Diastolic suction is impaired by bed rest: MRI tagging studies of diastolic untwisting

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Diastolic suction is impaired by bed rest: MRI tagging studies of diastolic untwisting. J Appl Physiol 104: 1037–1044, 2008. First published January 31, 2008; doi:10.1152/japplphysiol.00858.2006.—Bed rest deconditioning leads to physiological cardiac atrophy, which may compromise left ventricular (LV) filling during orthostatic stress by reducing diastolic untwisting and suction. To test this hypothesis, myocardial-tagged magnetic resonance imaging (MRI) was performed, and maximal untwisting rates of the endocardium, midwall, and epicardium were calculated by Harmonic Phase Analysis (HARP) before and after −6° head-down tilt bed rest for 18 days with (n = 14) and without exercise training (n = 10). LV mass and LV end-diastolic volume were measured using cine MRI. Exercise subjects cycled on a supine ergometer for 30 min, three times per day at 75% maximal heart rate (HR). After sedentary bed rest, there was a significant reduction in maximal untwisting rates of the midwall (−46.8 ± 14.3°/s to −35.4 ± 12.4°/s; P = 0.04) where untwisting is most reliably measured, and to a lesser degree of certainty in the endocardium (−50.3 ± 13.8° to −40.1 ± 18.5°/s; P = 0.09); the epicardium was unchanged. In contrast, when exercise was performed in bed, untwisting rates were enhanced at the endocardium (−48.4 ± 20.8° to −72.3 ± 22.3°/ms; P = 0.05) and midwall (−39.2 ± 12.2° to −59.0 ± 19.6°/s; P = 0.03). The differential response was significant between groups at the endocardium (interaction P = 0.02) and the midwall (interaction P = 0.004). LV mass decreased in the sedentary group (156.4 ± 30.3 to 149.5 ± 27.9 g; P = 0.07), but it increased slightly in the exercise-trained subjects (156.4 ± 34.3 to 162.3 ± 40.5 g; P = 0.16); (interaction P = 0.03). We conclude that diastolic untwisting is impaired following sedentary bed rest. However, exercise training in bed can prevent the physiological cardiac remodeling associated with bed rest and preserve or even enhance diastolic suction.

cardiac atrophy; bed rest deconditioning; magnetic resonance imaging with myocardial tagging; exercise; spaceflight

CARDIOVASCULAR UNLOADING ASSOCIATED with spaceflight and head-down tilt (HDT) bed rest results in a reduction in left ventricular (LV) size, eccentric cardiac atrophy, and decreased cardiac chamber distensibility (7, 28, 40, 42, 61). Coupled with a smaller plasma volume and a smaller LV end-diastolic volume (LVEDV), HDT bed rest leads to an excessive drop in upright stroke volume (SV) and orthostatic intolerance. The physiological adaptation to bed rest secondary to the loss of hydrostatic and gravitational gradients is initiated by a cephalic and intrathoracic redistribution of intravascular volume resulting in a transient augmentation in LV filling pressure and SV. Within the first 48 h, a prominent reduction in plasma volume due to salt and water diuresis ensues, and a new hemodynamic steady state is established. These changes result in a significant drop in LV filling, which is clearly evident after 2 wk (28, 40, 42, 59). As a result, orthostatic hypotension secondary to a decreased SV occurs when the gravitational gradients are restored. Interestingly, hypovolemia alone does not account entirely for the fall in SV following bed rest deconditioning (4, 17, 28, 42).

LV performance is impaired after HDT bed rest as suggested by a steeper Starling curve and a decreased SV for any given filling pressure below supine baseline (28, 40, 42). However, the relationship between LVEDV and SV remains normal, suggesting that the smaller SV after bed rest is a function of decreased filling not depressed contractility (28). Furthermore, LV distensibility is decreased with a shift to the left of the pressure-volume curve, and there appears to be a reduction in diastolic suction as suggested by a reduction in the equilibrium volume (V0) to the level of the LV end-systolic volume (LVESV) (28); but the impact of bed rest on diastolic suction remains uncertain.

Unfortunately, the limited methods used to study the dynamic process of diastole in the past had limited ability to accurately quantify the effect of HDT bed rest on diastolic suction. Therefore, in this study we utilized MRI with myocardial tagging to evaluate the impact of bed rest on diastolic function as assessed by velocities of untwisting. MRI with myocardial tagging directly evaluates diastolic untwisting, which occurs mostly before the opening of the mitral valve. As such, this characteristic is less affected by left atrial pressure or volume than other techniques that are highly preload dependent (6, 9, 13, 31, 52). Given the fact that exercise training leads to increases in both plasma volume and LV, resulting in eccentric LV hypertrophy (1, 10, 11, 12, 44) while improving cardiac compliance (1), we hypothesized that exercise may prevent the physiological cardiac remodeling associated with HDT bed rest and preserve diastolic untwisting.

METHODS

Subjects. Twenty-four previously sedentary but healthy subjects (21 men, 3 women) aged 34.8 ± 9.1 yr (range 19–49 yr) participated in this study. Each subject provided their voluntary written, informed consent. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
consent to participate in protocols approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

Study design (bed rest). All 24 subjects completed 18 days of strict -6° HDT bed rest as part of a larger study, parts of which have been previously published (23). They were recruited in a two-to-one balanced randomization stratified by age and sex to exercise vs. no exercise groups. Three additional sedentary subjects were added after initial data analysis to improve statistical power by partnering with another bed rest study at our institution. The exercise group (n = 14) cycled on a supine ergometer in a horizontal position for 30 min, three times a day at 75% of their maximum HR measured in an upright position according to standard bicycle exercise test protocol. This specific amount of training was calculated to normalize cardiac work compared with ambulatory periods (28). With the exception of the 90-min exercise session, all subjects were restricted to the HDT position at all times except for during meals when they were allowed to elevate on one elbow. Subjects were housed and supervised in the General Clinical Research Center at the University of Texas Southwestern Medical Center where they were given a standard diet of ~2,500 cal/day and ~3,500 mg of sodium/day, and fluids were allowed ad libitum. Intake and urine output were recorded, and caloric intake was increased appropriately for the exercise subjects to prevent weight loss.

MRI protocol. MRI with myocardial tagging was performed on all subjects immediately before and after bed rest at the Mary Nell and Ralph B. Rogers Magnetic Resonance Center at the University of Texas Southwestern Medical Center. Images were acquired by a 1.5-T Phillips NT MRI scanner. After completing the standard imaging protocol for the assessment of mass and volume (19, 26, 43), tagged short-axis, gradient echo, cine MRI sequences with a temporal resolution ranging from 30 to 55 ms were obtained.

Tagged images (linear tags) were obtained using the Spatial Modulation of Magnetization (SPAMM) encoding gradients (Fig. 1). The typical repetition time was 14.6 ms, the echo time was 9.0 ms, and the flip angle was 50°. The slice thickness was 8.0 mm with a gap of 2.0 mm spanning from the apex to the base of the heart. The image resolution was 256 × 256 with a 350-mm field of view. The tag width was 2–3 mm, and the tag spacing was 7–8 mm. In order for the tags to have the greatest resolution at early diastole when the untwisting rates (a function of diastolic suction) are maximal, the tags were placed at end systole at a fixed time after the R wave, which was ~55 ms.

Image analysis. LV volumes were calculated by manually identifying the endocardial border at both end-diastole and end-systole using the MRI-MR Analytical Software System (MEDIS, Leiden, The Netherlands) (36); the observer who read the cardiac MRI studies was blinded to the group assignments. End diastole was the first frame in every sequence, and end systole was defined as the frame with the smallest endocardial area (chamber area). LV volumes were then computed by summation using Simpson’s rule (22, 43). For the calculation of LV mass, the difference between endocardial and epicardial areas during diastole were calculated and multiplied by 1.05/g/ml, which is the density of myocardial muscle (26). Papillary muscles were included in the measurement of LV mass. This technique has been shown to be extremely accurate and reproducible in our laboratory with an intraobserver variability for LV mass and right ventricle mass of r = 0.98 with a SE of estimate (SEE) 3.8 g and r = 0.97 with a SEE of 2.1 g, respectively (19, 26, 40).

Harmonic phase analysis. All MRI studies were submitted to and read blindly by the Core MESA (Multi-Ethnic Study of Atherosclerosis) MRI Reading Center at Johns Hopkins Hospital where harmonic phase (HARP) analysis software (Diagnosoft, Palo Alto, CA) was used for determination of myocardial untwisting (5, 18, 20, 38, 39). The reproducibility of data for this type of analysis has been excellent by this specific MRI core reading laboratory (5). Untwisting rates were calculated for the endocardium, midwall, and epicardium at the midcavity level, and the midcavitory slice was defined by using the papillary muscles as a landmark. By tracking movements of the tag points, untwisting or rotation angles expressed as degrees were computed and plotted as a function of time as expressed in milliseconds (Fig. 2). Then, rotation rates were calculated using the formula:

\[
\text{Rotation rate} \left(^{\circ}/\text{ms}\right) = \frac{\text{angle 2} \left(^{\circ}\right) - \text{angle 1} \left(^{\circ}\right)}{\text{time difference (ms)}}
\]

By plotting the rotation rates vs. frame interval, maximal untwisting rates for each layer were identified as the most negative point on the curve, and maximal untwisting rates of all three layers were defined as the peak values of rotation across all segments (Fig. 3). With this approach, rotation rates are positive during systole (indicative of twisting) and negative during diastole (indicative of untwisting), and a more negative untwisting rate reflects an enhanced (or improved) diastolic function. To study the effect of bed rest and exercise on diastole, the maximal rates of untwisting expressed as degrees per second were compared.

Statistical analysis. The numerical data are presented as means ± SD. The differences between pre-bed rest and post-bed rest LVEDV, LV end-diastolic masses, and untwisting rates for both the deconditioned and exercise groups were compared by two-way repeated-measures ANOVA (group × time) with Bonferroni-corrected t-tests for post hoc comparisons. Because of the relatively small sample size, all individual P values are reported as per recommendation of the American Physiological Society (8). An alpha level of 0.05 was considered most clearly representative of statistical significance.

Fig. 1. A: MRI tagging images using Spatial Modulation of Magnetization (SPAMM). This is midcavity level and short axis. This individual’s maximal untwisting rate before (pre) bed rest was ~45.9, −31.8, and −19.2 °/s for the endocardium, midwall, and epicardium respectively, B: this individual’s maximum untwisting rate decreased to −22.5, −25.5, and −16.2 °/s for the endocardium, midwall, and epicardium, respectively, following (post) bed rest.
RESULTS

During 2 wk of HDT bed rest, there was a small reduction in LV mass (156.4 ± 30.3 to 149.5 ± 27.9 g; \( P = 0.07 \)). Conversely, the LV mass increased slightly after 2 wk of exercise during bed rest (156.4 ± 34.3 to 162.3 ± 40.5 g; \( P = 0.16 \)). The differential response between sedentary bed rest and exercise during bed rest on LV mass was significant (−7.0 ± 10.6 vs. 5.9 ± 14.8 g; interaction \( P = 0.03 \)). The LVEDV decreased prominently during 2 wk of sedentary bed rest (121.2 ± 19.3 to 102.1 ± 23.3 ml; \( P = 0.01 \)), and the LVEDV decreased by ~70% as much in the exercise group (106.2 ± 22.2 to 100.0 ± 22.0 ml; \( P = 0.07 \)). The differential response was significant (−19.1 ± 19.1 to −6.2 ± 11.7 ml; interaction \( P = 0.05 \)).

The \( V_0 \) was not calculated in this study. LVESV decreased by ~21% from 37.5 to 29.5 ml (\( P = 0.01 \)) in the nonexercise group and by only half as much, ~12% from 32.5 to 28.7 ml (\( P = 0.06 \)) in the exercise group; the ejection fraction (EF) did not change in either group (interaction, \( P = 0.30 \)). There was no apparent relationship between the change in LVESV, EF, and maximal untwisting after bed rest with or without exercise, although a relationship might have been demonstrable if we had measures of the difference between ESV and \( V_0 \).

Despite a similar reduction in LVESV after both bed rest and exercise during bed rest and no change in EF in both groups, the differential responses between the two groups in terms of maximum untwisting rates (interaction, \( P = 0.004 \)) and LV mass (interaction, \( P = 0.03 \)) were significant.

HR did not change in the control group (70.4 ± 12.4 to 68.3 ± 8.7 beats/min; \( P = 0.72 \)) or the exercise group (66.5 ± 7.3 to 68.4 ± 11.4 beats/min; \( P = 0.42 \)) (interaction \( P = 0.44 \)), and systolic blood pressure did not change in the control group (117.5 ± 6.6 to 115.8 ± 6.1 mmHg; \( P = 0.64 \)) or the exercise group (116.5 ± 11.9 to 118.6 ± 14.2 mmHg; \( P = 0.48 \)) (interaction \( P = 0.44 \)). Moreover, diastolic blood pressure did not change in the control group (69.2 ± 6.3 to 70.2 ± 7.9 mmHg; \( P = 0.71 \)) or the exercise group (69.1 ± 6.3 to 72.4 ± 10.4 mmHg; \( P = 0.14 \)) (interaction \( P = 0.54 \)), and lean body mass deceased slightly in the control group (61.2 ± 5.8 to 58.4 ± 6.9 g; \( P = 0.10 \)) and the exercise group (60.3 ± 10.4 to 58.1 ± 8.7 g; \( P = 0.02 \)) (interaction \( P = 0.67 \)).

Secondary to technical difficulties with data acquisition and file transfer for HARP imaging, the data from two subjects in the deconditioned group and three subjects from the exercise group could not be analyzed by HARP. Data were therefore available for 8 sedentary and 11 exercise-trained subjects.

At baseline before bed rest for all subjects, the average maximum untwisting rates were −49.3 ± 17.9, −42.6 ± 13.3, and −37.3 ± 12.3 °/s at the endocardium, midwall, and epicardium, respectively, and the differences of baseline maximum untwisting rates between the two groups were not significant for any of the three layers. After bed rest there was a significant reduction in the average maximal untwisting rates of the midwall (−46.8 ± 14.3 to −35.4 ± 12.4 °/s; \( P = 0.04 \)), where untwisting is most reliably measured, and to a lesser degree of certainty in the endocardium (−50.3 ± 13.8 to −40.1 ± 18.5 °/s; \( P = 0.09 \)). There was a minimal reduction of untwisting in the epicardium (−41.5 ± 13.5 to −36.8 ± 12.4 °/s; \( P = 0.34 \)) (Fig. 4A). In contrast, when exercise was performed during bed rest, average maximum rates of untwist-
ing were preserved or even increased at the endocardium (−48.4 ± 20.8°/s; P = 0.05), midwall (−39.2 ± 12.2°/s; P = 0.03), and epicardium (−33.9 ± 10.3°/s; P = 0.11) (Fig. 4B). The differential response was significant between groups at the endocardium (10.1 ± 14.4 vs. −23.9 ± 33.3°/s; interaction P = 0.02) and the midwall (11.4 ± 12.4°/s vs. −19.8 ± 24.0°/s; interaction P = 0.004), but it was less clearly so at the epicardium (4.7 ± 12.9°/s vs. −13.9 ± 24.7°/s; interaction P = 0.07) (Fig. 5).

However, one of the subjects from the exercise group had a baseline untwisting rate of −123.9°/s at the endocardium and −83.9°/s at the midwall. Given the fact that this subject’s baseline data were approximately three standard deviations greater than the mean, we concluded that this subject was a statistical outlier, possibly due to incorrect time stamping of the images. However, even when including this outlier in our analysis, the differential response was still significant between groups at the midwall (interaction P = 0.05), but it was not significant at the endocardium (interaction P = 0.14) or epicardium (interaction P = 0.09).

DISCUSSION

The principle new findings of this study include the following: 1) diastolic untwisting is impaired after sedentary short-term HDT bed rest suggestive of reduced diastolic suction; and 2) exercise training can prevent the physiological cardiac remodeling and atrophy associated with bed rest and preserve or even enhance diastolic untwisting. Hence, exercise appears to be not only an effective method to prevent cardiac remodeling during unloading conditions, such as spaceflight and bed rest, but it also augments diastolic untwisting resulting in improved diastolic suction and filling.

Numerous animal models have shown that chronic unloading leads to cardiac atrophy and remodeling (30, 34, 53, 59). LV morphological changes and prominent reductions in myo-
cyte size have been documented after as little as 7 days of microgravity in several small-animal models (14, 59). Chronic unloading of the heart in dogs by thoracic inferior vena caval constriction led to clear cardiac atrophy with a significant reduction in cardiomyocyte volume and LV mass (30). These changes primarily affect cardiac myocytes instead of the interstitium (54), increasing the relative concentration of collagen (33), which may be partly responsible for the decline in chamber distensibility associated with bed rest (32).

There are several mechanisms that might explain how unloading leads to cardiac atrophy. For example, short-term microgravity results in an inactivation of ANP synthesis (30) and changes in pretranslational regulation of contractile protein gene expression in cardiac muscle (53). Not only has the rate of protein synthesis been shown to decrease after as little as 18 h of tail suspension in rats but also there is a reduction in polypeptide synthesis, resulting in lighter polysomes and less ribosomes per mRNA (34).

Furthermore, multiple studies involving human subjects have shown that LV volume and mass decrease following as little as 18 days of strict bed rest deconditioning and after as little as 10 days of spaceflight (40). This reduction in LV volume after bed rest is not exclusively a product of dehydration; rather it is an adaptive response. Volume replacement does not completely prevent the orthostatic intolerance associated with bed rest or spaceflight (4, 17, 28, 42).

In fact, there is a unique leftward shift in the pressure-volume relationship and a larger reduction in the LV equilibrium volume after 15 days of HDT bed rest than after a similar degree of hypovolemia as simulated by acute volume loss induced by intravenous furosemide (42), providing further evidence that bed rest leads to cardiac remodeling and decreased cardiac distensibility rather than simply hypovolemia.

Previous studies by our group have suggested that this reduction in equilibrium volume after bed rest could theoretically impair diastolic suction (42). The V₀ is the volume of the fully relaxed LV when the transmural filling pressure equals zero (56). To utilize diastolic suction, the LV must contract below V₀ during systole to engage restorative forces (37, 57). Diastolic suction may become compromised if the end-systolic volume increases, if the equilibrium volume decreases, or both (28, 57). Thus in our laboratory’s previous studies, before bed rest calculated V₀ was significantly greater than the LVESV consistent with functional diastolic suction; but after bed rest, V₀ was reduced to the level of the LV end-systolic volume. This remodeling is consistent with, but not dispositive of, the possible loss of diastolic suction after bed rest or spaceflight (28). It also should be noted that this definition of V₀ is not entirely correct because it was derived from LV diastolic pressure estimated from the pulmonary capillary wedge pressure referenced to the atmosphere (28, 42) rather than to true transmural pressure. Moreover, some investigators have argued that diastolic suction is perhaps better defined in the closed-chest model in relative terms, in other words when LV pressure is decreasing at the same time that LV volume is increasing (dP/dV < 0) (27, 60). One implication of this definition is that the equilibrium volume may then be defined as a mechanical equilibrium (60), meaning the ventricular volume after release of stored elastic forces. Intriguingly, this definition of functional, closed-chest V₀ may end up being quite close to the estimates provided by previous studies in which V₀ was derived from pressures referenced to the atmosphere (28, 42). Finally, assessment of ventricular stiffness with lifelong deconditioning (i.e., sedentary aging) compared with young individuals or Masters athletes is completely independent of how intracardiac pressures are referenced (1). Regardless of the definition of equilibrium volume, however, the present study extends this previous research on ventricular chamber structure after bed rest and demonstrates the physiological consequences of cardiac atrophy, namely the decrease in untwisting rates highly suggestive of reduced diastolic suction.

There is limited research to date evaluating the dynamic process of diastole following unloading conditions. For example, peak early (E-) and atrial (A)-wave velocities are significantly reduced after both 10 and 21 days of −6 degrees of HDT bed rest, and the E/A ratio was decreased as well, although the difference was modest and quite variable (51). Although these Doppler indexes suggest that there might be a negative impact on diastolic filling, there are many limitations to relying on mitral inflow velocities for the assessment of intrinsic LV diastolic function (6, 9, 52). The majority of noninvasive modalities such as two dimensional echocardiography (mitral inflow variables) indirectly measure LV filling after the mitral valve opens and are thus highly dependent on preload and LV volume changes. Variations in left atrial (LA) pressure alter atrioventricular pressure gradients and thus confound estimations of relaxation. As a result, pulsed-wave Doppler echocardiography has poor sensitivity and specificity in the detection of diastolic dysfunction, and poor correlations have been found when Doppler measurements of diastolic function are compared with invasive measurements of ventricular filling (6, 9, 52). Despite claims to the contrary, color M-mode Doppler and tissue Doppler echocardiography are similarly preload dependent (45), although of course, “diastolic function” and ventricular filling in particular is an intrinsic preload phenomenon.

In contrast to mitral inflow velocities, MRI with tags placed at end systole measure the end-result of ventricular torsion, that is, the engagement of restorative forces that lead to diastolic suction (24, 25, 37, 57). The peak diastolic untwisting rates that are measured with this technique are obtained before the opening of the mitral valve, and thus are not substantially affected by left atrial pressure or LA-LV pressure gradients that drive mitral inflow (9, 31). Consequently volume infusion does not affect untwisting rates despite significant increases in LA pressure and is considered one of only a very few methods that can quantify the isovolumic relaxation phase of the cardiac cycle (9). To our knowledge, this is the first study to use myocardial tagging to measure the impact of HDT bed rest on the dynamic process of LV relaxation.

Interestingly, this study clearly demonstrated that the average maximal rate of untwisting at the midwall decreased by 33% following HDT bed rest, which further supports our hypothesis that unloading conditions result in physiologically significant cardiac atrophy and remodeling. Hence, the prominent fall in upright SV following microgravity exposure is due at least in part to decreased LV filling as a result of impaired diastolic untwisting and suction.

Diastolic suction is especially crucial for early diastolic filling in the setting of low filling pressures such was when standing upright. But the mechanism behind these restoring forces is poorly understood (58). Although restoring forces...
clearly originate within each myofiber due to the springlike action of the protein titin (3, 21), at the ventricular chamber level, others have argued that the negative and subatral pressure of the LV during early diastole results from the elastic energy that is generated during myocardial relaxation due to gross fiber rearrangement of the myocardial connective tissue network as the LV returns to the equilibrium or unstressed state (2, 46, 47). For example, using MRI with myocardial tagging in 10 open chest dogs, diastolic untwisting was found to occur during isovolumic relaxation, and as the LV returned to its configuration before the opening of the mitral valve, there was a release of restoring forces that were stored in elastic elements during systolic twisting (9, 24, 25, 37, 46, 47, 57). Diastolic suction is likely dependent on the recoil properties of the heart (59, 58), and it is decreased in certain conditions associated with less global elastic recoil such as in patients with dilated cardiomyopathies and in subjects following chronic unloading conditions (58).

The benefits of exercise training on LV compliance are well known (1, 29, 35, 49, 55). A small-animal model recently showed that endurance training augments the velocity of decline of LV pressure (dP/dt), decreases tau (τ), the time constant for relaxation, and reduces the contraction duration secondary to less relaxation time (29). Endurance training augments diastolic filling in humans by increasing early filling rates and lowering peak atrial filling velocities (29, 49). Exercise also prevents the decline in LV compliance associated with the aging process (1, 13, 29). Compared with age-matched sedentary seniors, LV mass, LVEDV, and LV compliance are all greater for Masters endurance athletes (1, 29). After 2 mo of exercise training, patients with nonsymptomatic cardiomyopathies had a significant increase in their untwisting rates compared with those in the control group as assessed by MRI with myocardial tagging (35).

Multiple mechanisms have been described to explain the improvement in diastolic function associated with endurance training, including enhanced calcium uptake by the sarcoplasmic reticulum, increased cytochrome-c oxidase levels, and fatty acid oxidation (29). Exercise preserves both myocardial viscoelastic properties and pericardial size. A study by Spiriti et al. (50) evaluated 947 elite athletes that participated in 27 different sports, and they demonstrated that endurance training of almost any type results in LV hypertrophy (50), which optimizes LV chamber geometry (eccentric ventricular hypertrophy). These changes are associated with improved compliance (1, 29, 41). In fact, a vast number of studies have shown that endurance training given an adequate duration and intensity leads to ventricular hypertrophy (10–12, 44, 50). Moreover, in this particular study, the LV mass-to-LVEDV ratio increased significantly after bed rest with exercise (1.5 ± 0.2 to 1.6 ± 0.4; P = 0.01). Perhaps this eccentric LV hypertrophy is a physiological adaptation to exercise that counterbalances the cardiac atrophy associated with unloading.

**Limitations.** Several studies utilizing myocardial tagging have established that recoil or untwisting rates are independent of atrial or ventricular volume (9, 31), but controversy regarding the effect of bed rest or spaceflight still remains. Critics maintain that the apparent reduction in diastolic filling following HDT bed rest is a function of a reduction in plasma volume and resultant preload rather than a result of cardiac remodeling, and there is no doubt that hypovolemia plays an important role. However, a recent study involving invasive hemodynamic measurements and myocardial tagging in canines found that diastolic untwisting rates during isovolumic relaxation are entirely independent of preload (9). Moreover, utilizing a beating heart preparation, MacGowan and coworkers (31) demonstrated that diastolic recoil is not affected by volume. In addition, LV end-diastolic volume decreased in both the control group (121.2 ± 19.3 to 102.1 ± 23.5 ml; P = 0.01) and in the exercise-trained subjects (106.2 ± 22.2 to 100.0 ± 22.0 g; P = 0.07), although clearly to a lesser degree after bed rest with exercise. Nevertheless, despite the reduction in LVEDV in both groups and the significant reduction in untwisting rates following sedentary HDT bed rest, the rates of diastolic untwisting actually increased following exercise training during bed rest. Although an earlier tagging study on canines demonstrated that dobutamine and catecholamines increase diastolic rates of untwisting (9), we minimized the influence of recent exercise by performing the post-bed rest MRI studies at least 24 h after the last training session.

This study could be faulted for not measuring atrial volumes or rates of ventricular filling. But untwisting rates are a measurement of isovolumic relaxation (fixed LV volume) and are less likely to be affected by LA pressure and volumes than other modalities that quantify diastole during LV filling (9, 31). Moreover, it is important to emphasize that in the supine position (in which the MRI studies were performed), HR is sufficiently slow, and there remains a sufficiently high LA-LV gradient that ventricular filling would not likely be compromised even if diastolic suction were completely absent. However, it is in the upright position that the clinical significance of the reduction in diastolic suction is most paramount and of course when orthostatic intolerance develops. Unfortunately, we were not able to measure rates of ventricular filling during the upright posture in this study.

There are a number of limitations to MRI tagging with SPAMM in a 1.5-T environment. For example, MRI tagging is dependent on the longitudinal relaxation time (T1) properties of the myocardium, and as a result, the tags tend to fade secondary to the rapid recovery of T1. Moreover, the definition of the tags becomes less with progression of the cardiac cycle, and it is quite difficult to evaluate the middle and late parts of diastole. However, in this particular study, we placed the tags in late systole to enhance our ability to see the tags more clearly during early diastole. There is a possibility that we did not always place the tags at exactly the same time point at end systole. However, the systolic time is quite stable under most circumstances, and thus less susceptible than diastolic period to changes in HR. In any case, because the goal of this experiment was to measure the maximal rate of untwisting at the earliest part of diastole, small variations in the time of tag placement or late tag decay would have no real impact on our data analysis.

We must also emphasize that we based our measurements on two-dimensional strain maps, and it is possible that HDT bed rest might affect the third dimension (long-axis strain). Thus the lack of incorporation of the long axis in our analysis limits the comprehensiveness of our findings. Moreover, two-dimensional analysis might suffer from some inaccuracies since regional movement in and out of the plane of measurement can be missed or at least under-represented. Unfortunately, the HARP approach, which standardizes and streamlines data analysis, at present can only analyze data in two dimensions.
Perhaps, future studies using more advanced tools when they become available should consider studying LV relaxation after bed rest utilizing 3D strain maps.

Despite heavy recruiting aimed at women, this study only enrolled three female volunteers and the impact of sex differences on untwisting rates is unknown. However, our laboratory recently demonstrated that men and women have a similar degree of cardiac atrophy and remodeling after 8 wk of HDT bed rest (10). Our laboratory has demonstrated recently that there are no major sex-related differences in orthostatic blood pressure control, including reductions in cardiac filling pressure, and corresponding increases in total peripheral resistance, mean sympathetic nerve activity (bursts/min), plasma norepinephrine levels, systemic vascular resistance, or diastolic blood pressure following graded HUT under both normovolemic or hypovolemic conditions, or during maximal lower body negative pressure to presyncope (15, 16). Finally, the response for the women was indistinguishable from the men, arguing against excluding the women from data analysis. Nevertheless, a larger study sufficiently powered to distinguish sex differences in untwisting rates would be required to be dispersive with regards to sex differences in this response.

Finally, the dataset in the present study was relatively small and the two groups were unbalanced in size, although the statistical comparisons seemed convincing.

Conclusions. In summary, 2 wk of sedentary bed rest leads to cardiac atrophy and remodeling sufficient to reduce rates of myocardial untwisting, which is indicative of reduced diastolic suction. Exercise training while in bed preserves cardiac structure, maintains optimal chamber geometry, and prevents the decline in diastolic suction associated with HDT bed rest. As a result, exercise training may be a potential countermeasure to the cardiac atrophy, orthostatic intolerance, and prominent reduction in SV associated with chronic unloading conditions such as spaceflight and bed rest.

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