The following is the abstract of the article discussed in the subsequent letter:

Merja A. Perhonen, Fatima Franco, Lynda D. Lane, Jay C. Buckey, 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 ± 2.2% (P = 0.005) after 6 wk with an additional atrophy of 7.6 ± 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 ± 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 ± 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 ± 2.7% (P = 0.06) and RV end-diastolic volume by 16 ± 7.9% (P = 0.06). After space-flight, LV mass decreased by 12 ± 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.

Lower body negative pressure vs. lower body positive pressure to prevent cardiac atrophy after bed rest and spaceflight. What caused the controversy?

To the Editor: In 2001, Dr. Perhonen and coworkers (4) published important material on cardiac atrophy after bed rest and spaceflight. In 2002, there was an interesting discussion between them and Dr. Watenpaugh (6) concerning the possibility of using lower body positive pressure to minimize cardiac atrophy. It appears strange that in this discussion, it was not mentioned that lower body negative pressure is used for simulating gravity—quite the contrary (7). What caused this contradiction in such an extremely advanced field?

In orthostasis, the gravity helps the arterial blood flow and impedes the venous return. During spaceflight/supine, this factor is absent, and the heart is commonly underloaded. The logical conclusion must be: first, the weight of the venous column is also overcome by the heart; second, despite the lower vein resistance, venous return is more energy consuming than the arterial flow, which hints to the fact that the gain on the venous side outweighs the loss on the arterial side. However, the cause of this underloading is not interpreted by this.

In Refs. 1, 2, 4, 5, and 6, there is speculation that physical factors are the main determinants of the orthostatic intolerance, but the question is not thoroughly examined with the mechanisms of venous return. The statement in Ref. 4 that it is not clear whether inactivity in a nonathletic population causes adaptive changes in left ventricular mass hints that venous return in the daily round may be enough exercise for the heart to prevent atrophy. It is correctly noted that cardiac work is a function of many factors, but in our view, the accent is incorrectly put on the reduced preload wall stress as the primary cause of atrophy. On this point comes the contradiction: it is acknowledged that the acute response of head-down-tilt bed rest transiently increases the cardiac filling pressure, without explaining the mechanism of the following adaptation and loss of plasma. Our concept on this is sketched below.

According to our theory for the blood circulation, in orthostasis, the heart has to overcome the weight of the venous column through transmural arterial pulsations, arteriovenous anastomoses, and arteriovenous capillary bridges. This effect cannot be achieved by factors external to the heart, as we stated in Ref. 3, challenging the present concept. The conclusion we made above that venous return is more energy consuming coincides well with the less-effective mechanism of transmural transmission of energy to the veins compared with direct pumping in the arteries.

The suggested transmural transmission of energy, which is similar to the mutual induction in electrical engineering, allows the changes in the blood flow conditions in the veins to be adequately sensed by the arterial side. Thus the enhancement of venous flow reduces primarily the left ventricular afterload, wall stress, and end-systolic volume, and leads to cardiac atrophy. The reduced energy transmission determines reduced blood volume necessary to create the correspondent mean circulatory filling pressure (to create the necessary vascular tone), reduced heart rate, and stroke volume because of the weaker pulsations needed for that transmission.

On the basis of our theory, we would propose, instead of the widely used −6° of head-down tilt as model of actual weightlessness, a legs-up, head-up position, in which the heart would remain in the lowest point in respect to the majority of the body. This would ensure maximally enhanced blood flow, by which the upper part of the body will be closer to real weightlessness as well. It could be speculated that in this position the required inclinations will be smaller than 6° and more comfortable for the astronauts.

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To the Editor: Dr. Panchev and colleagues suggest in their title that there is a controversy regarding the effect of lower body negative or positive pressure on cardiovascular hemodynamics. However, in my opinion, no such controversy exists. It is clear that hydrostatic gradients influence the distribution of pressure and volume within the circulation, with predictable effects on ventricular filling and consequent ejection (1). When a human stands up, blood pools below the heart, leading to reduced right and left ventricular filling volume, reduced transmural filling pressure, and reduced stroke volume—this is the primary effect of gravity on the upright human circulation. Conversely, when a previously upright human assumes the supine position, venous return increases, transmural filling pressure increases, and stroke volume increases with predictable effects on baroreflex control of heart rate and peripheral resistance. Counteracting the effects of gravity by using the skeletal muscle pump with the leg-crossing maneuver (12) or the respiratory muscle pump by using an impedance threshold device (4) leads to predictable increases in venous return, stroke volume, and blood pressure, with expected neurohumoral responses. These examples demonstrate clearly that hydrostatic gradients act in predictable ways in the circulation.

Bed rest serves as an appropriate model for spaceflight because it mimics the primary effect of gravity on the circulation—that is, elimination of head-to-foot (i.e., Gz) gravitational gradients. Lower body positive pressure applied in the upright position (8) simply provides the same hydrostatic stimulus and induces predictable and identical responses. Conversely, lower body negative pressure in the supine position allows the simulation of gravity without having to change body position, facilitating instrumentation and experimentation. Perhaps whatever confusion exists relates to the timing of circulatory changes with bed rest (the 6 degree head-down position is added to eliminate the modest effect of the shape of the thoracic and optimally eliminate Gz forces). With acute bed rest (or spaceflight), the elimination of hydrostatic gradients results in a central fluid shift, increasing transmural cardiac filling pressure (2, 23), left ventricular end-diastolic volume, and stroke volume. Chronically, neurohumoral compensation leads ultimately to decreased transmural filling pressure and a hemodynamic state that is about halfway between the supine and upright standing positions. When both groups of subjects stand up after this adaptation, both experience virtually identical reductions in stroke volume below the minimum observed before microgravity stimulus, associated with similar increases in heart rate and sympathetic activation (3, 13, 14, 19). It is this excessive reduction in stroke volume in the upright position that is the sine qua non of the cardiovascular adaptation to microgravity and has been observed in cardiac filling pressure, whereas in the standing position, regulatory pressure acts to retain salt and water. Thus, either lying at 30 degrees head up (50% Gz stimulus) or sitting down (18), approaches the “regulated” position for normal humans. It is this relative unloading compared with the supine position (along with reduction in physical activity from confinement) that, in my opinion, is the primary stimulus to a cardiac atrophy and remodeling that takes place over a few weeks with the ultimate adaptive goal to normalize wall stress (20).

It should be emphasized that cardiac mass is highly regulated in response to changes in loading conditions (6, 9–11, 21) with similar responses to volume or pressure load (5). Chronic volume loading of the LV is associated with eccentric hypertrophy and increased diastensibility, whereas volume unloading is associated with eccentric atrophy and decreased chamber distensibility (7, 24). When the unloading is marked (17), cardiac atrophy is rapid (within 7 days) and dramatic (40% decrease in heart weight and myocyte volume; Ref. 17). These adaptations appear to be localized exclusively to cardiac myocytes rather than changes in the interstitium (22). As a function of this decrease in myocyte volume, the relative concentration of collagen is increased (17), which contributes at least in part to increased chamber stiffness (16). A recent large-animal model of cardiac atrophy that matches the human bed rest deconditioning model quite closely confirmed that chronic reduction in LV volume (from IVC banding) causes a prominent reduction in LV mass and myocyte volume (15).

Finally, it is worth emphasizing that the current practice of employing -6 degree head-down tilt to simulate the acute and chronic exposure to the microgravity environment of space appears to be quite accurate. Figure 1 superimposes data drawn from two published papers in which I was an author and participated in data collection using the same equipment and subjects with similar demographics: a bed rest study (14) and three spaceflight studies (3). The figure demonstrates clearly that 2 wk of both spaceflight and bed rest lead to the same hemodynamic outcome—that is, a stroke volume that is halfway between supine and upright standing positions. When both groups of subjects stand up after this adaptation, both experience virtually identical reductions in stroke volume below the minimum observed before microgravity stimulus, associated with similar increases in heart rate and sympathetic activation (3, 13, 14, 19). It is this excessive reduction in stroke volume in the upright position that is the sine qua non of the cardiovascular adaptation to microgravity and has been observed in
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virtually every bed rest or spaceflight study in which it has been measured. “Occam’s razor” would argue that these straightforward hydrodynamic and mechanical explanations fit the available data simply and cleanly. Panchev and colleagues have not convinced me that any modifications of this paradigm are necessary.

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