Lower body negative pressure exercise plus brief postexercise lower body negative pressure improve post-bed rest orthostatic tolerance

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Watenpaugh DE, O’Leary DD, Schneider SM, Lee SM, Macias BR, Tanaka K, Hughson RL, Hargens AR. Lower body negative pressure exercise plus brief postexercise lower body negative pressure improve post-bed rest orthostatic tolerance. J Appl Physiol 103: 1964–1972, 2007. First published October 18, 2007; doi:10.1152/japplphysiol.00132.2007.—Orthostatic intolerance follows actual weightlessness and weightlessness simulated by bed rest. Orthostasis immediately after acute exercise imposes greater cardiovascular stress than orthostasis without prior exercise. We hypothesized that 5 min/day of simulated orthostasis [supine lower body negative pressure (LBNP)] immediately following LBPNP exercise maintains orthostatic tolerance during bed rest. Identical twins (14 women, 16 men) underwent 30 days of 6° head-down tilt bed rest. One of each pair was randomly selected as a control, and their sibling underwent 40 min/day of treadmill exercise while supine in 53 mmHg negative pressure exercise plus brief postexercise lower body negative pressure improved Tilt tolerance time in control subjects decreased significantly [34% (SD 10)] than in countermeasure subjects [13% (SD 20); P < 0.004]. Controls exhibited cardiac stroke volume reduction and relative cardioacceleration typically seen after bed rest, yet no such changes occurred in the countermeasure group. These findings demonstrate that 40 min/day of supine LBPNP treadmill exercise followed immediately by 5 min of resting LBPNP attenuates, but does not fully prevent, the orthostatic intolerance associated with 30 days of bed rest. We speculate that longer postexercise LBPNP may improve results. Together with our earlier related studies, these ground-based results support spaceflight evaluation of postexercise orthostatic stress as a time-efficient countermeasure against postflight orthostatic intolerance. Human; microgravity; spaceflight; countermeasure; cerebral blood flow

Both bed rest (20) and weightlessness (65) reduce orthostatic tolerance. When spacecraft reenter Earth’s atmosphere and land, vertical acceleration (+Gz) forces challenge cerebral blood flow, such that compromised orthostatic tolerance endangers crew members. This cardiovascular deconditioning also delays return to normal upright activities. For example, after return from spaceflights lasting months, Russian astronauts wear anti-G garments for up to 4 days (25).

Hypovolemia constitutes the most established cause of postflight orthostatic intolerance (65). Some investigators postulate that the chronic stroke volume (SV) reduction secondary to hypovolemia causes cardiac remodeling and atrophy (65), which in turn contributes to intolerance (40). The cardiac baroreflex appears to function appropriately in response to postflight hypovolemia because all astronauts exhibit accentuated postural tachycardia after flight (6, 39, 65). No increase occurs in leg compliance after spaceflight (6, 62), but some evidence suggests that problems with the vascular baroreflex arm contribute to postflight orthostatic intolerance (23, 24, 66). In weightlessness, gravitational pressure gradients never arise in the circulation, so cerebral blood flow continues unchallenged, and baroreflexive vasoconstriction remains chronically understimulated. Also, chronic lack of gravitational pressures in the lower body circulation may compromise local arteriolar structure and function (16, 65).

Most literature indicates that exercise training during bed rest does not protect orthostatic tolerance (20, 27, 29). However, based on the mechanistic information above, our laboratory previously hypothesized that addition of a gravity-like stress such as lower body negative pressure (LBPNP) during exercise would be effective (38, 64). Control subjects (no exercise) were compared with subjects who performed daily LBPNP exercise during 5 days of bed rest. LBPNP exercise consisted of 30 min/day of supine interval treadmill exercise at intensities up to 90% of maximum heart rate (HR), followed immediately by 5 min of resting LBPNP (i.e., ongoing LBPNP during recovery from the LBPNP exercise) (38). We added the 5-min postexercise LBPNP period as a pilot study of postexercise hypotension during bed rest; at the time of the study, it was not intended as a formal part of the countermeasure (S. M. C. Lee, unpublished observations).

Tilt tolerance time in control subjects decreased significantly (18%), yet tolerance tended to increase in LBPNP exercisers (9%, not significant). Hematocrit increased in controls, indicating substantial hemococoncentration; hematocrit did not increase in the exercisers. The countermeasure was then evaluated during 15 days of bed rest (53, 59). For this study, LBPNP exercise was prolonged to 40 min, but the 5-min postexercise LBPNP period was deleted: we assumed such a short period of LBPNP did not contribute to the positive results from the 5-day
Methods

Immediately following supine LBNP treadmill exercise, blood pressure responses by LBNP exercise (53). As in the 5-day study, the countermeasure maintained blood volume.

We confronted the possibility that a short resting LBNP period immediately following LBNP exercise may challenge orthostatic cardiovascular control mechanisms enough to maintain tolerance during bed rest. For a variety of reasons, orthostasis immediately after acute exercise imposes greater cardiovascular stress than orthostasis without prior exercise (11, 15, 22, 30, 31, 52). For example, Bjurstedt and coworkers (3) reported that five of six subjects experienced presyncope during 6 min of 70° head-up tilt (HUT) after exhausting exercise, whereas all six tolerated the test in preexercise conditions. Also, people sometimes faint when standing still after strenuous exercise when they otherwise have no such trouble (68). These findings imply that orthostatic stimulation imposed immediately following exercise may more efficiently train orthostatic cardiovascular control mechanisms than stimulation without prior exercise, because of the greater cardiovascular stress. Given the collective observations above, we hypothesized that daily exposure to short periods of simulated orthostasis that admits that daily exposure to short periods of simulated orthostasis than orthostasis without prior exercise (11, 15, 22, 30, 31, 52). For example, Bjurstedt and coworkers (3) reported that five of six subjects experienced presyncope during 6 min of 70° head-up tilt (HUT) after exhausting exercise, whereas all six tolerated the test in preexercise conditions. Also, people sometimes faint when standing still after strenuous exercise when they otherwise have no such trouble (68). These findings imply that orthostatic stimulation imposed immediately following exercise may more efficiently train orthostatic cardiovascular control mechanisms than stimulation without prior exercise, because of the greater cardiovascular stress. Given the collective observations above, we hypothesized that daily exposure to short periods of simulated orthostatic stress immediately following vigorous dynamic exercise maintains orthostatic tolerance during bed rest. The countermeasure protocol again included 5 min of resting LBNP immediately following supine LBNP treadmill exercise.

Subjects. University of California, San Diego (UCSD), University of North Texas Health Science Center, and National Aeronautics and Space Administration Institutional Review Boards approved this study. Fifteen pairs of healthy identical twins (14 women and 16 men) participated after providing informed, written consent. We employed identical twins, with one sibling as the control subject and the other as the countermeasure subject, to minimize genetic variability between control and countermeasure groups and thus strengthen our ability to ascribe intergroup differences to the countermeasure (5). Age ranged from 21 to 36 yr, weight from 43.7 to 84.1 kg, and height from 152 to 191 cm. Subjects provided their medical history and underwent physical examination and an exercise stress test to establish their healthy status.

Experimental design and conditions. The UCSD Hillcrest Hospital General Clinical Research Center housed, fed, and cared for subjects throughout their participation. The study occupied 6 days of familiarization and baseline data collection, 30 days of bed rest, and 3 days of post-bed rest testing and recovery. Siblings shared rooms and received diets containing 180 mmol Na/day. Water intake was ad libitum. Subjects abstained from caffeine and alcohol throughout the study. No subject used tobacco. Nonprescription medications such as analgesics and stool softeners were given as needed. Some female subjects used oral contraceptives. Menstrual cycle phase was not controlled or accounted for except that female subjects were at approximately the same phase of their cycle during pre- and post-bed rest testing because of the 30-day bed rest period.

Before baseline (pre-bed rest) data collection, subjects experienced all testing procedures to become fully familiarized with the study. All tests took place at the same time of day pre- vs. post-bed rest for a given subject, and all were at least 2-h postprandial. After completion of baseline data collection, twin siblings were randomly assigned to control or countermeasure groups. Group assignment after baseline data collection eliminated any possibility of group assignment influencing pre-bed rest results. Body weight did not vary significantly between groups or across bed rest. During the entire bed rest period, subjects remained at 6° head-down tilt except during periods for showers and training (0.5–1.5 h/day), when they were horizontal (0°). No training occurred on the day before end-bed rest orthostatic tolerance testing. All training and testing sessions occurred at room temperature (21–23°C).

LBNP exercise and orthostatic training. The LBNP exercise device consists of a vacuum control system connected to a rectangular chamber containing a vertically oriented treadmill. Earlier reports detail chamber construction and operation (21, 38, 59), and Fig. 1 further illustrates waist seal hardware and integration. Waist seal area was set to equal approximately twice a given subject’s waist cross-sectional area, such that the negative pressure necessary to produce one body weight equals ~50–60 mmHg (6.65–7.98 kPa). This larger waist seal reduces orthostatic stress and risks of LBNP (petechiae, hernia, syncope) by decreasing the LBNP necessary to generate a given level of footward force (58). Subjects wore inelastic shorts during countermeasure sessions to prevent abnormal LBNP-induced lower abdominal distension (4, 38, 59). The shorts held a 12 × 30-cm air bladder in place over the lower abdomen. A tube from the air bladder passed through the LBNP waist seal to outside the chamber. Therefore, the bladder automatically inflated to compress the lower abdomen in direct proportion to the magnitude of LBNP.

Countermeasure sessions consisted of 40 min of supine running exercise per day at 1.0–1.2 body weight of footward force, as

![Fig. 1. Schematic illustration of lower body negative pressure (LBNP) exercise chamber waist seal components. The subject dons the waist seal, the seal plates are juxtaposed in place on the chamber and clamped, and the waist seal is then affixed to the seal plate flange with an integral bungee cord. Multiple waist seals and paired waist seal plates produce a range of elliptical chamber orifices to accommodate different-sized subjects and tune the LBNP-to-footward force ratio. The waist belt and shoulder straps on the waist seal itself are not shown for simplicity.](http://jap.physiology.org/Downloadedfrom)
LBNP exercise, they were challenged to exercise at near-maximal RPE. As bed rest progressed and subjects acclimated to workloads during that session were adjusted as necessary to avoid workload remained there until the next scheduled interval. Subsequent water and wipe their face with a towel. HR and blood pressure were promptly following each exercise session (Fig. 1). During this time, weight.

Fig. 2. LBNP exercise protocol target workloads and actual heart rate and blood pressure were measured each minute. At any sign of presyncope, subjects were encouraged to move and stretch their legs, drink water, and wipe their face with a wet towel. In the rare cases where presyncopal signs continued after these measures, LBNP was stopped until all symptoms abated. LBNP was then restarted at the prescribed level and continued to completion of the session. Countermeasure subjects underwent the exercise and orthostatic training protocol 6 days/wk.

Orthostatic tolerance testing. Orthostatic tolerance tests consisted of combined HUT and LBNP (17). A semicylindrical Plexiglas LBNP chamber was attached to a tilt table. Subjects underwent three tests: familiarization, pre-bed rest baseline data collection, and post-bed rest data collection. After instrumentation for the orthostatic tolerance test, 5 min of supine resting cardiovascular data were collected. HUT to 60° (+0.87 Gz) then began and continued for 5 min. Thereafter, LBNP ensued at 10 mmHg (1.33 kPa) for 3 min, followed by stepwise 10-mmHg decrements for 3 min each until presyncope. We defined presyncope as drop of systolic pressure below 70 mmHg; sudden and progressive blood pressure reduction; sudden, obvious, and sustained drop in HR; sudden appearance or rapid worsening of presyncopal signs and symptoms (nausea, dizziness, tingling, clamminess, sweating, ashen face, weak legs, anxiety, unresponsiveness); or any combination of the above. Subjects stood on a footplate inside the LBNP chamber during HUT, and they were instructed and reminded as necessary to remain quiet, still, and relaxed throughout the test. Orthostatic tolerance time equaled the time from onset of HUT to presyncope. The same medical monitor judged presyncopal symptoms and called test endpoints pre- and post-bed rest. Baseline (pre-bed rest) data from this test were previously employed to investigate heritability of orthostatic cardiovascular function (46).

Orthostatic tolerance test instrumentation. Electrocardiography allowed determination of HR and monitoring for dysrhythmias. Doppler ultrasound from the suprasternal notch yielded beat-by-beat aortic outflow tract blood flow velocity (2-MHz probe, CFM750, GE/Vingmed, Horten, Norway), such that the integral of this signal provided cardiac SV. Aortic flow (cardiac output) was then calculated using outflow tract diameter as determined with standard echocardiography ( Hewlett Packard, Palo Alto, CA) (47). We measured finger arterial blood pressure continuously with a Finapres device (Ohmeda 2300, Englewood, CO) on the right hand, and left arm blood pressure was measured each minute with manual sphygmomanometric auscultation. The Finapres was adjusted before testing such that finger diastolic pressure was within 5 mmHg of arm diastolic pressure. Transcranial Doppler ultrasound permitted measurement of middle cerebral arterial blood flow velocity from a temporal cranial window (Transpect TCD, Medasonics, Mountain View, CA) (37, 47). Because of its influence on cerebral hemodynamics, end-tidal carbon dioxide was monitored (Ohmeda 5200, Englewood, CO) via nasal cannulas. Total peripheral resistance was calculated as mean arterial pressure divided by cardiac output. SV and cardiac output were converted to indexes by dividing by calculated body surface area. We calculated cerebral vascular resistance (CVR) as mean arterial pressure at eye level divided by cerebral blood flow velocity. This approach assumes minimal change in middle cerebral arterial diameter occurred such that velocity provided a reliable quantitative indicator of blood flow (47).

Statistical analyses. Multifactor repeated-measures ANOVA assessed independent and interactive effects of bed rest and the countermeasure for orthostatic tolerance test time. For physiological variables during the test, an additional factor (time) was included to analyze data from the three levels of orthostatic stress that all subjects achieved both pre- and post-bed rest: supine rest, HUT, and presyncope. Dependent variables were averaged over the fifth minute of supine rest, the fifth minute of HUT, and the minute before presyncope. Technical problems with aortic Doppler in specific subjects and during HUT plus LBNP led to significant loss of SV and thus blood flow and TPR data, so n = 10 for these variables (5 per sex), and they are not represented at presyncope. The sample size for sex compari-
sons was marginal, and they were deemed beyond the scope of this work. Tukey’s honestly significant difference post hoc tests determined which specific mean values differed from others for each variable. We accepted a finding as significant if $P < 0.05$. SAS software performed all statistical analyses (SAS Institute, Cary, NC). Values are expressed as means (SD) unless noted otherwise.

RESULTS

LBNP exercise and orthostatic training sessions. LBNP during training sessions averaged 53 mmHg (4) [7.05 kPa (0.50)]. All subjects progressively increased their footward force (LBNP) levels to at least 1.05 body weight, and as much as 1.2, as the 30-day study progressed. Mean treadmill speeds ranged from 5.5 km/h (0.8) to 9.2 km/h (1.5), and distance covered during a session averaged 4.6 km (0.8). Peak HR at the highest workload averaged 171 beats/min (15), which equaled 86% of subjects’ maximal HR as determined during pre-bed rest maximal upright treadmill exercise sessions (Fig. 2). RPE averaged 10 (4) after the 7-min warm-up, and the mean increased to as high as 17 (4) at the end of the second 3-min 80% interval (Fig. 2). HR increased 24 beats/min (20%) on average between the warm-up and end of LBNP exercise, yet treadmill speed was the same. Mean RPE of 12 (4) after the 5-min cooldown was also 20% greater than that after the 7-min warm-up. Mean HR decreased from 145 to 124 beats/min during 5 min of postexercise LBNP, such that resting HR was not reestablished before LBNP cessation.

Subjects tolerated LBNP exercise very well after resolution of any initial comfort problems (e.g., ankle and leg chafing from suspension system, waist chafing from seal, waist seal sizing, shoulder strap vs. waist seal pressure distribution, etc.). Less-fit subjects tended to spend the first few exercise sessions acclimating to regular vigorous activity. LBNP was stopped occasionally during postexercise LBNP periods because of presyncopal symptoms. This occurred more for women than for men, and more toward the beginning of the bed rest period than toward the end. At these stoppages, subjects enacted the remedies described above (see METHODS) until presyncope resolved, after which they continued the protocol to completion.

Orthostatic tolerance time. For this and other dependent variables, no significant control vs. countermeasure group differences existed prior to bed rest ($F < 2.39; P > 0.132$). Bed rest reduced orthostatic tolerance time in both groups ($F = 64.84; P < 0.001$; Fig. 3). However, countermeasure use attenuated loss of orthostatic tolerance during bed rest: the 13% (20) reduction of tolerance time seen in countermeasure subjects was significantly less than the 34% (10) reduction exhibited by control subjects ($F > 10.20; P < 0.004$). Figure 4 illustrates individual orthostatic tolerance data.

Cardiovascular responses to orthostatic stress. In control subjects, 30 days of bed rest reduced SV index by 13% (21) in supine posture and 28% (33) in HUT relative to pre-bed rest conditions ($F = 5.5; P = 0.025$; Fig. 5). Countermeasure subject SV index remained unchanged pre- vs. post-bed rest in both postures ($F = 0.05; P = 0.822$). HUT decreased SV index both pre- and post-bed rest, and it did so to a similar degree in both groups ($F > 47.8; P < 0.001$). After bed rest, control subjects exhibited higher HR than pre-bed rest in supine, HUT, and presyncopal conditions ($F = 8.87; P = 0.004$; Fig. 5). Post-bed rest control subject HR also exceeded post-bed rest countermeasure subject HR in all conditions, including at presyncope [control: 132 beats/min (31); countermeasure: 120 beats/min (19)].

Fig. 3. Orthostatic tolerance time before (black bars) vs. after (gray bars) bed rest in control (CON) and countermeasure (CM) groups. Values are means ± SD. Horizontal bars designate significant differences ($P < 0.004$). Bed rest reduced tolerance time in both groups, but CM subjects exhibited less loss of tolerance than CON ($n = 15$ per group).

Fig. 4. Individual orthostatic tolerance time data subdivided by group and sex (○, men; ●, women). Pre, before bed rest; Post, after bed rest. All control subjects exhibited reduced orthostatic tolerance after 30 days of bed rest. Tolerance increased post-bed rest in 4 of the 15 countermeasure subjects.
beats/min (27); $F = 9.06; P = 0.004]$. No significant pre- vs. post-bed rest difference appeared in countermeasure group HR ($F = 0.03; P = 0.866$).

HUT routinely decreased cardiac index ($F > 19.06; P < 0.001$), but no other main effects nor interactions emerged (Fig. 3). TPR increased during HUT ($F > 11.3; P < 0.003$; Fig. 6), but this increase did not vary with group or bed rest ($F < 2.66; P > 0.108$). Mean arterial pressure decreased at presyncope ($F > 26.9; P < 0.001$), but no other factor significantly affected this reduction (Fig. 6). CVR decreased with HUT and decreased still further at presyncope ($F > 19.52; P < 0.001$), and a trend emerged for CVR to decrease post-bed rest relative to pre-bed rest ($F = 3.69; P = 0.059$; Fig. 6). Orthostatic tolerance testing to presyncope consistently decreased mean cerebral artery flow velocity ($F > 30.0; P < 0.001$) with no variation of this response between groups or pre- vs. post-bed rest ($F < 1.53$; $P > 0.23)$. End-tidal CO$_2$ systematically declined with HUT and declined further at presyncope ($F > 12.19; P < 0.001$), but these responses also did not vary across group or bed rest ($F < 2.41; P > 0.11$).

**DISCUSSION**

Postexercise resting LBNP only partially preserved orthostatic function. These findings support, but do not fully confirm, our hypothesis: 5 min/day of resting LBNP immediately following 40 min of supine LBNP treadmill exercise attenuates the orthostatic intolerance associated with 30 days of bed rest. The countermeasure as is does not fully prevent loss of tolerance. However, compared with the negative orthostatic tolerance results from the 15-day bed rest evaluation of LBNP exercise, in which we used no postexercise LBNP (53), the present results are salient because benefits from only 5 min/day of orthostatic stress emerged despite doubling bed rest time from 15 to 30 days. There were no changes to the countermea-
Acute responses to training sessions. Previous work discusses responses to LBNP exercise per se (4, 59, 60). The present data confirm that the exercise portion of the protocol provides a vigorous workout (Fig. 2): peak HR averaged 86% of maximal levels. HR at a given treadmill speed and LBNP level at the end of an exercise session exceeded by 20% HR at the same speed and LBNP near the start of the session (after the 7-min warm-up). As discussed previously (59), multiple factors explain this cardiovascular drift, including 1) incomplete recovery from prior exercise at higher workloads, 2) fluid losses via respiration and sweat, 3) progressive LBNP-induced blood and extravascular fluid accumulation in the lower body (2, 60, 69), 4) cutaneous vasodilation from metabolic and LBNP chamber heat accumulation (59), and 5) synergistic interactions between the above factors. These acute responses to LBNP exercise set-up conditions for exaggeration of subsequent orthostatic stress.

Mechanisms of current observations. We sought to exploit postexercise hemodynamic conditions to train orthostatic blood pressure control mechanisms efficiently. Static upright posture immediately after strenuous exercise provides a substantially greater cardiovascular stress than orthostasis without prior exercise (68). Factors contributing to this observation include exercise-induced blood and extracellular fluid volume reduction (31), cessation of skeletal muscle pumping (10, 11), reduction of respiratory pumping (52), postexercise reduction of vasoconstrictive sympathetic nerve activity (15, 30), ongoing skeletal muscle vasodilatation to meet metabolic demands of exercise recovery (52), and cutaneous vasodilatation to dissipate residual heat from exercise (22).

Bjurstedt and colleagues (3) blamed low systemic resistance for postexercise orthostatic intolerance, because central venous pressure and thus cardiac filling remained at preexercise values during postexercise HUT. Indeed, Halliwill and coworkers (30) noted reduced sensitivity of both the arterial-sympathovascular baroreflex and the vasoconstrictive transduction of sympathetic activity following dynamic exercise. Therefore, ongoing vasodilatation during recovery from dynamic exercise accentuates the cardiovascular challenge imposed by orthostatic stress. In some ways, the postexercise condition mimics the hypovolemia and limited ability to vasoconstict seen after spaceflight.

Plasma and blood volume results from the present study are presented elsewhere, and they agree with earlier evaluations (38, 64): LBNP treadmill exercise prevents intravascular fluid volume loss during bed rest. This in turn helps normalize cardiac filling pressure during orthostasis and thus facilitates maintenance of orthostatic tolerance (13, 20, 48, 65). However, as noted above, maintenance of blood volume with LBNP exercise alone failed to prevent bed rest-induced loss of tolerance (53). The clearest physiological difference between the present control and countermeasure groups is the post-bed rest SV reduction and HR elevation in controls. This did not occur in countermeasure subjects. This maintenance of SV during bed rest suggests that the countermeasure prevented any cardiac remodeling that may contribute to loss of orthostatic tolerance (48, 65).

We saw no significant control vs. countermeasure group differences in TPR during HUT, but intersubject variability seemed to increase post-bed rest (Fig. 6), and technical problems limited sample size for these data. The countermeasure group exhibited an interesting trend toward reduced CVR after bed rest relative to pre-bed rest and control group values, including at presyncope (Fig. 6). Some evidence suggests that bed rest and spaceflight affect the cerebral circulation in ways that compromise brain blood flow during orthostasis, perhaps secondary to chronic elevation of cerebral circulatory and/or intracranial pressures (37, 65, 67, 71, 72). If so, the brief but strong stimulus offered by postexercise LBNP during bed rest may have reduced perfusion pressure and challenged autoregulation enough to help prevent maladaptive cerebral circulatory changes.

The present orthostatic tolerance results confirm and extend findings from our laboratory’s previous 5-day bed-rest study (38, 64). In that work, 5 min of postexercise LBNP applied daily appeared to fully preserve orthostatic tolerance during the relatively short bed rest period. Although the 5-min stimulus did not prevent degradation of orthostatic tolerance fully during 30 days of bed rest, it roughly halved the magnitude of degradation. We speculate that increasing postexercise LBNP duration may fully protect orthostatic tolerance during prolonged bed rest.

Alternatively, more accurate simulation of gravity may be necessary for full protection of tolerance. LBNP does not create a gradient of pressure in the circulation as does gravity, nor does it apply static +Gz vestibular stimulation (61, 65). Full preservation of orthostatic function may somehow depend on reproducing the gravitational pressure gradient between the cerebral circulation, carotid, and aortic baroreceptors. A literature search yielded no investigations of this idea. Vestibulovascular control mechanisms provide a more studied example of how gravity affects the circulation in ways that LBNP cannot duplicate. Many works suggest vestibular inputs to circulatory control may importantly influence orthostatic cardiovascular function (36, 43, 51, 70), whereas other findings question this contention (63). If future work confirms need for +Gz vestibular stimulation to protect orthostatic tolerance during bed rest, such results would suggest superiority of long-arm centrifugation over LBNP as a countermeasure.

Comparison to other countermeasures. Most current countermeasures against orthostatic intolerance either prove inadequate or take too much crew time. Toward the end of flights lasting months, astronauts on Mir spent 2–3 h/day exercising, yet they wore anti-G suits for up to 4 days postflight (26, 65). Vernikos and coworkers (57) reported that standing 4 h/day completely prevented, and 2 h/day partially prevented, reduction of orthostatic tolerance after 4 days of bed rest. Hyatt and West (33) found that 4 h of 30 mmHg (3.99 kPa) LBNP plus ingestion of 1 liter of isotonic beverage at the end of 7 days of bed rest restored LBNP responses to pre-bed rest levels.

Vernikos and coworkers (57) also reported that walking 2 or 4 h/day did not alleviate orthostatic intolerance. This and multiple other studies (20, 27, 29, 39), along with our laboratory’s results (53), document that exercise by itself offers little or no protection against loss of orthostatic tolerance during bed rest. Cerebral blood flow continues uncompromised or increases during even intense upright dynamic exercise (49), because of blood pressure elevation from sympathoexcitation and the skeletal muscle and respiratory pumps. Therefore, dynamic exercise by itself does little or nothing to train resting blood pressure control mechanisms for their task of maintain-
ing cerebral blood flow during gravitational stress. These collective observations suggest that protection of orthostatic tolerance during bed rest requires stimulation of orthostatic (resting) blood pressure control mechanisms. In this regard, our laboratory’s prior 15-day bed rest results (53) effectively provide an exercise-only control condition for the present study, because if LBNP exercise alone failed to protect orthostatic tolerance during 15 days of bed rest, no basis exists to expect it to protect tolerance during 30 days of bed rest.

A study by Engelke and colleagues (18) refutes the contention that exercise offers little benefit for orthostatic function. Their subjects performed a single bout of supine maximal cycling exercise after 15 days of bed rest. When LBNP tolerance was measured 24 h later (end of bed rest), subjects experienced less loss of tolerance after they had exercised than in control conditions. Although these findings are scientifically interesting, it is probably unrealistic to expect all crew members on a given flight to perform maximal exercise within 24 h before return from space, especially if return was unexpectedly urgent. Also, it may be unreasonable to expect occasional maximal exercise to counter the scope and degree of deconditioning seen after months in space (25, 45).

The simplicity of a pharmacological remedy for postflight orthostatic intolerance offers obvious advantages. Isotonic beverages provide limited and inconsistent benefit (6, 7) except when given in conjunction with prolonged LBNP (33). Fludrocortisone (55, 56) and midodrine (50) each proved effective for restoring orthostatic tolerance when given alone before the end of bed rest, but postflight results for fludrocortisone taken late in-flight were less promising (54). Although medications may perform well for orthostatic tolerance, they may not offer similar benefit for other systems and functions degraded by bed rest or spaceflight, and protected by LBNP exercise, such as spinal biomechanics (9), anti-G muscle strength, and upright exercise capacity (38, 59). Although a “drug cocktail” of agents could conceivably protect against all debilitating effects of spaceflight, no such combination of medications currently exists. Moreover, a LBNP treadmill system integrated with virtual environments offers recreation and other utility: such a system could be programmed to simulate the gravitational force and possibly even local terrain features of destinations such as Earth’s moon or Mars (42, 65).

Similarly, adjustment of centrifugation rate allows simulation of variable gravity. Also, centrifugation applies +G₁ force to the otoliths unless the head is at the center of rotation, and centrifugation more accurately duplicates gravitational pressure gradients in the circulation than LBNP (61). Neurolab shuttle flight results imply that even short-arm centrifugation may impose sufficient vestibular stimulation to aid postflight orthostatic function (44). Several interesting bed rest studies from Japan demonstrate that cycling exercise during short-arm centrifugation defends against cardiovascular deconditioning, including orthostatic intolerance (34), with efficacy rivaling LBNP exercise (1, 35). Also, Evans and colleagues (19) demonstrated that centrifuge training increases orthostatic tolerance in ambulatory subjects. Other works review the promise (8, 14) and recent progress (12, 14) of centrifugation as a countermeasure.

Safety and operational considerations. The muscle pumping and sympathoexcitatory stimuli practically always reversed the rare presyncope seen during postexercise LBNP. For operational implementation, a more proactive approach may employ brief scheduled applications of such stimuli. LBNP exercisers may easily and instantly stop LBNP by disengaging the waist skirt from the chamber, opening a vacuum release valve, or turning off the vacuum source. System operation could depend on physiologic feedback and/or active subject participation (e.g., a handgrip switch). Finally, the large chamber orifice over which the waist seal lies provides failsafe protection: a user who faints or is otherwise incapacitated would be drawn into the chamber, breaking the seal and thus stopping LBNP.

Although evidence suggests LBNP and centrifugation offer similar effectiveness as countermeasures, practical considerations favor LBNP. A human centrifuge on a spacecraft or a spinning spacecraft would be much larger, more complex, and expensive. The forces created by periodic operation of a human centrifuge would impose significant energy requirements and challenges to a spacecraft’s orientation control systems. LBNP exercise would require minimal purpose-built hardware and control systems: the spacecraft airlock could serve as a LBNP exercise chamber with existing pressure controls, vacuum vented to the spacecraft cabin, a waist seal installation, and a stowable treadmill inside (59).

We used treadmill exercise, as opposed to alternatives such as cycling, for multiple reasons presented previously (59). The present findings do not exclude other forms of exercise, and orthostatic training after shorter bouts of exercise than 40 min may also prove feasible. Concerning postexercise orthostatic training, methods other than LBNP exist to impose such stimulation in weightlessness, and our results do not exclude these options. Such methods include centrifugation (1, 8, 12, 28, 61) and thigh venous occlusion (32, 41). Thigh venous occlusion in particular offers the potential for immediate implementation: one simply applies venous occlusion pressure cuffs to the upper thighs following in-flight aerobic leg exercise and then inflates the cuffs to subdiastolic pressure for the prescribed time.

Limitations. In some subjects, signal quality problems prevented quantification of SV using aortic Doppler ultrasound. In others, as LBNP increased during orthostatic tolerance tests, insonation of the aortic outflow tract became unreliable. These problems limited the number of data points for SV, blood flow, and TPR data through HUT, and they disallowed inclusion of SV, blood flow, and TPR data at presyncope. Therefore, our ability to interpret and conclude from these data is restricted.

We employed identical twin subjects to minimize genetic variability between control and countermeasure groups. Hypothetically, this experimental design maximized our ability to detect and quantify effects of the countermeasure (5). However, despite their genetic identity, physiological and psychological differences between twin siblings occasionally emerged during baseline testing (46). Therefore, it did not seem appropriate to treat each twin pair as a single “subject” for statistical purposes, so we utilized the same statistical approach as one would with unrelated subjects. In these respects, the degree to which use of twins helped us test our hypotheses remains unclear but may have been overestimated. Twin subjects bring instant roommate rapport and an established support system to challenging studies such as this, which offers an advantage over use of unrelated strangers. In one case, the psychological support provided by a twin probably kept their sibling from dropping out of the study.
Our study design left out an LBNP-alone condition because 45 min of 50–60 mmHg resting LBNP exceeds the tolerance of most subjects (60, 69). Subjects tolerate sustained 50–60 mmHg LBNP with concomitant exercise because exercise increases LBNP tolerance (60). Bed rest is not physiologically identical to spaceflight (20, 65), so in-flight studies offer the only way to test whether post-exercise LBNP maintains orthostatic tolerance during spaceflight.

Conclusions. These results demonstrate that daily brief post-exercise orthostatic stress during bed rest attenuates bed rest-induced loss of orthostatic tolerance. Vigorous exercise followed by brief orthostatic stimulation appears capable of maintaining blood volume and orthostatic cardiovascular function near baseline levels. This strategy reduces the daily duration of orthostatic stress necessary for protecting orthostatic tolerance during bed rest from hours to minutes, and it appends time for orthostatic training to that already used for exercise countermeasures. Taken together with prior related work, these results support spaceflight study of orthostatic stimulation during recovery from exercise. Hardware currently exist in-flight to apply safely such stimulation in some form (32).

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