MANS’ CONTINUED INITIATIVE in space exploration will tax the human body, including the cardiovascular system. This system is exquisitely sensitive to loading conditions and neurohormonal stimuli and is adapted to function in normal gravitational environments (1 G). Both mechanical (muscle and diaphragmatic pumps) and neurohormonal regulatory mechanisms are critical in maintaining adequate blood pressure and flow to the brain to prevent syncope with the assumption of an upright posture, a stress that is continually imposed on the cardiovascular system here on Earth (1). In an environment of actual (space) or simulated microgravity [head-down-tilt bed rest (HDT)], the cardiovascular system works “just fine” as it adapts to lack of pressure gradients in both the arterial and venous system and a decreased load on the heart. It is, however, a return to an environment in which gravity is present that stresses a system that has been “remodeled” and whose compensatory mechanisms have been “tuned down.” This ultimately leads to orthostatic intolerance (OI) and (pre)syncope, a potential catastrophic outcome for a pilot or crew member. A significant decrease in stroke volume, as well as a failure to raise vascular resistance, are critical pathophysiological mechanisms underlying OI. Potential causes for a decreased stroke volume include a decrease in contractile function, an altered end-diastolic pressure-volume relationship, as well as a failure of regulatory mechanisms to increase preload. It is now well established that chronic exposure to actual or simulated microgravity results in cardiac atrophy and deconditioning (7, 8, 12). The high prevalence of OI among bed rest patients and astronauts may thus be due, in part, to the observed changes in cardiac morphology. Importantly, it has been reported that OI is more prevalent among female astronauts (15). Although there are hints as to the potential reasons for this divergence, the question arises as to whether it is a difference in the magnitude or rate of cardiac atrophy that could contribute to this phenomenon. Previous studies on cardiac deconditioning have failed to fully analyze the effects of HDT on female cardiac structure. Given that a full 20% of astronauts are women and approximately an equal amount of women are subject to bed rest as men, a study of cardiac deconditioning and atrophy in women during HDT was therefore warranted. Dorfman et al. (2) undertook this study and documented cardiac changes in women during 60 days of HDT bed rest.

Using state-of-the-art magnetic resonance imaging technology, Dorfman et al. (2) reported that bed rest resulted in significant reductions in left and right ventricular mass and volume in the HDT subjects. Interestingly, the degree (percent change) of cardiac atrophy was no different than that seen in men (2). This is an important finding because, although bed rest results in similar cardiac morphological changes and degrees of atrophy in both men and women, there remains a higher prevalence of OI among women. This suggests that although cardiac atrophy may contribute significantly to deconditioning, it does not explain the sex differences in OI susceptibility. What is it then that could explain this sex difference? Waters et al. (15) have demonstrated that female astronauts have lower peripheral resistance and hypoadrenergic responses compared with male astronauts following spaceflight. On the other hand, Fu et al. (5, 6) suggest that it is a decrease in cardiac filling rather than a decrease in sympathetic vasoconstrictor reserve (with failure to increase systemic vascular resistance) that distinguishes the sexes. Recently, we have demonstrated that orthostatically tolerant and OI astronauts can be stratified according to their arterial stiffness following spaceflight, with the tolerant group having a decreased arterial compliance (13). This “adaptive” change maintains preload by decreasing the resistance to venous return (13). It is thus possible that a difference in arterial stiffness between sexes [with female astronauts (or bed rest subjects) having a lower arterial stiffness or greater arterial compliance] contributes to OI. The mechanism for this difference might well be explained on the basis of the effect of estrogen on endothelial nitric oxide signaling and its downstream effects on enhancing endothelial function and increasing vascular compliance (9). This phenomenon of OI may also be exemplified in highly conditioned athletes, who not only have altered cardiac structure that predisposes them to increased falls in stroke volume with an orthostatic stress (4) but also have endothelial-dependent decreases in arterial stiffness, which contribute to the increased resistance to venous return (3, 11).

A further aim of Dorfman et al. (2) was to evaluate two separate potential countermeasures to cardiac atrophy: exercise and dietary protein supplementation. The exercise countermeasure was implemented by allowing the subjects to exercise on a horizontal treadmill in a chamber in which they were subjected to lower body negative pressure. The application of lower body negative pressure was intended to produce similar forces on the bedrest subjects in a horizontal position as those experienced during vertical exercise. The investigators demonstrated that this form of exercise during bed rest resulted in no significant changes in left or right ventricular volumes, but it did induce a significant increase in left and right ventricular mass. It remains unresolved, however, as to whether it is the exercise, or simply the lower body negative pressure with its unloading of the baroreceptors leading to sympathetic activation, that increases cardiac mass. It is well established that sympathoactivation is a critical trophic signal in the heart. This process is most likely mediated through α1-adrenergic receptors in the heart. Indeed, deletion of the cardiac α1-receptors prevents adaptive hypertrophic responses in mice with transverse aortic banding (10). Despite this question, the experimental exercise protocol represents an effective countermeasure to bed rest-induced cardiac atrophy in women. Additionally, this particular countermeasure, lower body negative pressure exercise, has the potential to be adapted for spaceflight applications to prevent microgravity-induced cardiac deconditioning.

The second countermeasure tested, protein supplementation, was shown to maintain right ventricular mass and volume and left ventricular mass at pre-bed rest levels with only a significant decrease in left ventricular volume during 60 days of bed rest. What is the possible mechanism underlying this preservation of ventricular mass by the supplementation of branched-chain amino acids? It is well established that cardiac hypertrophy resulting from increased cardiac load is mediated by mechanosensitive growth factor receptor-dependent transcriptional activation of protein synthesis within the cardiac myo-
cyte. In addition to mechanosensitive signals, branched-chain amino acid mixtures can mimic postprandial hyperaminoacidemia resulting in the activation of translational initiation factors [such as eukaryotic initiation factor 4G (eIF4G)] and resultant stimulation of myocardial protein synthesis (4). This simple countermeasure represents an effective way to prevent most of the cardiac deconditioning that occurs during bed rest at low cost and with minimal effort. What remains to be determined is whether this countermeasure can result in pathological remodeling with long-term use or whether it is effective in attenuating or preventing OI, the most critical end point in cardiovascular deconditioning.

In summary, in this important study, Dorfman and colleagues (2) have demonstrated that one of the “predictable” changes in cardiac structure, a change in volume and cardiac atrophy, occurs to the same degree in women as in men. What now remains to be determined are the mechanisms that underlie the divergence in responses that allow the phenotype, OI, to manifest. Some of the potential and well-studied mechanisms are summarized in Fig 1. We may, however, need to turn to our genes to further understand this phenomenon. For example, a common polymorphism in the β1-adrenergic receptor (b1Gly49) appears to be protective in idiopathic OI (a syndrome that has may features in common with microgravity-induced OI) (16). In addition, a mutation in a gene for the norepinephrine transporter, critical in the regulation of adrenergic signaling, may also contribute to OI (14). Furthermore, a genetic variant within the regulatory region of the endothelin-1 gene (endothelin is an important endothelial-dependent vasoconstrictor) is associated with a more “efficient hemodynamic response to standing” (17). Therefore, screening of astronauts for polymorphisms that are associated with a higher likelihood of OI may allow for specific and selective countermeasure interventions. Thus an intimate understanding of both genetic and sex similarities (as highlighted in this paper) or differences that contribute to OI will allow for the testing of both general and “designer” countermeasures. This will address both predictable and person-specific changes in cardiovascular structure and function following microgravity.

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Invited Editorial

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