Hypertension Research (2013) 36, 1037–1038

www.nature.com/hr

COMMENTARY

# Is gravitation your friend or foe?

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*Hypertension Research* (2013) **36,** 1037–1038; doi:10.1038/hr.2013.118; published online 12 September 2013

Gravitational forces are a prime reason why an obese person feels too heavy and experiences exercise intolerance. Moreover, gravitation promotes obesity-associated disease. As a result of gravitational forces, excess body mass imposes mechanical strain on the musculoskeletal system. Over the years, premature osteoarthritis may ensue. Restrictive ventilatory defects, obstructive sleep apnea, gastroesophageal reflux disease and other obesity-associated ailments all involve gravitational forces. Could gravitation also affect blood pressure regulation? A paper published by Schoenenberger *et al.*[1] in this issue of *Hypertension Research* and previous observations during long-term space flights support this provocative hypothesis.

Obesity-associated hypertension is a major health-care issue in many countries. Indeed, obesity can cause or exacerbate arterial hypertension. Given the steep increase in the prevalence of obesity in recent decades, it may be no surprise that approximately 25% of the adult population is affected by arterial hypertension and that the condition is increasingly diagnosed in younger people.[2] Among hypertensive participants in the Framingham Heart Study, the presence of obesity strongly predicted lack of blood pressure control below 140/90 mm Hg.[3] While obese hypertensive patients are prescribed more antihypertensive medications, their blood pressure tends to be less well controlled compared with normal-weight hypertensive patients.[4] Thus, most patients with treatment-resistant arterial hypertension are overweight or obese.[5] Finally, metabolic and cardiovascular risks associated with arterial hypertension and obesity may add up. For example, obesity and hypertension promote left ventricular hypertrophy, which is an established marker for cardiovascular organ damage.

Given the importance of obesity in the pathogenesis and management of arterial hypertension, the underlying mechanisms deserve our attention. Obesity-associated arterial hypertension is characterized by sympathetic nervous system and renin–angiotensin system activation. The neurohumoral activation tends to raise blood pressure through increased sodium retention.[6] To make matters worse, the systemic availability of blood pressure-lowering natriuretic peptides is reduced in obesity.[7] The imbalance between sodium-conserving and sodium-excreting mechanisms likely explains volume expansion and increased cardiac output, the typical hemodynamic abnormalities in obesity-associated hypertension.[8] However, the mechanisms triggering the neurohumoral activation in human obesity are not fully understood. Studies in genetically manipulated mice strongly suggest that adipose tissue-derived leptin can activate sympathetic efferent traffic through the melanocortin pathway.[6] Observations in patients with genetic melanocortin-4 receptor deficiency suggest a similar mechanism in humans. Hyperinsulinemia, adiponectin deficiency and low-grade systemic inflammation may amplify the pressor response to obesity. However, the idea that body mass itself could elicit a pressor response received little attention.

Schoenenberger *et al.*[1] studied otherwise healthy young to middle-aged men and women with a normal blood pressure or borderline hypertension and an average body mass index of 30 kg m$^{-2}$. The authors examined the blood pressure at rest and during exercise before and after 10 kg weight loss through a hypocaloric dietary intervention. To dissect out the individual contribution of the change in body mass, blood pressure measurements at rest and during exercise were repeated while subjects were wearing a 10-kg weight vest. Dietary weight loss was associated with a substantial reduction in blood pressure at rest and during exercise. When baseline body weight was restored through the weight vest, the beneficial effect on resting blood pressure was lost in part. Blood pressure during exercise completely relapsed when subjects wore the weight vest. Addition of weight also slightly raised blood pressure before the weight loss intervention.

A reduction in body mass is the only way that most humans can reduce the gravitational stress to the cardiovascular system. A few escape the earth's gravitational field during space flights, such that the cardiovascular system is exposed to microgravity. This condition is often referred to as weightlessness. The first days in space are characterized by volume redistribution toward the head among many other physiological and psychological adjustments. Most cardiovascular studies in space have been conducted during this acute phase. Hemodynamic investigations showed reductions in vascular resistance with compensatory increases in cardiac output, both with simulated microgravity during parabolic flights and after several days in space.[9] The authors suggested that space traveling might be healthy for the cardiovascular system. The few subjects tested during long-term space flights exhibited a similar response. Compared with baseline measurements, blood pressure decreased during several months in space, while heart rate remained unchanged.[10] Remarkably, the spontaneous respiratory rate also gradually decreased in space.[10] The reduction in blood pressure was rapidly reversed following return to earth.

In addition to affecting blood pressure, gravitational forces regulate cardiovascular

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structure, particularly left ventricular mass. In obese patients, body weight reduction through lifestyle interventions, medications or bariatric surgery reduces left ventricular mass. In this setting, the reduction is therapeutically desired because excessive left ventricular mass predisposes to heart failure and cardiac dysrhythmias. However, loss of ventricular mass secondary to reduced gravitation can also be maladaptive in that it impairs the capacity to adjust to acute hemodynamic challenges, such as standing. Prolonged bed rest, which is an established model to test influences of reduced gravity on the human body, and spaceflight led to reductions in the left ventricular mass.[11] Similar changes are likely to occur in many hospitalized patients. Therefore, too much and too little gravitational challenges to the cardiovascular system can have adverse cardiovascular health effects.

It is tempting to speculate that nature tuned the human cardiovascular system to work best with a normal body mass in the earth's gravitational field. If so, does the human body sense changes in mass or gravitational forces to maintain optimal mass and gravitational forces? The idea that body weight can be sensed and that this signal is fed into a loop regulating body weight is not new.[12] Weight-loaded animals lose weight, while the removal of the weight load elicits an opposite response.[13] Perhaps the leptin pathway is not the sole feedback loop regulating body weight. The rapid response to weight loading in Schoenenberger's study[1] suggests that the sympathetic nervous system could be part of the efferent loop of such a feedback mechanism. Yet, the mechanism sensing mass or gravitational forces remains mysterious. Vestibulo-sympathetic reflexes originating in otolith organs could be involved. Indeed, in experimental studies, vestibular nerve stimulation elicited sympathetic activation together with a pressor response.[14] Another possible explanation for the findings by Schoenenberger *et al.*[1] is that the added weight, while being supported by the bicycle saddle, nevertheless produced additional muscle activity in the upper body. Additional muscle activity may result from stabilization of upper body posture and increased respiratory work to overcome thoracic cage compression by the weight vest.

Overall, the literature suggests that when you are obese, gravitation is your foe. Given the important health-care implications of obesity and the tight association with arterial hypertension, the mechanisms underlying the gravitationally induced blood pressure increase should be studied in more detail. Because we cannot send our patients into space, weight loss remains the treatment of choice to ameliorate obesity-associated health issues. One way to escape excessive gravitational forces for a little while is water immersion, which allows obese patients to engage in physical exercise while relieving the musculoskeletal system. Perhaps the cardiovascular system is relieved as well through this intervention.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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