

Cardiac atrophy after bed rest and spaceflight

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Perhonen, Merja A., Fatima Franco, Lynda D. Lane, Jay C. Buckey, C. Gunnar Blomqvist, Joseph E. Zerwekh, Ronald M. Peshock, Paul T. Weatherall, and Benjamin D. Levine. Cardiac atrophy after bed rest and spaceflight. *J Appl Physiol* 91: 645–653, 2001.—Cardiac muscle adapts well to changes in loading conditions. For example, left ventricular (LV) hypertrophy may be induced physiologically (via exercise training) or pathologically (via hypertension or valvular heart disease). If hypertension is treated, LV hypertrophy regresses, suggesting a sensitivity to LV work. However, whether physical inactivity in nonathletic populations causes adaptive changes in LV mass or even frank atrophy is not clear. We exposed previously sedentary men to 6 ($n = 5$) and 12 ($n = 3$) wk of horizontal bed rest. LV and right ventricular (RV) mass and end-diastolic volume were measured using cine magnetic resonance imaging (MRI) at 2, 6, and 12 wk of bed rest; five healthy men were also studied before and after at least 6 wk of routine daily activities as controls. In addition, four astronauts were exposed to the complete elimination of hydrostatic gradients during a spaceflight of 10 days. During bed rest, LV mass decreased by $8.0 \pm 2.2\%$ ($P = 0.005$) after 6 wk with an additional atrophy of $7.6 \pm 2.3\%$ in the subjects who remained in bed for 12 wk; there was no change in LV mass for the control subjects (153.0 ± 12.2 vs. 153.4 ± 12.1 g, $P = 0.81$). Mean wall thickness decreased ($4 \pm 2.5\%$, $P = 0.01$) after 6 wk of bed rest associated with the decrease in LV mass, suggesting a physiological remodeling with respect to altered load. LV end-diastolic volume decreased by $14 \pm 1.7\%$ ($P = 0.002$) after 2 wk of bed rest and changed minimally thereafter. After 6 wk of bed rest, RV free wall mass decreased by $10 \pm 2.7\%$ ($P = 0.06$) and RV end-diastolic volume by $16 \pm 7.9\%$ ($P = 0.06$). After spaceflight, LV mass decreased by $12 \pm 6.9\%$ ($P = 0.07$). In conclusion, cardiac atrophy occurs during prolonged (6 wk) horizontal bed rest and may also occur after short-term spaceflight. We suggest that cardiac atrophy is due to a physiological adaptation to reduced myocardial load and work in real or simulated microgravity and demonstrates the plasticity of cardiac muscle under different loading conditions.

magnetic resonance imaging; left ventricular mass; left ventricular end-diastolic volume; right ventricular mass; right ventricular end-diastolic volume

CARDIAC MUSCLE IS WELL REGULATED in response to changes in loading conditions (9, 32, 34, 54). An in-

crease in cardiac muscle mass is the basic adaptive response to increased volume or pressure loading, which can be seen as specific molecular changes in contractile proteins (8, 30). The signaling processes that regulate myocardial mass have been studied intensively over the past few years, and many pathways involving hemodynamic, neurohumoral, and pathological stimuli that lead to myocardial hypertrophy have been identified (9, 14, 52, 62). Conversely, the mechanisms and pathways leading to the opposite response, i.e., cardiac atrophy, are less clear, in part because of the limited availability of physiologically relevant animal models (33, 34). For whole animals (including humans), chronic volume loading of the left ventricle is associated with eccentric hypertrophy (increased mass and volume, with preserved mass/volume ratio) and increased chamber distensibility, whereas volume unloading is associated with eccentric atrophy and decreased chamber distensibility (10, 61).

In the absence of manifest cardiovascular disease, one model of chronic circulatory unloading in humans is sustained exposure to microgravity, either directly (i.e., spaceflight) or as simulated by bed rest. Both horizontal or head-down-tilt bed rest can be used as an analog for the adaptive responses of real microgravity, leading initially to a central fluid shift, with activation of volume regulatory mechanisms, loss of plasma volume, and restoration of a new hemodynamic steady state about halfway between the upright and supine positions (17, 35, 36). Thus both spaceflight and head-down-tilt bed rest result in decreased relative (to the supine position) volume loading of the heart and may lead to cardiac atrophy (17, 25, 35, 36). Studies in rodents after short-term spaceflight have shown evidence of decreased cardiac myocyte size, which is consistent with cardiac atrophy (23). A recent study in our laboratory has shown a decrease in the equilibrium volume of the left ventricle (volume at pressure = 0 mmHg) and a trend for left ventricular (LV) mass to decrease during head-down-tilt bed rest for 18 days, suggesting cardiac remodeling during bed rest (36). However, the limited precision of the methods used to

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measure LV mass in that study (echocardiography) reduced the ability to demonstrate cardiac atrophy with confidence over this short time period. Moreover, there are no reports available regarding the changes in right ventricular (RV) mass and volumes after physical deconditioning such as bed rest.

To determine whether cardiac atrophy occurs in humans during exposure to real or simulated microgravity, we exposed sedentary (physically inactive) men to prolonged supine bed rest and short-term spaceflight. To obtain the most precise and accurate data regarding changes in cardiac structure, magnetic resonance imaging (MRI) was used to measure both LV and RV mass and end-diastolic volume after bed rest and LV mass after spaceflight. We hypothesized that the heart is extremely plastic in response to physiological loading conditions and would exhibit significant changes in ventricular mass with cardiovascular "deconditioning" induced by bed rest and/or spaceflight.

METHODS

Subjects

Five healthy men with a mean age of 31 ± 5 yr volunteered to participate in the bed rest study. All five subjects completed 6 wk of strict supine bed rest and three out of five completed the total of 12 wk of bed rest. LV mass data were also obtained from four male astronauts (40 ± 2 yr) who participated the second German Spacelab Mission (D-2) with a duration of 10 days. Five additional control subjects matched for age with the bed rest subjects were also studied at baseline and then after at least 6 wk of uncontrolled, routine daily activity. All the subjects were healthy and none had any chronic medical problems as determined by a medical history, physical examination, electrocardiogram (ECG), and echocardiogram. All the bed rest subjects signed an informed consent form approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center, Dallas, TX. In addition, all astronauts signed a consent form, approved by the Human Research Policy and Procedures Committee at the Johnson Space Center (Houston, TX), and the D-2 protocols were also approved by the review committee at the German Aerospace Research Establishment (Köln, Germany).

Experimental Designs

Bed rest study. The bed rest subjects were in complete supine bed rest for 6 wk ($n = 5$), and three out of five finished a total of 12 wk. These subjects are a subset of subjects who were enrolled in a study of the mineral metabolic effects of prolonged bed rest reported previously (60). Subjects were kept at strict bed rest and were not allowed to elevate their heads more than 30° above the horizontal level. Horizontal movement was allowed, bedpan or urinal was used, and daily sponge baths were taken. The subjects had full 7-day metabolic evaluations during a 1-wk ambulatory control period before the beginning of bed rest and during the last week of bed rest. The mean daily caloric value of the metabolic diet was 2,206 Kcal with 74 g of protein, 83 g of fat, and 291 g of carbohydrate. This metabolic diet was repeated for the last 4 days of each bed rest week. Otherwise the subjects had a standard diet. Subjects were housed in the General Clinical Research Center at the University of Texas Southwestern Medical Center. Control subjects were freely ambulatory and

pursued their usual occupational and recreational activities between the two MRI measurements.

Spaceflight study. The four astronauts studied included the payload crew for the D-2 mission (STS-55), which flew in space for 10 days in April 1993. This flight was a dedicated life-sciences mission and included 19 experiments from an international group of investigators with an emphasis on the cardiovascular, cardiopulmonary, and endocrine/metabolic effects of spaceflight. Submaximal exercise was performed by two subjects for brief periods (~ 10 min) on *flight days 1, 3, and 7* as part of other investigations, but because of time constraints, no routine "maintenance" exercise was performed by this crew.

Study Protocols

The measurements in the bed rest study were done in the supine position pre-bed rest and were repeated after 2, 6, and 12 wk of bed rest. Hemodynamic data were obtained after at least 30 min of quiet rest in the laboratory and were repeated every 5 min until consecutive measurements of cardiac output (Qc) were obtained that were within 500 ml of each other (usually 20–30 min). The results of these last two measurements were then averaged for each session. The MRI data from astronauts were obtained 5 mo before the spaceflight and within 12 h of landing after the 10-day Spacelab mission. The hemodynamic data for the astronauts were obtained in conjunction with an experiment examining the renal/neurohumoral responses to saline infusion and the experimental details regarding the preflight and in-flight data collection have been reported previously (42). In this study, hemodynamic data were obtained at 6 and 9 mo before spaceflight in the supine position and in-flight on *mission day 5*. During flight, the Spacelab was maintained at sea-level atmospheric pressure and gas composition. The crew members were asked not to alter their preflight exercise habits as reported previously (6).

MRI Measurements

Bed rest. For the bed rest studies, MRI was performed on a 1.5-T Philips NT MRI scanner (Best, The Netherlands) at the Mary Nell and Ralph B. Rogers Magnetic Resonance Center at the University of Texas Southwestern Medical Center at Dallas, TX. The subject was positioned supine on the MRI table, and ECG monitoring leads were placed on the chest. Short-axis, gradient-echo, cine MRI sequences with a temporal resolution of 39 ms were obtained to calculate LV volumes as previously described (28). The heart was sectioned in 8-mm slices with 2 mm of gap spanning apex to base. Images were obtained with a 256×152 matrix and a 350×350 -mm field of view. The repetition time was 14 ms, echo time was 8.1 ms, 2 phase encodes were acquired per cycle and the flip angle was 40° .

LV mass was computed as the difference between epicardial and endocardial areas multiplied by the density of heart muscle, 1.05 g/ml (31). Previous studies in our laboratory and others have demonstrated that MRI with Simpson's rule technique results in highly accurate and reproducible measurements of LV mass (21, 31). In our hands, a regression equation of true LV mass = $7.14 + 0.91 \times$ MRI mass estimate (in grams) has been reported, with a correlation coefficient between MRI and direct measurements of cadaver hearts of 0.99 and a standard error of estimate (SEE) of 6.8 g with intraobserver variability of 0.96, SEE 11.1 g (31). With the use of 10 short-axis slices through the heart at end diastole in the present study, the intraobserver variability for

LV mass was 0.98, SEE 3.8 g, and for RV mass $r = 0.97$, SEE 2.1 g.

For LV volume determination, the endocardial border of each slice was identified manually at end diastole and end systole, and volumes were calculated by summation (47). End diastole was defined as the first frame in each sequence and end systole as the frame with smallest endocardial area. LV volumes were calculated by using Simpson's rule technique as previously described (47).

Mean wall thickness (MWT) for the entire left ventricle included the papillary muscle and was calculated as follows. For each short-axis slice, the epicardial area (LV chamber plus myocardial wall) and endocardial area (chamber area) were determined by using software on the imaging device. The "average" radius for each area was calculated by approximating the cross section as a circle and using the equation for the area of a circle ($\text{Area} = \pi r^2$ or $r = \sqrt{\text{Area}/\pi}$). The MWT for each slice was obtained by subtracting the endocardial radius from the epicardial radius; the wall thickness for all the short axis images was averaged to obtain the LV MWT. These operations are summarized in the following equation

$$\text{LV MWT} = \sum_{\text{all slices}} [\sqrt{(\text{epicardial area}/\pi)} - \sqrt{(\text{endocardial area}/\pi)}]/n$$

For the measurement of RV free wall mass, the endo- and epicardial borders of the RV free wall were outlined manually at end diastole in each slice, and the interventricular septum, the moderator band, and the epicardial fat were not considered part of the RV free wall (4, 43). The value obtained for the entire free wall was multiplied by the specific density of the cardiac muscle, 1.05 g/ml. RV end-diastolic volume was calculated by summation as for the LV.

Spaceflight. A mobile 1.0-T magnet system manufactured by Picker International Medical Systems (now Marconi Medical, Cleveland, OH) was used for cardiac MRI studies before and after spaceflight. Breath hold, cardiac-gated long- and short-axis views of the heart were obtained by using a flow-compensated, gradient-echo (repetition time, 20 ms/echo time, 9 ms) segmented k -space or phase-encoding group technique. Specific parameters included 10-mm slices, a 38-cm field of view, a 192×256 matrix, undersampling with a total of 120 views, and a phase-encoding group of 5. This permitted cine imaging of a slice during a breath-hold of 24 cardiac cycles. Short-axis cine images were obtained at 10–12 levels to span the entire left ventricle. Images were then transferred to a workstation for analysis, which was performed by using the same techniques as for the bed rest study and therefore with the same accuracy and precision.

Heart Rate and Blood Pressure Measurements

Heart rate was monitored using the ECG (Hewlett-Packard). Blood pressure was measured in the arm by electro-sphygmomanometry (Suntech 4240) with a microphone placed over the brachial artery and detection of the Korotkoff sounds gated to the ECG.

Stroke Volume

In the bed rest study, \dot{Q}_c was measured with a modification of the acetylene-rebreathing technique using acetylene as the soluble gas and helium as the insoluble gas (36, 55). With this technique, pulmonary blood flow is calculated from the disappearance rate of acetylene in expired air, measured with a mass spectrometer (Marquette), after adequate mixing in the lung has been confirmed by a stable helium concentration. This method has been validated in our laboratory against standard invasive techniques, including thermodilution and direct Fick, over a range of \dot{Q}_c from 2.75 to 27.00 l/min, with an r^2 of 0.91 and an SEE of 1.1 l/min (44). For the D-2 mission, the same acetylene-rebreathing method was used, except that argon was used instead of helium as the inert gas (58). Stroke volume (SV) was calculated from \dot{Q}_c , and heart rate was measured during rebreathing.

Statistics

Data are expressed as means \pm SE. Statistical probability was assessed with one- or two-way repeated-measures ANOVA as appropriate, and the differences in means were evaluated by using the Student's paired t -test to test the difference between the values before and after each experiment. Actual P values are given in the text.

RESULTS

Hemodynamic Data

\dot{Q}_c and SV decreased ($P = 0.0009$ and $P = 0.02$, respectively) during the first 2 wk of bed rest (Table 1). Otherwise, horizontal bed rest did not cause significant changes in other hemodynamic variables. Both \dot{Q}_c and SV were also decreased ($P = 0.004$ and $P = 0.00001$, respectively) in-flight compared with preflight supine \dot{Q}_c and SV (Table 1).

LV Mass, MWT, and LV End-Diastolic Volume

LV mass decreased by 6 wk of bed rest by $8.0 \pm 2.2\%$ ($P = 0.005$, Fig. 1), and the three subjects who continued bed rest through 12 wk had an additional atrophy of $7.6 \pm 2.3\%$ (Fig. 2). In contrast, there was no change

Table 1. Hemodynamic data for the bed rest subjects and D-2 astronauts

	Bed Rest				Spaceflight	
	Base	2 wk	6 wk	12 wk	Pre-supine	In-flight
HR, beats/min	67 \pm 6	73 \pm 7	76 \pm 5	77 \pm 8	61 \pm 2	70 \pm 5
MAP, mmHg	84 \pm 3	76 \pm 3	78 \pm 1	73 \pm 4	88 \pm 4	93 \pm 2
\dot{Q}_c , l/min	7.1 \pm 0.7	5.9 \pm 0.2*	6.6 \pm 0.5	6.6 \pm 0.1	8.0 \pm 0.2	6.5 \pm 0.4*
SV, ml/min	110 \pm 20	83 \pm 11*	88 \pm 13	87 \pm 10	131 \pm 2	93 \pm 2*
TPR, dynes \cdot s \cdot cm ⁻⁵	956 \pm 85	1027 \pm 66	947 \pm 80	895 \pm 58	885 \pm 55	1119 \pm 73

Values are means \pm SE. All bed rest measurements were obtained in the supine position. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; \dot{Q}_c , cardiac output; SV, stroke volume; TPR, total peripheral resistance. *Statistically significant changes; see P values in text.

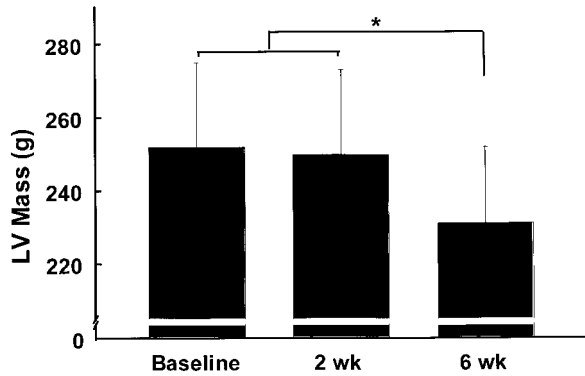


Fig. 1. Left ventricular (LV) mass measured by magnetic resonance imaging (MRI) at baseline and after 2 and 6 wk of supine bed rest on 5 subjects. * $P < 0.05$ compared with baseline and 6 wk of bed rest.

in LV mass for the control subjects (153.0 ± 12.2 vs. 153.4 ± 12.1 g, $P = 0.81$ for paired t -test; $P = 0.012$ for interaction statistic of two-way ANOVA comparing bed rest subjects with controls), and no individual subject had more than a 4.5-g (range 0.0–4.4 g) difference from one measurement to the other. Moreover, MWT decreased by $4 \pm 2.5\%$ ($P = 0.01$) after 6 wk of bed rest (Fig. 4). Similar to long-term bed rest, spaceflight for 10 days led to a trend toward decreased LV mass ($12 \pm 6.9\%$, $P = 0.07$) when compared with the preflight data (Fig. 3).

In contrast to LV mass, LV end-diastolic volume decreased ($14 \pm 1.7\%$, $P = 0.002$) when first measured at 2 wk of bed rest (Fig. 4). For the entire group, there was no further decrease in LV volume between 2 and 6 wk. In the subgroup who remained in bed for 12 wk, LV end-diastolic volume decreased an additional $8 \pm 4.2\%$ by 12 wk of bed rest (Fig. 2). The LV mass-LV end-diastolic volume ratio (2.09 ± 0.16 and 2.00 ± 0.11) was increased after 2 and 6 wk, respectively, compared with baseline (1.82 ± 0.11 , $P = 0.02$).

RV Mass and RV End-Diastolic Volume

RV mass was decreased by $10 \pm 2.7\%$ ($P = 0.06$) after 6 wk of bed rest (Fig. 5). There was a tendency to

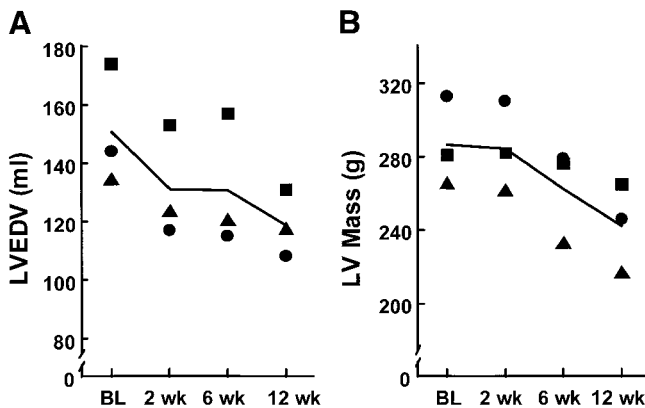


Fig. 2. Left ventricular end-diastolic volume (LVEDV; A) and mass (LV mass; B) measured by MRI at baseline and after 2, 6, and 12 wk on 3 subjects who completed a full 12 wk of supine bed rest. Lines connect arithmetic mean for each time point.

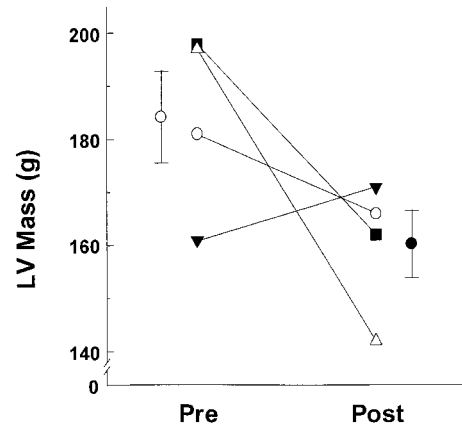


Fig. 3. LV mass measured by MRI before (Pre) and after (Post) the D-2 mission on 4 astronauts. Circles with error bars represent mean \pm SE before and after spaceflight.

decreased RV end-diastolic volume after 2 wk of bed rest, but the decrease ($16 \pm 8\%$, $P = 0.06$) was more prominent after 6 wk of bed rest.

DISCUSSION

The principal new finding of this study is that the human heart atrophies after bed rest and may also atrophy after spaceflight, presumably in response to decreased physiological loading. Specifically, we have shown that LV mass measured by MRI decreased clearly during prolonged strict supine bed rest in previously sedentary nonathletic men without cardiovascular disease, and a similar trend was observed after short-duration spaceflight. The decrease in LV mass noted first at 6 wk was associated with an earlier (2 wk) decrease in LV end-diastolic volume during bed rest, so that the LV mass-volume ratio increased acutely, resulting in a decrease in wall stress (i.e., load). In fact, the primary initial morphologic adaptation during bed rest was a decrease in LV end-diastolic volume that was most prominent when measured at 2 wk, secondary to the well-described loss of plasma volume during bed rest and spaceflight (17, 35). Thus

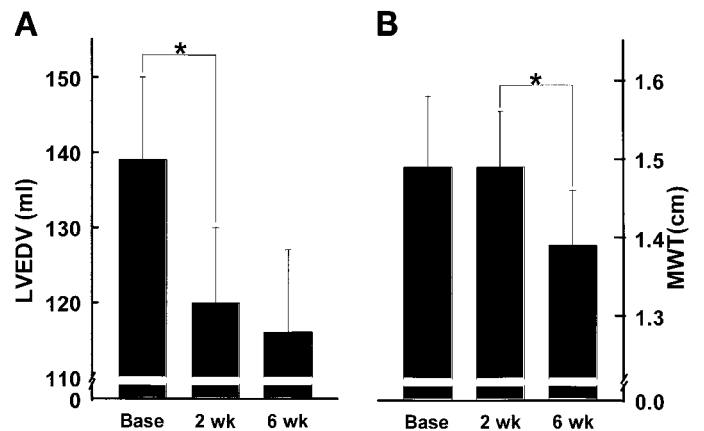


Fig. 4. LVEDV (A) and mean wall thickness (MWT; B) at baseline and after 2 and 6 wk of supine bed rest on 5 subjects. * $P < 0.05$ compared as shown with lines.

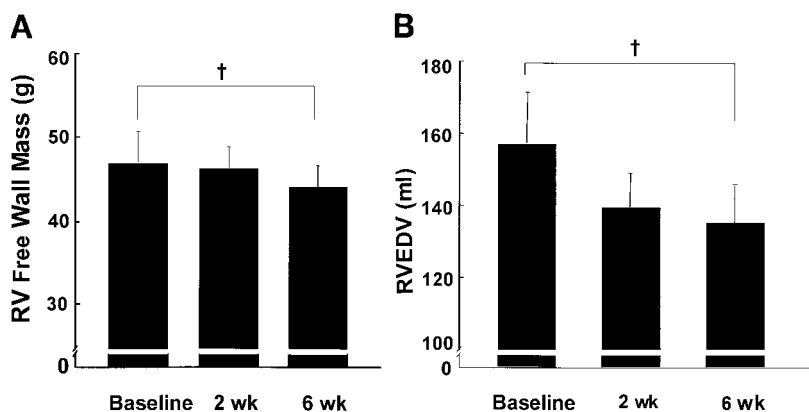


Fig. 5. Right ventricular free wall mass (A) and end-diastolic volume (RVEDV; B) at baseline and after 2 and 6 wk of supine bed rest on 5 subjects. † $P = 0.06$ compared between baseline and 6 wk.

bed rest deconditioning led to a remodeling (i.e., changes in cardiac morphology) of the heart first by changes in volume and secondarily via changes in muscle mass.

The changes in cardiac structure during short- and long-term bed rest have been under investigation for several years. Our present findings support earlier radiographic data that showed that the overall heart size (including both volume and mass) decreased after 3 wk of horizontal bed rest (50). Moreover, our previous studies in sedentary subjects undergoing head-down-tilt bed rest deconditioning for 18 days had significantly decreased resting supine LV end-diastolic volume and tended to have a decrease (5%) in LV mass after bed rest on the basis of measurements made by echocardiography. However, MRI provides better measurement precision than echocardiography (21, 31) and thus may be more sensitive for describing the morphological changes after bed rest or spaceflight. For example, it has been well documented that MRI has superior intraobserver variability compared with echocardiography for the purpose of measuring LV mass: intraobserver variability for MRI was 0.96, SEE 11.2 g, whereas for echocardiography $r = 0.89$, SEE 22.7 g (21). More recently, it has been demonstrated that the precision of LV mass measured with MRI (11 ± 8 g) is more than twice that observed with echocardiography (26 ± 49 g) (3). In addition, because MRI does not rely on geometric assumptions for the assessment of mass and volume, only MRI can be used accurately to study changes in the right ventricle after bed rest deconditioning. For these reasons, MRI is now widely considered to be the gold standard for the assessment of cardiac mass (11).

In comparison with bed rest, we detected a decrease in LV mass when using MRI in three out of four astronauts after spaceflight for only 10 days. Earlier radiographic data has shown that heart size decreases during short-term space missions similar to that observed after bed rest (25). However, the radiographic studies are not able to determine whether the changes in heart size reflect a change in heart volume or mass. Echocardiographic studies (M-mode) suggested an 8% decrease in LV mass in three Skylab 4 astronauts during an 84-day space mission, raising the possibility

that cardiac atrophy might occur with spaceflight (25). The present study extends these previous observations by demonstrating additional, supportive evidence of cardiac atrophy in three out of four astronauts after even short duration spaceflight, which in some cases may be profound.

The hemodynamic alterations in humans during bed rest or spaceflight are likely to play an important role in mediating the adaptation of myocardial mass. The acute hemodynamic response to head-down bed rest has been well described. With assumption of the head-down-tilt position, there is a cephalad fluid shift, resulting in significant increases in central venous pressure (CVP), LV dimensions, SV, and Q_c (19, 41). Within 24 h, there is a salt and water diuresis, with a reduction in CVP and SV below supine values. In one study, after 20 h of head-down-tilt bed rest, both SV and CVP were lower, and heart rate was higher during lower body negative pressure or upright tilt after compared with before bed rest, to a magnitude similar to that observed after more prolonged periods of bed rest (19). Although these subjects were not followed for longer periods, the authors suggested that the adaptation was essentially complete by the end of 24 h of head-down tilt.

A recent study carried out noninvasive hemodynamic measurements past 24 h, for the duration of 2 wk of -6° head-down-tilt bed rest (36). SV essentially doubled with the transition from standing to the supine position, with an additional 15% increase during acute head-down tilt that peaked after 30 min (36). Over the next 24 h, SV gradually decreased to below supine values, reaching a nadir at 48 h, with no further reduction over the next 2 wk. Heart rate and total peripheral resistance followed similar trends (36). These data confirm convincingly the hypothesis that the acute response to head-down-tilt bed rest involves removal of hydrostatic gradients, a central fluid shift, a transient increase in transmural cardiac filling pressure and SV, and then a rapid adaptation with loss of plasma volume that is mostly complete within 48 h of head-down tilt and does not progress over 2 wk, ultimately leading to a smaller heart with lower filling pressure and therefore reduced preload and myocardial work (17, 24, 25, 35, 36, 41).

In the present study, the short-term cardiac adaptation to supine bed rest was similar to these previous studies. Thus, when assessed after 2 wk, the LV end-diastolic volume measured by MRI, and SV measured by acetylene rebreathing was significantly decreased, although LV mass was minimally changed. As a consequence, the LV mass-volume ratio increased substantially, resulting in a marked attenuation of wall stress via Laplace's law ($\sigma = Pa/2h$; where σ = average circumferential wall stress, a = radius at the endocardial surface, P = intraventricular pressure, and h = wall thickness). In fact, we speculate that it is this change in wall stress that may well be one of the key stimuli to modify cardiac muscle mass during microgravity, as has been observed in pathological conditions such as hypertension and valvular heart disease (12). The fact that the LV mass-volume ratio remained elevated compared with baseline after 6 wk of bed rest may be one explanation for the continued atrophy in the three subjects who remained at bed rest for 12 wk.

In this regard, it also is important to emphasize that one of the unique aspects of bed rest is the absence of the normal night time "volume load" associated with the change from upright to the supine position. We speculate that the loading of the heart and increase in wall stress during the night may produce a stimulus similar to that of endurance exercise (39) and under normal circumstances may be at least partly responsible for the maintenance of cardiac mass and volume. Thus, although the heart volume during bed rest ultimately adapts to a level greater than upright but less than supine, it may be the absence of this peak volume load at night that plays a major role in regulating the mass and wall thickness required to normalize wall stress.

In contrast to bed rest, with acute spaceflight exposure, CVP referenced to atmospheric pressure decreases to near 0 mmHg (5, 16). Simultaneously, however, LV end-diastolic volume and SV increase, suggesting an increase in cardiac filling. This apparent paradox may be explained by a larger reduction in pericardial pressure than in CVP, presumably due to removal of restraining forces from the chest wall, such that transmural cardiac filling pressure actually increases similar to ground-based simulations (5, 59). Recent data from transient periods of microgravity during parabolic flight have confirmed this hypothesis (57), suggesting that the effects of spaceflight or bed rest on acute transmural cardiac filling pressure and volume, the primary determinants of diastolic wall stress, are similar.

Despite this apparent similarity in steady-state hemodynamics, the present study raises the possibility that there might be a more prominent reduction in ventricular mass after short-term spaceflight than after bed rest of the same duration. Thus we were unable to demonstrate a reduction in LV or RV mass after 2 wk of supine bed rest, despite a clear decrease in LV end-diastolic volume and a trend to decreased RV end-diastolic volume. Of interest, Russian investigators have suggested that adding -6° of head-down tilt is a

better model of actual weightlessness than supine bed rest, and this approach has become the standard for microgravity simulation on earth (17). In this regard, we have observed no change in LV and RV mass after 2 wk of supine bed rest, a 5% decrease in LV mass after 2 wk of head-down-tilt bed rest, and a 12% decrease after 2 wk of spaceflight, though it is important to note that none of these changes was consistent enough to meet conventional criteria for statistical significance given the small numbers of subjects studied. One possibility for this difference may be that the astronauts were fitter than the bed rest subjects and their results reflected the combination of detraining as well as microgravity exposure. However, although we did not have the opportunity to measure maximal oxygen uptake in the bed rest subjects, it was only 37 ± 7 ml \cdot kg $^{-1}\cdot$ min $^{-1}$ (range 25–43 ml \cdot kg $^{-1}\cdot$ min $^{-1}$) in the astronauts, making this possibility unlikely. We speculate that the differences in hemodynamic loading, particularly the removal of chest wall and pericardial constraint with spaceflight (5, 57, 59) may be responsible for differences in the rate of atrophy among these three conditions. However, larger numbers of subjects must be studied before such a speculation could be confirmed. Nevertheless, this study confirms conclusively that at least by 6 wk of strict, supine bed rest, the human heart does atrophy with a reduction in volume and mass of the left ventricle and similar trends for the right ventricle.

However, despite the reduction in volume loading of the heart after adaptation to microgravity compared with the supine position, it is important to note that the human heart remains well loaded during bed rest with a SV (and presumably LV end-diastolic volume) greater than during upright quiet standing, as well as normal arterial pressure. Thus the human heart during bed rest or spaceflight is clearly different from animal models examining a completely unloaded circulation, such as heterotopic heart transplantation to the ear or abdomen (20, 22, 33, 34). Therefore it is possible that factors other than preload may play a role in mediating the changes in ventricular mass during bed rest.

In addition to changes in volume loading conditions, both bed rest and spaceflight induce confinement, which reduces physical activity compared with more freely ambulatory periods. In the present study, physical activity was severely restricted during bed rest. For the astronauts, this level of activity control was not possible. However, they were asked not to alter their preflight exercise habits during spaceflight and did not have any programmed physical exercise during this mission. Preliminary data from our laboratory have shown that the heart is extremely plastic in relation to changes in physical activity (37), so that during long-term endurance training a clear hypertrophy of the heart is observed whereas during bed rest of 6 wk the heart atrophies as shown in the present study. This range of adaptability with changes in physical activity may approach a full third of the cardiac mass when

long-term bed rest is compared with long-term endurance training (37).

This plasticity of cardiac muscle during training and detraining also is well known in trained athletes. For example, cessation of intensive endurance training leads to a rapid (as quickly as 1 wk in studies in which early measurements were performed) atrophy of 10–22% in the exercise-induced hypertrophied heart seen as decreased LV wall thickness and LV mass measured by echocardiography (13, 15, 38). A decrease in presumed physiological hypertrophy was also detected in nonathletes 6 wk after cessation of a 6-wk exercise program (51). In addition, patients with high spinal cord lesions have a cardiac mass reduced by 25–35% compared with able-bodied nonathletic controls, which is reversible with electrically stimulated exercise training (40). The magnitude of this atrophy may represent a lower limit to the reduction in cardiac mass that can occur with cessation of all physical activity over a very prolonged period of time (years).

Animal studies designed to examine the mechanism of cardiac atrophy are consistent with the human data and indicate that regression of exercise-induced cardiac hypertrophy occurs rapidly (within 1–2 wk) after cessation of swimming training seen as decreases in LV mass by 15–30% and manifest as reduction in the width of myofibers, total protein content, RNA content, and total cytochrome *c* content (18, 26). In addition, models employing unloaded heterotopic heart transplants develop atrophy of about 40% within a week due to complete unloading (20, 33, 34). The mechanism of cardiac atrophy in these models has been presumed to be a reduction in cardiac work and follows the principle of symmorphosis, whereby the oxygen transport system maintains only the structural capacity necessary to match the functional demands placed upon it (27). Moreover, unloading of a single RV cardiocyte decreased the cardiocyte cross-sectional area and volume density of mitochondria and myofibrils within a week in untrained cats (54). Thus the rate of significant cardiac atrophy in sedentary humans during supine bed rest seems to be slower than in trained athletes who cease exercise training, in trained and/or untrained animals, or in heterotopic hearts.

At least one possible explanation for the differences in the rate and magnitude of atrophy in these different studies may be the relative magnitude of the reduction in cardiac work and loading conditions. Cardiac work is a function not only of wall stress (both preload and after-load) but also heart rate (chronotropic work) and contractility. Using changes in 24-h stroke work ($SV \times \text{blood pressure} \times \text{beats}/24 \text{ h}$) as an estimate of overall cardiac work during bed rest, our laboratory has estimated in our previous bed rest study that normal individuals reduce their cardiac work by as much as 18% compared with freely ambulatory periods (36). This reduction may be more or less in different individuals and could be modified by countermeasures such as exercise training (40, 45).

Although there is extensive literature regarding the molecular and cellular changes associated with cardiac

hypertrophy, the specific pathways involved in cardiac atrophy during decreased cardiovascular loading are less clear. It is not known whether the loss of muscle mass during bed rest and spaceflight in humans is due to changes in muscle cells (e.g., decrease in protein synthesis or even apoptosis), connective tissue, or both of these. However, microscopic studies show that the cross-sectional area of rat papillary myocytes decreases during a spaceflight for 2 wk, which is consistent with cardiac atrophy (18). Furthermore, changes in pretranslational contractile protein gene expression were detected in rat heart samples from the same space mission (53). These changes were associated with decreased growth hormone release from the anterior pituitary gland (29). Moreover, electron microscopic studies on rat cardiac cells after exposure to microgravity have shown an increase in the number of lipid droplets and the amount of glycogen, loss of mitochondria, and decrease in volume density in the mitochondria in ventricular tissue (48).

Ground-based animal models of microgravity exposure, for example tail suspension in rodents, also have been used to describe the mechanism behind cardiac atrophy due to unloading (7, 23). But the results suggest that tail suspension in quadrupeds may not be optimal for examining cardiovascular adaptations to microgravity because the dominant hemodynamics are fundamentally different from those in upright humans (49). Creative approaches to translating research at the basic level to intact humans therefore must be developed before the mechanism of cardiac atrophy during bed rest or spaceflight can be determined with certainty.

Clinical Implication

There is no evidence that physiological cardiac atrophy leads to impairment of systolic function. For example, spinal cord-injured individuals who have been immobilized for many years have normal systolic volumes for a given blood pressure, suggesting normal contractile function (40). Moreover, regression of LV hypertrophy due to hypertension or valvular heart disease usually results in improved rather than impaired ventricular function (12). Finally, even after spaceflights of 8 mo, Atkov and co-workers (1, 2) found normal LV contractile function, and similar observations have been made after bed rest studies lasting more than 1 yr (56). During the 3-mo Skylab mission, M-mode echocardiography revealed that, although LV end-diastolic volume and SV were reduced immediately postflight, plots of LV end-diastolic volume vs. SV appeared to be described by virtually identical linear regression equations, suggesting no deterioration in contractile function (25). Similar preservation of preload recruitable SV despite a decrease in LV end-diastolic volume has been demonstrated after bed rest by using more modern techniques (36).

However, one of the most important clinical consequences of cardiac atrophy may be for diastolic as opposed to systolic function. Invasive studies of cardiac

performance before and after 2 wk of head-down-tilt bed rest have shown that there is a leftward shift in the diastolic pressure-volume curve after bed rest, resulting in a smaller LV end-diastolic volume for any given filling pressure (36, 46). Furthermore, the equilibrium volume of the left ventricle (the volume at pressure = 0 mmHg) was significantly reduced, impairing the ability to use diastolic suction to fill the left ventricle. Together, these changes result in a greatly reduced end-diastolic volume and thereby SV during orthostasis, which is seen universally after bed rest or spaceflight and may play an important role in mediating the orthostatic intolerance observed frequently after such deconditioning (36, 46). We speculate that if cardiac atrophy is more severe with longer durations of bed rest or spaceflight, as suggested by the present study, then the impairment of diastolic filling may also be worse, providing a potential explanation for the anecdotal reports that orthostatic intolerance may be more severe after long-duration vs. short-duration space missions (J. Meck, unpublished observations).

In summary, this study shows that LV (and possibly RV) atrophy occurs during prolonged supine bed rest deconditioning and may also occur after spaceflight. We suggest that this response is an appropriate "physiological" adaptation to reduced myocardial work and loading conditions.

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