac contractility were assessed in a supine and a head-up tilt 80° position independently. Two-way repeated measures ANOVAs were used to test for main effects of HDBR and the exercise countermeasure on cardiac contractility in both body positions. (SigmaPlot 12.5, Systat Software Inc, Chicago IL, USA).

Results

All subjects, while in CON and RVE groups, successfully completed the HDBR. Image quality of the acquired images allowed obtaining reliable measurements for comparison among the different time point in 11/12 subjects in the CON group and 12/12 subjects in the RVE group. During the tilt there was not enough time during the 3 min at 80° to perform 4D analysis of Rad-St, Lg-Str, and Tw-Str. The Tw-Str parameter could not be collected in good condition in all subjects.

Effects of bed rest on LV function and strain

In Fig. 1, an example of speckle tracking analysis performed off-line on the acquired 4D volumetric echo in one subject before HDBR in supine position and at HDT18 at −6° head-down is reported for radial strain, in which it is possible to visually appreciate a reduction in yellow areas (higher strain values) with bed rest, confirmed by a reduction in total strain for this subject at HDT18.

In Fig. 2, the cumulative results relevant to LVDV and LVmass in both CON and RVE groups are presented. In the CON group, compared to BDC-2, at HDT18, LVDV was significantly reduced by 15% (98–83 ml) and LV mass by 17% (192–160 gr) ($p < 0.05$). On the contrary, no changes were visible in the RVE group. After bed rest, at R + 2, in the CON group, LVDV showed a not complete recovery to baseline levels in all subjects (86 ml, − 13% from pre HDBR, $p < 0.09$) as well as LVmass (174 mg, − 9%, $p < 0.08$).

In Fig. 3, the cumulative results relevant to total Rad-Str, total Lg-Sr, and total Tw-Str are shown. In the CON group, total Rad-Str at HDT18 was found decreased by 26% (from 431 to 321 a.u, $p < 0.05$), and it was not completely restored to pre-HDBR values at R + 2 (350 a.u, − 18%, $p = 0.05$).

While total Lg-Str did not change for both groups, at HDT18 or at POST, for the CON group an apparent increase in Tw-Str at both HDT18 (from 4 to 13 a.u, $p < 0.10$) and at R + 2 (4–42 a.u., $p < 0.11$) was noticed, while no changes were visible for the RVE group.

As from the previous results the main effect of bed rest was noticeable on total radial strain, we conducted a segmental analysis for this strain component to evaluate changes at the segmental level. In Fig. 4, the results of this analysis are reported, separately for the CON and the RVE groups. In both groups, a lower strain associated with apical segments was visible already before HDBR. At HDT18, a decrease

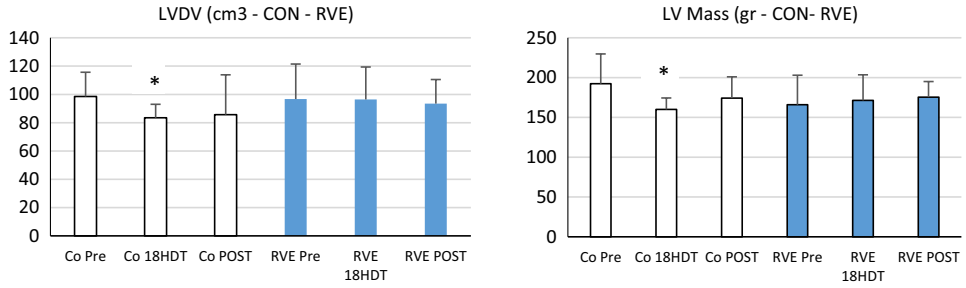


Fig. 2 Results obtained in the control (CON, white bars) and countermeasure (RVE, blue bars) groups relevant to left ventricle diastolic volume (LVDV, left panel) and left ventricle mass (right panel), at Pre-HDBR, at HDT18, and at post (*$p < 0.05$ vs Pre). Post-HDBR the significance was lower (LVDV $p < 0.09$ LVmass $p < 0.08$ vs pre)

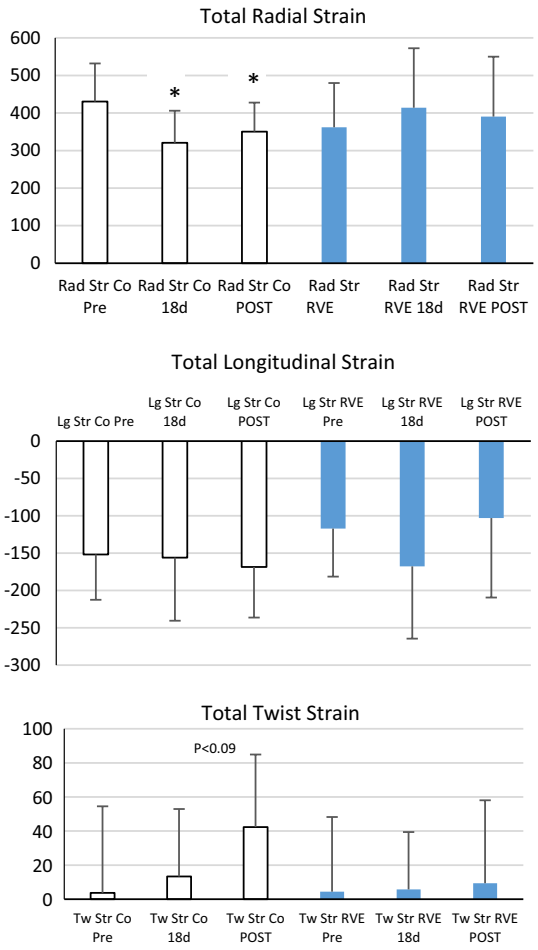


Fig. 3 Results obtained in the control (CON, white bars) and countermeasure (RVE, blue bars) groups relevant to left ventricle total radial strain (top panel), total longitudinal strain (center panel), Twist strain (bottom panel) at Pre-HDBR, at HDT18, and at post, all expressed in arbitrary units (*$p < 0.05$ vs Pre)

in radial strain in both basal and midventricular segments was visible in the CON group, while no apparent segmental changes were present in the RVE group.

Contractility at 80° tilt position (Fig. 5)

Figure 5 summarizes for both CON and RVE groups the results in LVDV, total Rad-Str, and total LG-Str obtained in the first minute of the 80° head-up step of the tilt, and at conclusion, both at pre-HDBR and at R + 2. The LVDV decreased in similar proportion during both pre- and post-HDBR tilt tests in both groups (in CON, pre-HDBR tilt pre: from 100 to 70 ml; post-HDBR tilt: from 86 to 62 ml. In RVE, pre-HDBR tilt: from 90 to 57 ml; post-HDBR tilt: from 91 to 59 ml), thus reaching similar values at pre- and post-HDBR tilt despite LVDV measured post-HDBR before tilt test started was lower in CON group than in RVE.

In 10 of the 11 CON subjects, the total Rad-Str decreased significantly ($p < 0.05$) during pre-HDBR tilt (from 435 to 299 a.u.) while this was not significant at R + 2 (from 346 to 296 a.u.), besides reaching a similar end-tilt value at 80° position pre- and post-HDBR. It is worth noticing that at post-HDBR, the total Rad-Str supine (right before being tilted) was reduced compared to the pre-HDBR.

In the RVE group, the total Rad-Str did not decrease during pre-HDBR tilt (from 389 to 367 a.u.), while it decreased at post-HDBR tilt (410–257 a.u.); however, it can be noted that the Rad-Str supine (just before being tilted) post-HDBR was higher than at pre-HDBR.

For Lg-Str, no changes were observable during tilt, both pre- and post-HDBR, in both groups. Thus the lowest level of Rad strain (at 80° post HDT) was similar for CON and RVE.

Discussion

The present HDBR study showed that in the control group, such a position maintained during 21 days induces a decrease in volemia, as exhibited by the significant decrease in left ventricle diastolic volume, in agreement with other reports of several bed rest and inflight studies. Additionally, the left ventricle myocardium mass was significantly

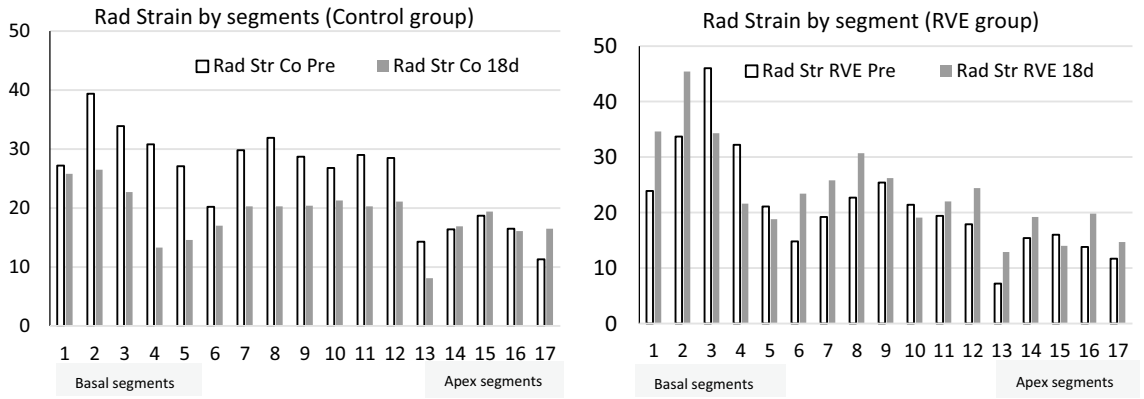


Fig. 4 Results obtained in the control (CON, left) and countermeasure (RVE, right) groups relevant to left ventricle radial strain for each of the 17 segments in which the 3D left ventricle was sub-divided, at Pre-HDBR (in white) and at HDT18 (in dark gray) (in % values)

decreased, which was also already described both as a result of bed rest and spaceflight (Arbeille et al. 2008; Caiani et al. 2014; Dorfman et al. 2007; Perhonen et al. 2001a, b).

The evaluation of the myocardial contractility along three orthogonal components by 4D speckle tracking analysis showed that only the radial contractility was affected by a significant reduction in HDBR, and this was concomitant with the observed drop in the left ventricle volume and mass. Nevertheless, it is difficult to state if such changes in radial strain were due to a real remodeling of the myocardium cellular structure or simply as the consequence of the myocardium atrophy and/or dehydration. Three days after the conclusion of HDBR (at R + 2), the left ventricle mass, end-diastolic volume, and total Rad-St did not completely recover, in agreement with the results obtained in a 60-day HDBR (Westby et al. 2016), thus suggesting that cardiac muscle atrophy could persist into recovery, as a result of real tissue transformation.

On the contrary, in a previous HDBR study of 5 days duration, the quick decrease in cardiac mass during HDT and the quick recovery within 2 days after the HDBR supported the hypothesis of a dehydration process related to the fluid shift effect induced by the HDBR (Caiani et al. 2014).

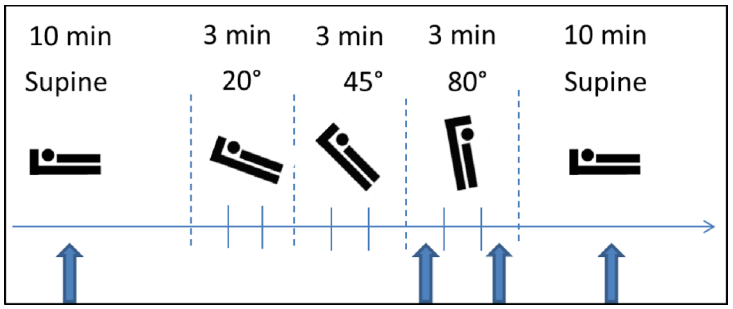
Most of the longitudinal strain evaluation during HDBR or spaceflight was performed using the Doppler tissue imaging (DTI) modality, reporting a decrease or no change in this parameter. In a 5-day HDBR, Caiani et al. 2014 found DTI velocities to reduce significantly after 5 days, and recover within 3 days after the conclusion, again supporting the hypothesis that the cardiac longitudinal contractility change was related to dehydration induced by fluid shift and the subsequent cardiovascular adaptation to the new homeostatic condition. Conversely, a 6-month spaceflight study (Integrated Cardio Vascular ISS program) performed onboard the International Space Station and a 2-week HDBR study did not find any significant change in longitudinal contractility (Negishi et al. 2017; Levine and Bungo, ICV unpublished data), despite that the fluid shift was present both during the flight and with HDBR, as confirmed by the significant dilation observed by vascular ultrasound in the jugular vein (Arbeille et al. 2001). Lastly, another 70-day HDBR study recently showed a decrease in Lg-Str (also evaluated by DTI) (Scott et al. 2018).

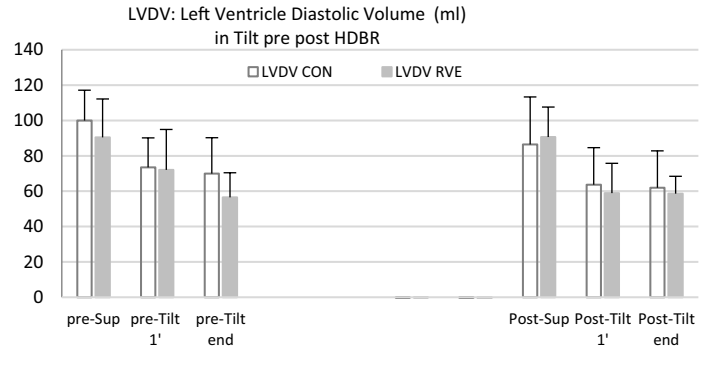
However, the DTI method used in these studies to estimate the longitudinal strain is based on the processing of tissue velocities on 2D views, as opposed to the speckle tracking mode used in this study, which measures movement of speckles over a 3D space (Arbeille et al. 2014): this difference in processing raw data could explain the weaker changes in Lg-Str and Tw-Str that we found in our study.

Two days after the end of the present 21-day HDBR, the radial strain was not completely recovered, thus not supporting the dehydration hypothesis. On the contrary, the fact that the longitudinal and twist contractility were not affected by HDBR does not support the hypothesis of true ventricular remodeling, as it should have affected strain in all directions.

As a result, we suggest that the observed changes along different directional strains might be related to different processes during the early period of adaptation and later on. Further studies relevant to strain assessment after longer bed rest studies, and in larger population, are needed to clarify further these points.

From the information relevant to strain in each of the 17 left ventricular segments, as represented in the polar maps as a result from the speckle tracking analysis, and described in Fig. 4, it is possible to observe that the Rad-Str changes induced by HDBR in CON group were significant and of similar amplitude in each cardiac segment, except for the basal segment numbers 1 and 6, and the apical segments 14th to 17th. This might partially explain why the longitudinal strain is less affected by HDBR than the radial strain. Conversely, the remaining segments showed higher strain





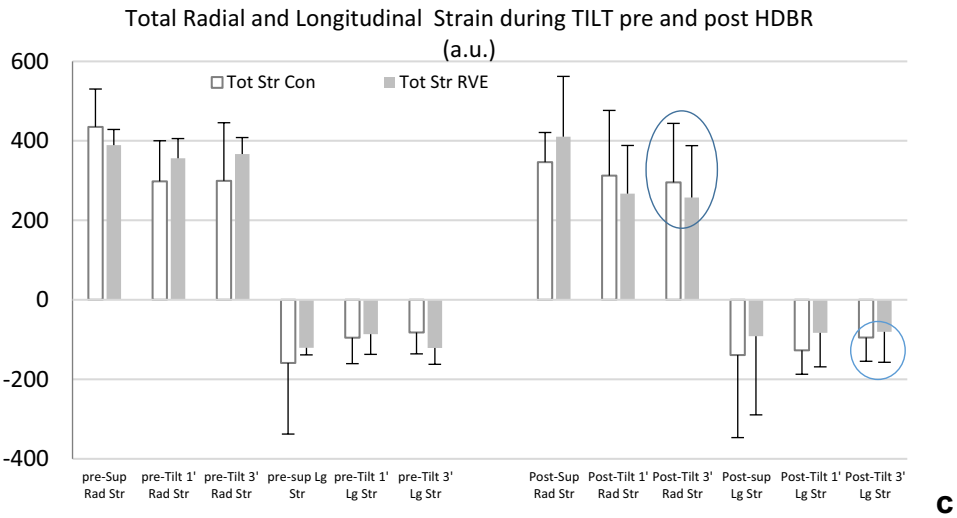


Fig. 5 Graded Tilt protocol (arrows indicate when 4D volumetric acquisition was performed) (**a**). Results obtained at Pre-HDBR (left), and after HDBR (right). In each case measures were performed before Tilt (supine: Sup), at 1 min of 80° tilt (Tilt 1′), and at the end of the tilt test (Tilt 3′), in the control (CON, white) and countermeasure (RVE, light gray) groups: Left ventricle diastolic volume (**b**), and Radial and Longitudinal strains (Rad-Str and Lg-Str (**c**). Only LVDV and Rad-Str (supine) in the control gr were significantly different pre vs post. No significant difference were found for the Rad-Str nor Lg-Str at post-HDBR Tilt 80° position between the CON and RVE groups (circle)

value (higher radial contractility) and were more affected by the HDBR.

Conversely, on the longitudinal strain polar map (not reported), the Lg-Str changes were of low amplitude in most of the segments and more heterogeneously distributed.

Lastly, the changes in radial strain (contractility) were quite homogenous around the left ventricle, which is not the case in coronary patient as the area affected is exclusively located downstream to the occluded artery. As a result of our observation, in healthy subjects such as astronauts or HDBR volunteers, if 4D echo is not available, the radial and longitudinal myocardium contractility could be evaluated using speckle tracking mode applied to a single apical two-chamber or multiple (mid and base left ventricle) parasternal short-axis views of the left ventricle, however, having the limitation of out-of-plane motion of the speckles that is solved by using a 4D volume.

The 4D echo and speckle tracking analysis have been previously used and validated in coronary patients, thus proving capable of locating the myocardium area with reduced contractility (using a color scale), evaluating the loss of contractility compared to healthy areas (by strain in each segment), and quantifying the level of recovery (increased strain) after coronary angioplasty. In these experimental

conditions, the largest increase was observed in the radial strain, compared to the longitudinal and twist strains, and associated not to myocardial mass change (as observed with bed rest in healthy volunteers) but to perfusion restoration (revascularization or liquid transfer) (Arbeille et al. 2013). Such observation supports the hypothesis that changes in contractility should be related to liquid transfer at the myocardium level (i.e., dehydration) (Caiani et al. 2014) at least between 24 h and some days of stimulation after the conclusion of HDBR.

While in the case of coronary patient there was no remodeling as the change in strain occurred within 24 h from reperfusion, in the case of mid-duration HDBR (21d) we cannot certify that the reduction in radial strain was just related to the myocardium atrophy without remodeling, or to a significant remodeling accompanying the myocardium atrophy.

On the other hand, skeletal muscle atrophy during hypoactivity (HDBR or dry immersion) has been associated with real tissue remodeling with a significant atrophy of type I muscle fibers and an increased proportion of hybrid, type I/IIX fiber co-expression. Additionally, after a 1-month spaceflight, leg muscle atrophy in mice was found associated with fiber-type redistribution, with structural alterations (Tascher et al. 2017; Demangel et al. 2017). Also, a histological study of the myocardium in tail suspended rats (for 30 days) reported the association of myocardium atrophy and deep rearrangement of the intracellular architecture and some destructive changes of the myocytes ultrastructure (Nepomniashchikh et al. 1985). These observations are in favor of a myocardium tissue remodeling, but until now no direct or indirect observation has confirmed that for the human heart.

Considering the results obtained in the tilt test at R + 2, both the ejection fraction and the stroke volume were maintained at an acceptable level in the RVE group, but surprisingly also in the CON group (except for 1 subject), despite that the left ventricle volume LVDV in supine was significantly lower than pre-HDBR, probably due to the limited decrease in contractility.

The contractility is mediated by the sympathetic nervous system which balance may be affected by the HDBR. Nevertheless it seems that the contractility at Tilt 80° position was sufficient to prevent the CON subject to be orthostatically intolerant, despite his values supine did not fully recover at R+2 (Arbeille et al. 2014).

A similar study, where tilt test was performed after a 2-week HDBR, reported that DTI showed similar changes in contractility during acute fluid shift as at pre-HDBR, while no changes in longitudinal strain were detected after 2-week HDBR at rest, in agreement with our study, thus suggesting a stiffer left ventricle after HDBR (Negishi et al. 2017). On the other hand, during acute fluid shift as that induced during zero G flights, the tissue velocity as measured by DTI was found preload dependent, while strain appeared to be preload independent, probably reflecting intrinsic myocardial properties (Caiani et al. 2007). As a conclusion, strain seems an appropriate parameter, even when measured by DTI, for evaluating changes in cardiac longitudinal contractility.

In the exercise RVE group, the left ventricle diastolic volume and mass remained unchanged during and after the HDBR. The radial, twist and longitudinal strain also remained unchanged, which confirm the efficiency of the resistive vibration exercise as a countermeasure acting as a cardiac protector in simulated gravity conditions.

Limitations

Despite that 4D speckle tracking method allowed visualization and quantification of the radial and longitudinal strain and twist for each cardiac segment, it suffers from some limitations when used in certain conditions such as the tilt test.

In fact, it allowed the evaluation of changes in radial or longitudinal contractility, but was less reliable for twist strain evaluation: this could be due to lower values of twist strain changes or because of difficulties in the detection of speckle movement to follow ventricular twist.

An additional limitation is related to imaging requirement for each 4D capture: (a) to find a good four-chamber apical view to ensure that the ultrasound sweep will cover the whole ventricle, (b) to wait some seconds for the 4D speckle processing and display, (c) to check that the whole volume has been properly insonated and that the left ventricle myocardial contours are well delimited. Considering that this process takes approximately 1 min, this explains why in several cases we could not get sufficient good data in some of the tilt especially for the Tw-Str.

A third limitation is related to the fact that during tilt test the subject was perfectly supine, and not leaning on his left side toward the operator, and this position in some cases made it difficult to capture the 4D echo.

Finally, in our analysis we did not focus on other temporal parameters (i.e., time to peak), as in previous studies we did not find significant changes; moreover, the computation of these parameters during loops could have been more prone to errors, due to the instability of the 4D speckle tracking pattern during the contraction. For these reasons, we decided to focus on the most robust and reliable parameter we could extract in our analysis.

Conclusion

The 4D echo with speckle tracking mode allowed evaluating directly and simultaneously the regional strain values along various directions in the 17 left ventricle myocardial segments, without using any complicated model or assumption, as implied by other 2D speckle tracking or DTI methods.

The 21-day HDBR induced in the control group a significant reduction in both the left ventricle volume and mass, associated with a significant drop in radial contractility (but not in longitudinal strain and twist). These changes in contractility were quite equally distributed among the basal and midventricular myocardial segments, thus suggesting a homogenous remodeling of the cardiac muscle, except at the apex where they were of lower amplitude. Unfortunately, these results do not allow concluding whether HDBR induced a real cellular remodeling or only a muscle atrophy. Resistive exercise countermeasure was able to preserve both cardiac mass and contractility during HDBR, thus proving its effectiveness to this aim. Nevertheless, the significant HDBR-induced changes observed in the CON group had only a limited effect on the level of cardiac contractility observed at the post-HDBR tilt 80° position.

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Compliance with ethical standards

Conflict of interest All authors declare they have no conflict of interest.

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