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Gary J. Hodges
Western University

Louis Mattar
Western University

Kathryn A. Zuj
Western University

Danielle K. Greaves
Western University

Phillipe M. Arbeille
University of Waterloo

See next page for additional authors

Experimental Physiology – *Research Paper*

WISE-2005: prolongation of left ventricular pre-ejection period with 56 days head-down bed rest in women

Gary J. Hodges[1], Louis Mattar[1], Kathryn A. Zuj[2], Danielle K. Greaves[2], Phillipe M. Arbeille[3], Richard L. Hughson[2] and J. Kevin Shoemaker[1,4]

[1] *School of Kinesiology and* [4] *Department of Physiology and Pharmacology, The University of Western Ontario, London, Ontario, Canada N6A 3K7*
[2] *Faculty of Applied Health Sciences, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1*
[3] *UMPS Medecine Physiologie Spatiale, Universite-Hopital, Trousseau, 37044 Tours, France*

This study tested the hypothesis that prolonged physical deconditioning affects the coupling of left ventricular depolarization to its ejection (the pre-ejection period, PEP_i) and that this effect is minimized by exercise countermeasures. Following assignment to non-exercise (Control) and exercise groups (Exercise), 14 females performed 56 days of continuous head-down tilt bed rest. Measurements of the electrocardiogram (ECG) and stroke volume (Doppler ultrasound) during supine rest were obtained at baseline prior to (Pre) and after (Post) the head-down tilt bed rest (HDBR) period. Compared with Pre, the PEP_i was increased following head-down tilt bed rest (main effect, $P < 0.005$). This effect was most dominant in the Control group [Pre = 0.038 ± 0.06 s (S.D.) *versus* Post = 0.054 ± 0.011 s; $P < 0.001$]. In the Exercise group, PEP_i was 0.032 ± 0.005 s Pre and 0.038 ± 0.018 s Post; $P = 0.08$. Neither the QRS interval nor cardiac afterload was modified by head-down tilt bed rest in Control or Exercise groups. Low-dose isoprenaline infusion reversed the head-down tilt bed rest-induced delay in the PEP_i. These results suggest that head-down tilt bed rest leads to a delayed onset of systolic ejection following left ventricular depolarization in a manner that is affected little by the exercise countermeasure but is related to β-adrenergic pathways. The delayed onset of systole following head-down tilt bed rest appears to be related to mechanism(s) affecting contraction of the left ventricle rather than its depolarization.

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Corresponding author J. K. Shoemaker: Neurovascular Research Laboratory, School of Kinesiology, The University of Western Ontario, London, Ontario, Canada N6A 3K7. Email: kshoemak@uwo.ca

A hallmark of prolonged head-down tilt bed rest (HDBR), or microgravity, is the reduction in stroke volume that is associated with decrements in exercise capacity and orthostatic intolerance (Levine *et al.* 1997). Potential causes of this reduced stroke volume include cardiac atrophy, reduced blood volume and/or reduced left ventricular compliance (Zile *et al.* 1993; Levine *et al.* 1997; Perhonen *et al.* 2001*a*; Dorfman *et al.* 2007). Previous reports show a reduction of left ventricular mass in both men (Perhonen *et al.* 2001*a*) and women (Dorfman *et al.* 2007) following exposure to real or simulated microgravity (e.g. HDBR). Nonetheless, beyond the reduction in stroke volume, the functional impact of microgravity on cardiac function remains poorly understood.

The cardiac pre-ejection period (PEP_i) describes the time interval from the onset of ventricular depolarization to the beginning of left ventricular ejection. This period is considered to depend primarily on cardiac afterload and contractility (Wallace *et al.* 1963; Weissler, 1977) but not blood volume *per se* (Kubitz *et al.* 2005) and has been used to study cardiac sympathetic innervation and contractility. Using this PEP_i, in conjunction with assessment of afterload and pharmacological treatments that affect cardiac inotropy, we examined whether HDBR affected this feature of systolic function, whether such an effect depended on cardiac remodelling, and whether this effect was minimized by an exercise countermeasure. The PEP_i was assessed using the R wave of the electrocardiogram to reflect left ventricular depolarization in conjunction with the upstroke of aortic stroke volume that marks ejection of blood from the left ventricle. These measures were made before and after 56 days of bed rest in a

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control group (HDBR only) and an exercise intervention group (HDBR + exercise). Pharmacological treatments were included to assess the responsiveness of the PEP_i to adrenergic stimulation and afterload changes. We also assessed the QRS complex to determine whether there were changes in the electrical activity of the heart. With this approach, we tested the hypothesis that prolonged HDBR reduces cardiac function in a manner that is dependent upon cardiac remodelling. Given evidence that exercise countermeasures prevent bed rest-induced cardiac remodelling (Dorfman *et al.* 2007), this hypothesis predicts that the PEP_i would be altered with HDBR and prevented with the exercise countermeasure.

Methods

Participants

Data were obtained from 14 healthy women (between the ages of 25 and 40 years) who participated in the WISE-2005 bed rest study, which was an international collaboration between the American, Canadian, European and French space agencies. All subjects had to be physically active with at least 'average' aerobic fitness (mean ± S.D.; maximal oxygen uptake 39 ± 4 ml kg^{-1} min^{-1}); competitive athletes were excluded. Subjects were 59 ± 4 kg and 166 ± 7 cm. Each subject completed 60 days of strict, supervised continuous 6 deg HDBR, with testing and monitoring before and after bed rest in the Space Medicine Research Facility of the Centre National d'Etudes Spatiales in Toulouse, France. All experimental procedures were approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Midi-Pyrénées (France), Committee for the Protection of Human Subjects at Johnson Space Center and local ethics committees, including the Office of Research Ethics, University of Waterloo. The entire study was conducted in accordance with the declaration of Helsinki. Each woman was aware of her right to withdraw from the study at any time for any reason.

Study design

As has been previously described (Edgell *et al.* 2007; Arbeille *et al.* 2008*b*; Schneider *et al.* 2009), subjects were randomly assigned to one of two groups, either a control group (Control) or an exercise intervention group (Exercise). Throughout the study, hydration was maintained with 60 ml kg^{-1} day^{-1}, and caloric intake was set at 120% of the calories dictated by resting metabolic rate. This was modified for the exercise group to account for increased fluid requirements and energy expenditure. No nicotine, alcoholic beverages or caffeine were permitted. The tests described here are a small subsection of a much greater collection of experiments. Baseline testing was conducted 7 days prior to the start of HDBR (pre-HDBR), and post-intervention testing was conducted following 56 days of HDBR (post-HDBR). In each session, baseline PEP_i data were obtained from a 5 min period of quiet supine rest, which was followed by the infusion of isoprenaline and noradrenaline (see below). Supine echocardiography measures were made during the week prior to HDBR and on day 55 of HDBR. For the exercise group, post-intervention testing took place ∼24 h after treadmill exercise.

Exercise countermeasures

The WISE-2005 exercise intervention has been previously described (Schneider *et al.* 2009). Briefly, subjects in the exercise group walked and ran three or four times per week in the supine position on a treadmill placed inside an lower body negative pressure chamber for 40 min at 40–80% pre-bed rest maximal oxygen uptake in an 'interval' fashion over the course of each session; the applied lower body negative pressure (−48 to −55 mmHg) provided 1 to 1.1 body weight of ground reaction force (Hargens *et al.* 1991; Boda *et al.* 2000; Cao *et al.* 2005; Schneider *et al.* 2009). The treadmill exercise was followed by 10 min of resting lower body negative pressure at the same level. This mode of exercise was chosen because supine treadmill exercise within lower body negative pressure provides weight bearing, muscle loads and cardiovascular responses that are equivalent to upright treadmill exercise on Earth and, importantly, simulates metabolic and kinetic features of upright exercise (Murthy *et al.* 1994; Boda *et al.* 2000). Furthermore, this exercise regime maintained peak oxygen consumption in men exposed to 5, 15 and 30 days of HDBR (Lee *et al.* 1997; Watenpaugh *et al.* 2000; Cao *et al.* 2005) and in these women (Schneider *et al.* 2009).

Subjects also performed resistive training of the knee extensor and plantar flexor muscle groups on a custom-built flywheel ergometer, modified for bed rest, every third day, and each training session included four sets of seven repetitions with each leg, performed with maximal effort using both concentric and eccentric contractions with a 2 min resting period between each set (Alkner & Tesch, 2004; Shackelford *et al.* 2004). The treadmill and flywheel exercises were normally not performed on the same day, and rest days were provided.

Drug infusion

Catheters were placed in the antecubital veins of the left arm for drug infusion. Following instrumentation, subjects were allowed to rest for 5 min before drawing the baseline blood samples. Drug infusion was always performed in the same order, with two doses of isoprenaline (Isuprel, Winthrop, Clichy, France) at

concentrations of 5 and 10 ng kg^{-1} min^{-1} diluted in 5% glucose for 5 min each. The isoprenaline infusions tested whether β-adrenergic stimulation affected the PEP_i delay and whether this was modified by HDBR. Infusion of isoprenaline was terminated if the increase in heart rate was greater than 35 beats min^{-1}. After the isoprenaline study, heart rate and blood pressure were monitored until they returned to the pre-isoprenaline baseline, and then two doses of noradrenaline (noradrenaline tartrate, Laboratoire Aguettant, Lyon, France) were infused for 5 min each at concentrations of 10 and 50 ng kg^{-1} min^{-1}, again diluted in 5% glucose. Infusion of noradrenaline was terminated if the systolic blood pressure increased more than 20 mmHg or if the reflex reduction in heart rate exceeded 20 beats min^{-1}.

Physiological measurements

Aortic root blood flow velocity was measured from the suprasternal notch by a hand-held 2 MHz Doppler ultrasound probe (Multigon, New York, NY, USA). Blood pressure waveforms were measured using finger-cuff plethysmography (Finometer, Finapres Medical, Amsterdam, The Netherlands), and heart rate was determined from the electrocardiogram. All blood pressure, ultrasound and ECG analog signals were sampled in real time at 1000 Hz with an online acquisition and analysis system (PowerLab, ADInstruments, Castle Hill, NSW, Australia) and stored on a computer for subsequent analysis.

Data analysis

The PEP_i was determined from the duration between the peak of the R wave of the ECG and the start of the upslope of the ultrasound measurement of left ventricular ejection (stroke volume). Twenty PEP_i values were obtained from a resting baseline phase and during the fourth minute of each drug infusion phase. To determine reliability of the approach, a second investigator independently obtained an additional twenty values selected randomly from each individual's pre-HDBR and post-HDBR baseline segment (without prior knowledge of the first investigator's selection sites).

The electrocardiogram was analysed for the QRS duration (duration of atrial-to-ventricular depolarization) and the total Q–T duration in order to assess whether the travel of electrical signals across the heart was modified by HDBR. The index of cardiac afterload was calculated as follows: afterload = (pressure × radius)/wall thickness, where pressure was diastolic blood pressure, radius was left ventricular radius at end diastole, and wall thickness was left ventricular wall thickness reported for these participants (Arbeille *et al.* 2008*b*). Based on a recent report from Hart *et al.* (2006), it was assumed that left ventricular end-diastolic volume was not affected by the drug infusions.

Left ventricle wall thickness, diameters and volumes were measured at end diastole and systole using two-dimensional echo ultrasound measures (GE Vivid I; 3.25 MHz transducer). Left ventricular fractional shortening was calculated as (LVSD − LVDD)/LVDD × 100, where LVSD and LVDD are left ventricular end-systolic and end-diastolic diameters, respectively. Stroke volume was calculated as the difference between left ventricular end-diastolic and systolic volumes.

Statistical analyses

The effects of HDBR and group were assessed using a one-way ANOVA in a mixed model. To assess the pharmacological studies, the effects of HDBR and drug dose, with subjects grouped accordingly, were assessed using a mixed two-way ANOVA (Statistical Analysis Software (SAS) version 8.01; SAS Inst. Inc., Cary, NC, USA). Significance was assumed when $P < 0.05$. Values are presented as the means ± S.D. Limits of agreement between the two sets of PEP_i data gathered at baseline were tested using a Bland–Altman mean difference analysis (Bland & Altman, 1986).

Results

Cardiac pre-ejection period

The baseline PEP_i data from the two independent investigator selections were similar (Fig. 1). Thus, these data were averaged in the final analysis. A main effect of HDBR ($P < 0.005$) was observed in PEP_i whereby, compared with pre-HDBR, post-HDBR PEP_i values were

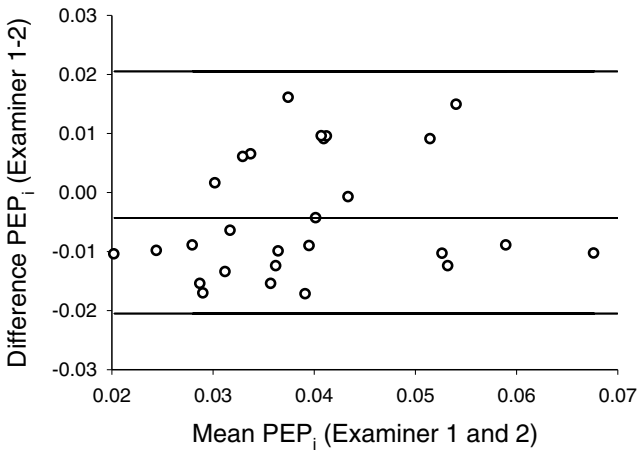

Figure 1. Bland–Altman (Tukey's mean difference) analysis of baseline pre-ejection period (PEP_i) data from two investigators
Values were obtained from 14 individuals during baseline data collection and after 56 days of head-down bed rest (HDBR).

Table 1. Effect of the exercise countermeasure on electrocardiogram periods, as well as cardiac structure and function, after 56 days of head-down tilt bed rest (HDBR)

	Control group		Exercise group	
	Pre-HDBR	Post-HDBR	Pre-HDBR	Post-HDBR
Heart rate (beats min^{-1})	63 ± 7	72 ± 11*	67 ± 9	64 ± 8
QRS complex (s)	0.06 ± 0.01	0.06 ± 0.01	0.07 ± 0.02	0.07 ± 0.02
Q–T interval (s)	0.35 ± 0.02	0.36 ± 0.04	0.37 ± 0.03	0.38 ± 0.2
Left ventricle wall thickness (mm)	6.13 ± 0.7	5.35 ± 0.4*	6.23 ± 0.7	6.15 ± 0.6
Fractional left ventricular shortening (%)	37 ± 2	37 ± 4	39 ± 3	39 ± 4
Stroke volume (ml)	68 ± 8	60 ± 7*	71 ± 10	75 ± 12
Systolic blood pressure (mmHg)	118 ± 13	121 ± 15	120 ± 8	119 ± 11
Diastolic blood pressure (mmHg)	65 ± 10	71 ± 17	69 ± 6	73 ± 9
Pulse pressure (mmHg)	53 ± 7	46 ± 6†	51 ± 5	46 ± 9†
Afterload (mmHg)	256 ± 28	270 ± 29	260 ± 54	261 ± 35

Values are means ± S.D. *Significantly different from pre-HDBR (group × time interaction; $P < 0.001$). †Significantly different from pre-HDBR (main effect of time; $P < 0.05$).

increased (Fig. 2). In Control participants, the mean PEP_i duration increased from 0.038 ± 0.06 s pre-HDBR to 0.054 ± 0.011 s post-HDBR (Fig. 2). In the Exercise group this delay was 0.032 ± 0.005 s before, and increased slightly to 0.038 ± 0.018 s after HDBR (Fig. 2).

Electrocardiogram

Neither HDBR nor group designation affected the duration of the Q–T or QRS intervals (Table 1).

Cardiac measures and afterload

Cardiac afterload at baseline was not different between Control and Exercise groups or between pre- and post-HDBR time points (Table 1). Neither systolic nor diastolic blood pressure was altered by HDBR. Compared with pre-HDBR, left ventricular wall thickness and stroke volume were reduced following HDBR in the Control but not Exercise group (group × time interaction, $P < 0.05$; Table 1). The smaller stroke volume in the Control group with HDBR (group × time interaction, $P < 0.001$) was a function of a smaller left ventricular end-diastolic volume in this group compared with the Exercise group (as reported earlier by Arbeille *et al.* 2008*a*). Left ventricular fractional shortening was not different between groups in the pre-HDBR tests and was not affected by the HDBR period in either group (Table 1).

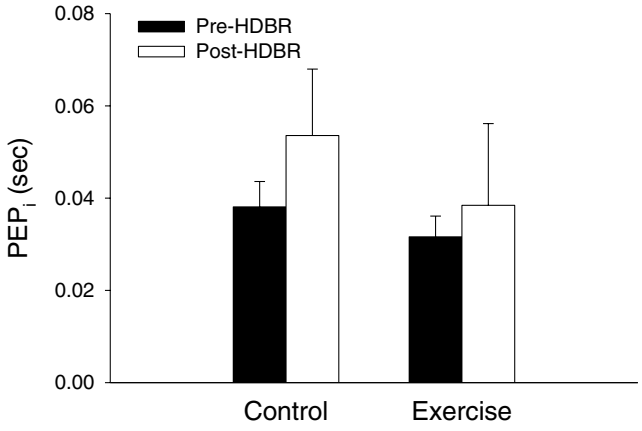

Figure 2. Mean PEP_i obtained during the pre-HDBR period and after 56 days of HDBR for the Control (filled bars) and Exercise training groups (open bars)
A main effect of HDBR was observed ($P < 0.005$). $n = 7$ in each group.

Pharmacological tests

In each of the pre- and post-HDBR tests, isoprenaline infusion decreased the PEP_i delay in a dose-dependent manner (Fig. 3). This effect of reducing the PEP_i delay was present in both groups, but a group × time interaction ($P < 0.05$) indicated that isoprenaline caused a greater reduction in PEP_i for the Control group following HDBR. In contrast, infusion of noradrenaline increased the PEP_i delay in a dose-dependent manner that was similar for the Control and Exercise groups (Fig. 3; $P < 0.05$). The effect of HDBR on the delayed PEP_i in the Control group persisted through each dose of noradrenaline ($P < 0.05$) and is probably explained by the elevated blood pressure and, therefore, afterload. Isoprenaline infusions did not affect either diastolic blood pressure or cardiac afterload (Table 2). The impact of noradrenaline on the increase in diastolic blood pressure ($P < 0.05$) and cardiac afterload ($P = 0.06$) was reduced in post-HDBR compared with the pre-HDBR measures (Table 2).

Discussion

The primary new finding from this study was that 56 days of HDBR increased the cardiac PEP_i, a change that was minimally affected by the exercise countermeasure.

Table 2. Blood pressure and cardiac afterload responses to 10 ng kg^{-1} min^{-1} isoprenaline and 50 ng kg^{-1} min^{-1} noradrenaline pre-HDBR and after 56 days of HDBR

	Control group		Exercise group	
	Pre-HDBR	Post-HDBR	Pre-HDBR	Post-HDBR
Isoprenaline				
ΔDBP (mmHg)	−0.73 ± 4.4	−0.64 ± 3.3	−0.68 ± 5.2	−1.76 ± 4.1
ΔAfterload (mmHg)	−3.57 ± 18	−2.53 ± 14	−3.82 ± 19	−7.36 ± 16
Noradrenaline				
ΔDBP (mmHg)	5.59 ± 2.23	1.92 ± 2.21*	4.81 ± 6.2	0.82 ± 9.3*
ΔAfterload (mmHg)	22 ± 9	7.64 ± 9.16†	19 ± 26	8.6 ± 36†

Values are means ± S.D. *Head-down bed rest effect on noradrenaline-induced changes in diastolic blood pressure (DBP) was $P < 0.05$. †Head-down bed rest effect on noradrenaline-induced changes in cardiac afterload was $P = 0.06$.

This increased PEP_i was not related to alterations in the electrocardiogram or to systematic elevations in cardiac afterload. Furthermore, this delayed PEP_i was 'corrected' with low-dose isoprenaline and this was most apparent in the Control group but was not related to drug-induced reductions in cardiac afterload or diastolic blood pressure. Together, these findings suggest the following: (1) there is an effect of HDBR on systolic timing that is difficult to minimize with exercise countermeasures; (2) the mechanism of the prolonged PEP_i lies within the inotropic properties of the left ventricle that can be modified by β-adrenoceptor activation; and (3) the change in PEP_i can occur independently from myocardial contractile function (e.g. fractional shortening) or left ventricular wall thinning.

The PEP_i is the time the ventricles spend in isovolumetric contraction, the cumulative effect of the time required for ventricular electrical activation, electrical–mechanical coupling and the initiation of the rise in left ventricular pressure. In addition to electrical delays reflected in the ECG, the PEP_i may be sensitive to changes in preload and in afterload, as well as intracardiac inotropic levels (Weissler, 1977; Mattar *et al.* 1991). Our analysis excluded any role of altered electrical patterns in the prolonged PEP_i. Furthermore, it is unlikely that cardiac preload affected the PEP_i with HDBR. Certainly, stroke volume and blood volume were reduced to a greater extent in the Control participants of this project, as reported earlier (Edgell *et al.* 2007). Yet, the reflex autonomic response to reduced preload might be expected to counteract any direct 'slowing' effect of reduced preload on systolic timing. Such counter-regulatory mechanisms might explain the lack of impact of acute changes in blood volume or expiratory pressures on PEP_i (Kubitz *et al.* 2005), left ventricular diameters or pressures (Nixon *et al.* 1979; Perhonen *et al.* 2001*b*).

An important determinant of PEP_i is cardiac afterload. In a manner that was consistent with earlier reports (Harris *et al.* 1967), peripheral vasoconstriction with noradrenaline infusion increased cardiac afterload and the PEP_i in all participants both before and after HDBR. Afterload is a function of diastolic blood pressure, left ventricular radius at end diastole and wall thickness; these variables form the initial basis for understanding bed rest-induced alterations in systolic timing. Diastolic pressure was not statistically different between test periods. Bed

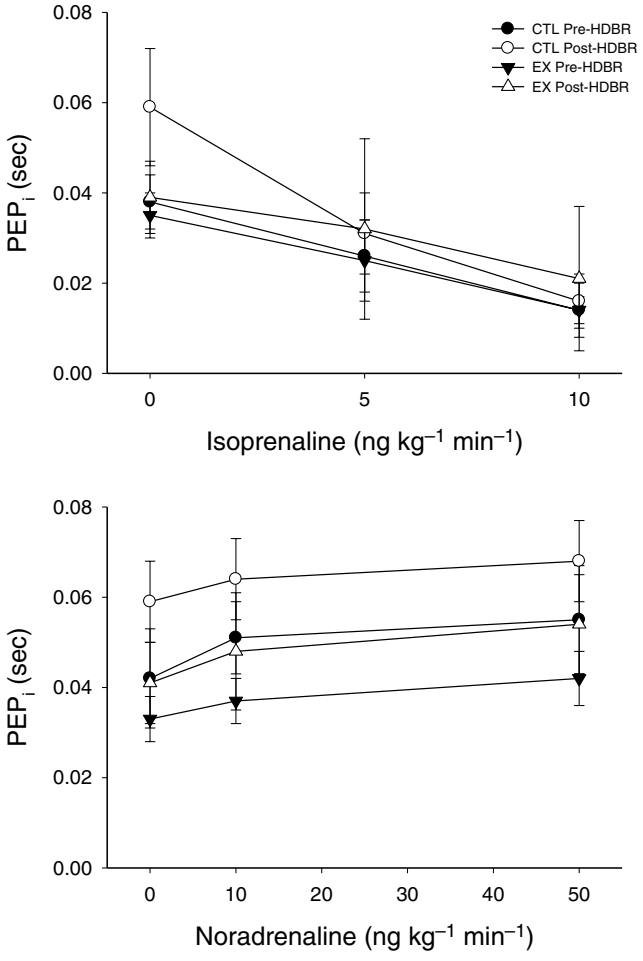

Figure 3. Effects of intravenous isoprenaline (top panel) and noradrenaline infusions (bottom panel) on the pre-ejection period (PEP_i) in Control and Exercise groups measured pre-HDBR and after 56 days of HDBR
Top panel, effect of drug ($P < 0.05$) and group × drug interaction ($P < 0.05$). Bottom panel, effect of drug ($P < 0.05$) and effect of HDBR ($P < 0.05$). $n = 7$ in each group.

rest-induced cardiac atrophy with thinning of the left ventricle wall (Dorfman *et al.* 2007) may offset the effect of reduced left ventricular end-diastolic volume (Perhonen *et al.* 2001*b*; Arbeille *et al.* 2008*a*) on cardiac afterload. Experimental studies that examine directly the impact of cardiac remodelling on systolic timing remain to be performed. However, it must be considered that such remodelling occurred only in the Control group of the present study, as assessed both by magnetic resonance imaging (Dorfman *et al.* 2007) and echocardiography (present study) and cannot explain the systematic effect of HDBR on prolonged PEP_i across both groups.

Thus, it appears that changes to cardiac inotropism must have been important factors in the HDBR-induced prolongation of cardiac PEP_i. In turn, this altered inotropic effect may be related to sympathetic activation and/or intrinsic characteristics of the left ventricle myocytes. At least in baseline conditions, the PEP_i has been used as an analogue of left ventricular contractility and a marker of cardiac sympathetic activation (Imrich *et al.* 2008). For example, therapeutic doses of β-blocker in patients with intact cardiac innervation caused a prolongation of PEP_i that was greater than what would have been predicted based on wall movement during isovolumic contraction (Chen & Gibson, 1979). In the present analysis, isoprenaline corrected the delayed PEP_i and this effect was not related to reductions in diastolic pressure or afterload. This effect was somewhat larger in the Control group, probably because of the slightly greater prolongation of PEP_i in this group compared with the Exercise group. However, the overall isoprenaline effect does not necessarily suggest that reduced baseline sympathetic activation or altered cardiac innervation formed the mechanism(s) of the augmented PEP_i. First, whereas patients with systematic autonomic failure and cardiac denervation are not able to decrease PEP_i reflexively, these same patients do not exhibit differences in baseline PEP_i from innervated hearts (Imrich *et al.* 2008). Second, although baseline sympathetic activation of the heart was not assessed in this study, peripheral measures of muscle sympathetic nerve activity were not different with HDBR in this group (Arbeille *et al.* 2008*a*). It could be that β-adrenergic sensitivity was reduced with HDBR in these groups. However, as reported previously in these participants (Edgell *et al.* 2007), the heart rate responses to isoprenaline infusion were augmented following HDBR but only in the Control group and these were related to the reduction in cardiac stroke volume. Similar patterns have been observed in men after 14 days of HDBR (Convertino *et al.* 1997). Thus, it appears that intrinsic post-receptor cardiac mechanisms contribute importantly to HDBR-induced prolongation of the PEP_i. While HDBR affected systolic timing, there was minimal impact on the fractional shortening of the left ventricle. Thus, prolonged bed rest deconditioning appears to have a specific effect on the timing of systolic events rather than systolic function *per se*.

Overall, the present observations provide a functional outcome of HDBR that emphasizes alterations in cardiac excitation–contraction coupling with mechanisms that appear to be independent of cardiac remodelling or β-adrenoceptor sensitivity. Although we cannot verify the mechanism behind the genesis of the prolonged PEP_i, this change must relate to wall movement in early systole that is affected by β-adrenergic activation. An interesting possibility comes from evidence that excessive pericardial fluid affects systolic function in the absence of clinical manifestations or ECG abnormalities (Spodick *et al.* 1983; Wayne *et al.* 1984). It is not known whether the prolonged head-down position produces pericardial fluid accumulation, but the headward translocation of fluid makes this option a relevant possibility.

Experimental considerations

The present study was performed on women, and additional studies in men remain to be reported. No participant had been using oral contraceptives for at least 2 months prior to the start of the experiment, and all had regular cycles on entry. Unfortunately, it was not possible to schedule testing based on the menstrual status of the participants. As an indication of relative cycle phase at the times of our testing, three subjects in each group were in the first 10 days of their menstrual cycle during the pre-HDBR tests, while four subjects from the Exercise group and two from the Control group were in the first 10 days of their cycle on day 56 of HDBR. Such a menstrual effect could only be resolved by a systematic large-scale study in which individuals were examined with regard to duration of HDBR and menstrual cycle phase (Edgell *et al.* 2007).

The increase in PEP_i reported here occurred within the context of long-term HDBR. The time course of the response is not known and the mechanistic basis of the response cannot be isolated, although it appears to relate to intracellular contractile behaviour. Whether or not similar alterations will develop during long-term space flight remains to be examined. Cardiac remodelling occurs in microgravity, but cardiac function is relatively sustained in the face of reduced diastolic blood pressure and blood volume (reviewed by Antonutto & Di Prampero, 2003).

Summary

Prolonged HDBR causes pronounced delay in the coupling of left ventricular excitation to contraction. The combination of aerobic and resistance exercise minimally affected this delayed PEP_i, suggesting that it was due to an independent effect of HDBR. The delay in PEP_i was reversed by low doses of infused isoprenaline.

Afterload and the QRS complex were unaffected by HDBR, reinforcing the suggestion that the delayed PEP_i was due to the effects of HDBR on the contractile properties of the heart rather than electrical or vascular factors. Thus, the cardiac PEP_i is a modifiable variable both acutely, in response to changes in cardiac contractility and/or cardiac afterload, and chronically, in response to physical deconditioning.

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