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Cardiovascular, Renal, Electrolyte, and Hormonal Changes in Man During Gravitational Stress, Weightlessness, and Simulated Weightlessness: Lower Body Positive Pressure Applied by the Antigravity Suit

Stein E. Kravik

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Stein E. Kravik, Ames Research Center, Moffett Field, California

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Space Administration

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Moffett Field, California 94035

DEDICATION

TO: C. W. Sem-Jacobsen—an exceptional friend. You exposed me to the exciting world of aerospace medicine.

TO: My mother and father. You encouraged me with great love and without pressure.

TO: My wife Sissel. Your infinite patience, inspiration and understanding have taught me the joy of living.

TO: My sons, Andreas and Erling. You make everything worthwhile.

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The Earth is the cradle of the mind,
but one cannot live in the cradle forever.

Konstatin Eduardovich Tsiolkovsky
1857-1935

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CARDIOVASCULAR, RENAL, ELECTROLYTE, AND HORMONAL CHANGES IN MAN DURING GRAVITATIONAL STRESS, WEIGHTLESSNESS, AND SIMULATED WEIGHTLESSNESS: LOWER BODY POSITIVE PRESSURE APPLIED BY THE ANTIGRAVITY SUIT

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1.0. INTRODUCTION

Gravity is one of the most important environmental elements on Earth which has remained unchanged since our planet was formed some four billion years ago, and which has affected and will continue to influence the structure, function, and behavior of animals as long as life exists on Earth.

It was indeed a bold venture when our ancestors left the aquatic environment and crawled on shore. Although not commonly recognized, the same daring enterprise of nature took place when man gradually rose to walk on his hind limbs. The gravitational force of Earth has tried to pull man down ever since.

Because of their erect posture, humans are more vulnerable to gravitational changes than any other animal. During standing or walking man must constantly use his antigravity muscles and his two columns—the legs—to balance against the force of gravity. At the same time, blood is surging downward to the dependent portions of the body, draining blood away from the brain and heart, and requiring a series of complex cardiovascular adjustments to maintain the human in a bipedal position.

Nevertheless, man has adjusted so well to gravity that very few people think of this force as harmful, maybe because gravity, unlike other natural phenomena, cannot be generated or interrupted at man's will; it cannot be touched, seen, or smelled.

Within the last three decades man has challenged another environment—space. Except for very short periods of weightlessness (1 min or less, Blomqvist and Stone, 1983) using a high-powered aircraft flying a parabolic maneuver (Keplerian flight trajectory), it was not until April 12, 1961, when Yuri Gagarin became the first human being to orbit Earth, that we could confirm man's ability to maintain vital functions in space—at least for 90 min. By May 1988, humans had logged more than 6800 days in space (U.S. News and World Report, May 16, 1988). Cosmonauts V. Titov and M. Manarov currently hold the manned spaceflight record with their 1-yr-long stay on board the Russian "MIR" space station ending Dec. 21, 1988 (Aviation Week and Space Technology, Jan. 2, 1989).

Except for space motion sickness (uncomfortable feeling, lack of initiative, dizziness, nausea, anorexia, and sometimes vomiting), which affects about 40-75% of the astronauts for the first 3-4 days of flight (Davis et al., 1988) humans appear to tolerate their new environment well.

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Nevertheless, man's adaptation to weightlessness entails the deconditioning of various organs in the body. Muscles atrophy, and calcium loss leads to loss of bone strength as the demands on the musculoskeletal system are almost nonexistent in weightlessness. Because of the lack of hydrostatic pressures in space, blood rushes to the upper portions of the body, initiating a complex series of cardioregulatory responses.

Deconditioning during spaceflight, however, first becomes a potentially serious problem when humans are returning to Earth and the cardiovascular system, the muscles and bones are suddenly exposed to the demanding counterforce of gravity—weight.

To understand human reaction to weightlessness and gravitational stress, various ground-based methods have been developed: water immersion, head-down tilt, and horizontal bed rest are classical "analogs of weightlessness" applied over the last two to three decades to simulate different effects of the weightless condition (Greenleaf, 1984).

One of the main purposes of our studies (referred to as PAPERS I-IX throughout the manuscript) was to test the feasibility of using Lower Body Positive Pressure (LBPP), applied with an antigravity suit, as a new and alternative technique to bed rest and water immersion for studying cardioregulatory, renal, electrolyte, and hormonal changes in humans.

Research related to human responses to gravity, weightlessness, and simulated weightlessness goes beyond the specific need to apprehend and support the human ability to live and work in space, and to readapt to the terrestrial environment. These studies also enhance our basic physiological knowledge, elucidate key questions regarding homeostatic mechanisms, and are relevant towards improving our current understanding of many clinical problems and processes applicable to preventive medicine.

2.0. CARDIOVASCULAR ADJUSTMENTS TO GRAVITY IN MAN

The effect of gravity upon man's circulatory system on Earth is easily recognized during postural changes. A sudden transition from recumbency to an erect position shifts some 700-900 ml of blood from the upper portions of the body to the legs and pelvic area (Sjöstrand, 1952, 1953; Rowell, 1986; Sandler, 1986).

2.1. Acceleration

According to Einstein's Principle of Equivalence, the inertial reaction derived from acceleration is physically equivalent and indistinguishable from a gravitational field of the same magnitude. Therefore, a centrifuge ride with head-to-foot direction of inertial force, or a pull-out from a dive in an airplane, will push even more blood into the lower vessels than assumption of the upright position does.

At this point it is timely to define the standard AGARD terminology accepted for accelerations and their inertial forces. According to this system, accelerations along the long axis of the body are called Gz-accelerations. A headward acceleration (with resultant head-to-foot direction of inertial force) is termed +Gz while "negative" Gz (–Gz) acceleration is in the opposite direction. Accelerations perpendicular to the Gz axis are defined as Gx (forward and backward) and Gy (lateral) accelerations (Pesman, 1971; Oyama, 1976; Sharp and Ernsting, 1978).

In human physiology we are mostly concerned with accelerations along the Gz axis since the inertial forces resulting from such accelerations either deprive the brain of blood (+Gz) or increase flow and intracranial pressure (–Gz).

The force exerted upon the body on the surface of the Earth is considered to be 1G. A human being is thus exposed to +1Gz while standing erect on Earth and to +1Gx during supine bed rest. The normal gravitational orientation for a quadruped animal is –Gx. No directional orientation exists in space (Oyama, 1976). Weightlessness is traditionally termed "zero gravity" (which is really a misnomer—see section 3.1.).

2.2. "Normal" Posture in Man

A healthy man spends about two-thirds of his life standing, walking or sitting. Groedel in 1908 (confer Gauer and Thron, 1965) and later Gauer (Gauer and Thron, 1965) proposed the erect posture as the natural resting "physiological" position. Still most physicians and researchers argue that the horizontal posture represents the best controlled condition for cardiovascular and blood measurements. Both views can be argued (Greenleaf, 1984).

2.3. Intravascular Pressures

The circulatory adjustments of a human upon assumption of erect posture are initiated by the sudden downward redistribution of blood and the creation of hydrostatic pressures generated by the weight of blood columns (Clark, 1934; Edholm, 1940; Carrier, and Rehberg, 1923; Hill, 1895; Hill et al., 1897; Hill and Barnard, 1897; Gauer and Thron, 1965; Rowell, 1983).

If the vessels were rigid, watertight tubes, nothing would happen during posture changes. The heart would simply keep pumping blood around a closed circuit of pipelines (veins and arteries) at the same rate independent of their position relative to the gravitational field. Such a system would be useless to the body. Instead, the vessels are elastic tubes made of smooth muscles which can alternate blood flow and their permeability for dissolved materials as needed by different organs (Amberson, 1943). The measured pressure within any vessel has three components:

2.3.A. Static Filling Pressure

The static filling pressure is interdependent upon the blood volume and the size of the vascular bed (distensibility) at zero flow. This is the dominant determinant of pressures in the low-pressure system (= systemic veins, the right heart, the pulmonary circulation) (Guyton et al., 1973). The filling pressure is modified by two other pressure components, the driving pressure and the hydrostatic pressure.

2.3.B. Driving Pressure

The driving pressure is a dynamic pressure generated by the heart and the resistance to flow (flow × resistance). This pressure characterizes the high-pressure arterial hemodynamics (McDonald, 1974).

2.3.C. Hydrostatic Pressure

The hydrostatic pressure, the third pressure component, is caused by the force of gravity. The hydrostatic pressure is equal to the weight of a blood column extending from the point of measurement to a level near the right atrium.

The hydrostatic pressures come into play with changing postures and can be added by the same amount to the dynamic venous and arterial pressures. Thus in standing man the venous and arterial pressures at the foot are approximately 100 Torr above the recumbent transmural venous (10-Torr) and arterial (100-Torr) pressures, respectively (Henry and Gauer, 1950).

2.4. Hydrostatic Indifferent Point (HIP)

During the time a human takes to stand up from a previously reclined position, the pressure in the upper and lower portions of the body decreases and increases, respectively. Consequently there is a cardiovascular pressure zone which remains unaltered pre- and post "tilt." Wagner in 1886 suggested that such an HIP existed and argued that this pressure-junction represents the natural hydrostatic reference point (confer Gauer and Thron, 1965). Gauer and Thron (1965) localized a "gravitational center for the cardiovascular system" approximately 5-8 cm below the diaphragm or 15 cm below the upper half of the right atrium.

HIP is not a static anatomical landmark. Rather it changes with the "fullness" of the bloodstream and its distribution in the vascular compartment. For instance HIP moves headward during a handstand (Wilkins et al., 1950), following hemorrhage (Gauer and Henry, 1964), or during exercise (action of the skeletal muscles of the legs (Rowell, 1986). It shifts downward during heat stress (vasodilation in the legs) (Rowell, 1983) and during +Gz acceleration (Gauer and Thron, 1965). HIP is also modified by

sudden changes in cardiac hemodynamics and may be located at a slightly different point in the low- and high-pressure system (Gauer and Thron, 1965; Smith and Guyton, 1963).

2.5. Orthostatic Plasma Volume (PV) Loss

Aside from orthostatic pooling of blood, man faces still another stress during upright posture: extravasation of plasma into the surrounding tissues below HIP. The magnitude of this PV loss varies between 6-18% (Harrison, 1985; Hinghofer-Szalkay, 1982; Hinghofer-Szalkay and Moser, 1986; PAPER IV). The outward PV filtration is caused by the hydrostatic pressure gradient, which at the feet can raise intracapillary pressure to 80-100 Torr during upright posture despite a significant increase in arteriolar resistance (Levick and Michel, 1978; Aukland and Nicolaysen, 1981).

In other words, as one stands erect from a previously recumbent position, the pull of gravity faces us with two problems: First 15% of the total blood volume is "bled" into the lower veins, resulting in increased mean transient time (Rowell, 1986). Second, the effective blood volume decreases by as much as 10-15% (Gauer and Thron, 1965; Hinghofer-Szalkay and Greenleaf, 1987) as a consequence of movement of plasma out of the leg capillaries. The heart depends on returned blood volume to keep pumping, and the greater the pooling of blood and PV loss, the less cardiac output.

2.6. Physiological Adjustments to Positional Body Changes

Humans have in the course of their evolutionary process developed reliable mechanisms to defend homeostasis during erect posture, intended for maintaining adequate blood supply to an organ positioned at a considerable distance above the HIP—the brain.

2.6.A. Mechanical Determinants

2.6.A.a. Contraction of Leg Muscles

Probably one of the most important factors to assert venous return during upright posture is contraction of the leg muscles, which squeezes blood back to the heart by emptying dependent veins (Stegall, 1966; Wang et al., 1960; Amberson, 1943). Rowell (1986) regards the muscle pump as the human's second heart.

Some sort of unconscious postural sway probably takes place even during "motionless" standing. "Standing is in reality movement upon a stationary base" (Hellebrandt, 1938). Supporting this hypothesis is the observation that passive head-up tilt (HUT) implies a greater stress to the circulation than does an actively achieved positional change (Hinghofer-Szalkay and Moser, 1986). In fact prolonged forced HUT is potentially lethal (Rowell, 1986).

2.6.A.b. Reduced Venous Compliance

According to Rowell (1986) reduced venous compliance (DV/DP) for intravascular pressures above approximately 50 Torr is crucial for orthostatic tolerance in man. The veins "stiffen" as transmural pressure increases and hinders further pooling.

2.6.A.c. Venous Leg Valves

Competent valves in the deep leg veins contribute to venous return by preventing backflow immediately following assumption of an upright posture. As the downward movement of arterial blood continues to "fill up" the dependent veins, their hydrostatic pressure increases. The caudad shift of approximately 900 ml of blood is completed when all the valves are open (Sjöstrand, 1952; Rowell, 1986).

2.6.A.d. Extravascular Tissue Pressure

Extravascular tissue pressure in the lower legs (caused by the hydrostatic pressure gradient) forms a circumferential counterpressure around the dependent vessels that tends to reduce the increase in orthostatic transmural pressure (Rowell, 1986). Further studies are needed to quantify this defense mechanism.

2.6.A.e. Intrathoracic Vessels

Intrathoracic vessels represent half the total compliance of the circulation (Gauer and Henry, 1976). The Central Blood Volume (CBV = volume of blood within the lungs and the four chambers of the heart (Rowell, 1983)) according to Gauer is an important blood pool to maintain adequate cardiac output the first few seconds after assumption of the upright posture, when venous return from below is transiently delayed (Gauer and Thron, 1965).

2.6.A.f. Respiratory Pump

The inspiration pressure gradient between the point where the inferior cava runs into thorax and the right atrium is increased because of the deepening of the breathing pattern in the upright posture. Hence venous return is aided (Moreno et al., 1967; Moreno and Burchell, 1982).

2.6.B. Dynamic Determinants—Pressure Receptors and Neurohormonal Regulation

These mechanisms are complex, and are not well understood. Only a brief summary of the problems will be addressed.

2.6.B.a. Carotid Sinus and Arterial Mechanoreceptors

Located in the walls of the carotid sinus and the aortic arch, these proprioceptors react to transmural pressures. Afferent fibers ascend to the cardio-inhibitory and vasomotor centers. Efferent traffic through vagus and sympathetic nerves reduces heart rate, contractility, and peripheral vasoconstriction, mainly in the splanchnic region (Paintal, 1973; Johnson et al., 1974; Rowell, 1986).

2.6.B.b. Cardiopulmonary Receptors

Cardiopulmonary receptors are located in the atria, pulmonary artery, and vein, and respond to increased filling pressure and wall tension (Bishop, 1983; Sandler, 1986). These receptors, also called low-pressure receptors, were once thought to play the major role in regulation of blood volume via the so-called Henry-Gauer reflex: Cardiopulmonary receptors would sense thoracic engorgement and

through vagus nerve stimulation inhibit the secretion of the antidiuretic hormone (ADH), resulting in diuresis (Gauer and Henry, 1951, 1963; Gauer et al., 1970; Smith, 1957). Subsequently Gauer and Henry proposed the same control mechanism for salt through inhibition of the renin-angiotensin-aldosterone system via decreases in sympathetic nervous activity (Gauer and Henry, 1976).

During recent years the Henry-Gauer theory has been seriously questioned. While probably still holding true in dogs, the same reflex does not seem to be as sensitive in nonhuman primates or in humans (Goetz, 1988; Gilmore and Zucker, 1978a,b; Greenleaf, 1983; PAPER III).

The interface between cardiopulmonary and arterial receptors is extremely difficult to assess in humans. The functional separation of the two reflexes is complicated by the fact that in any known experimental setting reduction in aortic pulse pressure invariably lowers central venous pressure (CVP) (Rowell, 1986).

By applying less than –20 Torr LBNP (which pools blood in the dependent parts of the body), the opposite experiment can, however, be carried out successfully: reduction in CVP without changing arterial blood pressure (Johnson et al., 1974; Ahmad et al., 1977; Zoller et al., 1972; Baisch et al., 1982). From these studies it is clear that an interaction between low- and high-pressure receptors exists.

At the risk of oversimplifying, the following probably holds true (Rowell, 1986; Bishop et al., 1983; Abboud and Thames, 1983; Abboud et al., 1979; Mark et al., 1983; Mark and Mancia, 1983; Mancia and Mark, 1983): It is a fact that upon assumption of the upright posture in humans CVP falls and aortic pulse pressure narrows: Heart rate (HR) increases owing to less activity in the high-pressure receptors. On the other hand vasoconstriction of the vessels in muscles and skin is mainly caused by excitation of the cardiopulmonary receptors (in humans)—measured as forearm blood flow. Splanchnic vasoconstriction is the result of both high- and low-pressure stimuli—mainly the former. Contractility of the heart muscle increases. There is strong sympathetic discharge and release of norepinephrine.

2.6.B.c. Plasma Renin Activity (PRA)

Orthostatic PRA augmentation has been observed by several investigators (Brown et al., 1966; Cohen et al., 1967; Davies et al., 1976; Gordon et al., 1967; Kimura et al., 1976; Oparil et al., 1970). There is, however, great individual variability (PAPER VII), and the postural increase may be related to the hydration status as rehydration attenuates the responsiveness (Harrison et al., 1986a).

2.6.B.d. Plasma Vasopressin (PVP)

An immediate postural rise in plasma vasopressin may depend on the simultaneous presence of elevated plasma osmolality. Standing per se does not influence osmolality (PAPER IV). Baylis and Heath (1977) found increased orthostatic PVP only when the subjects were dehydrated. Leimbach et al. (1984) reported similar results in subjects during LBNP tests. As compared with our results, these data are indicative of a more sensitive reflex control mechanism of vasopressin during dehydration (PAPER IV). However, the observation that orthostatic PVP did in fact increase during rehydrated HUT, in the absence of overt hypotension, is supportive of cardiopulmonary involvement (Harrison et al., 1986a).

In a recent study at the Stanford University School of Medicine, we applied LBPP to a cardiac transplant recipient and found no change in ADH or PRA responses as compared with healthy volunteers. The degree of innervation in cardiovascular transplants is unknown; however, assuming that innervation has been disrupted or is incomplete, these results are indicative of high-pressure receptor involvement in the regulation of ADH and PRA.

2.6.B.e. Atrial Natriuretic Factor (ANF)

A recently defined hormonal system complicates the control of blood pressure and volume even further. ANF is a peptide secreted from granula located in the myocytes of the atria (Goetz, 1988). The hormone is a powerful vasodilator and increases salt- and water-output by the kidneys (Ballerman and Brenner, 1986). Postural changes are reported, but the significance of ANF regulation during orthostasis is unknown (Hollister et al., 1986; Ogihara et al., 1986; Solomon et al., 1986).

2.6.B.f. Summary of Neurohormonal Regulation During Orthostasis

Orthostatic neurohormonal regulation is mainly aimed at volume preservation (ADH, PRA, Aldosterone) during prolonged upright stress (Gauer and Henry, 1976). However, the dramatic PVP rise in one of our subjects from 8.0 to 250 pg/ml, in a few minutes, indicates an important vasoactive role as well, possibly as a response to orthostatic hypotension or even insufficient brain perfusion (PAPER IV).

Clearly there is an interaction between low- and high-pressure receptors which is poorly understood. Nevertheless these pressure and neurohumoral reflexes play an important role in maintaining homeostasis during erect posture. Furthermore, a full comprehension of their reciprocal action is significant in studying fluid shifts and cardiovascular deconditioning during weightlessness (see section 3.0.).

2.6.B.g. Reflex Venoconstriction

Venoconstriction is controversial, but is probably not a constant counterregulatory factor during erect posture (Gauer and Thron, 1965; Rowell, 1986). Instead the venous volume may be modified by arteriolar vasoconstrictor regulation by diminished "delivery" to the veins (Amberson, 1943; Rowell, 1986).

2.6.C. Local Determinants

2.6.C.a. Precapillary Sphincter Control

As stated earlier PV decreases between 6-18% during assumption of an upright position, depending on individual variability and whether erect posture was achieved actively or passively (muscular activation or laboratory-induced HUT) (Hinghofer-Szalkay, 1982; Hinghofer-Szalkay and Moser, 1986; PAPERS IV and VI). PV loss is a direct consequence of increased transmural pressures in the vessels below HIP (Levick and Michel, 1978). Precapillary sphincter muscles are regulated by local reflex-activity sensitive to hydrostatic pressure gradients during positional changes (Henriksen et al., 1973). Increased precapillary sphincter contraction reduces the pre- to postcapillary pressure gradient by raising the arteriolar resistance (Aukland and Nicolaysen, 1981; Levick and Michel 1978). The orthostatic rise in the outward capillary filtration coefficient is thus disfavored (Hargens, 1981).

2.6.C.b. Shifted Fluid Density and Increased Lymph Flow

The filtrate which is displaced out the microvessels in an upright posture is hyponcotic as compared with that of plasma (Hinghofer-Szalkay and Moser, 1986; PAPER VI). By using a new density detection method Hinghofer-Szalkay and associates have repeatedly shown that some of the blood proteins escape into the interstitial space in the erect position (Hinghofer-Szalkay and Moser, 1986; Hinghofer-Szalkay and Greenleaf, 1987). This filtrate has a protein concentration of 40% of that in plasma (Hinghofer-Szalkay and Moser, 1986). Consequently the colloid osmotic pressure (COP) and in fact the colloid osmotic capacity in plasma (oncotic pressure × PV) increase (Hinghofer-Szalkay et al., 1981). The raised plasma protein concentration augments the counterforce against further outward filtration during prolonged standing (Hinghofer-Szalkay and Moser, 1986). Since the filtrate which is displaced from the blood vessels during upright posture is protein-poor, then extravascular COP must decrease.

Flow in leg-lymphatics is enhanced in erect posture since activation of antigravity muscles, distended veins (pooling), and increased contraction frequency in lymphatic vessels promote lymph return (Olszewski and Engeset, 1980; Olszewski et al., 1977; Olszewski, 1981). Elevated lymph flow and reduced COP in the interstitial space constitute an extremely important "safety" factor against orthostatic edema formation in the skin and subcutaneous tissue (Aukland and Nicolaysen, 1981).

2.7. Quantifications of Some Circulatory Parameters Upon Assumption of an Upright Posture

In the recumbent position in humans, 85% of the total blood volume (4250 ml of 5 liters) resides in the low-pressure system (systemic veins, the right heart, the pulmonary circulation, the left ventricle in diastole). The arterial system holds approximately 15% (~750 ml; 10% (~500 ml) is within the arteries and 5% (~250 ml) is in the capillaries). CBV contains 25% (~1250 ml; 10% (~500 ml) is in the lungs and 15% (~750 ml) is in the heart) (Gauer and Henry, 1963; Gauer and Thron, 1965; Åstrand and Rodahl, 1977; James et al., 1982; Sandler, 1986).

Upon assumption of the upright posture approximately 900 ml of blood rushes to the dependent parts of the body (600-700 ml to leg veins, 200-300 ml to splanchnic regions) (Sjöstrand, 1952, 1953; Rowell, 1986). CBV (heart/lungs) is depleted by some 400-500 ml of blood (Sandler, 1986). CVP falls from 6 to 0 Torr (with the barometric pressure as the reference point) (Liebenschütz et al., 1976; Eckberg, 1980).

When changing body posture from lying to standing mean arterial pressure (MAP) usually falls a few Torr and then may then stay constant or even increase because of peripheral vasoconstriction, which is probably the single most critical determinant in the cardiovascular defense line to maintain adequate brain perfusion during motionless upright position (Mengesha and Bell, 1979; Frey and Kenney, 1979; Hordinsky et al., 1980; Stevens, 1966; Rowell, 1986).

It is noteworthy that in 24-hr-dehydrated subjects MAP had decreased significantly by the third hour of standing (PAPER IV) while the pressure rose ($p < 0.05$) in euhydrated subjects during the same period (PAPER V). Aortic pulse pressure decreases in most studies, reflecting a general rise in diastolic blood pressure (Mengesha and Bell, 1979; Frey and Kenney, 1979; Hordinsky et al., 1980; Stevens, 1966; PAPER IV) and has to the author's knowledge never been reported to increase in erect posture. An immediate HR response to standing is normally not higher than 10~15 beats/min (Ewing et al., 1980). Prolonged standing for 3 hr appears to leave HR further unchanged (PAPERS IV and V). Orthostatic HR

increase of approximately 25% is not sufficient to offset a 40% reduction in stroke volume (SV), and cardiac output (CO) falls by about 20% (Gauer and Thron, 1965). Since MAP remains fairly constant during upright posture, and CO is reduced, it follows that total peripheral resistance (TPR) increases between 20-40% (Sandler, 1986; Gauer and Thron, 1965).

2.8. Venous Collapse in Upright Humans

Simple clinical inspection and palpation reveal collapse of neck veins when a person is tilted from recumbent to the upright posture. According to Gauer and Thron (1965) the point of orthostatic collapse of the venous channels is located approximately 5 cm above the upper half of the right atrium. Consequently transmural pressure in this 5-cm-long portion of the fluid column equals barometric pressure. Negative pressures have been recorded in veins above the collapse point—e.g., jugular veins (Henry et al., 1951; Patterson and Cannon, 1951; Patterson and Warren, 1952).

Undoubtedly the effective hydrostatic column is shorter than the length of the vascular bed and is modified by the total blood volume and capacity of the vascular system, environmental temperature (blood pooling) (Henry and Gauer, 1950), activity of antigravity muscles ("second heart"), and respiration. Venous pressure is only slightly affected by CO and TPR (Gauer and Thron, 1965).

2.9. Regional Blood Flow and Volume Adjustments During Posture Changes

Because of vasoconstriction in the upright posture, regional blood flow to the splanchnic organs (Culbertson et al., 1951); skeletal muscle (Brigden et al., 1950) and skin (Amberson, 1943; Johnson et al., 1974); and the kidneys (Hesse et al., 1978) is reduced as compared to the perfusion in the supine position. Kidney blood flow did not change significantly in seven healthy euhydrated subjects who stood for 3 hr. However, the supine values were not reported (PAPER V). The recording of volume changes in different organs as a consequence of the upright posture in humans is technically difficult. Future use of computer-assisted tomography will probably reveal exact measurements.

2.10. Cerebral Circulation During Upright Posture

Because of the brain's considerable distance above HIP during upright posture, MAP in head regions falls by 20-30 Torr (Henry et al, 1951; Patterson and Cannon, 1951; Patterson and Warren, 1952; Scheinberg and Stead, 1949). The driving pressure remains constant as venous pressure is reduced by about the same figure (Henry et al., 1951; Patterson and Cannon, 1951; Patterson and Warren, 1952). A collapse of the venous vessels inside the skull is prevented either by attachment of their walls to surrounding bone structures (noncollapsible sinuses) or by the paralleled drop in cerebrospinal fluid pressure (Patterson and Warren, 1952; Ranke, 1938; Rushmer et al., 1947; Lassen, 1959).

The brain's autoregulation is extremely important to maintain its perfusion over a wide range of blood pressures. Nevertheless cerebral blood flow falls by about 15-20% during upright posture, which is about half of what would be expected without autoregulation (Rowell, 1986). Loss of consciousness develops when MAP at eye level falls below 25 Torr, which marks a critical minimal cerebral flow of about 30 ml/min/100 g brain tissue (Henry et al., 1951; Finnerty et al., 1954).

2.11. Orthostatic Oliguria and Decreased Natriuresis

Orthostatic oliguria was first described by Edel in 1901 (confer Amberson, 1943). Low output of urine and salt during upright posture has been confirmed by several authors (Gauer and Thron, 1965; Selkurt, 1954; Smith, 1957; Thomas, 1957; Wesson, 1957; PAPER V).

3.0. WEIGHTLESSNESS—CARDIOVASCULAR DECONDITIONING AND ADAPTATION IN HUMANS

"Cardiovascular deconditioning" in space is the result of compensatory alterations which reflect an adaptation process of the circulatory system attuned to the weightless environment (deconditioning—meaning: Cause to lose fitness—Webster's Third New International Dictionary, Enlarged, 1965). The phenomenon is initiated immediately following rocket engine shutoff during orbital insertion, and is probably self-limiting after 5-6 wk in space (Levy and Talbot, 1983).

Manifestations of cardiovascular deconditioning, however, are not readily recognizable until after return to Earth, when the hemodynamic consequences of adaptation in space become inappropriate to cope with the effect of gravity on the surface of the Earth. The complexus of all the signs and symptoms resulting from circulatory alterations in weightlessness comprise the cardiovascular deconditioning syndrome (Blomqvist and Stone, 1983; Gauer et al., 1979; Levy and Talbot, 1983a; Howard, 1981).

3.1. Weightlessness—"Zero Gravity"—"Micro Gravity"

The terms zero gravity (0 G) and micro gravity (μG) are often used synonymously with weightlessness. Zero gravity implies an escape from the gravitational attraction of Earth, which is physically impossible. Micro gravity refers to inertial forces generated by instant thrusts of small rocket engines which continuously adjust the precise attitude of the spacecraft in its orbit.

The acceleration of any body, regardless of its size, falling free in vacuum at sea level under the influence of Earth's gravity is 1 G = 9.8 m/sec^2 and is denoted "acceleration of gravity." According to Newtonian physics a release from the gravitational field of Earth is impossible. Gravity is invariably present at any point above the surface of the Earth. The G is reduced as one moves away from Earth, but never becomes zero. Acceleration of gravity is inversely proportional to the distance from the center of the Earth (Howard, 1965).

An orbital flight of a spacecraft circling the Earth is a counterbalance between the acceleration of gravity, that is, the "G"-value, in that particular orbit, and the centrifugal acceleration generated by the motion of the spacecraft around the Earth. In a typical low Earth orbit at a height of 200 km G = 9.2 m/sec^2, which is 94% of the G-value at sea level (Howard, 1981). When the weight of any object (caused by the acceleration of gravity = gravitational weight) is cancelled out by any other inertial force acting on the object in the opposite direction, it is considered weightless (Howard, 1965).

Since weight is equal to mass times G, and G ≠ 0, then the term "weightless" is physically incorrect. According to Howard (1965) it is, however, the most acceptable expression because it indicates the loss of the subjective sensation of weight. The use of the phrases zero gravity, gravity-free, and micro gravity is widespread, and although the phrases are completely inaccurate, they will probably continue to be used. The term "nullified gravity" is suggested as a more appropriate term as a synonym for weightlessness (Pelligra, 1984).

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3.2. Abolished Hydrostatic Pressure Gradients

Owing to nullified gravity as the spacecraft circles the Earth, all hydrostatic pressure gradients within the body disappear, generating a new pressure equilibrium in the blood vessels. The absence of gravitational stress upon the blood volume, facilitated by tissue elasticity and muscle firmness (tonus) in the lower legs, evokes a cephalad redistribution of blood from the dependent regions into the upper portions of the body (Howard, 1981; Pace, 1977).

3.2.A. Headward Redistribution of Body Fluids

The cranial fluid shifts elicit a complex series of compensatory mechanisms that by nature are adaptative and are attuned to the environment in which the circulation is existing (Blomqvist, 1980; Blomqvist and Stone, 1983; Levy and Talbot, 1983a,b). Anthropometric calculations indicate a decreased leg volume (thigh + calf) of about 1 l within 2-3 hr after entering the weightless states. These measurements suggest a headward migration of interstitial (~1500 ml of water) and intravascular (~500-700 ml of blood) fluid close to 2 l from both legs (Thornton et al., 1977, 1987; Moore and Thornton, 1987; Kirsch and von Ameln, 1981).

3.3 Fluid Loss, Hypovolemia and Negative Water Balance

A weight loss in the range of 1-2 kg within the first few days of flight appears obligatory and correlates favorably with the measured girth decrements of the lower limbs. Such a rapid weight reduction must be comprehended as primarily loss of total body water (Blomqvist and Stone, 1983; Thornton et al., 1977; Nixon et al., 1979; Greenleaf, 1986). A progressive decline of PV seems to reach a plateau in about 3 days after launch and may stabilize at a 12-15% loss (approximately 300-500 ml) irrespective of flight duration (Blomqvist and Stone, 1983; Blomqvist, 1980; Nixon et al., 1979; Thornton et al., 1977; Thornton and Ord, 1977). There is a weightlessness-induced loss of urinary sodium (Leach and Rambaut, 1977).

3.3.A. Diuresis—Natriuresis and the Henry-Gauer Reflex in Space

A prominent hypothesis has focused on the Henry-Gauer reflex: In 1951 Gauer and Henry put forward a theory whereby blood volume is regulated as an independent parameter through stretch receptors in the low-pressure compartments (heart and lung) of the circulation. A sudden shift of body fluid from the legs and splanchnic regions into the thorax would be perceived as excessive fluid present in the body, and, via vagus stimulation, inhibit the antidiuretic hormone. This would lead to increased diuresis and loss of the perceived extra body fluids (Gauer and Henry 1951).

In 1976 Gauer and Henry suggested the same major pathway for salt regulation: Evoked receptors, following expansion of the intrathoracic blood volume, would convey information to the central nervous system (CNS). The CNS would respond and reduce renal activity. Suppressed secretion of renin would result and inhibit release of aldosterone from the adrenal cortex. Urinary salt loss would ensue. Such a proposed system is intriguing: Once adaptation to reduced gravity is completed, a new set-point for secretion of ADH and aldosterone should effectively reestablish a positive water balance. Several recent findings cast doubt on the significance of the Henry-Gauer reflex in humans (Sandler, 1986; Greenleaf, 1984; PAPER III). The Henry-Gauer reflex in weightlessness remains particularly obscure:

1. An early diuresis has not, until this time, been demonstrated in space (Leach and Johnson, 1985).

2. Data from Skylab missions (28, 59, and 84 days' duration) disclosed elevated levels of urinary aldosterone, indicating an increased activity of the renin-angiotensin mechanism, and at the same time a persistent sodium loss lasting throughout the flights (Leach and Rambaut, 1977).

Obviously mechanisms other than, or in addition to, the Henry-Gauer reflex are involved in the fluid and electrolyte metabolism in space.

3.3.A.a. Atrial Natriuretic Factor

A body of evidence tends to support the assumption that central fluid translocation is a stimulus for release of the atrial peptide (Goetz, 1988). Greenleaf recently proposed a role for the atrial peptide in the onset of negative water balance observed in space (Greenleaf, 1986): A transient elevation of CVP following orbital insertion releases atrial natriuretic peptides into the circulation. This results in renal loss of sodium which gradually facilitates a normal excretion of urine. The natriuretic response leads to hyponatremia. Hyponatremia was reported during Skylab, and Spacelab missions (Leach and Rambaut, 1977; Leach, 1979; Leach et al., 1986). Hyposmotic plasma, plus the observation that atrial peptides may be capable of shifting fluid from the intravascular to the interstitial compartments (Huxley et al., 1987; Trippodo et al., 1986), would explain the increased hematocrit recorded by Kirsch et al. (1984) throughout the Spacelab 1 mission. Osmotic pressure at the cell membrane would tend to increase as a consequence of outward filtration of hypotonic plasma, forcing fluid into the intracellular compartment. Cellular overhydration inhibits thirst, and may also explain the facial puffiness, swollen membranes, and the subjective feeling of "head fullness," reported by the astronauts (Thornton, 1987; Oman, 1984).

3.3.A.b. CNS Involvement

In all likelihood the regulation of salt and water is more intricate than is presently understood. A headward migration of fluid after sudden exposure to nullified gravity is comparable to a relative hypervolemia of the CNS. Therefore it is possible that baro-receptors exist in the CNS, and that hormones in the cerebrospinal fluid (CSF) regulate brain hydration primarily, and secondarily regulate peripheral salt and water balance (L. C. Keil, personal communication). Remember that very small variations in the volume of the CSF can generate large pressure changes, simply because the brain and the CSF are restricted by the skull.

3.3.B. Space Motion Sickness (SMS)

Nausea, lack of appetite, and sometimes repeated and vigorous vomits are symptoms and signs of the SMS phenomenon, which continues to impair crew comfort during the several first days of flight at an incident rate of 40-65% (Thornton, 1987; Moore and Thornton, 1987; Vanderploeg, 1986; Davis, 1988).

SMS probably contributes toward the early fluid and electrolyte loss of weightlessness (Yegorov, 1981; Greenleaf, 1986).

3.3.C. Lack of Thirst Sensation

Crewmembers have a tendency to reduce fluid intake before launch (voluntary dehydration) (Leach et al., 1986). Even during periods of negative water balance, the astronauts seem to lack the sensation of thirst and have to force fluid while in orbit (Gibson, 1977). Kravik et al. (PAPER III) reported five out of six subjects, who were moderately thirsty before neck immersion, but lost their conscious desire for water despite a progressive fluid deficit during immersion. There is evidence that reduced intrathoracic blood volume is a stimulus for thirst (Stricker, 1973). Perhaps headwards translocation of fluid during water immersion, as well as in weightlessness, involves cellular overhydration which inhibits thirst and drinking (Greenleaf, 1986).

3.3.D. Imbalance of Fluid Intake and Output

Against all expectations the early negative fluid balance, which has been observed uniformly both during Russian and American spaceflights, may not be a result of an overt water diuresis, but simply a consequence of reduced fluid intake, coupled with a normal excretion of urine. This hypothesis should be tested on future missions.

3.4. Central Hypervolemia and Extravascular Fluid Accumulation

There is discussion whether reduction in blood volume, associated with the cephalad fluid shift during transition to weightlessness, relieves the central circulation from continued engorgement. A persistent fluid overload of the heart and the pulmonary circulation could possibly lead to arterial hypertension and congestive heart failure over a period of months and years (Blomqvist, 1980; Gauer et al., 1979).

Abnormalities observed in the myocardium and coronary vessels of rats exposed to weightlessness for 30 days (Rokhlenko and Mul'Diyarov, 1981), as well as elevated pressure in the jugular veins, and increased left atrial diameter in cosmonauts during 175 days in space (Yegorov, 1981), are indicative of a hyperkinetic state of the circulation.

Norsk et al. (1987) recently documented augmented CVP (2.8 ±1.4 to 6.8 ±0.8 Torr) during transition from +2Gz to nullified gravity in 14 humans exposed to approximately 25 sec of weightlessness throughout the course of a Keplerian flight trajectory. This was done by using a 60-cm catheter positioned in an intrathoracic vein.

CVP increased by 2 Torr in a monkey that achieved orbit. Measurements were made in the vena cava and the right atrium (Biosatellite III in 1969) (Meehan and Rader, 1971). However, Kirsch et al. (1984, 1986) failed to demonstrate any rise in antecubital vein pressure in eight astronauts during two shuttle flights. No decrement in exercise capacity was observed in Skylab astronauts while orbiting the Earth up to 84 days, suggesting that ventricular filling pressure was not excessively augmented in space (Michel et al., 1977).

Changes in interstitial and vascular compliances in nullified gravity combined with variations in transcapillary filtration (deconditioning of precapillary sphincter contraction in space?) and lymphatic drainage, a different postcapillary venous pressure equilibrium, and altered neurohormonal regulation could conceivably lead to mobilization of extravascular fluid from the lower regions of the body and a

huge outward filtration into the tissues of the cervical and cephalic organs. This would explain a persistent rounding of the astronauts' faces and a subjective feeling of "head fullness" without a continuous CVP elevation (Gauer et al., 1979; Blomqvist and Stone, 1983; Kirsch et al., 1986; Greenleaf, 1986; Oman et al., 1984).

3.5. Hypokinesia in Weightlessness

Obviously there is musculoskeletal deactivation in space as the locomotor apparatus is not evoked to the characteristic (terrestrial) physiologic exercise in weightlessness (no compression forces on the long bones—no muscular contractions to overcome the effect of gravity). The importance of reduced muscle tone and "loss of the muscle pump" (see section 2.6.A.a.) in the genesis of weightlessness-induced circulatory dysfunction remains unclear (Levy and Talbot, 1983a). Physical inactivity is not, however, synonymous for cardiovascular deconditioning (Greenleaf, 1984):

1. Introduction of an on-board, well-disciplined, and rigorous physical training regimen is virtually ineffective in preventing decreased postflight exercise performance (reduced stroke volume and cardiac output) (Michel et al., 1977).

2. Half a year of moderately intense physical training did not improve HUT tolerance in five subjects after 6 hr of water immersion deconditioning (PAPER IX).

3. A few days of spaceflight (or even hours of water immersion) produces orthostatic intolerance equivalent to that induced by several weeks of restricted horizontal bed rest (Howard, 1981).

3.6. Return to Earth—"The Cardiovascular Deconditioning Syndrome"—Readaptation

The successful adaptional changes of the cardiovascular system to weightlessness become inappropriate upon return to Earth and exposure to the effect of gravity with the reappearance of hydrostatic columns in the circulatory system (Blomqvist and Stone, 1983).

Cardiovascular deconditioning comprises the hemodynamic changes which occur in space: loss of total body water, PV contraction, hyponatremia, and alterations in neurohormonal reflex mechanisms. Dysfunction of the autonomic nervous system (decrement in vascular tonus), shifts in vascular and tissue compliances, and a new equilibrium of microvessel filtration may add to the deconditioning process and attenuate the circulatory system further in its ability to cope with gravitational stress.

Many mechanisms remain unclear and much essential information is missing. For instance, is there myocardial atrophy in space (Levy and Talbot, 1983a; Sandler, 1986)? Manifestations of a reduced ability of the cardiovascular system to function effectively against gravitational stress following exposure to weightlessness can be characterized as the cardiovascular deconditioning syndrome. The syndrome represents signs and symptoms of a readaptation process to +1G environment on Earth.

3.6.A. Features of The Cardiovascular Deconditioning Syndrome

3.6.A.a. Retranslocation of Body Fluid

Interstitial fluid accumulated in the upper portions of the body in space is retranslocated to the lower parts following return to Earth. Inward transcapillary filtration in the cephalic and thoracic regions are evidenced by diluted blood (decreasing hematocrit) and a surprising elevated CVP (despite reduction in the circulatory blood volume of about 1/2 l) early during recovery (within hours after landing) (Kirsch et al., 1984). In fact two-thirds (~1300 ml) of the reduced leg volume during weightlessness (1000 ml of each lower extremity) is replaced within 1.5 hr after touchdown (Moore and Thornton, 1987). Subsequently CVP is decreasing as PV leaves the vessels in the legs and thighs and filtrates into dependent extravascular fluid compartments (Kirsch, 1986).

3.6.A.b. Assumption of an Upright Posture on Earth After Exposure to Weightlessness

An astronaut who has just returned from space and rises from recumbency to upright posture is likely to experience some degree of circulatory instability for the following reasons:

1. Reversal of extravascular fluid, which has been "stored" in the cephalic/thoracic regions during flight, into dependent body tissues, as just discussed (see section 3.6.A.a.).

2. An obligatory shift of some 900 ml of blood from the upper portions of the body to the lower extremities and splanchnic region takes place within seconds (see section 2.7.).

3. Conflicting results concerning compliance have been reported (Pourcelot et al., 1986). Presumably augmented vessel capacitance in the legs and abdomen (increased compliance in the lower body vessels—see section 2.6.A.b.) combines with the weightlessness-induced blood volume deficit (~500 ml), leading to enlarged blood pooling in the dependent veins and a state of functional hypovolemia. This fosters a more severe cardiovascular dysfunction (decreased venous return—reduced cardiac filling pressure, SV, and CO) than would otherwise be expected from the degree of reduction in the total circulating blood volume (500 ml).

4. Weakened or altered adjustments to hydrostatic effects of the erect posture may involve several of the homeostatic defense mechanisms that under normal circumstances ensure adequate brain perfusion (see section 2.6.).

For instance precapillary muscles, which ordinarily are sensitive to hydrostatic pressures, may lose some myogenic tonus leading to increased pre- to post-capillary pressure gradients which would favor outward capillary filtration and swelling in the dependent regions of the body (Hargens, 1981; section 2.6.C.a.). Attenuated responses of baroreflex control of the heart to postural changes upon return to Earth may be involved (Harrison, 1986c) as well as changed activity of the autonomic nervous system (Blomqvist and Stone, 1983).

3.6.A.c. Orthostatic Intolerance and Reduced Exercise Capacity

The astronauts' orthostatic tolerance is significantly reduced during passive standing and HUT. The tendency towards syncope during LBNP (–50 Torr) is increased. Tachycardia is invariably present and is appropriate in the face of reduced SV. Blood pressure responses are labile and pulse pressure narrows (Levy and Talbot, 1983a,b; Johnson et al., 1977). Stroke volume and CO during submaximal exercise tests after Skylab missions were reduced by 50 and 30%, respectively, as compared with preflight data (Gauer et al., 1979).

3.6.A.d. +Gz Deceleration Forces During Reentry

In a manned space capsule (earlier Vostok, Mercury, Voskhod, and Apollo, and the present Russian Soyus), the astronauts are typically positioned in such a way that the accelerating forces during reentry are directed from back-to-chest (forward acceleration = +Gx acceleration), with the result that the inertial force points toward the spine (section 2.1.). Cardiac output is not impaired during +Gx acceleration within the physiological range (Blomqvist and Stone, 1983).

With the advent of the American Space Shuttle in 1981, the accelerative forces acting on the astronauts through the landing phase changed from the +Gx to the +Gz direction. Shuttle reentry is similar to flying a glider along a steep landing path, and its occupants are seated like passengers in a commercial airliner. A headward +Gz acceleration vector pools blood in the lower portions of the body, draining blood away from central tissues. Of low intensity (+1.2 to +1.5 Gz) but of long duration (20 min), shuttle reentry poses a medical problem of some concern (Bungo et al., 1985). The two pilots must perform vital operational tasks during a period (35 min from entry interface to touchdown) when the deconditioning process, resulting from exposure to weightlessness, is unmasked. During this period the symptoms and signs of the cardiovascular deconditioning syndrome suddenly become manifest. For instance the heart rate is commonly increased, and the arterial blood pressure is lower than the duration and intensity of the deceleration forces during the landing phase would suggest (Howard, 1981).

3.6.A.e. Postflight—Thirst Sensation, Urine Volume, and Urinary ADH Output

Astronaut Gibson wrote after 84 days in space aboard Skylab 4: "We all felt very thirsty on the recovery ship despite the fact that we had really forced the fluids before we returned" (Gibson, 1977). Water ingestion is generally increased for several days postflight, while urine and salt excretion are depressed in accordance with a dehydrated state after periods of weightlessness (Leach et al., 1986).

These findings, however, are not consistent with a simultaneous low postflight output of urinary ADH. Maybe stimulation of oropharyngeal and gastric receptors, following substantial water intake for many days after landing, can help reconcile this apparent paradoxical phenomenon. We have recently reported that, in dehydrated humans, a rapid fall in PVP occurs after drinking, independent of plasma osmolality and plasma volume (PAPER VIII). Probably other factors are involved as well.

3.6.B. Measures to Prevent Cardiovascular Adaptation to Weightlessness, and to Improve Readaptation to Gravitational Stress

Because astronauts will return to Earth after exposure to weightlessness, a complete adaptation to this environment is not desirable. Various methods are currently under investigation, and some countermeasures are already utilized in an attempt to stabilize the cardiovascular system in a less deconditioned state, and thus minimizing cardiovascular incapacity during and following reentry (Levy and Talbot, 1983a).

3.6.B.a. Physical Condition Before Flight

Whether or not high levels of endurance physical training is an asset to manned spaceflights is presently a subject of debate (preflight countermeasure) (Pelligra, 1988; Greenleaf, in press). In fact athletes may be less tolerant to orthostatic stress than nonathletes (Klein et al., 1969a,b; 1977). In a recent study five untrained men underwent half a year of a moderately intensive exercise program. HUT tolerance following 6 hr of water immersion deconditioning did not change after the training period. Considerations regarding orthostatic tolerance in athletes versus nonathletes should include a possible genetic involvement as a cause of differences in the two groups rather than training per se only (PAPER IX).

3.6.B.b. In-flight Countermeasures

In-flight countermeasures include exercise prescription and intermittent downward displacement of venous blood by applying subatmospheric pressure below the iliac crests (lower body negative pressure—LBNP). Vigorous in-flight exercise does not prevent orthostatic intolerance after exposure to weightlessness (Garshnek, 1988). Compiled data from several flights indicate that in-flight physical training improved the time course for return to preflight exercise capacity during recovery (Johnson et al, 1977; Nicogossian, 1985). An in-flight exercise regimen is probably important for in-flight physical condition when extravehicular activity (EVA) becomes routine on future space missions (Greenleaf, personal communication). The Soviets currently emphasize the use of intermittent LBNP to generate gravitational loads (+Gz) on the cardiovascular system during the last 2-3 weeks of flight (Yegorov, 1981; Garshnek, 1988). Exposure to –40 to –50-Torr LBNP results in heart-rate and blood pressure responses similar to those occurring at 70° HUT and quiet standing (Wolthuis et al., 1974). Continued orthostatic stress on the cardiovascular system is, according to Gauer, extremely important for maintenance of adequate blood volume (Gauer and Thron, 1965; Meneely et al., 1947; Taylor et al., 1945). Hypovolemia, induced by the weightless condition, may be countered by in-flight application of LBNP, and thus prove to be an important in-flight countermeasure.

3.6.B.c. Prior-to-Reentry Countermeasure

Countermeasures prior to landing presently consist of oral saline rehydration ingested as salt tablets and water. The purpose of this procedure is to increase tonicity and expand blood volume (Bungo et al., 1985; Garshnek, 1988).

3.6.B.d. Reentry Countermeasure

The most effective reentry countermeasure is application of the antigravity suit, which, by providing LBPP, improves cerebral perfusion as the decelerative force increases during atmospheric descent, and causes excessive pooling of blood in the peripheral veins along the head-to-toe axis (Sandler, 1986; Howard, 1981; see section 3.6.A.d.).

3.6.B.e. Postflight Countermeasures

Reports indicate that Russian cosmonauts utilize the antigravity suit following long-duration space flights. The garment may assist deconditioned antigravity muscles by providing mechanical support during locomotion. At the same time the suit is reducing the tendency towards orthostatic hypotension (Yegorov, 1981; PAPERS II, IV, V, and VI). In addition Soviet researchers attach importance to post-flight countermeasures such as exercise, physical therapy, psychological support, and good nutrition to help regain preflight functional performance as soon as possible (Garshnek, 1988).

3.6.C. Time Course of Readaptation

There is great intersubject variability regarding the extent of cardiovascular deconditioning in space, and the time course of recovery upon return to Earth. A formula to estimate the degree of cardiovascular deconditioning has been adopted by the National Aeronautics and Space Administration in the U.S.: The Cardiovascular Index of Deconditioning (CID) (Bungo and Johnson, 1983; Bungo et al., 1985).

$$CID = \Delta HR + \Delta DSP - \Delta SBP$$

ΔHR = difference in standing heart rate pre- and postflight.

ΔDBP (diastolic blood pressure) = difference in standing diastolic blood pressure pre- and postflight.

ΔSBP (systolic blood pressure) = difference in standing systolic blood pressure pre- and postflight.

A high CID index upon return to Earth is an indication that a more profound cardiovascular deconditioning process has occurred in that particular astronaut as compared to a crewmember with a low CID value (Bungo and Johnson, 1983; Bungo et al., 1985). Following a long-duration flight (months), most astronauts experience vertigo and fatigue in the upright posture, and need assistance when walking during the first couple of days (Gazenko and Egorov, 1988; Garshnek, 1988). The time course for complete recovery to preflight baseline varies with subject and organ system, and may require anywhere between a few days to at least 45 days (Yegorov, 1981; Garshnek, 1988). The present comprehension indicates that cardiovascular dysfunction, resulting from long term exposure to weightlessness, is reversible upon return to Earth (Gazenko and Egorov, 1988; Garshnek, 1988).

4.0. TERRESTRIAL MODELS TO SIMULATE CARDIOVASCULAR EFFECTS OF WEIGHTLESSNESS

One of the most important premises for an understanding and resolution of the physiological problems related to the human ability to live and work in space is the development of ground-based research and simulation methods to complement investigations conducted in weightlessness (Robbins et al., 1988).

4.1. Cancelling of the Effect of the Earth's Gravitational Pull During a Keplerian Flight Trajectory

It is not possible to create true weightlessness on Earth because the effect of gravity is invariably present. One exception is to fly a parabolic or Keplerian flight trajectory whereby real weightlessness can be induced, but only for periods of less than 1 min (Blomqvist and Stone, 1983). The brief duration of this maneuver makes the useful time to conduct experiments extremely limited. However, this method has the advantage over actual spaceflights by an instant transition from +Gz to a weightless state. Body position before and during launch may interfere with early responses following orbital insertion (Norsk et al., 1987; Charles, personal communication).

4.2. Ground-Based Simulation Methods

Important insight into the reaction of the human body to nullified gravity can be obtained by utilizing Earth-based simulation models. There are currently two accepted concepts available to simulate particular stimuli which evoke physiological responses in the human body similar to those observed during weightlessness:

1. Absolute bed rest (BR)

2. Water immersion (WI)

4.2.A. Why Carry Out Ground-Based Research?

It must be strongly emphasized that neither BR nor WI can duplicate weightlessness. The weightless environment is inherent to space. No terrestrial equivalent to space exists. BR and WI are powerful "analogs of weightlessness" because those models simulate the effect on the body of certain physiological stimuli induced by the weightless habitat (Levy and Talbot, 1983a; Harrison et al., 1987).

For instance Earth-based models provide significant knowledge about cardiovascular deconditioning in space and how the human body adapts to the new environment (see section 3.0.). Terrestrial research enhances our understanding of the recovery process, and aids in the ongoing development of countermeasures to ensure adequate readaptation to gravitational stress following exposure to weightlessness.

Moreover BR and WI studies are important because the opportunities to carry out research in space are presently inadequate, and flight experiments are immensely costly. Also, technical constraints due to safety and other reasons before and during a mission make it difficult to obtain and interpret flight data, which often are nonconsistent and not easily reproducible. To improve the validity of flight data, future

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research planners should take into consideration measures to shield some of the crewmembers from performing important technical tasks early during the mission.

4.2.B. Characterization of the BR and the WI Models

It lies outside the scope of this thesis to characterize in detail the differences between and specific features of BR, WI, and the weightless state. This topic has been compiled in excellent reviews by several authors: Gauer and Henry (1976), Epstein (1978), Leach (1979, 1981), Blomqvist and Stone (1983), Greenleaf (1984), Sandler and Vernikos (1986), and Norsk and Epstein (1988).

4.2.B.a. Common Features of Ground-Based Models

A neutralized or decreased hydrostatic pressure in the lower portions of the body is the basis for using WI and BR as Earth-based simulation models to study cardiovascular, endocrine, and fluid and electrolyte effects of weightlessness. A new pressure equilibrium is generated within the circulatory system which results in the redistribution of blood. There is a reduction in the blood volume of the gravitationally dependent veins of the body, and central blood volume is increased. The headward translocation of fluid is the common feature of real weightlessness and various simulation techniques on the ground.

4.3. BR and Head Down Tilt (HDT)

Absolute BR studies go back more than 60 yr to a time when such regimens were used to evaluate clinical effects of immobilization (Sandler and Vernikos, 1986; Campbell and Webster, 1921; Cuthbertson, 1929; Harrison, 1944; Asher, 1947).

4.3.A. Horizontal BR as a Simulation Model of Weightlessness

With the advent of manned spaceflight, horizontal BR was quickly adopted as a simulation model of weightlessness. It became the most widely used technique to study physiological reactions to nullified gravity including cardiovascular effects as well as skeletal muscle atrophy and bone demineralization (Graveline and McCally, 1962; Chase et al., 1966; Greenleaf et al., 1977).

PV contraction during BR and weightlessness appears to be very similar and averages 10-15% (Blomqvist and Stone, 1983). However, a PV loss of up to 30% has been reported following 175 days in bed (Greenleaf, 1984). Circulatory, electrolyte and hormonal changes during BR are much slower in onset, and are of lower magnitude, sometimes only marginal, as compared to measurements conducted in space (Melada et al., 1975; Leach et al., 1973).

4.3.B. HDT as a Simulation Model of Weightlessness

In addition to SMS one of the earliest and most striking symptoms following entry into space is what the astronauts describe as a "feeling of head-fullness," or "just like hanging upside down" (Oman et al., 1984). Engorgement of neck veins and facial puffiness persisted throughout all the three Skylab missions (Thornton et al., 1977).

First adapted by the Russians, the antiorthostatic position, or HDT, has recently been introduced to mimic the same effects on Earth (Genin and Kakurin, 1972; Kakurin et al., 1976; Nixon et al., 1979). Four to 6 degrees HDT appears to reproduce to a greater extent the deconditioning effect of weightlessness than does horizontal BR. Cardioregulatory as well as endocrine and fluid and electrolyte changes occur more rapidly and are of greater magnitude (Dallman et al., 1984). Studies indicate that orthostatic intolerance following HDT is more pronounced than after horizontal BR (Genin and Kakurin, 1972; Kakurin et al., 1976).

4.4. Water Immersion

WI in thermoneutral water (34.5°C) has been utilized as a means of simulating weightlessness since the early 1960s (Beckman et al., 1961; Graveline and Jackson, 1962; Gauer, 1970; Gauer and Henry, 1963; Epstein, 1978).

4.4.A. Water Immersion—an Antagonist of Gravity

WI may be considered an antagonist of gravity on Earth (Gauer and Thron, 1965). Immersion to the level of the diaphragm elicits some of the same cardiovascular responses as those observed during recumbency, and is the "perfect" antagonist of orthostasis on Earth (Gauer and Thron, 1965). The blood in the vessels and the external water media exert identical hydrostatic pressure at any point along the vascular columns below the diaphragm, and effectively abolish hydrostatic pressure gradients in this region.

Increased water pressure during head out immersion (HOI) forces more blood into the central circulation (Löllgen et al., 1981). Therefore neck immersion (NI) is used as a tool to induce cardioregulatory and hormonal effects akin to changes triggered by exposure to weightlessness. However, NI cannot cancel out the effect of gravity completely, the reason being that the water media is unable to provide hydrostatic indifference in the thoracic vasculature (causing a negative pressure breathing effect) (Howard, 1981). Furthermore the gravitational traction exerted by internal organs on their vascular pedicles still persists.

4.4.B. Water Immersion—Stimulus Strength and Response Time

NI evokes much stronger and more rapid physiological responses within the cardiovascular, hormonal, and renal system than does BR or HDT (Greenleaf, 1984).

4.4.C. Water Immersion—Central Blood Volume, Central Venous Pressure, and Cardiac Output

CBV is augmented by some 700 ml (Arborelius et al., 1972) within 6 sec (Risch et al., 1978). CVP (right atrial filling pressure) is elevated by 12-18 Torr (Echt et al., 1974b; Aborelius et al., 1972). Stroke volume and CO increase by 35 and 32%, respectively (Arborelius et al., 1972; Lange et al., 1974; Gauer and Henry, 1976).

4.4.C.a. Sustained Cardiovascular Responses During WI

Unlike HDT the cardioregulatory responses during WI appear to persist as the intervention continues (Blomqvist and Stone, 1983).

4.4.D. Water Immersion—PV Contraction, Diuresis, and Natriuresis

4.4.D.a. PV Changes During WI

Following an initial increase of PV by 8-11%, which is caused by external hydrostatic counterpressure (von Diringshofen, 1948), there is a progressive decline beginning between 30 and 60 min of immersion (Greenleaf, 1984; Harrison et al., 1986d; PAPER III). PV contraction is averaging 10% at 8 hr of WI, but there is considerable variability (Greenleaf et al., 1980; PAPER III).

4.4.D.b. Urine Output and Sodium Excretion During WI

Immersion results in an acute and copious diuresis, which is usually manifest by hour 1, and often peaks between hours 3 and 4. The natriuretic response during immersion is somewhat different from that of the diuresis. Natriuresis remains elevated throughout WI, but is frequently delayed by 1-2 hr. Therefore, separate mechanisms may be responsible for the diuretic and natriuretic responses during immersion (Epstein et al., 1972, 1973, 1980; Epstein, 1978; PAPER III).

4.4.D.c. Voluntary Inhibition of Fluid Intake During WI

Kravik et al. (1984 (PAPER III)) reported that despite a sustained and significant fluid and electrolyte loss throughout 6 hr of HOI, all the subjects refused to drink while they were immersed. Water was available in sight of the subjects. In general, thirst sensation reappeared within 5 min after immersion ended.

4.4.E. The Antidiuretic Hormone and the Henry-Gauer Reflex During WI

A predominant hypothesis forwarded by Gauer et al. (1951) has been considered the main explanation for increased urine flow in humans during central hypervolemia. Left atrial mechanoreceptors have been suggested to sense the thoracic engorgement during immersion and via vagus nerve stimulation initiate the diuretic response through inhibition of ADH (Gauer and Thron, 1965; Gauer et al., 1970; Gauer and Henry, 1976; Epstein, 1978; see sections 2.6.B.b.; 3.3.A.). Within the last 10 yr, evidence has been obtained by several laboratories which cast doubt on the significance of this model as the only and major determinant for the control of blood volume and urine flow during WI (Norsk and Epstein, 1988; Greenleaf, 1984; PAPER III).

Several questions presently remain unanswered for a complete understanding of the mechanisms responsible for the immersion diuresis: Is ADH suppressed during WI? If the answer to this question is yes, which mechanisms, other than the Henry-Gauer reflex, could explain the reduced secretion of vasopressin? If the answer is no, which physiological factors could conceivably be involved in the immersion diuresis?

4.4.E.a. Is ADH Suppressed During WI?

Kravik et al. (1984 (PAPER III)) reported that PVP was not suppressed during 6 hr of WI. On the contrary, PV had increased significantly by hour 1 and remained elevated for the remainder of the experiment.

Harrison et al. (1986d) observed a decline in PVP only when the subjects were dehydrated. After rehydration vasopressin secretion was unaffected by immersion.

Norsk and Epstein (1988) recently reviewed PVP values obtained from 17 different immersion studies. They found that PVP was consistently suppressed only when the subjects were dehydrated and had not consumed water prior to or during immersion.

We have recently investigated the immediate effect of ingestion of water on plasma vasopressin. We found that vasopressin in plasma fell abruptly from 3.3 to 2.4 pg/ml within 3 min after drinking and further to 1.8 pg/ml 6 min later. The changes in PVP did not coincide with alterations in serum osmolality or in plasma volume (PAPER VIII). Our results have been confirmed by Davison et al. (1988).

The observation suggests that oropharygeal factors (receptors), alone or in combination with gastric stimuli, are implicated in the regulation of vasopressin secretion. Accordingly, even small amounts of water ingested prior to immersion may reduce PVP, and mask any further decline during immersion. In fact, the increase in PVP, which we observed in our subjects throughout NI, could conceivably be attributed to an early suppression of the hormone after drinking of 300 ml of water 2.5 hr before the experiment started. The strength of PVP inhibition caused by water ingestion is necessarily time-dependent. A weakened stimulus would tend to level off a later PVP suppression induced by immersion. Furthermore, suppression of PVP below 1 pg/ml introduces an increased possibility that measured vasopressin values are encompassed in random experimental errors.

Lack of experimental standardization between laboratories, especially the hydration levels, defining baseline, but also during the test condition, may explain some of the discrepancies in measurements of ADH reported during WI.

4.4.E.b. Mechanisms Other Than the Henry-Gauer Reflex Responsible for the Observed ADH Suppression During WI

Whereas PVP appears to be very responsive to stimulation of low-pressure receptors in dogs, the same reflex may not be as sensitive in primates, including humans. Gilmore and Zucker (1978b) distended the left atrium in anesthetized monkeys with a balloon, but failed to demonstrate a diuresis or natriuresis. However, another group of monkeys responded to WI with elevated CVP and continuous urine flow similar to that in humans (Gilmore and Zucker, 1978a). Arnauld and co-workers (1977) found in conscious monkeys that a blood volume reduction of 20% did not increase PVP until a fall in arterial blood pressure occurred. Results from recent immersion studies by Norsk et al. (1985, 1986a, 1986b) indicate that receptors in the carotid sinus and aortic arch are stimulated, and may contribute significantly in mediating a PVP response during immersion (high-pressure receptor theory).

Assuming that atrial innervation in cardiac transplant patients has been disrupted, or is incomplete, the following studies are pertinent to elucidate the role of the Henry-Gauer reflex in humans: Drieu et al. (1986) found a significant difference in PVP response between heart transplant patients and normal subjects exposed to HUT stress. Plasma vasopressin rose in the normal group, but remained unaltered in the transplant patients indicating that left atrial receptors played a major role in the ADH response to PVC contraction. However, in another experiment PVP suppression in the two groups did not differ when they were subjected to HDT (Convertino et al., 1984). In a recent study Myers et al. (1988) reported a significant diuresis and natriuresis in cardiac transplant recipients undergoing WI.

We are in the process of studying heart transplant patients during exposure to LBPP. Preliminary results suggest no difference in the ADH response between the two groups.

4.4.E.c. Factors Other than Reduced ADH Which May Explain Immersion Diuresis

An atrial natriuretic peptide (ANP) has received much attention during the last few years (Goetz, 1988) (see sections 2.6.B.e.; 3.3.A.a.).

Central hypervolemia during WI probably induces release of the atrial peptide from granula located in the cardiocytes of both atria. Accumulating evidence indicates that ANP may play a substantial role in both the diuretic and natriuretic response during immersion (Greenleaf, 1984; Ogihara, 1986; Pendergast, 1987; Anderson, 1986; Epstein, 1987; Lee et al., 1987; Kurosawa et al., 1988). In addition to accelerating urinary excretion of sodium, the peptide may modulate urine output by inhibiting ADH and thereby increase the free water clearance (Dillingham and Anderson, 1986).

5.0. LOWER BODY POSITIVE PRESSURE APPLIED BY THE ANTIGRAVITY SUIT: CLINICAL USE, EFFECTS ON +Gz ACCELERATION, AN INVESTIGATIVE TOOL TO STUDY PHYSIOLOGICAL MECHANISMS, AND A NOVEL SIMULATION MODEL OF WEIGHTLESSNESS

5.1. Brief History of Positive Pressure Applied to the Lower Body

In 1733 Stephen Hales observed in an experimental setting that pressing the bellies of dogs with a hand would immediately increase the height of the blood column in a tube connected to an artery of the dog. Roy and Adami (1888) reported that compression of the abdomen in dogs increased the quantity of blood "thrown" out by the heart by about 30%. The use of an abdominal belt to compensate for the effect of gravity and thereby elevate the venous return of blood to the heart was suggested by L. Hill in 1895.

The antigravity suit was invented by the American neurosurgeon George W. Crile (1903, 1909) who, in 1903, described the use of an "inflatable rubber suit" to counteract the force of Earth's gravity to maintain adequate blood pressure during neck surgery in the reclined position. Crile's pneumatic rubber suit was later modified several times. Wood et al. (1946) perfected the inflatable aviator's "antiblackout suit" in the 1940s as a means of reducing the effects on pilots of +Gz acceleration which occurs in sharp turns or when pulling out of dives at high speed.

LBPP has been utilized to control intractable abdominal hemorrhage and circulatory shock, and in the treatment of orthostatic hypotension (Pelligra and Sandberg, 1979; PAPER I).

An antigravity suit, the military antishock trouser (MAST), has been commercially available since 1973 and is now a widely used lifesaving device in the prehospital and hospital setting (Frumkin, 1985). The MAST was invented by B. H. Kaplan, and was used successfully during the Vietnam Conflict (Cutler and Daggett, 1971; Kaplan et al., 1973). (The term MAST has been claimed as a trade name by one manufacturer.) In 1972 the American College of Surgeons chose Pneumatic Antishock Garment (PASG) as a name which better describes the suit's action. The terms circumferential pneumatic pressure (Gardner and Storer, 1966) or circumferential pneumatic counterpressure (CPC) (Pelligra and Sandberg, 1979) are interchangeable with antigravity suit pressure, anti-G-suit pressure, G-suit pressure, or LBPP.

5.2. Techniques in LBPP

5.2.A. Positive and Negative Pressure

In accordance with physical laws, pressure is always positive, and the terms hyperbaric and hypobaric are more accurate nomenclature than positive and negative pressure. Hyperbaric and hypobaric pressure refers the actual pressure to the environmental atmospheric pressure, and the barometric pressure serves as the reference point. However, the handy use of the acronyms LBPP for hyperbaric (positive) pressure and LBNP for hypobaric (negative) pressure is deep-rooted and prevailing and their usage will remain.

5.2.B. The Antigravity Suit

LBPP is often applied by an antigravity suit. The antigravity suit consists of a trouser which contains one or several inflatable rubber bladders enclosing each leg, thigh, and abdomen from the foot to the costal margin. The bladders are usually pressurized with air.

Instead of inflating the antigravity suit with gas, another design permits filling the trouser with water, which provides hydrostatic pressure to the body surface, decreasing from the ankle and reaching zero Torr at the upper edge of the suit (Howard, 1965; Egan et al., 1983).

5.2.C. Pressurized Air Chamber

Alternately LBPP may be applied by enclosing the lower body in a pressurized air chamber sealed around the subject at the inferior rib cage margin (Kass and Moore-Ede, 1982; Bennett, 1982; Echt et al., 1974a).

5.3. Application of the Antigravity Suit

The present range of uses of the antigravity suit falls within two general categories: (1) clinical application and (2) use in aviation medicine.

5.3.A. Use of the Antigravity Suit in Clinical Application

Current therapeutic uses of the antigravity suit demonstrate three characteristic effects:

1. To reduce and arrest abdominal and gynecological/obstetrical bleeding from venous as well as arterial sites. Specific applications include the control of

    a. Retroperitoneal bleeding (Brooks and Grenvik, 1973)

    b. Pelvic fracture hemorrhage (Flint et al., 1979)

    c. Postoperative intraabdominal bleeding (Burdick et al., 1975)

    d. Ruptured abdominal aneurysm (Burn et al., 1972)

    e. Pediatric application (Brunette et al., 1987)

    f. Uncontrollable urologic bleeding (Ryan et al., 1986)

    g. Uncontrollable gynecological/obstetrical bleeding (Sandberg and Pelligra, 1983)

2. To increase CO and MAP to counteract circulatory shock in the prehospital setting. Specific applications include

    a. Prehospital critical hypotension following massive war injuries (Cutler and Daggett, 1971)

b. Prehospital civilian use (Kaplan et al., 1973)

3. To improve cerebral perfusion during states of orthostatic hypotension (+1 Gz environment). Specific applications include

a. Bilateral sympathectomy and diabetes (Sieker et al., 1956)

b. Bilateral percutaneous cordotomy (Fox, 1971)

c. Traumatic quadriplegia and paraplegia (Vallbona et al., 1963)

d. Neurosurgery in the sitting position (Crile, 1903; Freuchen, 1959)

e. Inoperable brain tumor (Burton, 1975)

f. Shy-Dräger syndrome(PAPER II)

5.3.B. Use of the Antigravity Suit in Aviation Medicine

LBPP has been used as a means of reducing the effects of +Gz acceleration on pilots since the early years of World War II (see section 5.4.E.).

5.4. Mode of Action of the Antigravity Suit

A number of mechanisms are responsible for the different effects of LBPP. The mode of action of the antigravity suit is complex and confounded by factors such as (1) degree of hydration and volemia of the subjects as well as body position relative to the force of gravity (PAPERS IV and V); (2) suit pressure (Pelligra and Sandberg, 1979); (3) sequential filling pattern (Begin et al., 1976); and (4) increased gravitational-inertial force environment (+Gz acceleration) (Howard, 1981).

5.4.A. Control of Bleeding by the Antigravity Suit

Numerous animal studies have confirmed clinical experience that LBPP is extremely efficacious in controlling severe bleeding in areas encompassed by an inflated antigravity suit. The mechanisms by which LBPP arrests hemorrhage, including repair of major abdominal arteries, are not well understood. The fact that both clinical and experimental results clearly document a hemostatic effect also when intravascular pressure exceeds suit pressure is puzzling. Most of the underlying work for an understanding of how CPC affects the bleeding site was reported in the 1960s (Gardner and Storer, 1966; Gardner, 1969; Ferrario et al., 1970; Wangensteen et al., 1968a,b,c; Ludewig and Wangensteen, 1969a,b; Eddy et al., 1968).

Based on in vivo experiments, Gardner and Storer (1966) hypothesized that external counterpressure reduces wall tension by decreasing transmural pressure and vessel radius and thereby renders smaller the defect in the wall of the artery or vein (Laplace's Law: $T = P \times R$, where T = wall tension, P = transmural pressure, R = vessel radius). Wangensteen et al. (1968a) demonstrated in dogs that femoral blood flow was reduced by an average of 33% when an external counterpressure of 40 Torr was applied. The

combined consequence of reduced wall tension and flow may have a favorable influence on the clotting process and the prevention of further blood loss beneath the suit (Pelligra and Sandberg, 1979; Wangensteen, 1968a,b,c; PAPER I).

5.4.A.a. Hemostatic Effect Related to the Magnitude of LBPP

A substantial body of evidence indicates that LBPP in the range of 10-30 Torr represents optimal pressure to bring about a desired hemostatic effect (Gardner and Storer, 1966; Gardner, 1969; Ferrario et al., 1970; Cutler and Daggett, 1971; Pelligra, 1970; Pelligra and Sandberg, 1979; Sandberg and Pelligra, 1983; Burdick et al., 1975; Batalden et al., 1974; Brooks and Grenvik, 1973; Åberg et al., 1986). Higher suit pressure may precipitate development of a lower extremity compartment syndrome if application is prolonged in the supine position (1 Gx environment) (Chisholm and Clark, 1984; Hargens et al., 1984; see section 5.4.B.c.).

LBPP varying between 8 and 33 Torr (33 Torr for the first 2 hr, 26 Torr for the next 18 hr, and varying between 8 and 15 Torr for the remaining 76 hr) throughout 96 hr of continuous use was recently reported with excellent results and without detrimental effects in a 3-yr-old child initially admitted in shock after being hit by a school bus (Brunette et al., 1987).

5.4.B. The Antigravity Suit—Headward Redistribution of Body Fluid, Cardiac Output, and Blood Pressure

There is universal consensus among researchers and clinicians that LBPP increases MAP. However, whether the augmented MAP is the result of elevated CO or TPR, or a combination of the two, remains a subject of different opinions (Ransom and McSwain, 1984; Niemann et al., 1983).

Based on our own studies, clinical experience, and review of current literature, this research team is firmly convinced that pneumatic LBPP translocates fluid to the upper regions of the body, provided the stimulus is applied correctly, and the results are interpreted according to variables such as (1) degree of volemia (Bellamy et al., 1984); (2) body position (Seaworth et al., 1985; Mannering et al., 1986; PAPERS IV, V); (3) whether or not the suit has been inflated sequentially from below (Jennings et al. 1986; Begin et al., 1976); and suit pressure (see section 5.4.C.).

We feel confident that LBPP is capable of inducing a sustained hyperkinetic state with increased CVP and CO. The following authors have concluded that a headward redistribution of blood is a result of exposure to LBPP: Kass and Moore-Ede, 1982; Echt et al., 1974a; Bellamy et al., 1984; Wilkins et al., 1986; Sanchez et al., 1987; Mannering et al., 1986; Ransom and McSwain, 1984; Streeten et al., 1985; Bennett et al., 1982; Jabbour et al., 1986; Mittal et al., 1982; Seaworth et al., 1985; Segel et al., 1973; Sackner and Dougherty, 1973; Nagano et al., 1987; Roth and Rutherford, 1971; Weissler et al., 1957b; Begin et al., 1976; Goldsmith et al., 1984; and PAPERS IV, V, and VI.

In an ongoing study, using Doppler cardiography, we have measured CO in five standing, dehydrated subjects before, during, and following exposure to LBPP (60 Torr in the leg bladders, 30 Torr in the abdominal bladders). CO increased significantly during garment inflation—from 4.2 l/min before inflation to 5.8 l/min during external counterpressure. CO fell immediately upon deflation of the antigravity suit to a mean value of 4.4 l/min. The 38% (1.6 l/min) increase in CO during LBPP is close to a 32% rise

in CO during WI (Gauer and Thron, 1965). Heart rate decreased significantly during inflation, and the increase in CO was therefore due entirely to augmented stroke volume which was obviously a consequence of increased preload (Kravik et al., unpublished data).

The peripheral resistance in the vascular territory beneath the suit is augmented because the driving blood pressure increases and vessel lumen, and thereby flow, decreases (Wangensteen et al., 1968a). However, the total peripheral resistance may increase, remain unchanged, or actually decrease, depending on alterations in CO and whether resistance vessels not encompassed by the suit are dilated as a result of shifted blood from the capacitance veins of the legs and splanchnic regions to the upper body (Ferrario et al., 1970; Mannering et al., 1986; Niemann et al., 1983; Gaffney et al., 1981).

5.4.B.a. Hemodynamic Effects of LBPP Applied During Hypovolemia and Circulatory Shock

Ransom and McSwain (1984) found in hypovolemic and hypotensive bled dogs that 30% of the total blood volume was shifted to the central circulation when the dogs were exposed to LBPP of 60 Torr. Bellamy et al. (1984) showed no change in central hemodynamics when normovolemic anesthetized swine were exposed to LBPP which increased CO (41%), coronary perfusion (50%), and cerebral blood flow (33%) only after hemorrhage.

Presumably LBPP brings about changes in central hemodynamics during a state of hypovolemia while there is almost no net cephalad shift of blood in a normovolemic subject in the supine position. This is in agreement with the fact that left ventricular function in normovolemia is along the flat portion of the curve, and changes in venous return have little impact on CO (Braunwald and Ross, 1979). It also corresponds with the observation that in humans the heart is maximally dilated in the recumbent (or slightly HDT) position (Gauer and Thron, 1965; Wilkins et al., 1950). Therefore, LBPP may not cause any significant increase in cardiac output in the supine position.

5.4.B.b. Magnitude of LBPP During Hypovolemia and Circulatory Shock

Kaplan et al. (1973) and later McSwain (1980) and Wayne and Macdonald (1983), and others (Frumkin, 1985), have advocated suit pressures in the range of 100 Torr when used to counteract circulatory shock. They reasoned that "the only thing which matters is the patient's blood pressure."

Pelligra and Sandberg (1979) have reviewed 174 cases in which CPC was applied to control massive intraabdominal bleeding from various organs. They concluded that inflation pressure of 15-20 Torr is effective in inducing hemostasis and increases blood pressure in hypovolemic shock patients.

Thirsk et al. (1980) and Roberts (1971) found in volunteers during supine recumbency that circumferential compression at 20 Torr to a lower extremity collapsed the leg veins, and positive pressure above 20 Torr did not expel more blood from the calf.

By exposing reclined subjects to various levels of LBPP between 0-60 Torr (air alone) Echt et al. (1974a) recorded no further increase in CVP as external counterpressure exceeded 30 Torr. They inferred that LBPP of 30 Torr was sufficient to translocate the maximum volume of available blood from the lower body to the central circulation.

5.4.B.c. The Compartment Syndrome and LBPP

The compartment syndrome is caused by elevated tissue pressure which interferes with and severely reduces the microcirculation, producing ischemia and injury to the skeletal muscles within a confined region (Hargens et al., 1984). Compartment syndromes of the leg have been linked to the use of LBPP (Brotman et al., 1982; Maull et al., 1981). Christensen (1986) demonstrated that external counterpressure exceeding 30 Torr applied to one lower extremity of humans in the supine position compromised the microcirculation, leading to tissue anoxia and increased risk of precipitating a compartment syndrome.

The comparison between the effects on the circulation of an air splint encompassing one leg only (Christensen's experiments) and the antigravity suit is somewhat halting because LBPP usually augments the driving blood pressure, which helps to maintain flow through narrowed vessels (Wangensteen et al., 1968a). Nevertheless, application of suit pressure in the range of 100 Torr during dorsal recumbency obviously increases the danger of developing a compartment syndrome and should be avoided (Chisholm and Clark, 1984). Lower extremity fracture combined with reduced flow and decreased tissue perfusion may render hypotensive patients more liable to incur myoneural damage at high external counterpressure (Templeman et al., 1987; Ransom and McSwain, 1979).

5.4.C. Optimal LBPP in a 1-G Recumbency Position with Reference to Myocardial Function During Hypovolemia and Circulatory Shock

Hypovolemia denotes reduced blood volume. Circulatory shock is caused by a generalized insufficiency of blood flow throughout the body to the extent of cellular damage due to lack of oxygen (Guyton, 1981).

Cardiac work (CW) is the product of CO and MAP (CW = CO × MAP). Work output of the heart is reduced during hypovolemia, the most common cause being hemorrhage (Guyton, 1981). According to Guyton (1971), the major determinant of the circulatory shock syndrome is CO. CO falls during hypovolemia because less blood is returned to the heart (Frank and Starling's law of the heart). Generally arterial pressure decreases because of reduced CO. Serious hypotension is detrimental to the heart because decreased coronary perfusion leads to a diminished oxygen supply to the myocardium (Abboud, 1982). The antigravity suit may improve coronary blood flow by increasing MAP and CO (MAP = CO × TPR). The same amount of CW (see above) is executed with less myocardial oxygen consumption if CO rather than arterial blood pressure becomes the determinant of the work output of the heart (Guyton, 1971). Heart outflow resistance (= aortic resistance, which is determined principally by TPR) is one of the major determinants of cardiac afterload (ventricular wall tension during ejection). Afterload is directly related to myocardial oxygen consumption (Cohn, 1982; Braunwald and Ross, 1979). High inflation pressure of the antigravity suit (100-Torr range) augments TPR (Pelligra and Sandberg, 1979; Niemann et al., 1983 (see section 5.4.B.)). In other words, increased inflation pressure increases MAP at the sacrifice of increased myocardial oxygen demand. Mannering et al. (1986) found in 10 normal subjects at 30° HUT that MAP rose proportionally more than CO when the subjects were exposed to LBPP above 20 Torr. The results imply that myocardial oxygen consumption increased in a nonlinear fashion and relatively more and more in the direction of the final inflation pressure. In another study a suit pressure of 30 Torr mobilized the maximum volume of available blood in the dependent regions of the body, and inflation pressure higher than 30 Torr did not shift more blood cephaladly (Echt et al., 1974a). An elevated myocardial oxygen demand without increase in oxygen supply means deterioration of heart

function (Maroko and Braunwald, 1976). Consequently, a high suit pressure may actually prove detrimental to the work output of the heart.

In conclusion we strongly emphasize earlier recommendations by Pelligra and Sandberg (1979) that LBPP should not exceed 20-25 Torr, independent of indication, when LBPP is applied to the human body in a horizontal position in a 1-G environment (1 Gx).

5.4.D. The Antigravity Suit—Orthostatic Hypotension

If a normal, healthy man remains passively standing, or if he is tilted head-up on a tilt-board, he will ultimately faint. Unconsciousness will occur despite a number of intricate regulatory mechanisms which defend homeostasis during orthostasis (see section 2.6.). Fortunately, the body assumes a horizontal position during this occurrence and restores adequate cerebral perfusion (Gauer and Thron, 1965). An attempt to prevent assumption of the horizontal posture can be lethal.

The following sequence of events probably plays a major role in the development of orthostatic hypotension leading to unconsciousness.

As the body stands up from a previous recumbent position gravity pulls 7-900 ml of blood into the splanchnic and leg/thigh regions (Sjöstrand, 1952, 1953; Rowell, 1986; Sandler and Vernikos, 1986). The heart and lungs are depleted by some 4-500 ml of blood (Sandler and Vernikos, 1986). In addition, because of the hydrostatic pressure component during upright posture, outward capillary filtration in the dependent regions amounts to 6-18% (Harrison, 1985; Hinghofer-Szalkay, 1982; Hinghofer-Szalkay and Moser, 1986; PAPERS IV and VI). Stroke volume and CO gradually fall and pulse pressure narrows. Peripheral vasoconstriction becomes more and more severe in all vascular beds of the body (Gauer and Thron, 1965).

At some point during orthostatic or HUT exposure, and usually within seconds following symptoms of profuse sweating, stomach awareness, nausea, and paleness, the arterial blood pressure drops instantly to very low levels. Bradycardia is invariably present, perhaps triggered by receptors in the left ventricle as the heart contracts forcefully with less and less blood available (activation of the Bezold-Jarisch reflex in humans?). Unconsciousness ensues if it is not prevented by assumption of the horizontal position (Gauer and Thron, 1965; Abboud, 1982; PAPERS IV, V, and VI).

5.4.D.a. Orthostatic Intolerance in Normal Individuals

Various conditions may attenuate orthostatic tolerance and predispose toward "vasovagal syncope." Hemorrhage (Gullbring et al., 1960); dehydration (Harrison et al., 1986b); varicose veins of the legs (Bevegård and Lodin, 1962; Chapman and Asmussen, 1942); general vasodilation (Wilkins et al., 1937; Weissler et al., 1957a); muscular exhaustion (Allen et al., 1945); hot climate (Rowell, 1983); and exposure to BR, WI, and weightlessness (see sections 3.0.; 4.0.) make the body more susceptible to fainting during prolonged motionless standing.

We have recently reported that individuals who become orthostatically intolerant at an early point during erect posture or HUT ("fainters") appear to have a generally lower MAP and elevated concentration of renin activity (measured as angiotensin I) in venous blood (PAPER VII).

5.4.D.b. Orthostatic Intolerance as a Pathological Condition

Another group of primary mechanisms causing orthostatic hypotension and circulatory failure is related to abnormal reflex responses of the cardiovascular system. Although venous pooling of blood in dependent regions is not greater than in normal people, postural vasoconstriction is slight or absent, and orthostatic increase in heart rate and sympathetic discharge are often missing (Blomqvist and Stone, 1983). The Shy-Dräger syndrome identifies patients with such a disturbance of the vegetative system. An uneventful catastrophic fall in arterial blood pressure occurs almost immediately upon assumption of the upright position (PAPER II).

5.4.D.c. Control of Orthostatic Intolerance by LBPP

The antigravity suit improves orthostatic tolerance (see section 5.3.A.; PAPERS II, IV, V, VI, and IX). LBPP reduces vascular capacity beneath the inflated antigravity suit and therefore augments static filling pressure (Guyton et al., 1973; Ferrario et al., 1970; section 2.3.A.). Consequently, venous return is enhanced (Guyton et al., 1973). Peripheral resistance in areas encompassed by the suit rises (section 5.4.B.). The aftermath of increased CO and MAP ameliorates cerebral blood perfusion above a critical value of about 30 ml/min/100 g brain tissue (Finnerty et al., 1954), which prevents loss of consciousness.

5.4.D.d. Reduction of Orthostatic Capillary Filtration by LBPP

One of our studies (PAPER VI) revealed that the antigravity suit prevented about 50% of orthostatic hemoconcentration during 60° HUT. This suggests that the total PV loss was only half (–6.0%) in the tilt LBPP period compared to the subsequent postdeflation time (–12.4%). In another study (PAPER IV), we showed that inflation of the antigravity suit during the second of 3 hr of passive standing restored PV to values that were not significantly different from baseline levels, indicating that external counterpressure mobilized fluid from the interstitial compartment.

The capacity of LBPP to reduce outward capillary filtration in the upright posture has to our knowledge not previously been reported and delineates an additional mechanism whereby the suit aids a steady state of the circulation during orthostasis and HUT. Not only does the antigravity suit protect the central blood volume during erect position by inducing a significant headward fluid shift, but it appears to delay the orthostatic loss of plasma water at least transiently. Similar to the effect of elevated hydrostatic counterpressure during WI, PV decreases as the stimulus of pneumatic counterpressure continues because excretion of urine and sodium is increased during prolonged application of the antigravity suit (PAPER V).

5.4.D.e. Use of LBPP to Improve Orthostatic Tolerance Following Exposure to Weightlessness

The antigravity suit may prove to be a protective device of considerable benefit for the astronauts as the deconditioning effect of the weightless exposure is unmasking during landing and the first hours following touchdown (see sections 3.6.A.d.; 3.6.B.d.; 3.6.B.e.). Evidently the bulk of the cephalad fluid, which accumulates in the upper body in space, has returned to the splanchnic area and the legs within 1.5 hr after the mission ends (Moore and Thornton, 1987). Kirsch et al. (1986) found in one astronaut that the plasma water had filtrated out of the intravascular compartment leaving a low CVP 4 hr after landing.

This indicates a tremendous dynamic process striking the cardiovascular system as the effect of the force of gravity interferes with the circulation following exposure to weightlessness.

It is highly conceivable that LBPP would afford protection during landing and following assumption of the erect posture postlanding by (1) increasing CBV, CO, and MAP, and consequently improving cerebral blood flow; (2) delaying outflux of plasma water exerting a favorable effect on total blood volume; and (3) supporting deconditioned skeletal antigravity muscles and thereby aiding both the muscle pump in returning blood to the right side of the heart and walking itself. We therefore propose that the astronauts don and activate the antigravity suit before entry and keep the suit pressurized for at least the first few hours after landing.

5.4.D.f. Magnitude of LBPP in the Upright Position (+1 Gz)

The inflation pressure during orthostasis must compensate for the hydrostatic component of the blood pressure (see section 2.3.C.) Ideally the distribution of suit pressure should exactly counterbalance the hydrostatic pressure at every level below the heart owing to the height of blood above this level (refer to WI, section 4.4.A.). We are in the process of designing a suit consisting of a series of independent bladders which, through manifolds, would allow inflation from below and a stepwise decrease in suit pressure in the cranial direction. Because such a suit is yet not available, we have made an approximation using a protocol which requires inflation of 60 Torr in the leg/ thigh bladders and 30 Torr in the abdominal bladder—the leg/thigh compartments of the suit being inflated before the abdominal bladder to avoid trapping blood in the lower extremities. These suit pressures apply only when the subjects are in the vertical or near-vertical (HUT) position (PAPERS IV, V, and VI).

5.4.E. Use of the Antigravity Suit to Improve Cerebral Perfusion During +Gz Acceleration

5.4.E.a. Franks' Water-Filled "Flying Suit"

The Franks' water-filled flying suit (after the inventor W. R. Franks) was developed by the Royal Canadian Air Force at the outset of World War II (Howard, 1965). Franks claimed that the suit added a 3-G protection, but true effectiveness was probably less than 1.5 G (Wood et al., 1946; Wood, 1987; Howard, 1965, 1981). Franks' garment was the first antigravity suit to be tested in combat in 1941. However, the pilots found it inconvenient and cumbersome in practical use. The water-filled suit exerted a continuous external hydrostatic counterpressure to the lower body from the time before takeoff to after landing. Such a physiological stimulus may have resulted in elevated urine production through reduced secretion of the antidiuretic hormone (The Henry-Gauer reflex—see section 4.4.E.). In fact, pilots often reported a feeling of distended bladder and urge to urinate after wearing the suit for some time, not exactly an advantage when flying combat missions (Howard, 1981).

5.4.E.b. The "Antiblackout Suit"

Inflatable antiblackout suits (blackout meaning temporary blindness) were developed by Wood and Lambert (Wood et al., 1946; Lambert and Wood, 1946) at the Acceleration Laboratory of the Mayo Aero Medical Unit, Rochester, Minn., in the United States in the early 1940s. The suit was hooked up to a source of compressed air in the airplane and inflated (activated) through a specially designed gravity-sensitive valve only when the pilot increased the G-load higher than 1.5-2 G in the headward direction

(+Gz) (Wood, 1987; Howard, 1981). The final design adopted by American pilots in 1943-44 was a cut-away version which could be worn over the usual flight coverall. The concept of the present G-suit worn by fighter pilots all over the world is virtually unchanged from the old prototype (Wood, 1987). The suit usually consists of five interconnecting bladders—one over each leg and thigh and one over the groin and lower abdomen. It fills rapidly with air from above through the abdominal bladder. Protection added is between 1.2 and 1.5 +Gz. This means that a relaxed pilot is able to maintain adequate cerebral perfusion when the weight added to the blood column in a standing posture is 1.2-1.5 times that of normal hydrostatic pressure at every point below the heart.

5.4.E.c. +Gz Acceleration Tolerance in Humans

Human tolerance to positive acceleration along the long axis of the body (= headward acceleration = +Gz acceleration) with the resultant head-to-toe direction of inertial force depends on the magnitude of force applied, duration of force applied, and rate of onset of force applied.

The subjective sensations of increased +Gz acceleration in a relaxed, unprotected individual spinning on a centrifuge (Lambert and Wood, 1946; Wood, 1986) are at +2.5 Gz, impossible to rise from a sitting position and at +4.0 Gz, barely possible to lift an arm and leg.

The following symptoms and signs will occur within 5-10 seconds after reaching maximum G-load in 3 sec:

1. 3.0 to 4.0 +Gz — Dimming of peripheral light
2. 3.5 to 4.5 +Gz — Loss of peripheral light
3. 4.0 to 5.0 +Gz — Complete loss of vision = blackout; hearing and consciousness intact; vision returns promptly when force is terminated
4. 4.5 to 5.5 +Gz — G-induced loss of consciousness (GLOC); loss of orientation as to time and place; recovery may take 30 sec; convulsive jerks may occur during recovery

Within the last decade loss of several high-performance aircraft was related to "pilot error." The GLOC phenomenon has played a primary role in several recent fatal pilot incapacitations (Wood, 1987; Gillingham, 1988).

Not only the magnitude of the +Gz acceleration (Lambert and Wood, 1946), but factors such as pilot hydration level (PAPER VII) and pilot mental stress capacity are important for GLOC tolerance. Sem-Jacobsen and Sem-Jacobsen (1963) reported that great variability existed among pilots to withstand +Gz acceleration. They also pointed out that in the same aviator exposure to identical acceleration may entail different tolerance depending on the hostility of the environment in which the stress is applied. Riding a centrifuge is a totally different matter compared to the serious challenge of a combat mission. In the former situation the pilots know that they are "coming home for dinner" the same day. Flying a high-performance aircraft through difficult maneuvers remains a risky undertaking and requires selection of the excellent pilots (C. W. Sem-Jacobsen, personal communication).

5.4.E.d. Magnitude of LBPP During +Gz Acceleration

The G-suit is typically pressurized in a linear fashion of 1 psi/G (1 psi = 52 Torr), with activation at 2 G and a cutoff pressure set at 10.5 psi (546 Torr), which happens at +9 Gz (Gillingham, 1988). In fact a +9 Gz maneuver is about the limit of human tolerance to headward acceleration which a trained pilot may sustain for a few seconds provided (Gillingham, 1988) that:

1. The pilot is using an antigravity suit pressurized as described above (adding about +1.5 Gz to a relaxed +3.5-Gz tolerance).

2. The pilot is performing a special Valsalva maneuver: forceful exhalation against a partially closed glottis and in addition tensing all skeletal muscles—repeated every 3-5 sec. These straining measures are very effective and may add up to a +4-Gz tolerance by raising intrathoracic pressure, which increases arterial pressure (but reduces venous return—see below).

3. The pilot is resting in a seat with a reclined back, which reduces the vertical distance between the base of the brain and the heart and thereby alleviates the influence of the hydrostatic pressure component on the arterial blood pressure at eye-level. A 30° seatback angle in the F-16 aircraft (plus somewhat elevated legs) adds about 0.5 to 1.0 +Gz protection.

The antigravity suit adds about 1.2 to 1.5 +Gz acceleration tolerance independent of the magnitude of the applied acceleration (Wood, 1987). The mode of action of the aviator's G-suit may differ somewhat from that of the antigravity suit used in a 1-G environment (see section 5.4.). The G-suit inflates rapidly to a very high pressure, compensating for the increased weight of blood during a progressive headward acceleration. More important, despite a sensitive G-value, the inflation lags a fraction of a second behind the onset of the acceleration. The delayed pressurization, in addition to filling from above through a narrow bladder compressing only the lower parts of the abdominal wall, may actually trap blood in the legs and splanchnic regions.

The mechanisms by which the G-suit affords protection during headward acceleration are complex and their relative contribution may be quantitated as follows:

1. Reduction of the hydrostatic distance between the heart and the base of the brain by prevention of downward descent of the diaphragm (1 cm at +2 Gz), accounting for an increased +0.3-Gz protection (Howard, 1981; Seiker et al., 1953; Burns et al., 1986).

2. Prevention of venous pooling in the dependent regions of the body, adding +0.3 Gz protection (Howard, 1981).

3. Augmented resistance to arterial inflow of blood in the lower extremities and increased intra-abdominal pressure, annexing about a +0.6-Gz acceleration tolerance (Rushmer, 1947).

4. Inhibition of rapid extravasation of plasma water into the interstitium (section 5.4.D.d.). The significance of reduced capillary filtration during +Gz exposure of only a few seconds is not known.

According to Wood (1986) the effectiveness of the antigravity suit to counteract headward acceleration is directly proportional to its ability to raise intraaortic pressure at heart level so that the blood column can reach the brain with sufficient pressure to adequately perfuse cerebral tissue during the increased gravitational-inertial force environment. The venous return is probably not a major determinant of the human +Gz acceleration tolerance (Wood, 1987). However, the antigravity suit reduces venous pooling of the splanchnic regions and of the legs as the weight of the blood increases with applied acceleration forces.

5.5. Use of LBPP as a Research Tool to Study Physiological Mechanisms

By applying CPC to the lower body of dehydrated subjects during the second of 3 hr of passive standing, we were able to study the immediate responses of ADH to a failing arterial blood pressure triggered by rapid deflation of the antigravity suit (PAPER IV). Severe presyncopal signs and symptoms were indicative of a vasovagal reaction developing soon after removal of the LBPP stimulus (section 5.4.D.). Ordinarily, vasopressin is thought to play a role in long-term regulation of blood volume (Gauer and Henry, 1976). Our results are almost proof positive that the antidiuretic hormone must contribute significantly in the homeostasis to prevent unconsciousness when arterial blood pressure is dropping to very low levels. Presumably increased vasopressin concentrations in the plasma exert extensive vasoconstrictor activity throughout the vascular beds in a last resort to regain cardiovascular control. This is in accordance with recent findings by Cowly et al. (1980) and Cowley (1982). In one of our subjects PVP increased more than 30 times in a few minutes from 8.0 to 250 pg/ml. It must be emphasized, however, that
since we did not measure CVP, the discriminatory contribution of high- and low-pressure receptors to the regulation of vasopressin during loading and unloading cannot be distinguished (section 2.6.B.).

Study seven (PAPER VII) disclosed that orthostatically intolerant individuals appear to have lower blood pressure and increased plasma renin activity before the symptoms manifest themselves. We propose that a protocol combining dehydration and HUT or passive standing with the use of the LBPP may provide a valuable physiological model to study mechanisms of orthostatic hypotension.

Study six (PAPER VI) dealt with applying LBPP and HUT to further investigate fluid exchange in tissues (Starling balance).

Thorough investigations (using LBPP) of the renal and electrolyte systems were undertaken, and the results are presented in PAPER V.

Experiments conducted by our group and by various research teams clearly demonstrate that LBPP may interfere with and disturb the normal control and regulation of major organs of the body. The antigravity suit may be used to elucidate mechanisms within the cardiovascular, fluid and electrolyte, endocrine and renal systems during both physiological and pathological conditions (Hesse et al., 1978; Wilkins et al., 1986; Jabbour et al., 1986; Julius et al., 1982; Sanchez et al., 1987; Streeten et al., 1985; Kass and Moore-Ede, 1982; Bennett et al., 1982).

5.6. LBPP Applied by the Antigravity Suit—A New Tool for Studying Physiological Effects of Weightlessness

As stated in earlier sections (sections 3.0.; 4.0.), one of the most noticeable effects of weightlessness on the human body is the cranial migration of body fluids. For this reason the changed hydrostatic pressure equilibrium within the circulatory system and the resulting redistribution of blood to the upper body become the most prominent common feature of our ground-based analogs of weightlessness (section 4.2.B.a.).

Ground-based research is imperative for a better understanding of the deconditioning effects of weightlessness (Robbins et al., 1988). There is presumably not one single model which is ideally suited to simulate every phase of weightlessness. Rather, WI, HDT, and horizontal BR represent different ground-based analogs which induce cardiovascular deconditioning of various stimulus strength and response time (sections 4.3.A.; 4.3.B.; 4.4.B.), each model perhaps conforming best with certain phases of the adaptational process of real weightlessness (for instance, short-term versus long-term adjustments to weightlessness) (Gazenko and Egorov, 1988).

It is a continuous and pressing task to improve existing models and to search for new and cost-effective methods for a full understanding of the many unresolved questions regarding physiological deconditioning in space. For several years the author has been inspired by an idea that circumferential pneumatic counterpressure applied to the lower body in the upright posture may serve as an alternative to existing methods for studying hemodynamic, endocrine, and fluid and electrolyte effects of weightlessness (Kravik et al., 1983). Our preliminary results show promise for the use of an air-filled antigravity suit in the upright posture to induce a sustained cephalad redistribution of body fluid comparable to that seen with WI (PAPERS IV, V, and VI, and section 5.4.B).

The fluid and electrolyte changes are similar to data obtained during WI. CO appears to increase more than 30%, an observation almost identical to responses occurring in NOI. Hormonal measurements are indicative of a headward fluid shift. An immediate and brisk elevation of urine flow and increased natriuresis are sustained throughout inflation. Upon activation of the suit, several subjects noticed an immediate sensation of blood rushing to their heads, one of the most prominent and earliest symptoms reported by an almost unanimous astronaut corps (Oman et al., 1984).

5.6.A. The Antigravity Suit Model as a Ground-Based Analog of Weightlessness

Several essential features constitute our model for using the antigravity suit as a tool to simulate physiological effects of weightlessness and for elucidating mechanisms contributing to the adaptation process in space. We think our particular protocol is a premise for the clarity of the data reported for (1) subjects in an upright or HUT position and correct hydration level (section 5.4.B.a.), and for (2) a suit inflated to 60 Torr within the leg bladders and 30 Torr within the abdominal bladder (sections 5.4.C.; 5.4.D.f.).

The following rationale was used for designing this protocol. By clinical experience and physiological experiments with the MAST garment we have noticed that LBPP appears to bring about significant changes in central hemodynamics during hypovolemia, while alterations in a supine, normovolemic state are generally nonsignificant. This is in agreement with the observation that the operating point for the left ventricle in a state of normovolemia is along the flat portion of the curve (Braunwald and Ross,

1979; Frye et al., 1960; Robinson et al., 1966). It also corresponds with measurements showing maximal heart size in the recumbent or slightly head-down position (Gauer and Thron, 1965; Wilkins et al., 1950), and that therefore LBPP may not cause any further increase in CO (Bellamy et al., 1984).

Because of gravity, assumption of the upright posture shifts some 7-900 ml of blood from the upper regions of the body to the dependent veins of the abdomen and lower extremities (Sjöstrand, 1952, 1953; Rowell, 1986; Sandler and Vernikos, 1986). This pooling of blood may be regarded as a functional hemorrhage into the leg—and splanchnic vessels. As prolonged standing continues, there is approximately a 10% decrease in the effective circulating blood volume (Hagan et al., 1978; Ziegler, 1980; Fawcett and Wynn, 1960; Sjöstrand, 1976; Henriksen et al., 1973). The decrease is a result of increased hydrostatic pressure in the erect position and the ensuing outward filtration of plasma from the capillaries in the lower parts of the body (Harrison, 1985; Hinghofer-Szalkay, 1982; Hinghofer-Szalkay and Moser, 1986; PAPER IV). In addition to passive standing or HUT, some of our subjects were dehydrated over a period of up to 24 hr supplemented with a dry diet containing 6 g of NaCl (Harrison, 1986b; PAPERS IV, V, VII).

These stresses contributed to a state of functional hypovolemia, a fall in central blood volume, and diminished return of blood to the right side of the heart (preload). We have found that the headward translocation of fluid afforded by the antigravity suit has a much greater impact on the extent (quantity) and clarity (quality) by which some parameters change when preload is reduced by the upright and dehydrated condition.

5.6.B. Differences and Similarities in Application of the Antigravity Suit Model Versus BR and WI as Ground-Based Analogs of Weightlessness

A headward shift of fluids can be induced in head-down, horizontal, seated, or standing positions and can be maintained during ambulation if desired. This eliminates the postural restrictions that accompany BR and WI.

On the whole the effects of the antigravity suit model appear to be quite similar to those seen with the WI model, i.e., the antigravity suit model represents a strong stimulus with a short response time (sections 4.3.A.; 4.3.B.; 4.4.B.).

Similar to WI and unlike HDT, the antigravity suit model does not change the direction of the hydrostatic pressure component within the circulatory system. Neither does it lead to a reorientation of reflexes caused by afferent impulses from different organs and tissues exposed to a change of direction from the pull of gravity.

A clear advantage over the use of WI and BR is the elimination of the cumbersome water tank and auxiliary equipment for temperature control and possible infection by contaminated water.

The antigravity suit can be donned and doffed easily and quickly without need for highly trained personnel.

Pressures within the antigravity suit can be adjusted quickly to accommodate a wide range of experimental conditions.

The unit is relatively inexpensive and does not have the operating costs or space requirements of WI or a BR facility.

Unlike the BR and WI models, the antigravity suit unit is portable.

The possibility of orthostatic hypotension and loss of consciousness in experiments utilizing LBPP is related to the conditions of the experiments or the natural propensity of certain individuals to faint rather than to the use of the antigravity suit itself. In fact, LBPP is an extremely effective method for preventing orthostatic intolerance (section 5.4.D.). However, just as in BR or WI, too rapid removal of the subject from the experimental stimulus can lead to sudden pooling of blood in the depending portions of the body and to fainting. Actually, since orthostatic hypotension is a potential serious problem facing returning astronauts from space the antigravity suit can be used to study this problem as well as a postflight countermeasure (sections 3.6.B.d.; 3.6.B.e.; 5.4.D.a.; 5.4.D.e.).

Discomfort related to mechanical pressure on soft tissues, blood vessels, or joints is related to the magnitude of external counterpressure and was discussed in length in sections 5.4.B.b.; 5.4.B.c.; 5.4.C.; and 5.4.D.f.

The antigravity suit model is not a replacement for WI or BR. On the contrary, the antigravity suit complements the two present models.

Paper I

Bruk av anti-G-drakt til kontroll av kritisk intraabdominal blødning

Bruk av såkalt anti-G-drakt til å stanse vanskelig traktabel intraabdominal blodning har til nå vært lite akseptert og blir sjelden benyttet. Ikke desto mindre er idéen gammel. Crile[1] anvendte i 1903 en oppblåsbar gummidrakt til å presse mot huden fra ankel til midje. Dermed kunne han hindre hypotensjon under neurokirugiske inngrep i sittende stilling. I 1909 behandlet han en pasient i blodningssjokk etter samme prinsipp.[2] Drakten, som ble satt under trykk ved hjelp av en sykkelpumpe, var laget av indiagummi, og det forekom stadig lekkasjer. Dessuten ble blodtransfusjoner snart tilgjengelig, og metoden ble oppgitt.

Uttrykket «anti-G» skriver seg fra tidlig under annen verdenskrig, da drakten ble tatt i bruk av amerikanske flyvere for å hindre skjebnesvangre bevissthetstap ved krappe manovrer, som for eksempel uttrekning av stup (pull-out). Ved denne tilstand er flyveren ut-

[1]Crile, G. W.: J. B. Lippincott Co., Philadelphia 1903, 288–291

[2]Crile, G. W.: D. Appleton & Co., New York 1909, 139

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satt for såkalt «positiv-G-akselerasjon», idet akselerasjonsbelastningen adderer seg til gravitasjonskraften. Blodet samles dermed i underekstremitetene med den følge at blodgjennomstrømningen til retina og hjernen blir for liten. Synet blir uskarpt (grey-out), og øyeblikket senere oppstår reell synkope (black-out). Anti-G-drakt brukes i alle moderne jagerfly i dag og hindrer effektivt synkope hos flyveren. En gummiblære innebygd i drakten er tilkoblet flysystemet og blir automatisk blåst opp ved vinkelakselerasjon. Anti-G-drakt har ingen effekt ved rettlinjet horisontal akselerasjon. Drakttrykket motvirker den økte gravitasjon, derav navnet «anti-G (gravitasjon)». På den måten oppnår man redusert vaskulær kapasitet i nedre kroppsdeler med betydelig bedret cerebral gjennomstrømning.[3]

I slutten av 1950-årene tok Gardner[4] til å eksperimentere med drakten på nytt, og den fikk igjen medisinsk interesse, uavhengig av Criles arbeid 50 år tidligere. I 1958 brukte Gardner[5] anti-G-drakt til å stanse en blødning post partum etter at alle andre forsøk hadde slått feil. Det forelå placenta percreta. Da kvinnen ble iført drakten, hadde hun fått 55 blodtransfusjoner i løpet av 18,5 timer via 4 vener samtidig, var laparotomert 2 ganger, hysterektomert, og det var anlagt elastisk bind rundt underekstremitetene. Det forelå sikker disseminert intravaskulær koagulasjon. Blodtrykket var 80/40 med blødningssjokk og situasjonen ansett som håpløs. Etter bare minutter med et drakttrykk på 20 mm Hg våknet pasienten, blodtrykket steg til 114/80, og diuresen kom i gang igjen. Blødningen stanset gradvis i løpet av noen timer, og drakten ble fjernet etter 24 timer uten at det oppsto ny blødning.[5]

Senere er anti-G-drakt i 174 rapporterte tilfelle benyttet til å stanse intraabdominale blødninger i forbindelse med aortaaneurysmer, bekkenfrakturer, disseminert intravaskulær koagulasjon og andre koagulopatier, militære traumer samt obstetriske og gynekologiske komplikasjoner.[4-7] I de tilfelle man har tydd til drakten, har som regel utgangssituasjonen vært håpløs og slaget ansett som tapt. Anti-G-drakt har vært siste redningsmulighet i en situasjon hvor det ikke forelå noe annet alternativ.

Inntil nå har behandling av ortostatisk hypotensjon vært det viktigste indikasjonsområde. (Se for øvrig egen artikkel på annen plass i dette nummer av «Tidsskriftet».)

Hvorfor er bruken av anti-G-drakt ikke mer anerkjent? Den viktigste grunnen synes å være at man mangler adekvate kliniske kontrollforsøk. Alle rapportene bygger på *inntrykk* av at anti-G-drakt medførte hemostase, men det kan oftest ikke bevises at andre faktorer ikke har spilt inn. Dette har medført at draktens effektivitet er blitt møtt med skepsis, selv i siste instans når situasjonen har vært katastrofal.

Fra 1909 til 1969 er drakten beskrevet brukt 5 ganger sammenlignet med 169 rapporterte tilfelle fra 1970 og frem til i dag. Dette viser tydelig den økende interesse for drakten som har funnet sted i de siste årene, noe som først og fremst skyldes at man blant spesialtrenede førstehjelpere i USA (såkalte paramedics) har fått øynene opp for nytten av anti-G-drakten i akutte situasjoner. En kommersiell utgave av drakten i polyvinylfabrikat brukes til å kontrollere livstruende blødning og hypotensiv krise mens pasienten er på vei til videre behandling.[7]

Man er enig om at draktens evne til å heve et lavt blodtrykk skyldes kompresjon mot huden under diafragma og dermed redusert vaskulær kapasitet i dette området. Det skjer en autotransfusjon fra nedre kroppsdeler til organer over diafragma, sannsynligvis i størrelsesområde 750–1 000 ml.[4,7,8]

Klinisk observeres bedre ansiktsfarve og distensjon av halsvener. Blodtrykkstigningen er mest uttalt ved hypovolemisk sjokk, men kan også iakttas hos normovolemiske pasienter.[8,9]

Drakttrykket er oftest ikke høyere enn 20–25 mm Hg, og perfusjonen i underekstremitetene er hele tiden god.[8,9] Betydelig vanskeligere er det å forklare det paradoksale faktum at et eksternt trykk mot huden, langt under gjennomsnittlig blodtrykk, kan stanse en intraabdominal blødning fra så vel venøs som *arteriell* blødningskilde. To velkjente lover fra fysiologien gir en sannsynlig forklaring:

LaPlaces lov ($T = P \cdot R$, hvor T er veggtensjonen, P er trykkdifferansen mellom hydrostatisk trykk i blodkaret og extravaskulært trykk (= transmuralt trykk), R er karets radius) går i korthet ut på at veggtensjonen i et fleksibelt kar er en funksjon av transmuralt trykk og karets radius. Det er først og fremst veggtensjonen som får kantene i en intramural lesjon til å sprike. Jo høyere tensjon, desto større er avstanden mellom sårkantene, og blødningen fortsetter. Ved at drakten presser på huden, øker det intraperitoneale trykk slik at transmuralt trykk avtar. Dermed reduseres veggtensjonen, og sårkantene nærmer seg hverandre.[4,6-8,10]

I tillegg kommer at drakttrykket distribueres likt i hele abdomen og fører til innsnevring av kardiameter.[8,10] Reduksjon i kardiameter vil ytterligere bidra til fallende veggtensjon (LaPlaces lov).

Av kanskje større betydning er at blodgjennomstrømningen i området under diafragma avtar ganske kraftig: Poiseuilles lov ($Q = \Delta P \, r^4/8 \, n \, l$, hvor Q = gjennomstrømning, P = perfusjonstrykket, r = radius, n = blodets viskositet, l = karets lengde) fastslår at selv en li-

[3]Gillies, J. A.: A textbook of aviation physiology, Pergamon Press 1965
[4]Surg Gynecol Obstet 1966, 123, 792–798
[5]JAMA 1958, 167, 985–986
[6]Aerosp Med 1970, 41 (8), 943–945
[7]JAMA 1979, 241, 708–713
[8]Surg Gynecol Obstet 1971, 133, 637–643
[9]Surg Gynecol Obstet 1968, 127, 253–258
[10]Am Surg 1969, 35, 635–637

ten reduksjon i karradius medfører markert mindre gjennomstrømning.[7]

Det er derfor sannsynlig at den kombinerte effekt av redusert blodgjennomstrømning og veggtensjon fører til at pasientens egen, ofte marginale, koagulasjonsmekanisme blir tilstrekkelig til å ta over, og blødningen stanser.[7]

Enkelte forfattere har registrert redusert nyrefunksjon ved bruk av anti-G-drakt, andre en bedret eller uendret diurese. Espinosa[11] har målt nedsatt vitalkapasitet på ca. 17% hos friske mennesker ved et drakttrykk på 20 mm Hg. Wangensteen[12] har observert alvorlig metabolsk acidose på hunder i hypovolemisk sjokk ved et drakttrykk på 40 mm Hg over 4 timer. Funnet er ikke bekreftet i andre dyreforsøk og er aldri registrert hos mennesker. Hjertefrekvensen avtar, noe som antas å skyldes økt aortatrykk og økt venøs tilbakestrømning som registreres av baroreseptorer på arcus aortae, sinus caroticus, lungene og begge sider av hjertet.[7]

På grunn av økt venøs tilbakestrømning og dermed økt fylningstrykk i høyre atrium, vil slagvolumet stige (Starlings lov). Som følge av økt slagvolum skulle man forvente økt minuttvolum. På grunn av samtidig reduksjon i hjertefrekvens vil imidlertid minuttvolumet oftest forbli uendret.[7] Perifer karmotstand i området som dekkes av drakten øker på grunn av redusert karradius, avtagende blodgjennomstrømning og økende perfusjonstrykk. Den totale karmotstanden, derimot, er avhengig av minuttvolumet og eventuell distensjon av venøse kar over diafragma.[7] Med et drakttrykk helt opp i 40 mm Hg er det hos hunder registrert en økning på 20% blodgjennomstrømning i a. carotis og samtidig en reduksjon på 33% i a. femoralis.[9]

Under ingen omstendighet synes bivirkninger i forbindelse med bruk av anti-G-drakt å representere noe klinisk problem. De fleste observasjoner tyder i retning av at uheldige virkninger øker med økende drakttrykk, og at man ikke oppnår fordeler ved å overskride 30 mm Hg. Kanskje motsatt av hva man kunne vente, er det nemlig hverken klinisk eller teoretisk grunnlag for å hevde at blodtrykket vil øke i takt med økende drakttrykk. Dette gjelder spesielt hypovolemiske pasienter.[7]

Anti-G-drakt bør anvendes med forsiktighet hos pasienter med underliggende nyre- eller lungelidelse.

På grunn av shunteffekten av blod fra nedre til øvre kroppsdeler, er drakten vanligvis kontraindisert ved hjerneødem, lungeødem, hjertesvikt og ved blødning over diafragma. McSwain[13] har imidlertid observert god respons i forbindelse med blødning fra a. pulmonalis og tillegger denne effekten bedret oksygenering og vevsperfusjon til tross for at det teoretisk burde foreligge økt blødning fra såret. Han har også fremsatt en meget interessant teori om at siden intrakraniell skade og hypotensjon gir hjerneødem, skulle bruk av anti-G-drakten i virkeligheten redusere en cerebral ischemi. Effekten av anti-G-drakt ved blødninger over diafragma er ikke klarlagt, og her gjenstår videre klinisk utprøving.

Akutt diffus erosiv hemoragisk gastritt er ofte en fatal sykdom som oppstår hos pasienter i en fysiologisk stress-situasjon (alvorlige brannskader etc.). Multiple og diffuse blødningskilder i hele ventrikkelen gjør kirurgi til en tvilsom behandlingsform. Bruk av anti-G-drakt ved denne tilstanden er uprøvet. Før man går til et så mutilerende inngrep som total gastrektomi, burde det imidlertid være all mulig grunn til å prøve drakten.

Etter å ha gjennomgått en del litteratur om anti-G-drakten synes vi det er klart at den burde være et trygt, effektivt og aktuelt supplement til eksisterende kirurgiske metoder i akutte blødningskriser, og spesielt i en førstehjelpssituasjon. I sistnevnte tilfelle kan drakten settes under trykk ved hjelp av en vanlig håndpumpe, og kontroll av trykket er ikke kritisk. Et lavt trykk er imidlertid absolutt å foretrekke.[7] Når drakten brukes over lengre tid i forbindelse med blødningskriser som ikke lar seg overvinne kirurgisk, er det nødvendig å kontrollere drakttrykket nøye. I de aller fleste tilfelle er det ikke nødvendig å overskride et trykk på 20–25 mm Hg for å oppnå hemostase. Dette reduseres gradvis etter ca. 24 timer, men må individualiseres. Det er meget viktig at det er sørget for adekvat væske/elektrolyttkorreksjon og at eventuell koagulopati er behandlet før drakten avlastes.[7]

Luftforsvarets Forsyningskommando på Kjeller har laget en kontrollenhet slik at drakttrykket kan innstilles nøye. Kontrollenhet og en anti-G-drakt oppbevares nå ved Sentralsykehuset i Akershus og kan om nødvendig rekvireres med helikopter.

En punktvis rettledning i bruken av drakten følger:[7]

1) Grundig eksaminering av huden som dekkes av drakten – incisjoner, decubitus
2) Innlegging av blærekateter
3) Mekanisk ventilasjon hvis mulig
4) Maksimalt trykk i drakten: 20–25 mm Hg = 272–340 mm H_2O
5) Tid under trykk: I medisinsk litteratur varierer vanligvis tiden mellom 24 og 48 timer
6) Iaktta:
   a) Blodtrykk, puls, respirasjon
   b) Væskeinntak/diurese
   c) Arteriell syre/basestatus
7) Før drakten avlastes:
   a) Adekvat væske/elektrolyttkorreksjon

NB

   b) Laboratoriebekreftelse på at eventuell koagulopati er korrigert
8) Drakten avlastes gradvis over en periode på 30–60 minutter.

Stein Kravik og *Knud Landmark*

[11] Arch Surg 1970, 101, 36–39
[12] Ann Surg 1969, 170, 187–192
[13] J Trauma 1977, 17 (9), 719–724

Paper II

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Behandlingsopplegg ved våre sykehus

Her presenteres behandlingsopplegg ved aktuelle sykdommer, slik det praktiseres ved en del av våre sykehus
Det publiserte behandlingsopplegg gjør naturligvis ikke krav på å være det eneste rette
Kommentarer og spørsmål mottas med takk og vil eventuelt bli publisert i «Korrespondansespalten»
Ønskes stoff i denne spalte omtalt i massemedia, ber vi om at det skjer i samråd med Redaktøren

Bruk av anti-G-drakt i behandlingen av idiopatisk ortostatisk hypotensjon

Idiopatisk ortostatisk hypotensjon (Shy–Dragers syndrom) er karakterisert ved fallende blodtrykk og manglende pulsøkning i stående stilling, noe som tyder på en forstyrrelse i det autonome nervesystem. I tillegg til svimmelhet og synkope er tilstanden karakterisert ved varierende grad av affeksjon av nervesystemet. Vanlig medikamentell behandling kan føre til en viss bedring, men som oftest er den uvirksom. Hos 3 pasienter med idiopatisk ortostatisk hypotensjon har vi forsøkt anti-G-drakt, og dette førte til en tydelig reduksjon i blodtrykkfallet og en bedring av plagene ved overgang fra liggende til stående stilling. Imidlertid syntes 2 pasienter at drakten i lengden var ubehagelig å bære. Anti-G-drakten representerer et alternativt behandlingsprinsipp ved en vanskelig traktabel sykdom som idiopatisk ortostatisk hypotensjon representerer.

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Idiopatisk ortostatisk eller primær postural hypotensjon (Shy–Dragers syndrom) er en sjelden lidelse som er karakterisert ved blodtrykkfall i stående stilling og manglende reflektorisk pulsøkning, dvs. en forstyrrelse i den autonome regulering av blodtrykk og hjertefrekvens. Dette fører til nedsatt minuttvolum og fall i perifer karmotstand, den cerebrale blodgjennomstrømning avtar, noe som fører til svimmelhet og eventuell synkope (3, 4, 9). I tillegg finnes som regel blære- og rectumforstyrrelse, impotens, irisatrofi, ekstern oftalmoparese, tremor, distal muskelatrofi, anhidrose og EMG-forandringer (6). Disse symptomene kan ofte manifestere seg først flere år etter debut av hypotensjonen (12). Tilstanden, som gjerne debuterer i 50–70-års alderen (11), er jevnt, men langsomt progredierende. Menn affiseres oftere enn kvinner. Patologisk-anatomisk er det funnet tegn til primær sentralnervøs degenerasjon med affeksjon av det autonome nervesystem i medulla spinalis, basalganglier og i cerebellum (6, 11). Aminoff & Wilcox (1) har funnet holdepunkter for sentral/perifer lesjon i det sympatiske nervesystem. Chokroverty og medarbeidere (4) fant i tillegg dysfunksjon i det parasympatiske nervesystem. Terapien er symptomatisk, og man har forsøkt forskjellig medikamentell behandling som Effortil (2, 6), Florinef (9-α-fluorohydrokortison) (6), MAO-inhibitorer kombinert med noradrenalinfrigjørende substanser (8) og efedrin kombinert med propranolol (7), alle med noe varierende, men ikke overbevisende effekt. Det er beskrevet god nytte av anti-G-drakt (3, 9). I løpet av de siste 2 år har vi hatt innlagt i vår avdeling 3 pasienter med idiopatisk ortostatisk hypotensjon. Hos disse har vi forsøkt anti-G-drakt, og vi vil her redegjøre for våre erfaringer med dette behandlingsprinsipp.

Materiale

Tre pasienter, to menn og én kvinne i alder 60–65 år med 1–6 års sykehistorie med symptomer på idiopatisk hypotensjon, har vært innlagt i Medisinsk avdeling B, Rikshospitalet, i tidsrommet 1976–1978. De viktigste subjektive og objektive funn er vist i tabell 1. To pasienter hadde i tillegg til svimmelhet og synkopetendens også til dels uttalte neurologiske symptomer. Vanlige laboratorieprøver og EKG var normale, ingen hadde tegn på hjerte- eller karsykdom. Renin i perifert blod var normalt. Alle de 3 pasientene hadde før innleggelsen i avdelingen vært hospitalisert lokalt og bl.a. forsøkt Effortil, Florinef og salttilførsel uten sikker effekt. I liggende stilling hadde pasient nr. 1 og 2 normale blodtrykkverdier, mens pasient nr. 3 hadde forhøyede verdier (tab 2). Alle ble raskt svimle når de sto opp, blodtrykket falt betydelig uten at det kom noen reflektorisk pulsøkning. Ingen ble svette eller klamme. Pasient nr. 1 falt etter ca. ½ minutt i stående stilling sammen med snorkende respirasjon, det var ingen kramper eller ufrivillig avgang av urin eller fæces, blodtrykket var ikke målbart. Han ble lagt i seng og våknet raskt opp. Hos de tre pasientene ble det forsøkt anti-G-drakt

Tabell 1 Symptomatologi ved idiopatisk ortostatisk hypotensjon

Pasient nr.	1 (mann)	2 (mann)	3 (kvinne)
Svimmelhet	+	+	+
Synkope	+	+	÷
Blæreforstyrrelser	+	÷	+
Fascikulasjoner i ekstremitetene	+	÷	+
Tremor	+	÷	÷
Distal muskelatrofi	+	÷	+
Dysartri	÷	÷	+
Usto gange	+	÷	+
EMG	+	+	
EEG	+	÷	+
Reflekser	normale	normale	normale

EMG + = tegn på perifer neurogen lesjon, EEG + = tegn på cerebral dysrytmi

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Tabell 2 Blodtrykkverdier med og uten anti-G-drakt hos 3 pasienter med idiopatisk ortostatisk hypotensjon

	Uten drakt		Med drakt	
	BT	Puls	BT	Puls
Pasient nr. 1				
Liggende	115/80	64	130/80	
Stående	0	64	80/55	
Pasient nr. 2				
Liggende	125/70	74	150/95	80
Stående	60/35	88	80/55	80
Pasient nr. 3				
Liggende	240/140	76	240/140	
Stående	95/70	76	120/100	

(CSU-3/P).[1] Hos pasient nr. 1, som var mest plaget av sin sykdom, resulterte dette i en dramatisk bedring. Ved overgang fra liggende til stående stilling falt nå blodtrykket fra 130/80 til 80/55 uten at han ble svimmel (tab 2), og han ble i stand til å ta turer i korridoren (fig 1). Også hos de to andre pasientene ble blodtrykkfallet redusert, pasient nr. 2 anga at svimmelheten ble borte, pasient nr. 3 at den ble mindre uttalt. Begge disse pasientene anga for øvrig at drakten i lengden var ubehagelig å bære.

Diskusjon

Medikamentell behandling av idiopatisk ortostatisk hypotensjon, som er en jevnt progredierende lidelse (4, 11, 12), har stort sett gitt dårlige resultater (2, 6–8), noe som også var tilfelle for våre pasienter. Tidligere er også forsøkt elastisk bandasje på underekstremitetene, og en viss temporær effekt har vært oppnådd.

Crile (5) brukte i 1903 et nytt prinsipp for å forhindre kritisk hypotensjon under neurokirurgisk inngrep på hode og nakke i sittende stilling: En buksedrakt med oppblåsbar gummiblære klemte direkte på huden fra ankelregionen til diafragma. Under 2. verdenskrig ble jagerflyene stadig raskere, og synkope hos flygerne under uttrekning av stup forekom hyppigere. Blodet samlet seg i de nedre kroppsdeler, og dette resulterte i for liten flow til retina (grey-out) og øyeblikket senere til reell synkope (black-out). For å motvirke synkopetendensen konstruerte amerikanske flymedisinere den såkalte anti-G-drakten. De benyttet derved nøyaktig samme prinsipp som Crile (5) hadde anvendt på sine pasienter 50 år tidligere. Navnet anti-G (gravitasjon) uttrykker akkurat hensikten: En gummiblære innebygd i drakten omslutter huden fra ankelregionen til mellomgulvet. Satt under trykk (20–30 mm Hg) reduseres vaskulær kapasitet i de nedre kroppsdeler, og det skjer en autotransfusjon til organer ovenfor diafragma (10), slik at venøs tilbakestrømning og minuttvolum kan opprettholdes (9). Perfusjonen i underekstremitetene er hele tiden god (10), idet drakttrykket ligger langt under blodtrykket. Anti-G-drakt har vært brukt i behandlingen av idiopatisk ortostatisk hypotensjon av flere forfattere med tilfredsstillende resultat (3, 9). Det er vist at tilstanden er ledsaget av til dels betydelig fall i minuttvolumet (3, 4, 9), således fant Rosenhamer & Thorstrand (9) hos en pasient med idiopatisk ortostatisk hypotensjon et fall i minuttvolumet fra 4,6 l til ikke målbare verdier i oppreist stilling; ved bruk av anti-G-drakt var fallet 1,6 l.

Hos våre tre pasienter, som tidligere hadde forsøkt forskjellig medisinsk behandling uten sikker effekt, fikk man subjektiv og objektiv bedring av symptomene på idiopatisk ortostatisk hypotensjon etter oppblåsing av anti-G-drakten. Én pasient ble utskrevet med drakten, de to andre syntes at denne i lengden var ubekvem å bære. Vi mener til tross for dette at anti-G-drakt representerer et brukbart alternativt behandlingsprinsipp for en vanskelig traktabel sykdom som idiopatisk ortostatisk hypotensjon.

[1]Utlånt fra Luftforsvarets Forskningskommando, Kjeller

Fig 1 Pasient iført anti-G-drakt under trykk

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Litteratur

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Paper III

Immersion diuresis without expected suppression of vasopressin

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KRAVIK, S. E., L. C. KEIL, J. E. SILVER, N. WONG, W. A. SPAUL, AND J. E. GREENLEAF. *Immersion diuresis without expected suppression of vasopressin.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 57(1): 123–128, 1984.—To investigate fluid, electrolyte, and plasma vasopressin (PVP) and renin activity (PRA) responses, six men (20–35 yr) were immersed to the neck (NI) in water at 34.5°C for six h after overnight food and fluid restriction. Diuresis was 1,061 ± 160 (SE) ml/6 h during immersion and water balance was −1,285 ± 104 ml/6 h. Preimmersion PVP was 0.7 ± 0.2 pg/ml and increased to 3.0 ± 0.6 pg/ml ($P < 0.05$) at 6 h. PVP was unchanged at 1.2 ± 0.1 pg/ml in the 6-h seated nonimmersion experiment at 25°C. Plasma volume increased by 7.8 ± 1.6% ($P < 0.05$) at 60 min of NI and decreased thereafter. Serum osmolality was constant (292 ± 1 mosmol/kg) throughout NI, whereas PRA decreased progressively from 1.9 to 0.5 ng angiotensin I·ml^{-1}·h^{-1} ($P <$ 0.05) at the end of immersion. In spite of moderate thirst just before NI, thirst sensations were attenuated and no water was consumed ad libitum during immersion. These data indicate that PVP is not suppressed when there is no fluid intake during immersion and suggest that the action of factors other than PVP suppression are necessary to explain the mechanism of immersion diuresis.

plasma vasopressin concentration; plasma renin activity; serum osmolality; thirst

DURING BED REST, water immersion, and presumably during weightlessness, there is a shift of blood from the lower parts of the body to the thoracic circulation (1, 27). On Earth this central fluid shift is associated with a profound diuresis (6, 20, 21), but the mechanism is not well understood. A prominent hypothesis has involved the Henry-Gauer reflex; i.e., volume receptors located in the atria of the heart sense the thoracic engorgement and inhibit vasopressin secretion via vagus nerve stimulation (14). However, the ability of this reflex to induce diuresis in man is still in question. Recent results from our laboratory indicate that plasma vasopressin is not suppressed significantly during neck immersion (19), but these findings have not been confirmed.

In monkeys, bilateral cervical vagotomy (15) and elevation of left atrial pressure using balloons (16) and snares (5) failed to alter renal function. In addition acute blood volume expansion did not alter plasma vasopressin (PVP) concentration (17).

In view of these findings the present study was designed to measure plasma vasopressin, fluid, electrolyte, and plasma renin activity (PRA) responses in subjects with normal preimmersion PVP concentrations.

PROCEDURE AND METHODS

Six men (20–35 yr) volunteered for the study after they had passed an extensive clinical examination (Table 1). All the subjects were nonsmokers and did not use drugs or medication.

The subjects did not consume fluid or food from 2300 h the day before the experiment until 2.5 h prior to water immersion. They arrived at the laboratory at 0700 h, and at 0715 h they urinated and ate a light breakfast consisting of two pieces of dry wheat toast with honey. At 0740 h the subjects ingested 300 ml of water containing NaBr for measurement of extracellular volume (data not reported due to technical problems), were seated, and rested for 2 h at room temperature (25°C). Nude body weight and the initial urine and blood samples were obtained before they entered the water tank at 0945 h. The subjects sat in a tank (1.1 × 1.3 × 1.6 m) filled with tap water. External hydrostatic counterpressure was approximately 75 Torr at their feet, ~30 Torr over the splanchnic region, and zero Torr at the neck. The subjects wore bathing suits, and water temperature was maintained at 34.5° ± 0.5°C. To determine whether fluid loss by diuresis during immersion induced thirst, the subjects were offered tap water ad libitum but were not specifically encouraged to drink. Blood was drawn from the brachial or median cubital vein with the arm out of the water at 30, 60, and 360 min of immersion. Urine samples were collected hourly with the subjects standing briefly; urine sampling did not coincide exactly with blood drawing. The subjects were dried and weighed immediately after immersion.

Within a period of 2 mo after the first study, the same six subjects underwent an identical control study where they sat nonimmersed for 6 h at room temperature (25°C). However, blood samples were taken less frequently: at time zero, 120, and 360 min. Urine samples were collected hourly.

Serum and urine were analyzed for sodium and potassium (Instrumentation Laboratory digital flame photometer, model 643) and osmolality (Advanced Instruments Digimatic freezing point osmometer, model 3DII).

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TABLE 1. *Anthropometric, water-balance, and thirst-sensation data*

Subj	Age, yr	Height, cm	Preimmersion Wt, kg	Postimmersion Wt, kg	Water Balance, g/6 h	Thirst Sensation		
						Preimmersion	During immersion	Postimmersion
GLI	34	185.4	78.82	77.27	−1,550			
GRI	35	177.8	82.09	80.89	−1,200	++	0	0
GRO	20	178.4	74.38	73.15	−1,230	++	++	+
HAL	33	167.6	82.96	81.91	−1,050	+	0	0
KRA	32	179.7	72.54	70.90	−1,640	++	0	0
RID	25	174.0	62.47	61.43	−1,040	++	0	+
Mean	30	177.2	75.54	74.24	−1,285			
±SD	±6	±6	±7.61	±7.58	±254			

Thirst sensation: 0, none; +, mild; ++, moderate; +++, intense.

Plasma vasopressin (24) and renin activity (New England nuclear kit) were analyzed by radioimmunoassay. Hemoglobin (Hb) concentration was determined with the cyanomethemoglobin method (Coulter Hb analyzer). Microhematocrit (Hct) was measured in quadruplicate with a modified capillary-tube reader after centrifugation for 10 min with an International centrifuge, model MB. Raw hematocrit values were corrected for trapped plasma and for whole-body Hct by multiplication with the factor 0.874 (0.96 × 0.91, respectively).

Percent changes in plasma volume (% ΔPV) at 60 and 360 min of immersion were calculated from Hct and Hb concentrations (18). Osmotic clearance (C_{osmol}) was calculated from the urinary osmotic excretion ($U_{osm}\dot{V}$)-to-serum osmolality (S_{osmol}) ratio and free water clearance (C_{H_2O}) from urinary excretion rate ($\dot{V}$) minus C_{osmol}.

The sensation of thirst was estimated before, during, and immediately after immersion according to the scale: 0, none; +, mild; ++, moderate; and +++, intense.

The data were analyzed with the Wilcoxon matched-pairs sign-rank test. The null hypothesis was rejected when $P < 0.05$, and nonsignificant differences were denoted by NS. Values are means ± SE unless noted otherwise.

RESULTS

PVP and PRA responses. Mean plasma vasopressin concentration went from 0.7 ± 0.2 pg/ml before immersion to 3.0 ± 0.6 pg/ml ($P < 0.05$) by the end of immersion; PVP was unchanged during the nonimmersion chair-rest control period and ranged from 0.9 ± 0.4 to 1.3 ± 0.5 pg/ml (Figs. 1 and 2). PRA declined progressively from 1.9 ± 0.4 before immersion to 0.5 ± 0.2 ng angiotensin I (Ang I)·$ml^{-1}·h^{-1}$ ($P < 0.05$) at the end of immersion, and was unchanged during the nonimmersion experiment with a range of 2.0 ± 0.3 to 2.1 ± 0.3 ng (Ang I·$ml^{-1}·h^{-1}$) (Fig. 2).

Serum osmotic, electrolyte, and plasma volume changes. Immersion did not alter either serum osmotic or sodium concentrations, which averaged 292 ± 1 mosmol/kg and 142.0 ± 0.4 meq/l respectively, compared with 292 ± 2 mosmol/kg and 141.9 ± 0.4 meq/l before immersion (Fig. 2). Serum potassium concentration increased from 4.01 ± 0.19 to 4.35 ± 0.09 meq/l ($P < 0.05$) at the first hour

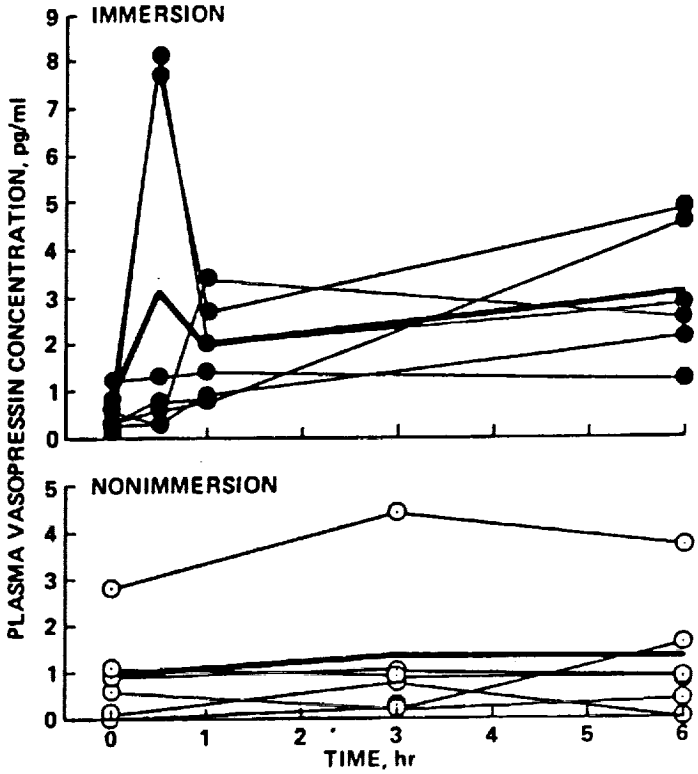

FIG. 1. Individual and mean (*heavy line*) plasma vasopressin concentrations during immersion and nonimmersion experiments.

of immersion, but it returned to base-line values (4.05 ± 0.07 meq/l) by *hour 6* (Fig. 2). Compared with preimmersion values plasma volume (PV) showed a transient increase with a peak value of 7.8 ± 1.6% ($P < 0.05$) after 60 min and decreased to −2.9 ± 1.1% ($P < 0.05$) at the end of immersion.

Urine volume and electrolyte excretion. Immersion resulted in acute and copious diuresis, natriuresis, and kaliuresis (Table 2, Fig. 3). A significantly elevated urine flow ($\dot{V}$) of 3.5 ± 0.5 ml/min ($P < 0.05$), compared with a preimmersion value of 1.1 ± 0.4 ml/min, was measured within the first hour; it increased to a maximal rate of 3.7 ± 1.3 ml/min ($P < 0.05$) between *hours 3* and *4* and declined thereafter to 1.4 ± 0.2 ml/min (NS) by *hour 6*. In contrast $\dot{V}$ decreased steadily from 1.1 ± 0.2 to 0.7 ± 0.1 ml/min ($P < 0.05$) during 6 h of chair-rest in air (Table 2).

Urine sodium excretion increased from 120 ± 30 μeq/min before immersion to 330 ± 40 μeq/min ($P < 0.05$) by *hour 1*, remained elevated throughout, and was 260 ± 40 μeq/min ($P < 0.05$) at the end of immersion (Fig. 3). Natriuresis decreased from 161 ± 11 to 113 ± 10 μeq/min ($P < 0.05$) at the end of the nonimmersion period. In contrast significant kaliuresis was limited to the first 3 h of immersion and decreased to preimmersion levels by *hour 4*; it was unchanged during nonimmersion. The urine Na^+/K^+ excretion ratio was unchanged at about two units during nonimmersion but increased significantly from two to five units from *hour 3* to *hour 6* of immersion (Fig. 3). This increase was due to the reduction in K^+ excretion as Na^+ excretion was essentially constant.

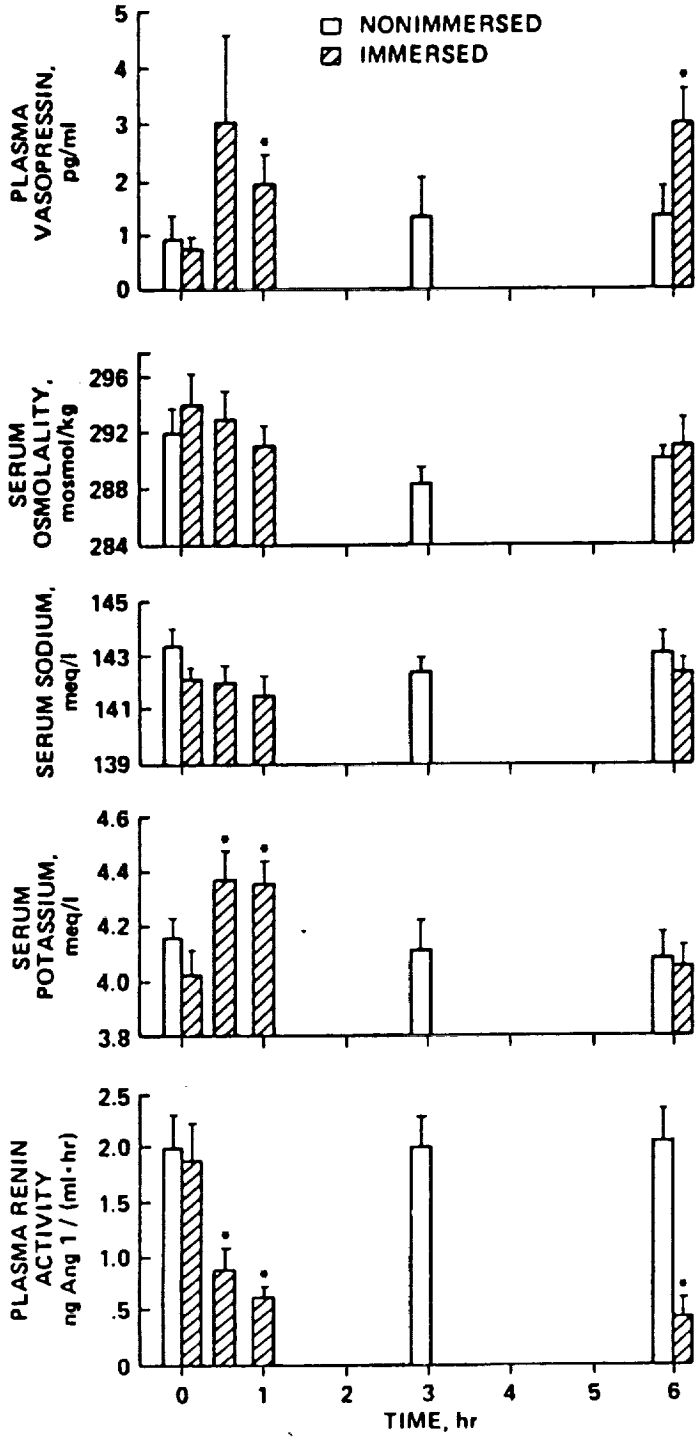

FIG. 2. Plasma vasopressin, serum osmolality, Na^+, K^+, and plasma renin activity during immersion and nonimmersion experiments. Values are means ± SE. * $P < 0.05$ from 0-h value.

Urine osmolality decreased significantly throughout immersion but increased significantly from *hour 2* to *hour 6* in the nonimmersed condition (Table 2). The subjects were moderately hydropenic as immersion progressed, and the increased $\dot{V}$ was due mainly to increased C_{osmol}. Urine osmotic clearance was generally higher and C_{H_2O} generally lower during immersion, whereas both variables were unchanged during nonimmersion. Free water clearance was negative throughout immersion but was less negative as time progressed. It was -1.9 ± 0.3 ml/min at base line and -1.1 ± 0.5 ml/min ($P < 0.05$) at *hour 6* (Table 2) in spite of a significant loss of body wt by 1,285 ± 104 g (Table 1).

Thirst and drinking. No subject drank water during immersion even though water was available in sight of the subjects. All subjects were mildly to moderately thirsty just before immersion; with the exception of the *subject GRO* thirst disappeared during immersion (Table 1). In general thirst did not reappear within 5 min after immersion as the subjects assumed the horizontal position immediately after emerging from the tank.

DISCUSSION

There is general agreement that an increase in central (thoracic) blood volume (1, 6) and the accompanying absolute increase in PV (19) (i.e., hypervolemia of 7.8% in the present study) provide the stimuli for the renal responses during immersion. These fluid shifts increase central venous (right atrial) pressure (27) and cardiac output (1, 27, 28). The increase in central blood volume in less than 6 s (28) suggests that the major response is the cephalad shift of blood from the lower extremities as a result of *1*) reduced venous capacitance caused by increased external hydrostatic counterpressure and 2) a pseudonegative-pressure breathing effect (6) caused by upward displacement of the diaphragm by the water pressure.

Immersion produces intense diuresis, natriuresis, and kaliuresis in hydrated subjects drinking water during immersion (8, 9, 21) and somewhat attenuated responses in water-deprived subjects not drinking during immersion (12, 19). It is still unclear how thoracic volume expansion induces increased fluid and electrolyte excretion. Gauer et al. (14) have proposed that signals from left atrial distension stimulate the hypothalamus to suppress vasopressin release, which instigates the diuresis. Subsequently some evidence has indicated that in hydrated immersed subjects there is suppression of antidiuretic hormone activity in urine (10), that injection of vasopressin attenuates urine flow (7, 25), and that PVP concentration is significantly decreased (20, 21).

In a recent investigation Epstein et al. (12) demonstrated that PVP decreased in 8 of 12 men during 8 h of NI. The question still remains whether the statistically significant decline in PVP by 0.5 pg/ml (from 1.5 to 1.0 pg/ml), clearly within the normal range, was the only factor that could have accounted for the observed diuresis. Epstein et al. (7) also infused aqueous vasopressin into subjects during immersion and observed that indeed the hormone did suppress diuresis. However this observation is not proof that diuresis is a consequence of suppression of this hormone. Injection of a pharmacological dose of vasopressin will presumably reduce urine flow regardless of other physiological factors which may be involved. The effect of infused vasopressin is difficult to interpret, since no values of plasma concentrations of the hormone were given either before or after administration.

In the present study mean PVP was 0.7 ± 0.2 pg/ml

TABLE 2. *Urine composition in seated subjects during 6 h of water immersion or nonimmersion*

	Base Line	Immersed or Seated Outside Water Tank					
	−2 h	+1 h	+2 h	+3 h	+4 h	+5 h	+6 h
$\dot{V}$, ml/min							
Immersed	1.1 ± 0.4	3.5 ± 0.8*	2.9 ± 0.6*	3.5 ± 0.7*	3.7 ± 1.3*	2.2 ± 0.4*	1.4 ± 0.2
Nonimmersed	1.1 ± 0.02	1.1 ± 0.1	1.0 ± 0.1	0.8 ± 0.1*	0.8 ± 0.1*	0.8 ± 0.03*	0.7 ± 0.1*
U_{osm}, mosmol/kg							
Immersed	639 ± 97	550 ± 132*	483 ± 90*	533 ± 123*	423 ± 62*	518 ± 69*	545 ± 62*
Nonimmersed	728 ± 80	735 ± 72	776 ± 73*	795 ± 68*	802 ± 67*	809 ± 66*	815 ± 65*
C_{osm}, ml/min							
Immersed	3.1 ± 0.3	5.1 ± 0.3*	3.9 ± 0.4	5.7 ± 0.7*	4.2 ± 0.4*	3.4 ± 0.2	2.7 ± 0.5
Nonimmersed	2.7 ± 0.3	2.7 ± 0.4	2.8 ± 0.4	2.1 ± 0.3	2.2 ± 0.3	2.1 ± 0.2	1.9 ± 0.1
C_{H_2O}, ml/min							
Immersed	−1.9 ± 0.3	−1.6 ± 0.7	−1.1 ± 0.4*	−1.7 ± 0.8	−0.4 ± 1.0*	−1.0 ± 0.5	−1.1 ± 0.5*
Nonimmersed	−1.6 ± 0.3	−1.6 ± 0.3	−1.8 ± 0.3	−1.3 ± 0.2	−1.4 ± 0.2	−1.4 ± 0.2	−1.2 ± 0.1

Values are means ± SE. $\dot{V}$, urinary excretion rate; U_{osm}, urine osmolality; C_{osm}, osmotic clearance; C_{H_2O}, free water clearance. * $P < 0.05$ from 2-h base-line value.

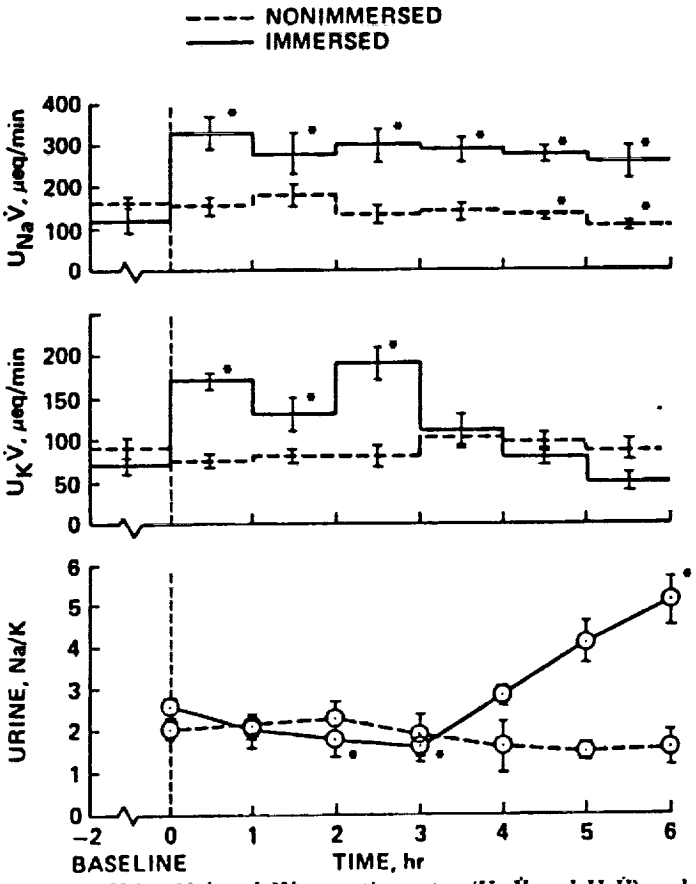

FIG. 3. Urine Na^+ and K^+ excretion rates ($U_{Na}\dot{V}$ and $U_K\dot{V}$) and urine Na^+/K^+ during immersion and nonimmersion experiments. Values are means ± SE. * $P < 0.05$ from base-line value.

(well within the normal range) before immersion. It rose significantly by the first hour, presumably remained elevated throughout immersion, and reached 3.0 ± 0.6 pg/ml at 6 h. Clearly there was no hint of PVP suppression in this study. The two increased PVP values at 30 min were probably due to emotional stimuli, possibly painful hypodermic needle insertions. We observed no apprehension or other untoward responses in the subjects that would result in elevated PVP levels. In the nonimmersion experiment mean PVP varied from 0.9 to 1.3 pg/ml.

Two disturbing observations emerged from our previous studies (20, 21). First, PVP suppression occurred during chair-rest in air (21) which suggests that perhaps the suppression was caused by water consumption. Results from a subsequent study in our laboratory indicate a significant suppression of PVP, from 3.3 to 2.4 pg/ml within 3 min of drinking water, by mildly dehydrated subjects with no change in serum osmolality (G. Geelen, unpublished data). Thus drinking during immersion may contribute to PVP suppression. Second, while PVP was reduced significantly by the second hour in subjects drinking during immersion, PVP increased toward preimmersion levels during the remainder of the 8-h immersion period (20). Results from a subsequent study (19), in mildly dehydrated subjects who drank no water within the first 2 h of immersion, strongly suggest that the nonsignificant drop in PVP at 30 min was due at least in part to the initial hypervolemia. No significant PVP suppression was evident during that study.

Our findings are in general agreement with those of Gilmore et al. (17) who failed to demonstrate a consistent change in PVP following an acute (15%) volume expansion in monkeys despite a substantial elevation by 17.1 cmH_2O of left-ventricular end-diastolic pressure. Another group of monkeys responded to the same (15%) hypervolemia with a significant salt and water excretion (5). Also, Boasberg et al. (4) observed unchanged serum vasopressin levels in two normal subjects who underwent a 4-h water immersion, whereas vasopressin concentration rose in two immersed patients with intrathoracic carcinoma. Whereas PVP seems to be very responsive to stimulation of low-pressure receptors in dogs, the same reflex may not be as sensitive in monkeys (2, 17) or in man. Arnauld and coworkers (2) found in conscious monkeys that a blood volume reduction of 20% did not increase PVP concentration until a fall in arterial blood pressure occurred. This high-pressure-receptor theory is consistent with the unchanged PVP observed in the present study where blood pressure has been reported to remain essentially constant during immersion (1, 12).

Despite a sustained fluid and electrolyte loss throughout the 6-h immersion period that resulted in a negative

water balance, all the subjects refused to drink while they were immersed. The lack of a conscious desire for water combined with the progressive fluid deficit is puzzling. However, there is evidence that reduction of intrathoracic blood volume is a stimulus for thirst and that the renin-angiotensin system may be a mediator of the thirst sensation (29). It is therefore possible that the suppression of PRA in our subjects contributed to the reduction in thirst despite the significant decrease in blood volume.

Although the elevated concentration of plasma potassium during the initial hours of immersion is difficult to explain, it has been observed repeatedly (19, 20, 21). The concomitant kaliuresis that occurred during the first hours of immersion may have been a direct response to elevated extracellular fluid potassium ion concentration by increased potassium tubular secretion (22).

Several immersion studies have included the simultaneous measurement of plasma aldosterone (PA) and PRA (11, 13). In the present study PRA was suppressed significantly at 30 min of immersion and had declined by 74% by the end of the experiment. If we assume that PA concentrations followed the fall in PRA, then perhaps the significant rise in sodium excretion was the result of a reduction in PA secretion. There is, however, strong evidence against this explanation because the natriuresis was accompanied by increased excretion of potassium during the first half of immersion. This concomitant loss of sodium and potassium is contrary to the accepted action of aldosterone on electrolyte excretion. Nevertheless, as pointed out by Korz et al. (26) whose results agree with ours, a continued inhibition of PA secretion could explain the renal handling of electrolytes during the final half of immersion when the kaliuresis decreased while sodium excretion remained elevated (Fig. 2). However, by measuring PA and sodium excretion in conscious monkeys over a longer period of time, Kass and Moore-Ede (23) demonstrated that initial PA suppression during lower body positive pressure at 20 Torr was restored to control values 24 h later, whereas sodium continued to be excreted at a high rate throughout the 4-day study. Although cardiac output is enhanced throughout immersion (1, 3), renal blood flow and glomerular filtration rate are unaltered, and natriuresis is mediated independently of changes in renal perfusion (9). Administration of deoxycorticosterone acetate failed to suppress sodium excretion during immersion (8). It is clear from these results that sodium excretion during immersion may be independent of aldosterone action.

Results of these experiments indicate that PVP was not suppressed by water immersion in normally hydrated subjects and that other factors may be responsible for the diuresis.

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Paper IV

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Effect of antigravity suit inflation on cardiovascular, PRA, and PVP responses in humans

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KRAVIK, S. E., L. C. KEIL, G. GEELEN, C. E. WADE, P. R. BARNES, W. A. SPAUL, C. A. ELDER, AND J. E. GREENLEAF. *Effect of antigravity suit inflation on cardiovascular, PRA, and PVP responses in humans.* J. Appl. Physiol. 61(2): 766–774, 1986.—Blood pressure, pulse rate (PR), serum osmolality and electrolytes, as well as plasma vasopressin (PVP) and plasma renin activity (PRA), were measured in five men and two women [mean age 38.6 ± 3.9 (SE) yr] before, during, and after inflation of an antigravity suit that covered the legs and abdomen. After 24 h of fluid deprivation the subjects stood quietly for 3 h: the 1st h without inflation, the 2nd with inflation to 60 Torr, and the 3rd without inflation. A similar control noninflation experiment was conducted 10 mo after the inflation experiment using five of the seven subjects except that the suit was not inflated during the 3-h period. Mean arterial pressure increased by 14 ± 4 (SE) Torr ($P < 0.05$) with inflation and decreased by 15 ± 5 Torr ($P < 0.05$) after deflation. Pulse pressure (PP) increased by 7 ± 2 Torr ($P < 0.05$) with inflation and PR decreased by 11 ± 5 beats/min ($P < 0.05$); PP and PR returned to preinflation levels after deflation. Plasma volume decreased by 6.1 ± 1.5% and 5.3 ± 1.6% ($P < 0.05$) during *hours 1* and *3*, respectively, and returned to base line during inflation. Inflation decreased PVP from 6.8 ± 1.1 to 5.6 ± 1.4 pg/ml ($P < 0.05$) and abolished the significant rise in PRA during *hour 1*. Both PVP and PRA increased significantly after deflation: Δ = 18.0 ± 5.1 pg/ml and 4.34 ± 1.71 ng angiotensin $I \cdot ml^{-1} \cdot h^{-1}$, respectively. Serum osmolality and Na^+ and K^+ concentrations were unchanged during the 3 h of standing. These data indicate a headward redistribution of blood during inflation, and the antigravity suit may provide an alternative to bed rest and water immersion for examining some early responses of humans to weightlessness.

lower body positive pressure; presyncope; blood pressure; pulse rate; plasma volume; serum osmolality; serum sodium; serum potassium

ANTIGRAVITY GARMENTS have been utilized successfully in the treatment of hemorrhagic shock (7, 9, 27) and postural hypotension (24) and as a tool for studying the physiological characteristics of orthostatic insufficiency (5). Medical antishock trousers have been available commercially since 1973 and are a widely used lifesaving device in emergency medicine (16).

Results from numerous studies emanating from extensive use of the antigravity suit during the last 80 years have shown that circumferential pneumatic counterpressure applied to the legs and abdomen opposes the hydrostatic gravitational stress which acts on the circulatory system of humans in the upright position (21). But it is evident that many of the physiological effects of counterpressure remain unclear.

The purpose of this study was to determine the effect of lower body and abdominal pressure, exerted by an antigravity suit, on blood pressure, pulse rate, fluid and electrolyte shifts, plasma vasopressin, and plasma renin activity in healthy human subjects in the upright posture.

METHODS

Healthy subjects, five men and two women (20–50 yr), gave their informed consent to participate in the study. The subjects were nonsmokers with no history of cardiac or renal disease; they did not use drugs or medication.

To standardize fluid and salt intake, each subject undersent a 24-h fluid deprivation period supplemented with a dry diet containing 6 g of sodium chloride; they arrived at the laboratory at 0800 h. A flexible Teflon catheter (Vicra Quick-Cath, Travenol Laboratories) was inserted into a large antecubital vein. The subjects then donned the medical antishock trousers (MAST III-A, David Clark), an antigravity suit. Two experiments were conducted: an inflation experiment and a control noninflation experiment. In the inflation experiment, the test subjects (*I–VII*) stood upright at room temperature (25°C) for 3 h; a natural postural sway was allowed, but the subjects tried to stand as quietly as possible. The antigravity suit was worn throughout the 3-h study period. The suit was not inflated during the 1st h, was inflated to 60 Torr throughout the 2nd h, and was again deflated for the 3rd h. The control noninflation experiment was conducted 10 mo after the inflation experiment. The test procedure was the same, except that the antigravity suit was kept deflated throughout the 3-h standing period, and *subjects II* and *VII* did not participate. Blood samples were taken at the same time of day in both experiments. The one female subject (*III*) who participated in both experiments was tested on both occasions midway between her menstrual cycles.

The suit consisted of an abdominal bladder, which extended from the xiphoid to the pubis, and two separate thigh-leg bladders. The garment was secured with Velcro fasteners. The leg bladders were always inflated before

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the abdominal bladder to avoid trapping blood in the lower extremities (2). The suit was filled with air, and a regulator made it possible to control the pressure at 60 ± 5 (SE) Torr. This inflation pressure selected was determined, from previous experience, to be that above which no further normal significant physiological effects were induced. Pain and discomfort occurs at pressures above ~65 Torr. The inflation procedure took <1 min, and the pressure was released in a few seconds. The abdominal and leg bladders were deflated simultaneously.

Radial pulse rate (PR) was monitored, and brachial blood pressure was measured with a mercury sphygmomanometer (W. A. Baum) by the same observer at times before inflation of −60, −45, −30, −15, −10, and −2 min; at times after inflation of +1, +3, +5, +10, +15, +30, +45, and +60 min; and at times after deflation of +61, +63, +65, +75, +90, +105, and +120 min. The lower arm was rested on a table so that the middle third of the upper arm remained at heart level. Diastolic blood pressure (DBP) was recorded as the Korotkoff sound disappeared. Pulse pressure (PP) was systolic blood pressure (SBP) minus DBP. Mean arterial blood pressure (MAP) was DBP + ⅓PP. Blood samples were taken at experiment times −60, −30, −15, −2, +5, +10, +15, +30, +45, +60 +65, +75, +90, and +120 min; 280 ml of blood were removed during each experiment.

Serum was analyzed for Na^+ and K^+ (Instrumentation Laboratory digital flame photometer model 643) and osmolality (Advanced Instruments Digimatic freezing-point osmometer model 3DII). Plasma vasopressin (PVP) (17) and plasma renin activity (PRA) (New England Nuclear kit) were measured by radioimmunoassay. Hemoglobin (Hb) concentration was determined with the cyanomethemoglobin method (Coulter Hb analyzer). Microhematocrit (Hct) was measured in quadruplicate with a modified capillary-tube reader after centrifugation with an International centrifuge (model MB). Raw Hct values were corrected for trapped plasma and for whole-body Hct by multiplication with the factor 0.874 (0.96 × 0.91), respectively. Mean corpuscular Hb concentration (MCHC) was 100 [Hb]/(Hct × 0.96). Percent change in plasma volume (%ΔPV) was calculated from the Hct (13).

Two values (±SE) were calculated: the mean of individual values for each time that data were collected; and the group mean value for which data for all subjects in each hour were averaged and then means calculated. The data were analyzed with the Wilcoxon matched-pairs signed-ranks test. The null hypothesis was rejected when $P < 0.05$, and nonsignificant differences were denoted by NS.

RESULTS

Presyncopal signs and symptoms. Four of the seven subjects (*II, III, IV,* and *VII*) were presyncopal from 5 to 30 min after deflation (Table 1). The subjects complained of lightheadedness and epigastric distress; sweating was usually evident. No subject lost consciousness. *Subjects III* and *IV* had several presyncopal episodes during the control noninflation experiment (Table 2). During the episodes, MAP fell, PP narrowed, and bradycardia occurred. During the presyncopal episodes the changes in blood pressure and pulse rate were often more pronounced than indicated in Tables 1 and 2, which show readings taken after the subjects had been seated or returned to the horizontal position. PVP and PRA always increased shortly after subjects reported impending symptoms of fainting. During inflation, no presyncopal signs or symptoms developed and all subjects expressed feelings of well being.

Blood pressure and pulse rate. During the 1st h of the inflation experiment, MAP and PP decreased from 92 ± 4 to 85 ± 4 Torr ($P < 0.05$) and from 33 ± 4 to 27 ± 3 Torr ($P < 0.05$), respectively; PR remained unchanged (Table 1). Group mean MAP and PP values were 86 ± 5 and 29 ± 3 Torr, respectively, for the 1st h, increased to 100 ± 4 and 36 ± 2 Torr ($P < 0.05$) with inflation, and decreased to 85 ± 4 and 23 ± 2 Torr ($P < 0.05$) after deflation (Fig. 1). Following suit inflation, group mean PR was 67 ± 4 beats/min, which was lower ($P < 0.05$) than pre- and postinflation values of 78 ± 6 and 82 ± 5 beats/min, respectively (Fig. 1). During the control experiment, group mean MAP was 95 ± 4 Torr and the PP was 31 ± 6 Torr during the 1st h, 89 ± 6 (NS) and 26 ± 4 Torr ($P < 0.05$) during the 2nd h, and decreased further to 86 ± 6 ($P < 0.05$) and to 22 ± 2 Torr (NS) during the 3rd h. Group mean PR (75 ± 0.5 beats/min) was unchanged over the 3-h control experiment (Fig. 1).

Serum osmotic, electrolyte, endocrine, and plasma volume responses. Inflation did not alter serum osmotic (Fig. 2), Na^+, or K^+ concentrations, which averaged 299 ± 0.3 mosmol/kg, 144 ± 0.2 meq/l, and 4.3 ± 0.02 meq/l, respectively, during the 3 h of standing; mean values during the control experiment were 293 ± 0.4 mosmol/kg, 142 ± 0.1 meq/l, and 4.3 ± 0.03 meq/l, respectively. Neither 3 h of prolonged standing nor inflation of the suit changed the MCHC, which was 35.2 ± 0.1 and 36.7 ± 0.1% during the inflation and noninflation experiments, respectively.

During the preinflation periods (*hour 1*) PVP rose from 3.7 ± 0.5 to 9.3 ± 2.1 pg/ml ($P < 0.05$) in the inflation experiment and from 4.2 ± 0.8 to 10.1 ± 3.8 pg/ml ($P < 0.05$) in the control experiment (Tables 1 and 2, Fig. 2). PVP decreased significantly with inflation during *hour 2* of the inflation experiment and reached ~5 pg/ml; it increased massively during *hour 2* of the noninflation control experiment and remained elevated during *hour 3*. PVP increased significantly during 3rd-h deflation in the inflation experiment (Fig. 2). The group mean data reflected these PVP responses (Fig. 3).

PRA increased from 2.32 ± 0.60 to 5.06 ± 1.11 ($P < 0.05$) and from 1.31 ± 0.60 to 3.56 ± 1.23 ng angiotensin I (ANG I)·ml^{-1}·h^{-1} ($P < 0.05$) during the 1st h of the inflation and control experiments, respectively (Tables 1 and 2). During the 2nd h, PRA continued to rise slightly in the control experiment but showed no further change on inflation in the inflation experiment; it increased significantly, to between 6.5–7.0 ng ANG I·ml^{-1}·h^{-1} during the 3rd h in both experiments (Tables 1 and 2, Fig. 3).

TABLE 1. *Cardiovascular, plasma vasopressin, and plasma renin activity responses: inflation experiment*

	Subj No.	Time, Standing, min																				
		−60	−45	−30	−15	−10	−2	+1	+3	+5	+10	+15	+30	+45	+60	+61	+63	+65	+75	+90	+105	+120
MAP, Torr	I	110	108	107	105	101	102	118	120	117	118	118	118	118	119	109	112	104	103	104	102	104
	II	78	70	73	73	73	73	87	83	84	81	84	87	85	86	77	77	77§	70§	68	70	75
	III	93	80	79	79	79	78	102	101	101	101	105	107	107	103	76	78	82	82	63§	77	77
	IV	90	83	85	85	84	85	105	102	97	95	94	93	97	97	83	82	81	77	84§	81	85
	V	98	97	97	95	94	94	100	99	103	101	102	103	103	103	93	93	97	90	93	92	90
	VI	90	83	86	89	88	85	100	100	100	100	101	101	101	102	89	91	91	89	89	88	91
	VII	87	87	78	81	80	78	100	98	97	98	95	96	95	97	76	77	65§	77	77	80	82
	Mean	92	87*	86*	87*	86*	85*	102‡	100‡	100‡	99‡	100‡	101‡	101‡	101‡	86†	87†	85†	84†	83†	84†	86†
	±SE	±4	±5	±5	±4	±4	±4	±3	±4	±4	±4	±4	±4	±4	±4	±5	±5	±5	±4	±5	±4	±4
PP, Torr	I	45	40	42	45	33	35	40	38	35	40	38	40	37	34	28	20	32	25	32	31	32
	II	25	15	25	23	25	23	50	38	31	34	36	35	30	33	20	20	20§	30§	25	30	30
	III	25	30	28	27	26	25	35	36	34	30	30	35	37	40	18	25	20	20	25§	20	20
	IV	30	25	17	15	19	20	30	35	35	38	37	33	31	31	10	20	18	20	17§	19	20
	V	44	41	34	31	35	34	44	37	44	37	42	41	40	41	18	29	26	29	27	23	23
	VI	45	40	33	32	30	37	45	45	45	38	43	40	41	42	20	28	28	28	28	25	26
	VII	20	20	18	17	18	18	30	25	27	25	28	24	28	26	17	20	15§	20	20	18	20
	Mean	33	30	28	27*	27*	27*	39‡	36‡	36‡	35‡	36‡	35‡	35‡	35‡	18†	24†	22†	25†	25†	23†	24†
	±SE	±4	±4	±3	±4	±3	±3	±3	±2	±3	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
PR, beats/min	I	88	84	86	84	86	86	78	80	82	82	80	80	80	80	96	90	86	88	90	96	94
	II	88	70	100	100	90	90	58	70	74	70	65	75	76	77	85	70	96§	58§	80	90	96
	III	90	86	86	85	86	84	60	64	64	68	70	68	74	74	100	102	100	87	70§	78	85
	IV	74	72	74	72	70	74	58	58	56	57	60	64	62	60	76	78	79	78	70§	68	70
	V	84	86	84	82	85	82	66	75	81	80	80	82	80	82	100	108	100	96	100	100	100
	VI	50	60	52	52	50	52	46	48	48	46	46	48	47	46	66	60	60	56	58	58	60
	VII	82	80	74	80	82	84	64	66	64	64	65	66	68	66	84	82	60§	75	76	74	80
	Mean	79	77	79	79	78	79	61‡	66‡	67‡	67‡	67‡	69‡	70‡	69‡	87†	84†	83†	77†	78†	81†	84†
	±SE	±5	±4	±6	±6	±5	±5	±4	±4	±5	±5	±5	±4	±5	±5	±5	±7	±7	±6	±5	±6	±6
PVP, pg/ml	I	4.3		4.6	5.6		6.3			3.3	3.2	3.9	3.8	5.6	4.9			3.7	4.8	7.4		7.4
	II	4.4		4.0	7.3		7.8			5.0	5.5	5.5	6.8	4.1	7.8			19.3§	13.7§	10.7		10.7
	III	1.6		11.6	13.4		18.0			10.0	8.9	6.5	4.5	4.4	2.6			4.8	8.0	250.0§		20.4
	IV	4.7		13.3	6.3		8.8			7.2	7.3	8.6	8.2	8.6	11.4			13.8	18.8	34.8§		16.1
	V	4.7		9.2	7.6		16.2			11.4	6.0	7.3	8.7	9.0	8.7			11.3	16.6	14.5		14.8
	VI	3.4		7.1	3.1		5.0			4.5	4.4	3.7	4.3	3.3	1.6			4.2	4.8	5.2		5.9
	VII	2.5		2.6	2.7		3.3			3.1	2.6	2.5	2.0	2.3	2.1			49.5§	27.1	25.8		5.3
	Mean	3.7		7.5*	6.6*		9.3*			6.4‡	5.4‡	5.4‡	5.5‡	5.3‡	5.6			15.2†	13.4†	49.8†		11.5†
	±SE	±0.5		±1.5	±1.3		±2.1			±1.2	±0.8	±0.8	±0.9	±1.0	±1.4			±6.1	±3.1	±33.6		±2.2
PRA, ng ANG I·$ml^{-1}·h^{-1}$	I	1.58		2.23	2.24		2.06			2.48	2.32	2.04	2.17	2.40	2.33			2.55	2.72	2.79		3.00
	II	3.86		5.73	2.75		6.48			6.00	4.99	5.32	6.62	6.78	6.94			8.69§	9.20§	7.53		7.91
	III	4.79		7.09	7.67		7.91			7.47	6.15	6.21	5.86	6.24	5.26			6.72	7.80	20.21§		15.86
	IV	2.26		3.97	7.37		7.58			7.18	5.62	5.46	4.98	5.27	6.02			6.81	10.41	14.54§		13.49
	V	1.12		2.58	3.29		4.50			4.00	3.80	3.94	4.41	3.98	4.50			4.96	6.73	8.03		8.31
	VI	0.15		0.22	0.21		0.22			0.18	0.32	0.16	0.21	0.16	0.26			0.21	0.25	0.35		0.35
	VII	2.51		4.28	4.84		6.66			5.84	4.45	3.63	3.49	3.23	3.40			5.61§	5.62	5.64		4.66
	Mean	2.32		3.73*	4.05*		5.06*			4.47‡	3.95‡	3.82‡	3.96	4.01	4.10			5.08†	6.10†	8.44†		7.65†
	±SE	±0.60		±0.87	±1.04		±1.11			±1.01	±0.77	±0.81	±0.84	±0.88	±0.87			±1.08	±1.36	±2.59		±2.10

Antigravity suit inflated to 60 Torr. *Subjects II* and *III* are female. MAP, mean arterial pressure; PP, pulse pressure; PR, pulse rate; PVP, plasma vasopressin; PRA, plasma renin activity. * $P < 0.05$ vs. ambulatory (−60 min). † $P < 0.05$ vs. values at +60 min. ‡ $P < 0.05$ vs. values at −2 min. § Presyncopal signs and symptoms.

TABLE 2. *Cardiovascular, plasma vasopressin, and plasma renin activity responses: noninflation experiment*

	Subj No.	Time, Standing, min																				
		−60	−45	−30	−15	−10	−2	+1	+3	+5	+10	+15	+30	+45	+60	+61	+63	+65	+75	+90	+105	+120
MAP, Torr	I	115	115	112	109	107	107	107	109	106	106	106	105	106	104	104	104	104	104	104	104	104
	III	92	90	90	80§	81	83	79	81	81	72§	58§	75	72	68	65	67	63§	72	68§	75	61§
	IV	91	91	93	90	89	88	88	91	93	88	75	77§	81	85	84	79	75	82§	83	76	79§
	V	93	93	88	88	87	90	88	88	95	92	95	90	92	95	92	93	93	93	88	88	88
	VI	95	95	97	97	94	94	94	90	97	97	93	93	90	93	93	95	88	87	87	87	87
	Mean	97	97	96	93	92*	92*	91	92	94	91	85	88	88	89	88	88	84	86	86	86	84†
	±SE	±5	±5	±4	±5	±4	±4	±5	±5	±4	±6	±8	±6	±6	±6	±6	±7	±7	±6	±6	±5	±7
PP, Torr	I	45	38	42	43	37	37	35	35	33	36	33	35	32	32	34	32	32	32	32	32	32
	III	20	22	23	7§	19	16	13	10	10	20§	10§	15	20	25	22	20	8†	12	10†	15	10†
	IV	28	19	17	15	20	25	18	17	18	18	15	20§	20	22	24	16	20	20†	23	18	20†
	V	55	55	55	40	35	45	40	40	30	35	30	30	35	30	35	25	25	25	25	25	25
	VI	30	30	27	27	29	29	30	30	25	27	25	25	30	25	25	22	25	22	22	22	20
	Mean	36	33	33	26*	28*	30*	27	26	23‡	27	23‡	25‡	27	27	28	23	22	22	22	22	21†
	±SE	±6	±6	±7	±7	±4	±5	±5	±5	±4	±4	±4	±4	±3	±2	±3	±3	±4	±4	±4	±3	±4
PR, beats/min	I	84	84	84	86	86	88	86	84	86	88	90	86	88	90	90	90	92	94	92	92	92
	III	78	80	84	82§	84	86	76	80	80	70§	62§	76	70	78	72	70	58§	64	66§	80	80§
	IV	64	64	66	62	72	70	70	70	72	74	74	72§	70	70	72	72	70	68§	70	74	70§
	V	78	86	90	86	88	84	84	84	84	92	84	88	86	96	92	86	90	86	92	98	102
	VI	54	56	54	54	56	56	56	54	52	54	58	62	56	61	57	58	58	59	60	60	63
	Mean	72	74	76	74	77*	77*	74	74	75	76	74	77	74	79	77	75	74	74	76	81	81
	±SE	±5	±6	±7	±7	±6	±6	±5	±6	±6	±7	±6	±5	±6	±6	±6	±6	±7	±7	±7	±7	±7
PVP, pg/ml	I	3.8		4.6	5.6		5.9			5.5	5.0	6.9	5.9	4.0	4.2			4.8	4.5	5.0		7.0
	III	5.1		5.4	8.6§		24.3			25.4	55.3§	175.2§	35.2	50.6	71.5			130.8§	58.3	68.2§		60.0§
	IV	6.7		8.6	10.6		10.8			12.0	13.9	14.3	52.5§	30.6	18.5			34.6	40.3§	21.1		33.7§
	V	2.6		5.1	6.6		6.0			6.0	5.4	6.5	7.4	5.7	6.2			6.6	9.7	7.6		10.7
	VI	3.0		3.6	3.0		3.3			3.6	4.0	3.9	3.5	2.4	2.4			3.1	4.9	41.1		5.1
	Mean	4.2		5.5*	6.9		10.1*			10.5	16.7	41.4‡	21.0	18.7	20.6			36.0†	23.5	17.2		23.3
	±SE	±0.8		±0.8	±1.3		±3.8			±4.0	±9.8	±33.5	±9.8	±9.5	±13.0			±24.4	±10.9	±8.3		±10.5
PRA, ng ANG I·$ml^{-1}·h^{-1}$	I	2.34		2.45	2.43		2.76			2.88	2.84	3.02	3.13	3.08	3.33			3.38	3.18	3.39		3.34
	III	3.45		5.32	5.70§		7.27			8.79	8.31§	11.14§	11.18	10.17	11.24			16.56§	13.90	14.07§		13.29§
	IV	1.61		3.76	4.13		5.17			5.42	5.71	5.45	8.71§	8.81	8.55			7.85	8.71§	8.44		9.19§
	V	0.46		1.81	2.29		2.51			2.74	2.98	3.13	3.73	3.79	4.18			4.03	4.92	5.87		5.86
	VI	0.21		0.26	0.23		0.21			0.16	0.20	0.41	0.40	0.27	0.26			0.26	0.46	0.29		0.51
	Mean	1.61		2.72*	2.96*		3.56*			4.00	4.01	4.63‡	5.43‡	5.22‡	5.51‡			6.42	6.23	6.41		6.43†
	±SE	±0.60		±0.86	±0.92		±1.23			±1.46	±1.38	±1.81	±1.97	±1.85	±1.95			±2.81	±2.34	±2.34		±2.23

Subjects II and *III* are female. MAP, mean arterial pressure; PP, pulse pressure; PR, pulse rate; PVP, plasma vasopressin; PRA, plasma renin activity. * $P < 0.05$ vs. ambulatory (−60 min). † $P < 0.05$ vs. values at +60 min. ‡ $P < 0.05$ vs. values at −2 min. § Presyncopal signs and symptoms.

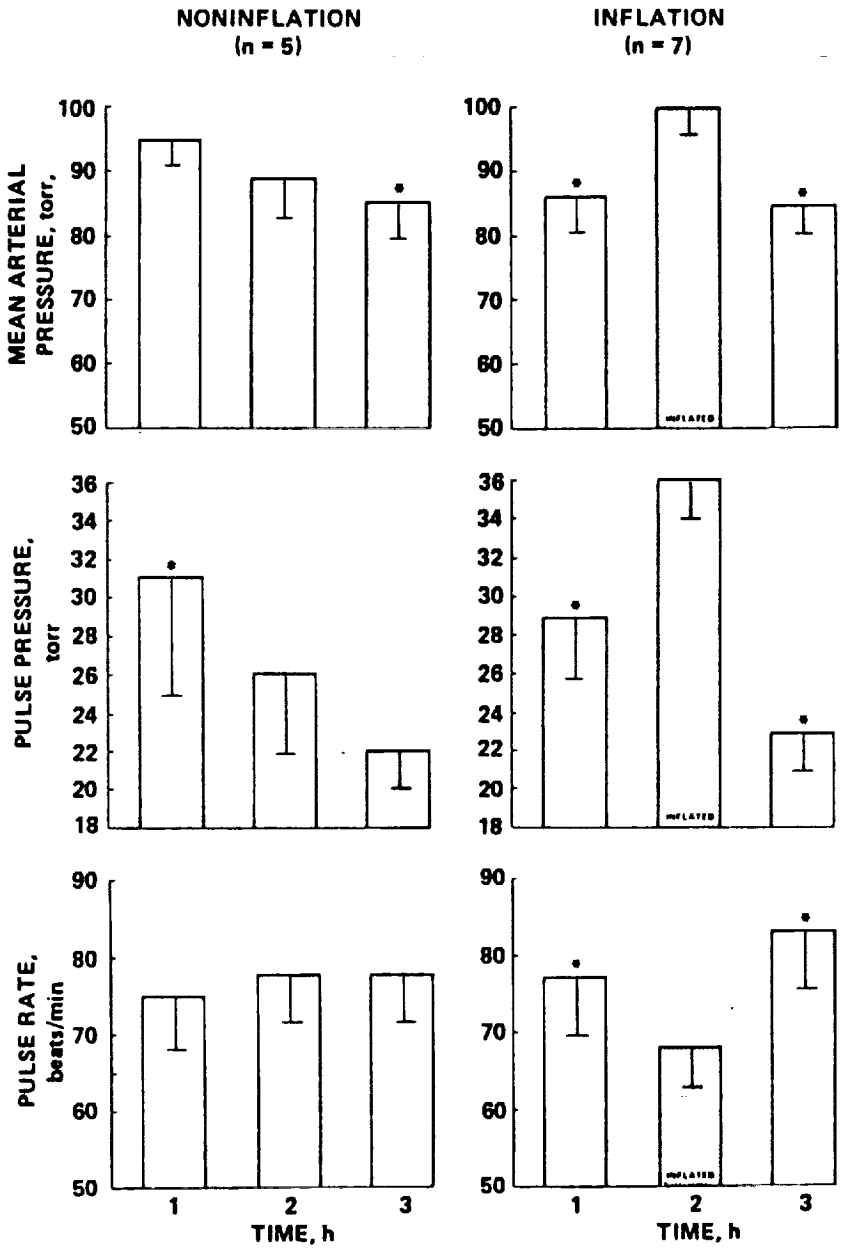

FIG. 1. Group mean arterial pressure, pulse pressure, and pulse rate during 3 h of quiet standing in noninflation (control) and inflation experiments. Values are group means ± SE. * $P < 0.05$ from *hour 2*.

During the control experiment, PV decreased by 8.2 ± 0.9% ($P < 0.05$) by the end of the 1st h of standing but did not change further thereafter (Fig. 3). In the inflation experiment, PV was restored during inflation such that the deflation losses of 6.1 ± 1.5% (*hour 1*) and 5.3 ± 1.6% (*hour 3*) were reduced significantly to only 2.2 ± 1.3% with inflation (Fig. 3). With an assumed PV of 3,000 ml, the difference between losses of 8.2 and 2.2% is 180 ml.

DISCUSSION

Because of gravity, assumption of the upright posture shifts 500–700 ml of blood from the thoracic compartment into the dependent veins of the abdomen and legs (10, 25). This pooling of blood may be regarded as a functional hemorrhage into the leg and splanchnic vessels. As prolonged quiet standing continues there is an 11–15% decrease in the effective circulating blood volume; the decrease is a result of increased hydrostatic pressure and the ensuing filtration of fluid from capillaries in the lower parts of the body (10). In addition to standing for 3 h, our subjects had undergone a 24-h fluid deprivation period (with a dry diet supplement containing a total of 6 g of NaCl). These stresses contribute to a state of hypovolemia that requires circulatory adjustments (4).

Four of the seven subjects were presyncopal between 5 and 30 min after the suit was deflated, and two of the five subjects had several presyncopal reactions during the control experiment. The onset was always unpredictable and occurred almost instantly. A concomitant bradycardia, abrupt fall in blood pressure, and narrowing of the pulse pressure were consistent findings. That inflation of the antigravity suit attenuated presyncopal responses was clearly illustrated. All subjects expressed feelings of well being, and no presyncopal episodes developed during inflation of the suit. During orthostatic

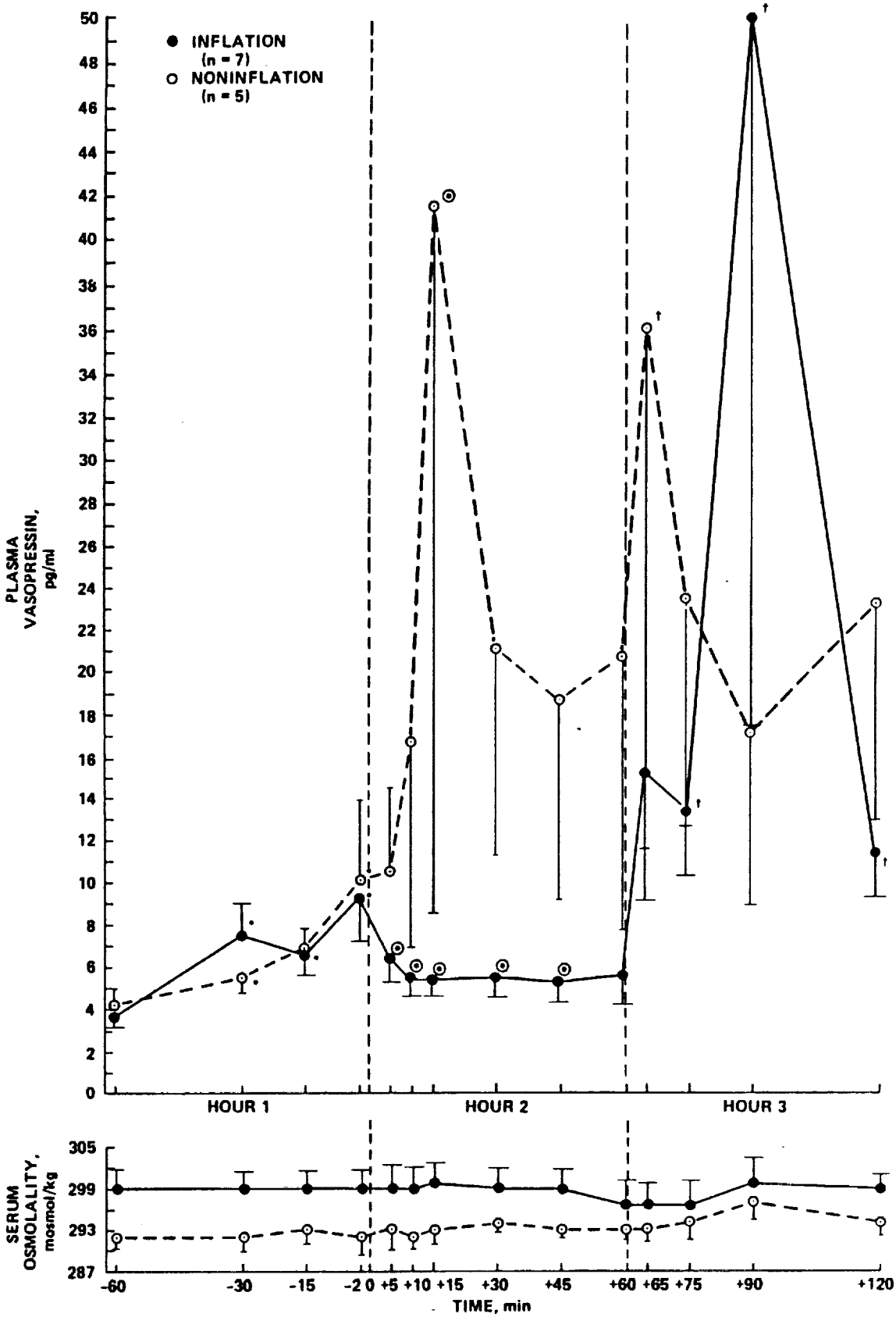

FIG. 2. Mean plasma vasopressin and serum osmolality during 3 h of quiet standing in noninflation (control) and inflation experiments. Suit was inflated only during *hour 2* in inflation experiment. Values are means ± SE. * $P <$ 0.05 from −60-min value; * $P < 0.05$ from −2-min value; † $P < 0.05$ from +60-min value.

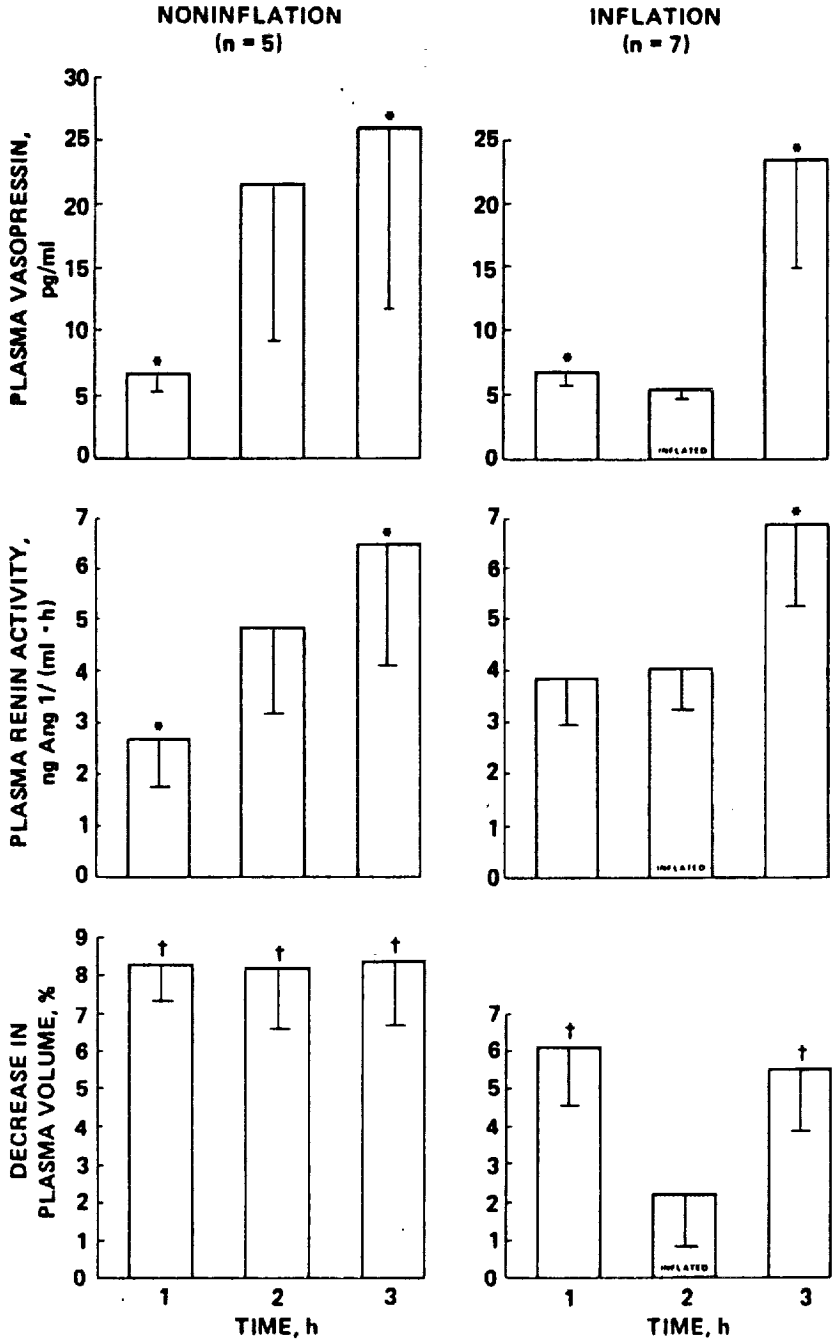

FIG. 3. Group mean plasma vasopressin, renin activity, and decrease in plasma volume during 3 h of quiet standing in noninflation (control) and inflation experiments. Values are group means ± SE. * $P <$ 0.05 from *hour 2*; † $P < 0.05$ from 0.

fainting, the immediate circulatory events appear to be provoked by a gradual fall in central blood volume that elicits a reflex whereby systemic resistance, heart rate, and arterial pressure decrease to a point at which brain perfusion becomes insufficient (4). Central blood volume depends on the distribution of blood and effective blood volume. Inflation of an antigravity suit causes a cephalad shift of blood by reducing venous capacitance beneath the suit (26). There is disagreement as to the precise volume of translocated fluid from the lower extremities and abdomen to the central circulation during external counterpressure. Values differing from 3 (3) to 17 (22) ml/kg have been reported. A less recognized but important effect of the counterpressure is a marked effect on the total blood volume. In the present study, inflation restored PV to values that were not significantly different from base-line levels, suggesting that the counterpressure induced fluid mobilization from the extravascular space (Fig. 3).

These results do not answer the fundamental question of how the antigravity suit counterpressure modifies blood pressure. The significant pressure responses observed are in general agreement with the clinical observation that counterpressure in hypovolemic subjects is more effective for improving arterial pressure than it is in normovolemic subjects (21). Ferrario et al. (8) demonstrated a significant increase in MAP, from 30 ± 13 to 110 ± 20 Torr, during counterpressure extending from the epigastrium to the knees in hypovolemic anesthetized mongrel dogs, but the same suit pressure (30 Torr) in

normovolemic dogs caused no change in blood pressure. In the hypovolemic dogs the vascular resistance actually fell significantly during inflation, and the elevated blood pressure was due entirely to significantly increased cardiac output ($\Delta = 109 \pm 12\%$). Some investigators (15) have found that the blood pressure during external counterpressure was solely a consequence of increased peripheral resistance, whereas others (3, 23) have shown that inflation enhanced both cardiac output and peripheral resistance. It is probable that some interaction among the degree of hypovolemia (3, 8), baroreceptor activity (23), various suit pressures (22), and the rate of sequential inflation upward from the leg bladders (2) determine whether cardiac output, systemic resistance, or even neurogenic control (15) becomes the deciding factor whereby external counterpressure raises blood pressure.

In both of the experiments reported herein, the inflation experiment and the control noninflation experiment, significant rises in PVP and PRA occurred during the 1st h of standing. During the 2nd h these responses were entirely different in the two experiments: although both PVP and PRA continued to increase during the control experiment, PVP actually decreased significantly and a further increase in PRA was abolished during inflation. Deflation of the suit resulted in an immediate rise in both PRA and PVP concentration, especially in PVP that increased by 171% within 5 min.

Baylis and Heath (1) suggest that the magnitude of PVP increases, when subjects are in the upright posture, appears to be related to the severity of the presyncopal symptoms. In *subject III*, who nearly fainted 28 min following suit deflation, PVP concentration rose to 250 pg/ml, which was measured in blood drawn 2 min after onset of the syncopal reactions. Increased PVP concentration increases peripheral resistance to help counteract falling blood pressure (6). Cardiopulmonary and arterial baroreceptors are involved in the reflex regulation of vasopressin (6) and renin activity (19) in humans. However, Goldsmith et al. (11) found no PVP suppression when applying external counterpressure that increased both central venous pressure and MAP. But their subjects were in a relaxed supine position and only moderately dehydrated (plasma osmolality was 288 mosmol/kg). Since neither quiet standing nor external counterpressure had any influence on serum osmolality or Na^+ or K^+ concentrations in the present study, osmolar changes were probably not responsible for the observed responses in PVP. Baylis and Heath (1) reported a postural rise in PVP only if the subjects were dehydrated. Leimbach et al. (18) reported similar results in subjects undergoing lower body negative pressure; unloading arterial baroreceptors resulted in increased PVP levels only when serum osmolality was increased. Compared with our results, these data indicate that in humans the reflex control of vasopressin is more sensitive during circulatory insufficiency (dehydration).

Our results confirm the observation that external counterpressure eliminates the increased PRA response during orthostasis (14, 20), but they do not indicate whether the hormonal and enzyme responses to inflation and deflation or the antigravity suit were caused by volume receptors, or high-pressure receptors, or if both types of baroreceptors participated. However, recent evidence indicates that unloading of arterial and cardiac baroreceptors by lower body negative pressure increases PVP significantly, whereas unloading only cardiac baroreceptors does not (18). Alternatively, we suggest that the dramatic rise in PVP during presynope may also reflect insufficient brain perfusion, since hypoxia can cause antidiuresis in conscious humans and PVP release in sheep (12).

The physiological effects of inflation and deflation of the antigravity suit described in this study demonstrate a technique that can cause prolonged and substantial cardiovascular and neurohumoral changes in humans. The successful use of the suit as a potent nonpharmacological and noninvasive stimulus has several implications. The technique is a powerful investigative tool for studying orthostatic insufficiency and the physiological characteristics of the circulatory system. The observed hormonal, enzyme, and blood pressure changes during inflation suggest a headward redistribution of blood; therefore, external counterpressure may provide an alternative method to bed rest and water immersion for examining some early responses of humans to weightlessness.

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Paper V

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Antigravity suit inflation: kidney function and cardiovascular and hormonal responses in men

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GEELEN, GHISLAINE, STEIN E. KRAVIK, AOUMEUR HADJ-AISSA, GEORGES LEFTHERIOTIS, MADELEINE VINCENT, CHARLES-ALBERT BIZOLLON, CARL WILHELM SEM-JACOBSEN, JOHN E. GREENLEAF, AND CLAUDE GHARIB. *Antigravity suit inflation: kidney function and cardiovascular and hormonal responses in men.* J. Appl. Physiol. 66(2): 792–799, 1989.—To investigate the effects of lower body positive pressure (LBPP) on kidney function while controlling certain cardiovascular and endocrine responses, seven men [35 ± 2 (SE) yr] underwent 30 min of sitting and then 4.5 h of 70° head-up tilt. An antigravity suit was applied (60 Torr legs, 30 Torr abdomen) during the last 3 h of tilt. A similar noninflation experiment was conducted where the suited subjects were tilted for 3.5 h. To provide adequate urine flow, the subjects were hydrated during the course of both experiments. Immediately after inflation, mean arterial pressure increased by 8 ± 3 Torr and pulse rate decreased by 16 ± 3 beats/min. Plasma renin activity and aldosterone were maximally suppressed ($P < 0.05$) after 2.5 h of inflation. Plasma vasopressin decreased by 40–50% ($P < 0.05$) and plasma sodium and potassium remained unchanged during both experiments. Glomerular filtration rate was not increased significantly by inflation, whereas inflation induced marked increases ($P < 0.05$) in effective renal plasma flow (ERPF), urine flow, osmolar and free water clearances, and total and fractional sodium excretion. No such changes occurred during control. Thus, LBPP induces *1*) a significant increase in ERPF and 2) significant changes in kidney excretory patterns similar to those observed during water immersion or the early phase of bed rest, situations that also result in central vascular volume expansion.

lower body positive pressure; blood pressure; diuresis; natriuresis; free water clearance; renal blood flow; plasma renin activity; aldosterone; plasma vasopressin

CLINICAL (28), as well as more basic (1, 4, 10, 15–17, 21, 34), studies have shown that application of lower body positive pressure (LBPP) with antigravity suit or medical antishock trousers (MAST) results in an increase in blood pressure and a headward redistribution of fluid. However, the underlying mechanisms of these responses remain unclear. Kravik et al. (24) studied healthy human subjects rendered mildly hypovolemic by standing upright before MAST inflation. The results confirmed the headward redistribution of blood during inflation with increased mean arterial pressure (MAP) and pulse pressure (PP), reflex bradycardia, correction of the hypovolemia, and decreased plasma renin activity and vasopressin concentration. However, fluid also shifts headward during weightlessness, as well as during bed rest and water immersion, with important resulting effects on kidney function and fluid and electrolyte balance (5, 18). LBPP thus appeared to be a useful procedure for studying kidney function. In addition, few investigators have studied the renal aspect of LBPP (22, 25). Therefore the purpose of the present study was to investigate the effects of LBPP on kidney function in normal men during head-up tilting while certain cardiovascular and neurohormonal responses were controlled.

PROCEDURE AND METHODS

Nine healthy males, 35 ± 2 (SE) yr and 67 ± 2 kg, volunteered as test subjects. Seven subjects participated in the inflation experiment, and a similar noninflation (control) experiment was conducted 12 mo later on seven subjects, five of whom had participated in the inflation experiment. All had a negative history for arterial hypertension and cardiovascular and kidney diseases. The protocol was approved by the Human Research Committee (Université Claude Bernard). Informed consent was obtained after the subjects had been fully briefed as to the purpose and nature of the experiments. The experiments were always performed at the same time of day (between 0800 and 1300 h) in a laboratory maintained at 25°C. Each subject fasted (no food or drink) from 2200 h the evening before the experiment and reported to the laboratory at 0745 h the next morning. He was weighed nude, donned the MAST (MAST III A, David Clark), and rested sitting upright for 30 min while eating a light breakfast consisting of six crackers and jam with 360 ml tap water (Fig. 1). Then flexible Teflon catheters (Quick Cat, Travenol Laboratory), one for blood sampling and another for *p*-aminohippurate (PAH) and inulin infusion were inserted into the antecubital vein of each forearm. In the inflation experiment, he then stood at 0830 h on a tilt table with a footboard at 70° [70° head-up tilt (HUT)] for 4.5 h. This 4.5-h period consisted of a 0.5-h

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infusion period (for inulin and PAH) followed by 1 h of quiet standing and then 3 h of standing with inflation (diuresis may peak as late as the 3rd h of inflation) (Fig. 1). Pressure was 60 Torr in the thigh-leg bladders, which were always inflated before the abdominal bladder to avoid trapping blood in the lower extremities, and 30 Torr in the abdominal bladder. Those pressures were compatible with comfort and easy voiding. The suit was filled with air, and separate regulators connected to each of the three bladders made it possible to control the pressure continuously. Inflation took <1 min. In the noninflation experiment, each subject wore the suit and stood on the tilt table at 0830 h (70° HUT) for 3.5 h including the 30-min infusion period (Fig. 1). In both experiments, 0900–1000 h is *h 1*, 1000–1100 h is *h 2*, and so on.

To prevent symptoms of orthostatic intolerance when the suit was not inflated, the subjects were asked to gently contract their leg muscles when necessary.

To provide adequate urine flow, the subjects ingested 360 ml tap water at 0800 h with breakfast and 170 ml at the start of each hour thereafter. Net fluid intake (drink + infusion-blood) was 500 ml during *h 1* and 200 ml during each of the following hours. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured with inulin and PAH clearance (C_{In} and C_{PAH}), respectively. Inulin (Polyfructosan, Inutest, Levosan Gesellschaft) and PAH (sodium *p*-aminohippurate, Nephrotest) were infused in isotonic glucose with a loading dose of 0.03 and 0.015 g/kg, respectively. Infusion occurred between 0830 and 0842 h at a rate of 10 ml/min, followed by a constant infusion throughout both experiments at doses of 0.040 and 0.030 g/kg, respectively, at a rate of 1 ml/min.

Urine was collected hourly after the 0900-h voiding. Urine flow ($\dot{V}$), osmolar and free water clearances (C_{osm} and C_{H_2}), and total sodium and potassium excretion ($U_{Na}\dot{V}$ and $U_K\dot{V}$), as well as fractional sodium excretion (FE_{Na}), were measured or calculated.

Blood samples (21 ml each) were taken at 0835, 0900, 0930, 1000, 1030, 1130, 1230, and 1300 h in the inflation experiment, and starting at 0835 h every 30 min until 1200 h in the noninflation experiment. The blood samples were placed in chilled heparinized tubes and centrifuged immediately at 4°C for 15 min. Plasma samples were aliquoted for the different hormonal measurements and stored immediately at −80°C. Other determinations on the remaining plasma were made the same day. Plasma samples were analyzed for Na^+ and K^+ (Instrumentation Laboratory flame photometer), osmolality (OR T Fiske osmometer), and inulin and PAH (Autoanalyzer I F 121) with automated techniques adapted from Galli et al. (11) and Bratton and Marshall (2). Plasma vasopressin (PVP), plasma aldosterone (PA), and plasma renin activity (PRA) were measured by radioimmunoassay (23, 31).

Radial pulse rate (PR) was taken, and brachial blood pressure was measured (mercury sphygmomanometer), with the subject's arm hanging down, by the same observer every 10 min during the final 60 min of the control period in the inflation experiment, every 20 min during inflation, and every 10 min throughout the noninflation experiment. Mean arterial pressure (MAP) was calculated: MAP = DBP + 1/3(SBP − DBP), where SBP and DBP represent systolic and diastolic blood pressure, respectively.

Data treatment. Values are means ± SE. For MAP, PP, and PR, the hourly mean value was the average of all values during that hour. The data within each experiment were analyzed with the Wilcoxon matched-pairs

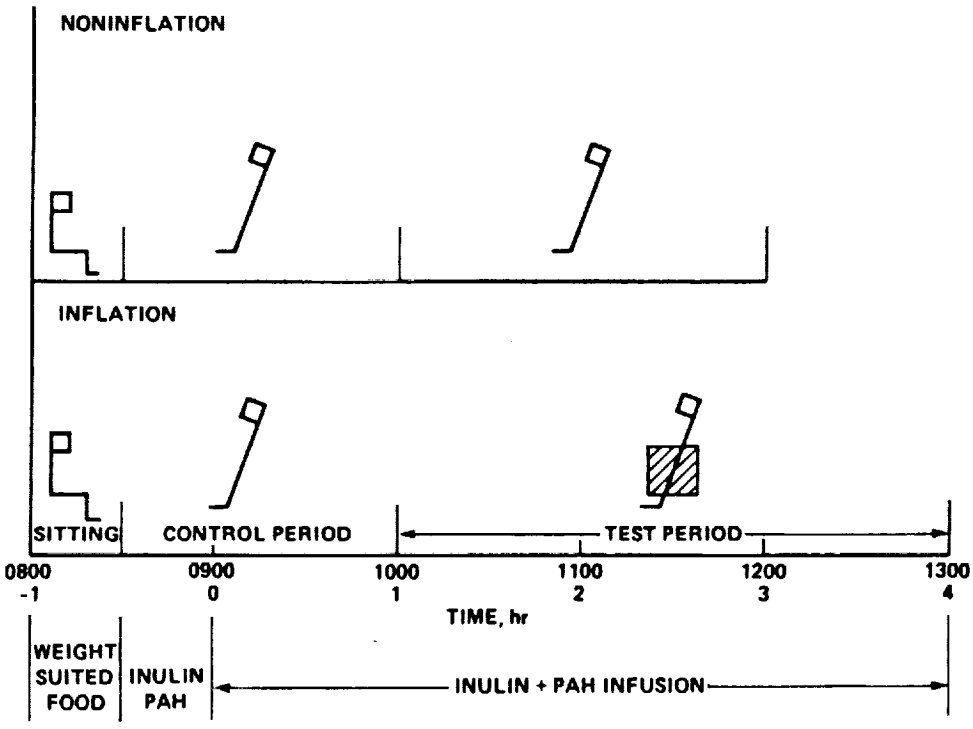

FIG. 1. Experimental design. PAH, *p*-aminohippurate.

sign-rank test. The null hypothesis was rejected when $P < 0.05$. Data from *h 2* and *3* of the inflation vs. noninflation experiments were compared using a two-way analysis of variance, and significance between means was determined with the Newman-Keuls multiple-range test. Nonsignificant differences are denoted by NS.

RESULTS

HUT was well tolerated. No subject was presyncopal during the first 1.5 h of the inflation experiment or during the 3.5 h of the noninflation experiment. During the latter, only one subject complained of light-headedness after 105 min of tilt and was subsequently returned to the horizontal position for 10 min, then retilted. No presyncopal episodes developed during inflation; all subjects expressed feelings of well-being, except during the last 30 min when the pressure of the suit on the knees was reported as becoming uncomfortable.

Blood pressure and pulse rate. Within the 1st h of the inflation experiment (suit noninflated), MAP and PR remained unchanged, while PP decreased from 35 ± 1 to 29 ± 2 Torr ($P < 0.05$). One minute after inflation, MAP and PP rose to 101 ± 3 and 38 ± 3 Torr ($P < 0.05$), respectively, while PR decreased to 72 ± 3 beats/min ($P < 0.05$). MAP remained elevated and essentially stable during *h 2–4*, reaching 109 ± 2 Torr ($P < 0.05$) by the end of *h 4*. Group mean MAP during inflation was 101 ± 1, 104 ± 1, and 108 ± 2 Torr ($P < 0.05$), respectively. PP and PR remained essentially unchanged during the 3 h of inflation, reaching 38 ± 2, 39 ± 1, and 41 ± 3 Torr, respectively, and 72 ± 3, 71 ± 3, and 69 ± 3 beats/min, respectively (Fig. 2). In the noninflation experiment, MAP, PP, and PR remained essentially unchanged during the 3 h of tilting (Fig. 2). During *h 3*, the group mean data were as follows: MAP, 91 ± 4 Torr ($P < 0.05$); PP, 38 ± 2 Torr (NS); and PR, 82 ± 4 beats/min (NS). During both *h 2* and *3* of inflation, MAP increased ($P < 0.01$) and PR decreased ($P < 0.01$) compared with their respective noninflation group mean values (Fig. 2).

Plasma electrolyte, osmotic, and endocrine responses. Throughout both experiments, plasma Na^+ and K^+ concentrations remained constant, averaging 136.5 ± 0.2 and 4.3 ± 0.03 mmol/l and 137.5 ± 0.4 and 4.2 ± 0.03 mmol/l during the inflation and the noninflation experiments, respectively (Table 1). In both experiments plasma osmolality (P_{osm}) decreased significantly ($P < 0.05$) during the first 90 min and remained stable thereafter so that a dissociation between plasma Na^+ concentrations and osmolalities occurred. PRA and PA were significantly increased ($P < 0.05$) while PVP was decreased at the 90th min of tilt in both experiments (Table 1). Inflation resulted in substantial decreases of PRA and PA concentration starting 30 min after inflation and becoming more pronounced thereafter (Fig. 3). Compared with the preinflation value at *h 1*, PRA and PA were maximally suppressed ($P < 0.05$) to 46.2 ± 14 and 37.2 ± 7% after 2.5 h of inflation. PVP decreased significantly ($P < 0.05$) between 0.5 and 2.5 h of inflation; the lowest value was 49 ± 11% at 1.5 h after inflation. Interestingly, PVP returned to the preinflation level by 1300 h (Table 1, Fig. 3). During *h 2* and *3* of noninflation, PRA and PA remained unchanged compared with the maximal values they had reached at 1000 h after 90 min of tilt, whereas PVP had decreased significantly ($P < 0.05$) during *h 3*.

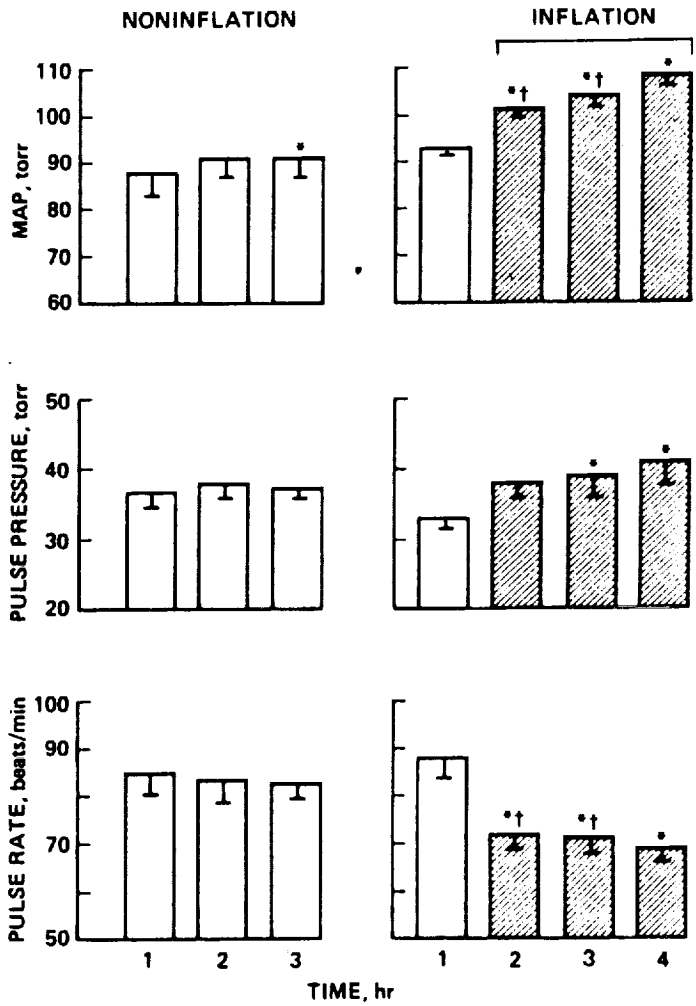

FIG. 2. Group mean (±SE) arterial pressure (MAP), pulse pressure, and pulse rate during 70° head-up tilt in inflation and noninflation experiments. * $P < 0.05$ from corresponding value at *h 1*; † $P < 0.05$ from corresponding noninflation value.

Kidney hemodynamics. During the inflation experiment, inulin clearance (C_{In}) (corrected to 1.73 m^2 body surface area) increased significantly ($P < 0.05$) from 105.6 ± 8.7 (*h 1*) to 131 ± 4.8 ml/min (*h 2*) then was 137 ± 10 (*h 3*, NS) and 115 ± 3 ml/min (*h 4*, NS) (Fig. 4*A*). The PAH clearance (C_{PAH}, corrected to 1.73 m^2 body surface area) increased significantly ($P < 0.05$) from 535 ± 45 (*h 1*) to 736 ± 50 ml/min (*h 2*) then decreased to 644 ± 24 ml/min (*h 3*, $P < 0.05$) and was 583 ± 36 ml/min (*h 4*, NS).

During the control experiment, C_{In} remained unchanged at 116 ± 7, 129 ± 11, and 121 ± 8 ml/min at *h 1*, *2*, and *3*, respectively. C_{PAH} remained unchanged at 592 ± 40, 553 ± 29, and 530 ± 24 ml/min at *h 1*, *2*, and *3*, respectively (Fig. 4*A*). There was no significant influence of inflation on C_{In}, whereas C_{PAH} was increased significantly ($P < 0.01$) during *h 2* and *3* of inflation compared with the corresponding values of the noninflation experiment.

TABLE 1. *Effect of inflation and noninflation during tilting on plasma electrolytes, osmolality, and hormonal concentrations*

			h 1		*h 2*		*h 3*		*h 4*	
	0835	0900	0930	1000	1030	1100	1130	1200	1230	1300
P_{Na}, mmol/l										
I	137±0.9	136±0.6	136±0.5	137±0.6	136±0.8		136±0.4		136±0.3	137±0.6
NI	138±0.6	138±0.5	139±0.6	138±0.2	137±0.3	137±0.5	137±0.5	137±0.6		
P_K, mmol/l										
I	4.5±0.1	4.3±0.1	4.3±0.1	4.3±0.1	4.2±0.1		4.5±0.1		4.3±0.1	4.2±0.1
NI	4.1±0.1	4.1±0.1	4.2±0.1	4.2±0.1	4.3±0.1	4.3±0.1	4.2±0.1	4.1±0.1		
P_{osm}, mosmol/kgH_2O										
I	289±2*	289±2*	286±2	284±2	281±2		282±4		282±2	278±2
NI	278±2*	278±2*	276±1	275±1	273±1	273±1	273±1	273±1		
PRA, ng Ang I·l^{-1}·min^{-1}										
I	184±52*	183±40*	255±76	238±47	200±57		135±50*†		110±35*	128±50*
NI	258±69	289±74	349±82	342±58	309±43	292±45	306±54	397±55		
PA, pmol/l										
I	260±88*	279±82*	371±71	544±86	436±84*		238±40*†		203±40*	214±39*
NI	259±105	345±111	417±89	561±104	662±112	609±116	583±131	565±143		
PVP, pg/ml										
I	6.1±3.0*	2.0±1.0	1.5±0.7	1.2±0.3	0.7±0.2*		0.6±0.1*		0.7±0.1*	1.2±0.2
NI	3.0±2.0	3.9±2.0	3.3±2.0	1.8±0.5	1.9±1.0	1.3±0.4*	0.8±0.3*	0.9±0.2*		

Values are means ± SE. P_{Na}, plasma sodium; P_K, plasma potassium; P_{osm}, plasma osmolality; PRA, plasma renin activity; PA, plasma aldosterone; PVP, plasma vasopressin; I, inflation; NI, noninflation; ANG I, angiotensin I. * $P < 0.05$ from comparable 1000 h value. † $P < 0.01$ from corresponding NI value.

Kidney excretory patterns. During the inflation experiment, $\dot{V}$ increased significantly ($P < 0.05$) from 0.9 ± 0.3 ml/min before inflation (*h 1*) to 2.5 ± 0.6 (*h 2*) and 7.5 ± 1 ml/min (*h 3*) and decreased to 2.5 ± 0.7 ml/min (NS vs. *h 1*) at *h 4*, which corresponds to 2.5- and 6.8-fold increases during the first 2 h of inflation compared with the corresponding values of the control experiment. C_{osm} increased significantly ($P < 0.05$) during each of the 3 h of inflation while C_{H_2O} became highly positive ($P < 0.05$) during *h 2* (Fig. 4*B*). $U_{Na}\dot{V}$ increased significantly ($P < 0.05$) from 42.6 ± 4.8 (*h 1*) to 74.3 ± 9 (*h 2*), 116.6 ± 14 (*h 3*), and 123 ± 21 μmol/min (*h 4*), corresponding to 2- and 3.5-fold increases during the first 2 h of inflation compared with the corresponding excretions of the control experiment. FE_{Na} also increased significantly ($P < 0.05$) in similar fashion from 0.28 ± 0.02 (*h 1*) to 0.4 ± 0.05 (*h 2*), 0.6 ± 0.07 (*h 3*), and 0.74 ± 0.1 (*h 4*). $U_K\dot{V}$ increased transiently ($P < 0.05$) during the *h 3* of inflation (Fig. 4*C*).

During the noninflation experiment, $\dot{V}$ was <1 ml/min, C_{osm} remained unchanged, and C_{H_2O} was constantly negative (Fig. 4*B*). $U_{Na}\dot{V}$ displayed a continuous decrease, which became significant ($P < 0.05$) by the end of *h 3*, whereas FE_{Na} remained unchanged. $U_K\dot{V}$ increased transiently ($P < 0.05$) during *h 3* (Fig. 4*C*), as did FE_K (not shown). Comparison of data for the same times in both experiments showed inflation to cause a significant rise ($P < 0.01$) in $\dot{V}$, C_{osm}, and C_{H_2O} in *h 3* and in $U_{Na}\dot{V}$ and $F\Xi_{Na}$ during *h 2* and *3*.

DISCUSSION

Since their clinical use was introduced by Crile in 1903, antigravity garments and antishock trousers have been used in emergency medicine (28) and in the treatment of postural hypotension (33), as well as to counteract the hemodynamic effects of positive end-expiratory pressure (27). LBPP has also been used to increase blood pressure by noninvasive and nonpharmacological means (21). However, after 85 years of utilization, the physiological effects of LBPP application are still not completely delineated and the underlying mechanisms of its beneficial effects are still a matter of controversy. To date, the majority of studies designed to explore such effects in humans (4, 10, 15–17, 28, 32) and animals (1, 9, 21, 30, 31, 34) have dealt with hemodynamic mechanisms. On the other hand, since increased blood pressure and headward redistribution of blood are now established responses to LBPP (1, 4, 10, 15–17, 21, 28, 34), the subsequent renal changes have not been studied thoroughly (20, 22, 25). These reasons prompted the present investigation into kidney function under LBPP in humans. In the present study, inflation to 60 Torr on the legs and 30 Torr on the abdomen resulted in an immediate, significant, and sustained increase of 8 ± 3 Torr in MAP and an immediate, significant and sustained decrease in PR of 16 ± 3 beats/min. Similar findings have been observed in standing subjects who had been dehydrated for 24 h (24). This LBPP-induced increase in MAP, although not necessarily sustained, is a consistent finding for subjects in the standing (10, 17, 24, 32) and supine (1, 4, 9, 10, 15–17, 21, 30, 34) body positions. This increase has been ascribed to a number of mechanisms that are not mutually exclusive. First, it may be mainly if not solely a consequence of increased peripheral resistance (4, 10, 21). However, others (1, 30) have shown that inflation can enhance both peripheral resistance and cardiac output ($\dot{Q}$), since reduction of venous capacitance beneath the suit causes a cephalad shift of blood (an "autotransfusion" effect) from the lower extremities and the splanchnic circulation (9, 30, 34). The effect on $\dot{Q}$ is complex; the level of the preexisting blood volume appears to be an important determinant because Bellamy

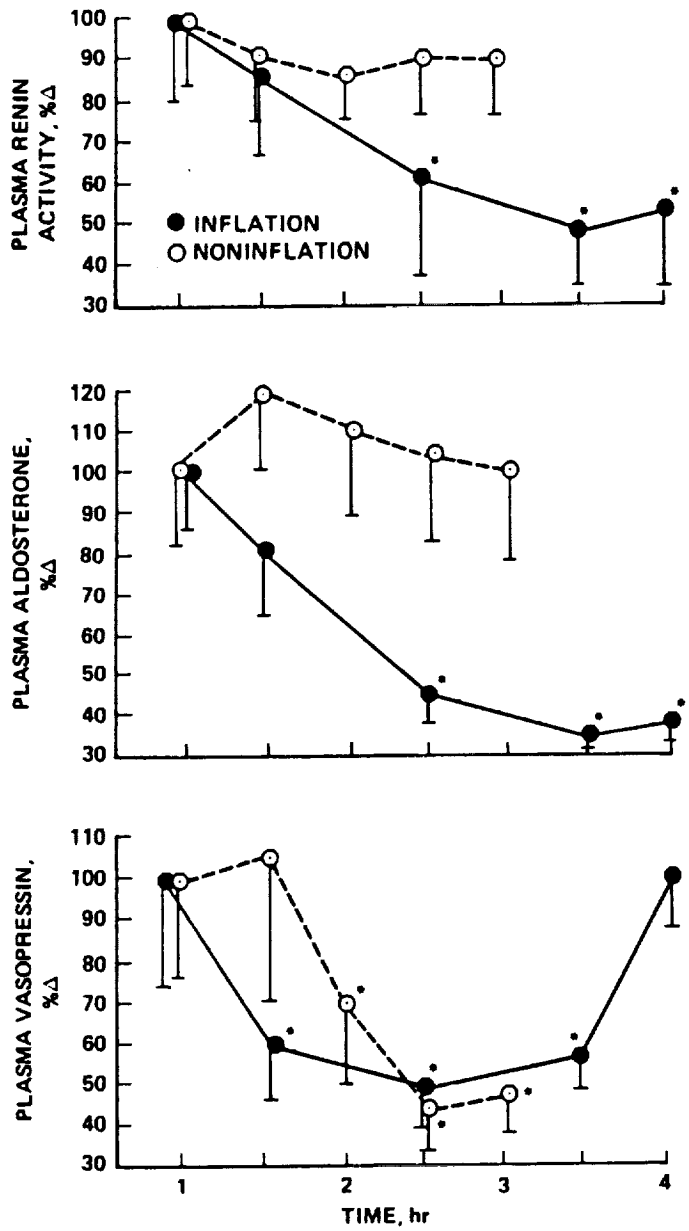

FIG. 3. Group mean (±SE) percent changes in plasma renin activity and aldosterone and vasopressin concentrations in inflation and noninflation experiments. * $P < 0.05$ from value at 1000.

et al. (1) reported a dramatic increase in $\dot{Q}$ only when LBPP was applied in hypovolemic swine. In a previous experiment during the last 20 min of a 45-min period of 70° HUT, blood and plasma volumes decreased by 4.3 ± 0.3 and 7.6 ± 0.3%, respectively, in rehydrated subjects (2.5 ± 0.15 liters tap water drunk per subject) compared with a decrease of 6.5 ± 0.5 and 10.9 ± 0.6%, respectively, when dehydrated (19). Even though blood volume was not measured in the present study, inflation of the suit in subjects rendered mildly hypovolemic by standing (24, present study) is likely to be more effective than its normal use on supine normovolemic subjects, thus providing a plausible explanation for the finding of no substantial effects of LBPP on kidney function (25).

In our studies (24, present study), the inflation-induced increase in blood pressure was always associated with reflex bradycardia, a rather uncommon finding of other studies (17, 34). Baroreceptor-mediated compensatory response to the headward redistribution of blood, which is the common feature of bed rest, water immersion, and antigravity suit inflation, was associated with a significant suppression of tilting-stimulated PRA and PA, which is in keeping with earlier findings (3, 5, 6, 12, 14, 18, 24).

In the present study, the decrease in PVP must be interpreted with caution. During the first 90 min of both experiments, the decrease in PVP seems to follow the decrease in P_{osm}. After inflation, as well as during the corresponding hours of the noninflation experiment, P_{osm} remained unchanged and PVP decreased significantly, so that there was no significant difference between both experiments. Such results suggest that the postinflation decrease in PVP is not inflation induced, with the restriction that the decrease in PVP after 1000 h occurs faster during inflation than during the noninflation experiment. On the other hand, we had shown in a previous study (24) an inflation-induced decrease in PVP in a situation of stimulated vasopressin, since inflation occurred after 1 h of standing in 24-h dehydrated subjects. In the present study, the stimulating influence of posture before inflation on arginine vasopressin secretion was probably counterbalanced by water administration. Drinking per se suppresses PVP before any change in P_{osm} probably because of the involvement of oropharyngeal or gastrointestinal receptors (13); this may have occurred during the second half of both experiments where PVP decreased significantly without any change in P_{osm}, as well as during the first half in addition to the influence of decreased P_{osm}.

Therefore, it is clear that, in the face of increased MAP and decreased PR together with decreased PRA, PA, and PVP, i.e., under conditions very similar to those resulting from LBPP application in normal, standing humans (24), the predictable changes in kidney excretory patterns do occur: $\dot{V}$, $U_{Na}\dot{V}$, C_{PAH}, C_{osm}, and C_{H_2O} were dramatically increased. Interestingly, similar increases in $\dot{V}$, natriuresis, and kaliuresis together with a decrease in urine osmolality have been observed during the first 12 h of LBPP in conscious squirrel monkeys (22). Moreover, the renal excretory changes brought about by LBPP appear to be similar in nature and magnitude to those observed during water immersion and the early phase of bed rest (5, 6, 18).

The decreases in PRA, PA, and PVP and the renal effects of bed rest and immersion have been viewed mainly as a consequence of the involvement of the atrial pressure receptors, since immersion and bed rest do not usually cause an increase in blood pressure. However, increased blood pressure has been reported in two immersion studies; Epstein et al. (8) noted a 6-mmHg increase at 180 min of immersion and Norsk et al. (26) noted that systolic pressure increased significantly by 8–10 mmHg (9%) at *h 3* and *4* of immersion. As shown previously and verified in this study, LBPP is consistently associated with increased MAP, which suggests the participation of both low-pressure (atrial) and high-pressure (carotid and aortic arch) baroreceptors, although we have no way of discriminating between the two. The

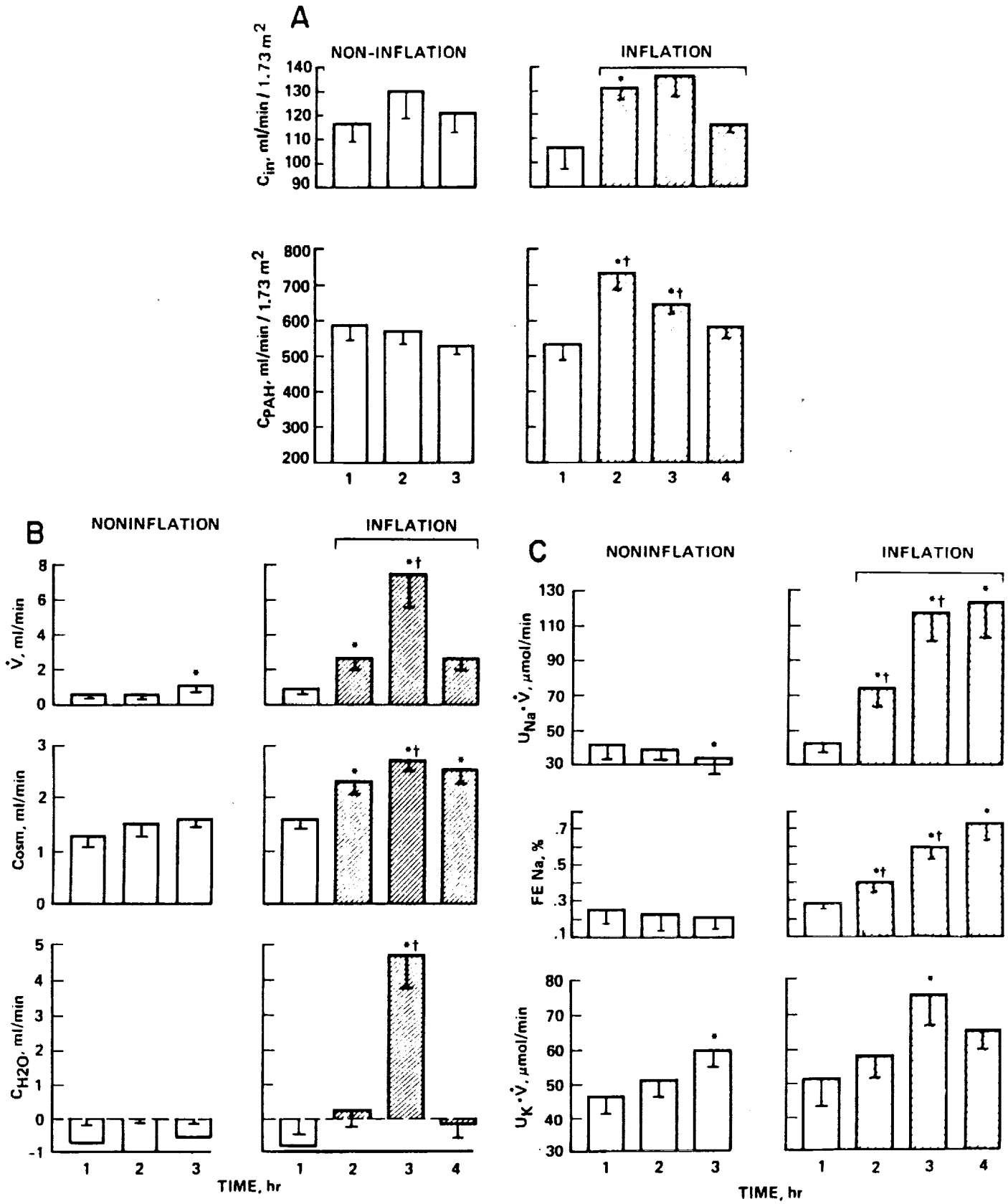

FIG. 4. *A*: group mean (±SE) inulin (C_{in}) and *p*-aminohippurate (C_{PAH}) clearances (corrected for body surface area) during 70° head-up tilt in inflation and noninflation experiments. *B*: group mean (±SE) urine flow (V̇) and osmolar (C_{osm}) and free water (C_{H_2O}) clearance during 70° head-up tilt in inflation and noninflation experiments. *C*: group mean (±SE) total (U_{Na}V̇) and fractional (FE_{Na}) excretion of sodium and potassium (U_KV̇) during 70° head-up tilt in inflation and noninflation experiments. * $P < 0.05$ from corresponding value at *h 1*. † $P < 0.01$ from corresponding noninflation value.

question arises now as to the mechanisms of the inflation-induced changes in kidney function.

Although C_{PAH} may not be an accurate index of renal plasma flow under all experimental circumstances (7), C_{PAH} was significantly and markedly increased during inflation but not in the noninflation experiment. This finding suggests that compression of the abdominal area with 30 Torr does not cause impaired blood flow distribution, which could have depressed the function of the kidney and other organs encompassed by the suit. A possible explanation for this increased ERPF was the increase in systemic arterial pressure, which probably induced a baroreceptor-mediated decrease in sympathetic nerve activity, including renal nerve response, that subsequently caused renal vasodilation.

C_{In} was not significantly increased by inflation; this result is in agreement with responses during bed rest (18) and water immersion (5, 7, 18). Changes in inflation-induced excretory patterns are probably not mainly a consequence of changes in the GFR.

$\dot{V}$ was increased throughout inflation, with a marked peak during *h 3* concomitant with the peak in C_{H_2O}. The inflation-diuresis mechanism is most certainly multifactorial; if one cannot exclude a participation of the slight although insignificant increase in GFR, it appears that the inflation-diuresis mechanism is influenced by the increases in both C_{osm} and C_{H_2O}, the increase in C_{H_2O} in hydrated subjects being the major determinant as in water immersion (5). In addition, since LBPP application is associated, among other responses, with increased MAP and ERPF, a pressure-diuresis mechanism may be involved, since increases in arterial pressure in the autoregulatory range are able to inhibit tubular reabsorption of sodium and water independently of changes in ERBF or GFR (29) and thus cause diuresis by a mechanism intrinsic to the kidney. Lastly, decreased PVP also accounts for part of the diuresis.

Natriuresis was also a constant finding throughout inflation, although its time course was somewhat different from that of diuresis. Natriuresis occurred during the 1st h of inflation and increased markedly and constantly thereafter, particularly during *h 3* when the diuresis had decreased by 65%. Three factors can be put forward to explain the increase in FE_{Na} during the first 2 h of inflation: *1*) an increase in filtered load (which is likely to play a modest role), *2*) a pressure-natriuresis mechanism (29), and *3*) a change in peritubular Starling forces due to increased ERPF without any significant increase in GFR, with a subsequent decreased tubular reabsorption. During the last hour of inflation, natriuresis was still increasing and systemic blood pressure remained elevated, while ERPF and GFR had returned to baseline levels. At the same time, PRA and PA concentrations were maximally decreased concomitantly with a trend toward kaliuresis. The natriuresis of *h 3* of inflation can thus be viewed as a consequence of the aldosterone suppression. Other hormonal mechanisms are also probably involved in inflation natriuresis. Although plasma atrial natriuretic factor was not measured in this study, it increases transiently during MAST application (35).

Since kaliuresis was increased significantly during the *h 2* of inflation and also during the control experiment, the response was probably a posture effect rather than a consequence of external pressure.

In conclusion, in standing, mildly hypovolemic subjects, application of LBPP by means of a pressure suit modifies kidney function via increased $\dot{V}$, $U_{Na}\dot{V}$, C_{osm}, C_{H_2O}, and ERPF. Therefore, external counterpressure may prove a valuable alternative technique to bed rest and water immersion for studying blood volume regulation and for examining certain early cardiovascular, hormonal, and renal responses to simulated weightlessness. On the other hand, the use of LBPP suits can have clinical applications for the treatment of edematous states associated with hypovolemia and decreased GFR in nephrotic and cirrhotic patients.

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Paper VI

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Effect of lower-body positive pressure on postural fluid shifts in men

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Summary. To quantify the effect of 60 mm Hg lower-body positive pressure (LBPP) on orthostatic blood-volume shifts, the mass densities ($\pm 0.1\ g \cdot l^{-1}$) of antecubital venous blood and plasma were measured in five men (27–42 years) during combined tilt table/antigravity suit inflation and deflation experiments. The densities of erythrocytes, whole-body blood, and of the shifted fluid were computed and the magnitude of fluid and protein shifts were calculated during head-up tilt (60°) with and without application of LBPP. During 30-min head-up tilt with LBPP, blood density (BD) and plasma density (PD) increased by $1.6 \pm 0.3\ g \cdot l^{-1}$, and by $0.8 \pm 0.2\ g \cdot l^{-1}$ ($\pm$SD) ($N = 9$), respectively. In the subsequent period of tilt without LBPP, BD and PD increased further to $+3.6 \pm 0.9\ g \cdot l^{-1}$, and to $+2.0 \pm 0.7\ g \cdot l^{-1}$ ($N = 7$), compared to supine control. The density increases in both periods were significant ($p < 0.05$). Erythrocyte density remained unaltered with changes in body position and pressure suit inflation/deflation. Calculated shifted-fluid densities (FD) during tilt with LBPP ($1006.0 \pm 1.1\ g \cdot l^{-1}$, $N = 9$), and for subsequent tilt after deflation ($1002.8 \pm 4.1\ g \cdot l^{-1}$, $N = 7$) were different from each other ($p < 0.03$). The plasma volume decreased by $6.0 \pm 1.2\%$ in the tilt-LBPP period, and by an additional $6.4 \pm 2.7\%$ of the supine control level in the subsequent postdeflation tilt period. The corresponding blood volume changes were $3.7 \pm 0.7\%$ ($p < 0.01$), and $3.5 \pm 2.1\%$ ($p < 0.05$), respectively. Thus, about half of the postural hemoconcentration occurring during passive head-up tilt was prevented by application of 60 mm Hg LBPP.

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Key words: Specific gravity — Mechanical oscillator technique — Venous blood — F_{cell}-ratio — Orthostatic hemoconcentration — Posture — Antigravity suit — Capillary fluid shifts

Introduction

Antigravity garments which apply external pressure to the legs and lower abdomen have been used successfully as life saving devices in emergeny medicine; they provide an effective procedure for counteracting postural hypotension (Sieker et al. 1956) and for the treatment of hemorrhagic shock (Wayne and MacDonald 1983). In addition, the garments can be used to study disturbed cardiovascular regulation and orthostatic insufficiency in standing man (Bevegård et al. 1962). The major mechanism of action of antigravity suit inflation is to oppose the hydrostatic gradient which causes about one tenth of the total blood volume to move from the thoracic compartment into the veins of the legs (Gauer and Thron 1965). However, during application of lower body positive pressure (LBPP), the physiological responses which act to oppose this fluid shift remain partly obscure. Few investigators have studied the relationship between the level of LBPP and volume regulatory readjustments quantitatively.

The purpose of the present study was to measure changes in hemoconcentration in the supine and upright postures with and without application of lower body positive pressure, to compute the density of the filtrated fluid, and to quantify the influence of changes in whole body to large vessel hematocrit (F_{cell}-ratio).

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Material and methods

Subjects. Five healthy men, aged 27—42 years, fully briefed as to the purpose of the experiment, volunteered as test subjects. They were familiar with the procedure from participation in previous similar experiments.

Protocol. Each experiment started between 1300—1500 hr. The subjects were placed horizontally on a tilt table in a laboratory at 20±1°C. A catheter (Quick-cath™, Travenol Labs., Inc.) was inserted into an anticubital vein, and the supine posture was maintained for 60 min. Blood was drawn 10 and 5 min before changing to the head-up position. The antigravity suit was placed around the subject at the beginning of the supine control period and was inflated to 60 mm Hg immediately before tilting the subject to the +60° head-up tilt position. Blood samples were taken at min 1, 5, and 29 of the tilt/LBPP period. At min 30, the antigravity suit was deflated while tilting continued; blood was drawn at min 31 and 36, and the last sample was obtained either when presyncopal symptoms occurred or at min 90.

Density measurements. The density measuring apparatus (DMA 55/602M, Mettler/Paar) was used for determining blood and plasma densities (mass/unit volume) at 37.0±0.02°C (Kratky et al. 1966; Kenner 1982). An ultrathermostat (Exacal EX-100 UHP, Neslab) was used because the density of blood and plasma changes by 0.4 $g \cdot l^{-1} \cdot °C^{-1}$ (Hinghofer-Szalkay 1985). The DMA's glass tubings were siliconized to prevent deposition of protein and corpuscular elements (Hinghofer-Szalkay 1986a). Complete temperature equilibration was tracked using an electronic thermometer and a Gould pen recorder. The precision of the density measurement was ±0.04 $g \cdot l^{-1}$.

Blood density was measured immediately after blood withdrawal. 1 µl of heparin solution (density: 1050 $g \cdot l^{-1}$ at 37°C) was added to 1 ml of blood prior to measurement. Plasma was prepared by adding 1 µl of heparin solution (density: 1019 g/l at 37°C) to 0.3 ml of blood which was separated for 30 min at 1500 g. The heparin solutions were brought to the desired density by concentrating commercial heparin solutions (density approx. 1010 $g \cdot l^{-1}$) using a vacuum chamber.

The microhematocrit (Ht) was measured in triplicate. Samples were spun for 12 min at 11500 rpm (International™ Centrifuge model MB). The measurement error was ±0.2%. The raw mean Ht was corrected for trapped plasma by multiplying by 0.96.

Calculations

Transvascular fluid shifts. During head-up tilt, a certain fluid volume (FV) with a certain fluid density (FD) is filtrated from the circulating blood. According to the mass equation (mass = density × volume),

$$FD \times FV + PD_u \times PV_u = PD_s \times PV_s \quad (1)$$

and

$$FD \times FV + BD_u \times BV_u = BD_s \times BV_s \quad (2)$$

where: PV and BV refer to plasma volume and blood volume respectively; u refers to the upright postfiltration state (either at the end of the suit inflation period at min 30 of tilt, or at the final sampling); s refers to the supine control state; and $BV_s = BV_u + FV$. From Eqs. (1) and (2), the FV shift can be calculated from the plasma density (PD) and blood density (BD) changes (Hinghofer-Szalkay and Moser 1986):

$$FV_P = 100 \times \frac{PD_s - PD_u}{PD_u - FD} PV_s \quad (\% PV_s) \quad (3)$$

and

$$FV_B = 100 \times \frac{BD_s - BD_u}{BD_u - FD} BV_s \quad (\% BV_s) \quad (4)$$

Erythrocyte density. Red cell density was calculated (Hinghofer-Szalkay and Holzer 1979) from

$$ED = PD + (BD - PD)/Ht \quad (g \cdot l^{-1}) \quad (5)$$

where: ED is the erythrocyte density, and hematocrit is given as volume fraction.

Density and hematocrit data. With unchanged ED, the observed PD increase during tilt is due exclusively to fluid efflux from the plasma to the extravascular compartments. The FD can be calculated (Hinghofer-Szalkay and Moser 1986) from:

$$FD_P = PD_s - \frac{Ht_s(1 - fc \times Ht_u)}{(Ht_u - Ht_s)} (PD_u - PD_s) \quad (g \cdot l^{-1}) \quad (6)$$

where: fc is the correction factor for whole body hematocrit, i.e. the F_{cell}-ratio. If fc would change in the course of an experiment, all Ht values in Eq. (6) would have to be multiplied by the corresponding appropriate fc value.

Fluid density may also be computed from the BD changes. Because of the lower whole body hematocrit compared to the antecubital Ht, the calculated whole body blood density (BBD) was employed. Since the measured blood density (BD) = ED × Ht + PD(1 − Ht), then

$$BBD = ED \times fc \times Ht + PD(1 - fc \times Ht)$$

and the fluid density is computed from

$$FD_B = BBD_s - \frac{Ht_s}{Ht_u - Ht_s} (BBD_u - BBD_s) \quad (g/l) \quad (7)$$

according to Eq. (6).

Varying F_{cell}-ratios. To assess the influence of changing F_{cell}-ratios, values of fc ranging from 0.90 to 0.93 (Harrison 1985; Gaehtgens 1984) were used to calculate the corresponding values of FD from Eqs. (6) and (7).

Data analysis. The data from min 1, 6, 29, 31, 36 and the final minute were compared to the mean of the two supine control samples. For single groups, arithmetic means ±SD are indicated. Linear regressions were computed with a Texas Instruments 51 II calculator, analysis of variance of data as a function of time was performed by calculating least significant differences (LSD) between periods corresponding to $p = 0.05$, and the Mann-Whitney U test was applied for hypothesis testing.

Results

Four of the five subjects participated twice each in the experiments; three showed no presyncopal

symptoms during the full 90 min period (five experiments). One subject (Nr. 3) displayed presyncopal symptoms immediately after suit deflation at min 30 (two experiments), and another (Nr. 5) at min 40 and min 60. Thus, fore each data point in the tilt/LBPP period (min 1, 6, and 29), $N=9$; for the subsequent postdeflation tilt period (min 31, 36, and final), $N=7$. All possible combinations of BD, PD, and Ht were linearly correlated ($p<0.001$). Erythrocyte density did not change with body position and pressure suit inflation/deflation ($p>0.2$).

Figure 1 shows the time course of PD, BD, and Ht (supine control, minute -10 to minute 0; head-up tilt with the suit inflated, minute 0 to 30; and head-up with the suit deflated, minute 30 to 90). Figure 2 presents corresponding mean relative values and the levels of least significant difference (LSD) of $p=0.05$. Compared to the supine control, all changes were statistically significant after 6 min tilt/LBPP. After 29 min, BD had increased by 1.6 ± 0.3 g·l^{-1}, and PD by 0.8 ± 0.2 g·l^{-1} ($p<0.05$). In the subsequent period of tilt without LBPP (deflated), the densities and Ht were further increased ($p<0.05$) at min 36 (Fig. 2). At the final sampling (not shown), BD and PD had increased by $+3.6\pm0.9$ g·l^{-1} and by $+2.0\pm0.7$ g·l^{-1}, respectively, compared to supine control. These results were significant when compared to both the supine control ($p<0.01$) and the 29 min levels ($p<0.05$).

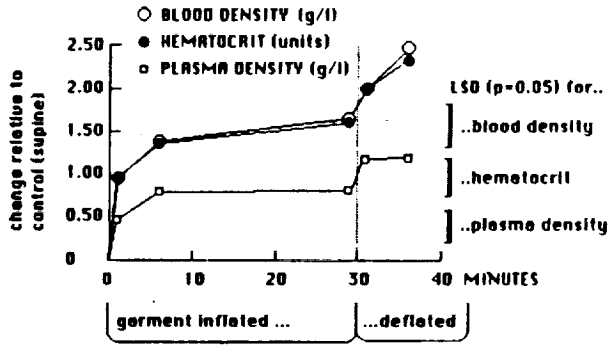

Fig. 2. Average time-course of changes in plasma and blood densities and hematocrit during the first 36 minutes of head-up tilt. After supine control, least significant differences (LSD) are indicated for $p=0.05$

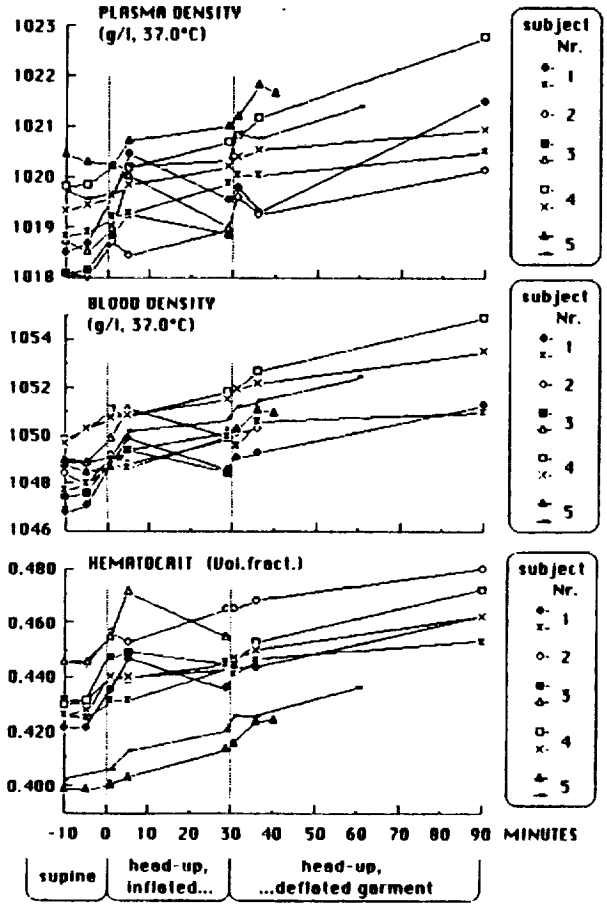

Fig. 1. Individual plasma densities, blood densities and hematocrits during the supine control, upright/LBPP, and postdeflation upright periods

Using the data from min 29 versus supine control ($N=9$), and the final data versus min 29 ($N=7$), FD averaged 1006.0 ± 1.1 g·l^{-1} for tilt with LBPP, and 1002.8 ± 4.1 g·l^{-1} after garment deflation (assuming unchanged F_{cell}-ratios). Fluid density differed for tilt/LBPP and post-deflation tilt ($p<0.03$). Blood and plasma density data gave virtually the same results from Eqs. (6) and (7). Assuming unchanged F_{cell}-ratio levels ranging between 0.90 and 0.93, essentially identical results ensue from FD computations (Fig. 3).

Plasma volume decreased by $6.0\pm1.2\%$ ($p<0.05$) in the head-up tilt/LBPP period, and by an additional $6.4\pm2.7\%$ ($p<0.05$) of supine control in the subsequent postdeflation tilt period

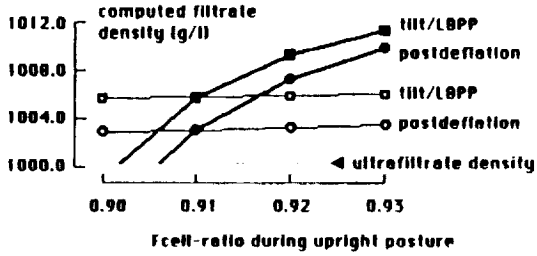

Fig. 3. Computed mean filtrate density values for min -10 to 29 *(upper curves: tilt/LBPP)* and 29 to final *(lower curves: postdeflation tilt)* with the F_{cell}-ratio either unchanged *(flat curves)* or varying with changing conditions *(thick curves)*

(Eq. (3)). The corresponding blood volume increases (Eq. (4)) were by $3.7 \pm 0.7\%$ ($p < 0.05$) and by an additional $3.5 \pm 2.1\%$ ($p < 0.05$) of the supine control, respectively. During the first 30 min of tilt, therefore, half the total orthostatic plasma volume (-12.4%) and blood-volume decreases (-7.2%) were prevented by application of 60 mm Hg LBPP.

Discussion

"Positive" pressure. From a physical point of view, all pressure is positive, and the terms hyperbaric and hypobaric (with the respective barometric pressure serving as the actual reference point) should be preferred usage rather than the terms "positive" and "negative". However, the use of the acronyms LBNP for hypobaric ("negative") pressure, and LBPP for hyperbaric ("positive") pressure applied to the lower body is widespread and will probably continue to be used.

Use of antecubital blood. There was no muscular activity in the arm from which the venous blood samples were taken, and thermoregulatory shunt flow probably contributed a major part to the overall perfusion of the extremity. Therefore it is likely that adverse local influences on the properties of antecubital blood were minimal under the experimental conditions of the study. However, it might be questioned whether blood taken from the antecubital vein can be considered as representative of the blood throughout the circulation, although venous blood is routinely used for most human studies.

Blood volume changes. Compared with the supine control level, the total average plasma volume decrease was 12.4%. From a previous study, the calculated plasma volume loss while tilted 70° upright (without garment) for 45 min after equilibration in the supine position exceeded 16% (Hinghofer-Szalkay and Moser 1986). During upright tilting after equilibration in the sitting or supine postures, hemoconcentration occurs because of outward filtration of protein-poor fluid caused by high hydrostatic capillary pressures in the dependent parts of the body.

Plasma density increased due to changes in the volume and density of the shifted fluid. Blood density increased proportionally to both the increasing plasma density and the rise in hematocrit which follows the plasma volume contraction. The time course of orthostatic fluid accumulation the legs can be traced by ultrasound echo tissue thickness measurements (Kirsch et al. 1980). This method, however, records the total effect of interstitial volume gain plus venous engorgement, whereas density changes in the plasma reflect solely fluid shifts across the interface between the vascular and the interstitial/lymph compartments. The rise in plasma and blood densities in normal subjects, when moved to the tilted posture, may exceed 2 and 4 $g \cdot l^{-1}$ respectively (Hinghofer-Szalkay 1980).

If LBPP were applied to a subject in the supine position before being tilted to the upright position, the orthostatic rise in transmural pressure across the vessel walls in the dependent legs would be reduced because the external positive counterpressure would oppose the increase in intravascular hydrostatic pressure. The circulatory effects of LBPP are comparable to those when the body is immersed in a water bath; LBPP increases central venous pressure (Goldsmith et al. 1984) to a similar extent as when immersed to the neck (Gauer and Thron 1965). With immersion, no significant changes in Ht and hemoglobin concentrations are observed if the subjects are supine before immersion (Epstein 1978; Epstein et al. 1972). If standing is chosen as the basal condition, subsequent immersion reverses this hemoconcentration, leading to a marked expansion in plasma volume. This was predicted from theoretical reasoning (von Diringshofen 1948) and later confirmed experimentally (Greenleaf et al. 1983; McCally 1964). Net fluid transfer to the intravascular compartment may cause a decrease of interstitial fluid pressure, which has been reported during immersion (Khosla and DuBois 1981). However, it is not known how changes in interstitial fluid pressure contribute to fluid shifts during LBPP application.

Red cell density. We found no change in red cell density, in agreement with results from earlier investigations on the influence of orthostasis in euhydrated man (Hinghofer-Szalkay and Moser 1986) and of induced hypovolemia in animals (Hinghofer-Szalkay 1986a). During head-up tilt, red cell density changed neither with LBPP nor after garment deflation. This result supports the assumption that no net fluid shift occurred between the plasma and erythrocyte compartments, and that fluid volume and fluid density calculations are not compromised by additional net fluid exchange across the red cell membranes. In addition, plasma osmolality is unchanged during application of LBPP in mildly dehydrated subjects

(Goldsmith et al. 1984), and the mean erythrocytic volume remains unchanged after postural changes in euhydrated humans (Harrison 1985).

Filtrate density. If the fluid which leaves the intravascular compartment contains no protein, then the fluid density equals the density of protein-free ultrafiltrate; i.e., 1000.3 $g \cdot l^{-1}$ at 37°C (Hinghofer-Szalkay et al. 1980). If protein moves with the filtrate, then the filtrate concentration is greater than zero for any accompanying protein content and fluid density is greater than 1000.3 $g \cdot l^{-1}$. In the present study, fluid density ranged from 1001.7 to 1008.3 $g \cdot l^{-1}$ in the nine experiments. The mean fluid density during the first standing period with the garment inflated (1006.0 $g \cdot l^{-1}$) was close to fluid density values reported from ear lobe blood in an earlier study (1008.3 $g \cdot l^{-1}$) which investigated the effects of 70° head-up tilt after supine equilibrium (Hinghofer-Szalkay and Moser 1986). In the present study, post-deflation fluid density was lower (1002.8 $g \cdot l^{-1}$) than in the predeflation (tilt/LBPP) periods (1006.0 $g \cdot l^{-1}$, $p < 0.03$). This fluid density decrease was probably caused by a lower protein content of the fluid filtrated after cessation of LBPP during tilt.

F_{cell}-ratio. For unchanged levels of F_{cell}-ratios in the physiological range, the computation of filtrate density from blood or plasma density shifts results in virtually identical FD values. However, there are significant differences in the resulting fluid density values from Eqs. (6) and (7) if different F_{cell}-ratios are used for the supine control, upright inflated, and upright deflated conditions (Fig. 3).

A possible decrease of the F_{cell}-ratio during the post-deflation tilt period would yield lower (compared to the preceding tilt/LBPP phase) fluid density results. This reduction could be due to a tissue depressurizing effect at min 30 (garment deflation), rendering the lower body microvessels more compliant than before. Since blood in the microvessels has a lower average hematocrit than that in large vessels, the result would be a lowered F_{cell}-ratio because of an increased plasma volume fraction in the microvascular compartment. Conversely, an increase of the F_{cell}-ratio with garment inflation, assuming the microvessels were "squeezed out" in part by compression effects of the LBPP maneuver, cannot be dismissed. Such an effect would increase the computed fluid density values above the real filtrate density. Therefore, direct measurement of the F_{cell}-ratio before, during, and after LBPP, with and without additional postural changes, are needed to determine to what extent a shift in net microvessel filling may contribute to changes in hematocrit and blood density in venous blood.

This F_{cell}-ratio condition applies to all experiments where hematologic changes in large vessel blood are taken when measuring fluid shifts across microvascular interfaces (Harrison 1985). Our fluid density data suggest a mean protein concentration of ~29 and ~13 $g \cdot l^{-1}$ (two-fifths and one-fifth of the normal plasma protein concentration) during the first (tilt/LBPP) and second (postdeflation tilt) periods, respectively (Hinghofer-Szalkay et al. 1980). The confounding influence of possible intra-experimental shifts in the F_{cell}-ratio is quantified in Fig. 3. At least a major part of the decrease in hematocrit and blood density of the present study was caused by an outward fluid shift and decrease in plasma volume, however, since there was a significant increase in plasma density and, hence, plasma protein concentration.

In conclusion, application of +60 mm Hg garment pressure on the lower body (LBPP) during 60° head-up tilt prevented approximately 50% of orthostatic hemoconcentration in euhydrated human subjects. The mass density of red cells remained unchanged during tilting with and without LBPP compared to supine control conditions. This finding validates the computation of volume shifts and filtrate densities from blood density and plasma density measurements. The filtrate density results for head-up tilt with LBPP, and during continuation of tilting after garment deflation were different. This difference could be the result of different protein concentrations in the filtrated fluid during the two periods, and/or with changes in the ratio of whole body to large vessel hematocrit. Direct determination of the F_{cell}-ratio could answer the question whether redistribution of blood between microvascular and large vessel compartments, which differ in their average hematocrit, occurs during combined pressure garment and body tilt maneuvers.

H. Hinghofer-Szalkay was a European Space Agency fellow on leave from the Physiological Institute, Karl Franzens-University, A-8010 Graz, Austria.

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Paper VII

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Blood Pressure and Plasma Renin Activity as Predictors of Orthostatic Intolerance

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HARRISON MH, KRAVIK SE, GEELEN G, KEIL L, GREENLEAF JE. *Blood pressure and plasma renin activity as predictors of orthostatic intolerance.* Aviat. Space Environ. Med. 1985; 56:1059–64.

Some physiological responses to head-up tilt and 3 h standing were evaluated in 13 dehydrated subjects. Seven of the subjects proved to be orthostatically intolerant (INT), exhibiting presyncopal symptoms. Before the symptoms manifest themselves the INT subjects had consistently lower ($p < 0.05$) systolic blood pressures, generally lower diastolic and pulse pressures, and elevated ($p < 0.05$) plasma renin activity (PRA) compared to the tolerant (TOL) subjects. Plasma vasopressin usually increased more in the INT subjects, but appeared to be related to the severity of presyncopal symptoms rather than to the upright posture per se. It is concluded that systolic and pulse pressures, with PRA, may allow discrimination between TOL, and potentially INT individuals; i.e., predict orthostatic intolerance. It is suggested that dehydration could provide a valuable physiological model for elucidating the causes of orthostatic intolerance.

REDUCED ORTHOSTATIC tolerance has invariably been observed postflight in American and Soviet spacecrews (16). This is generally ascribed to "cardiovascular deconditioning"; i.e., an alteration of cardiovascular control mechanisms induced by the hypogravic conditions of spaceflight (4). However, some astronauts appear to have a greater resistance than others to this deconditioning process (13).

Within the general population there is also considerable variability in physiological responses to orthostasis, with some otherwise healthy individuals being more susceptible to postural hypotension than others; for example, endurance-trained athletes may be less tolerant of gravitational stress than nonathletes (12). A question which has not been addressed is whether the physiological basis of this orthostatic intolerance is the same as that for orthostatic intolerance induced by spaceflight, or by simulated weightlessness as in water immersion (14) and in bedrest (18). This may be because those physiological factors which predispose humans toward orthostatic intolerance have not been precisely identified (3).

Incidental observations from two studies we have recently conducted have some bearing on this issue. During investigations of effects of dehydration on endocrine responses to orthostasis, it happened by chance that about half of the subjects were orthostatically intolerant (INT). Consequently, we were able to test the experimental hypothesis that the means of the orthostatically intolerant (INT) and tolerant (TOL) groups represented two distinct populations. This paper describes the physiological factors which differed significantly between the two groups.

METHODS

Six male subjects aged 30 to 51 years, and weighing 57 to 86 kg, took part in Study 1. Five males and two females, aged 20 to 50 years, and weighing 64 to 85 kg, took part in Study 2. All were healthy volunteers, nonsmokers, using no drugs or medication at the time of the studies, and fully briefed as to the purpose and nature of the experiments. Most importantly, none had a history of syncope. All but one subject were physically active, and of above average physical fitness.

The experiments were always performed at the same time of day (between 0800 h and 1300 h) in a laboratory maintained at 24°C. In both studies the subjects were

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dehydrated by 26 h of total abstinence from all liquids, and a dry, but otherwise normal diet supplemented by 6 grams of sodium chloride.

Subjects were regarded as orthostatically INT if at some point during either head-up tilt (HUT) or free standing they exhibited presyncopal signs and symptoms; i.e., pallor, dizziness, sweating, and nausea. No subject fainted.

Study 1. The purpose of the study was to determine the effect of hydration status on plasma vasopressin (PVP) and plasma renin activity (PRA) during HUT. Each experiment comprised four 45-min periods, the first two being separated from the last two by a 1-h period of rehydration. This was with tap water, heated to 36.5 ± 0.5°C to prevent any change in core temperature. The subject was allowed to leave the tilt table to drink the water, but remained seated until a supine position was resumed 55 min after the end of period two, and 30 min before taking the first blood sample in period three. The volume of water the subject was asked to consume was calculated from predicted insensible and measured urine losses over the 26 h, and not from change in body weight (BW). This was because of uncertainty regarding the contribution of variations in food intake to the decline in BW during dehydration. To ensure over- rather than underhydration, a volume of water equivalent to 0.5%of the predehydration BW was added to the calculated volume.

In periods 1 and 3 the subjects were supine on a tilt table and in periods 2 and 4 they were in a 70° head-up position supported on a footboard.

Study 2. The purpose of the study was to determine the effect of inflation, i.e., lower body positive pressure (LBPP), and deflation of an antigravity suit on cardiovascular and hormonal responses to standing. Subjects stood upright, unsupported, for 3 h wearing the antigravity suit. During the first and third hours the suit was deflated; during the second hour the suit was inflated to 60 mm Hg. A control experiment was performed 6 months later in which five of the seven subjects stood for 3 h wearing the deflated antigravity suit.

Measurements. Heart rate (fH) was determined either from a 30-s ECG recording, or by the palpation of the radial pulse. Brachial blood pressure (BP) was measured with a mercury sphygmomanometer, always by the same person. The arm rested on a raised table so that a constant reference point with respect to the heart was maintained. Diastolic pressure was recorded as the Korotkoff sounds disappeared. In Study 1 measurements of fH and BP were made every 5 min, and in Study 2 approximately every 10 min.

Blood was sampled via a flexible teflon catheter (Quick-Cath, Travenol Laboratories Inc.) inserted 3 cm into an antecubital vein. In Study 1, 18-ml blood samples were removed after 25-, 35-, and 45-min supine, and after 1, 5, 10, 15, 25, 35, and 45 min HUT. In Study 2 a similar volume was removed after 15, 30, 45, and 58 min standing within each hour. Of the many determinations made, only the PVP and PRA data are presented here.

Blood used for radioimmunoassay was collected over EDTA. The plasma was immediately separated in a refrigerated centrifuge and frozen (−60°C) to await analysis. Vasopressin was assayed according to Keil and Severs (10), and PRA according to Haber *et al.* (9). The sensitivities of the radioimmunoassays were 0.3 $pg \cdot ml^{-1}$, and 2 $pg \cdot ml^{-1} \cdot h^{-1}$ of angiotensin 1, respectively; the coefficients of variation of repeated assays on the sames samples were ±11% for low and ±3% for high plasma levels of PRA, and ±9% for PVP.

Within 6 weeks of the completion of Study 1, an estimate of the subjects' absolute blood volume was obtained using T-1824.

Treatment of results. Analysis of variance was used to compare values from INT subjects with TOL subjects. Comparisons were first made using data from each study separately, and treating the LBPP and control data from Study 2 as separate studies (since the same subjects were used for each). Values are presented in tables and figures as the means plus or minus a standard error of the mean (SEM) derived from the residual variance estimate. The number of observations (n) upon which the means are based is indicated by the product (n_1 x n_2), where n_1 = number of subjects, and n_2 = number of observations on each subject.

RESULTS

Study 1. As determined from estimated insensible and measured urine water losses, the mean dehydration was 3.04 ± 0.34%; as determined from loss of BW from day 1 to day 2, the mean dehydration was 2.37 ± 0.41%. Between periods 2 and 3 the subjects drank 2.48 ± 0.15 L of water. This raised their BW to 0.26 ± 0.18% more than the predehydrated, day 1 value—less than the target level of +0.5%, but still representing overhydration.

During dehydration HUT, three subjects were INT. During rehydrated HUT, one of these subjects still reported mild discomfort. While supine, both dehydrated and following rehydration, systolic, diastolic, and pulse pressures were lower ($p < 0.001$) in the INT group compared to the TOL group, but fH was similar (Table I). The INT group also had lower systolic and pulse pressures during dehydrated HUT ($p < 0.001$ and $p < 0.05$, respectively) and rehydrated HUT ($p < 0.01$ and $p < 0.001$, respectively). Heart rate increased more during dehydrated HUT in the INT subjects ($p < 0.01$), but not during rehydrated HUT.

Plasma renin activity was higher ($p < 0.001$) during all four experimental periods in the INT group (Fig. 1a). Plasma vasopressin increased more during dehydrated HUT in the INT group ($p < 0.05$), but not during rehydrated HUT (Fig. 1b). Levels of PVP were similar in the two groups before dehydrated HUT, but were elevated in the INT subjects prior to rehydrated HUT ($p < 0.01$).

Study 2. The level of dehydration was not assessed, but may be assumed to have been similar to that in Study 1.

Deflation of the antigravity suit at the start of the third hour of standing provoked presyncopal symptoms in four of the seven subjects. During the control study in which five of the subjects stood for 3 h, two of the four INT individuals began to experience discomfort after the first hour. The other two INT subjects were unavailable

TABLE I. HEMODYNAMIC CHARACTERISTICS OF ORTHOSTATICALLY TOLERANT (TOL) AND INTOLERANT (INT) SUBJECTS BEFORE AND DURING HEAD-UP TILT WHEN DEHYDRATED AND FOLLOWING REHYDRATION. Mean ± S.E.M. (n = 3 x 6)

Variables	Group	Supine		Head–up Tilt	
		Dehydrated	Rehydrated	Dehydrated	Rehydrated
SP	TOL	130±1	130±1	127±1	126±2
	INT	121±1	120±2	112±2	118±3
	p<	0.001	0.001	0.001	0.01
DP	TOL	82±1	89±1	91±1	91±1
	INT	78±1	83±1	90±2	93±2
	p<	0.001	0.001	NS	NS
PP	TOL	48±1	35±1	41±1	35±1
	INT	43±1	22±1	37±1	25±2
	p<	0.01	0.001	0.05	0.001
fH	TOL	55±1	53±1	66±1	64±2
	INT	59±2	54±2	73±2	66±2
	p<	NS	NS	0.01	NS

SP = systolic pressure (mm Hg); DP = diastolic pressure (mm Hg); PP = pulse pressure (mm Hg); fH = heart rate (bpm^{-1}); NS = not statistically significant; p = probability; n = (number of subjects) x (number of observations per subject).

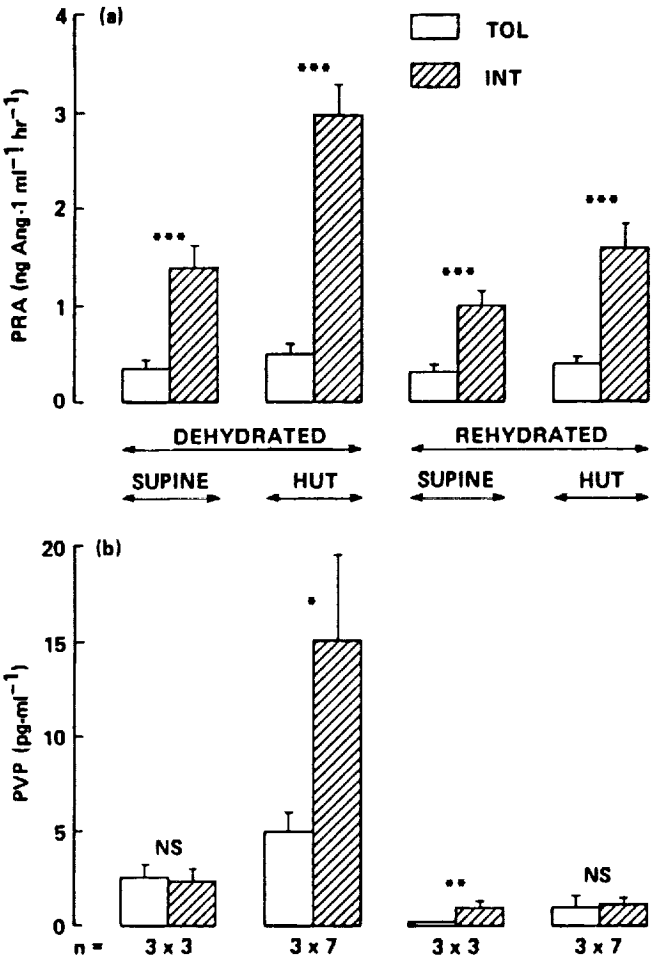

Fig. 1. Comparison of (a), plasma renin activity (PRA), and (b), plasma vasopressin (PVP), in three orthostatically tolerant (TOL) and three orthostatically intolerant (INT) subjects before (supine) and during head-up tilt (HUT) dehydrated and 1 h later following rehydration. Vertical bars represent standard errors. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$. n = (number of subjects) × (number of observations per subject).

for the control study. Mean values for systolic, diastolic, and pulse pressures, and for fH, are given in Table II. Data are presented as means for each hour during the control and LBPP phases of the study.

Systolic and pulse pressures were consistently lower ($p < 0.01$) in the INT group, and diastolic pressures were lower ($p < 0.001$), except for the first hour of the control phase. Heart rate sometimes differed significantly, but not always in the same direction.

Plasma renin activity was consistently higher ($p < 0.001$) in the INT subjects (Fig. 2a). Plasma vasopressin increased to very high levels in the two control subjects who experienced presyncope periodically through the last 2 h of standing ($p < 0.001$; Fig. 2b). By contrast, when LBPP was applied at the start of the second hour, no increase in PVP was observed until that pressure was released at the start of the third hour ($p < 0.05$; Fig. 2b).

Combined analysis. Classifying the subjects within each study as either orthostatically INT or orthostatically TOL produced very small subgroups. Consequently, the statistical analysis was biased by the ratio of the large number of observations per subject to the small number of subjects. This allowed any one subject to have a disproportionate effect on the mean response, which account for the sometimes higher and sometimes lower values for fH seen in the INT group compared to the TOL group in Study 2 (Table II). Nevertheless, the consistency with which BP and PRA differed between the two groups, even before presyncopal signs became evident, was impressive. Therefore, despite the dissimilar protocols followed, the data were combined for an evaluation of overall differences between the INT and TOL subgroups.

Table III provides the results of an analysis of variance performed on the means of observations from each of the INT and TOL subjects for the dehydrated supine control period in Study 1, and for the first hour of standing in Study 2 (i.e., observations

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TABLE II. HEMODYNAMIC CHARACTERISTICS OF DEHYDRATED ORTHOSTATICALLY TOLERANT (TOL) AND INTOLERANT (INT) SUBJECTS DURING 3H OF STANDING WITH AND WITHOUT LOWER-BODY POSITIVE PRESSURE DURING THE SECOND HOUR. Mean ± S.E.M.

Variable[a]	Group	1st Hour		2nd Hour		3rd Hour	
		Control[b]	Control	Control	LBPP	Control	Control
n[c]	TOL	3 x 6	3 x 6	3 x 8	3 x 8	3 x 7	3 x 7
	INT	2 x 6	4 x 6	2 x 8	4 x 8	2 x 7	4 x 7
SP	TOL	125±3	121±2	118±2	134±2	113±2	114±2
	INT	101±2	95±1	90±2	117±1	85±3	91±1
	p<	0.001	0.001	0.001	0.001	0.001	0.001
DP	TOL	86±2	84±2	86±1	93±2	86±1	87±2
	INT	83±1	73±1	77±2	84±1	72±3	70±2
	p<	NS	0.001	0.001	0.001	0.001	0.001
PP	TOL	39±2	38±1	29±1	40±1	25±2	27±1
	INT	20±1	22±1	17±1	33±1	17±1	21±1
	p<	0.001	0.001	0.001	0.001	0.01	0.001
fH	TOL	90±1	74±4	91±1	68±2	91±1	84±4
	INT	75±3	82±2	73±1	66±1	70±2	80±2
	p<	0.001	0.05	0.001	NS	0.001	NS

[a] For key to symbols, see Table I.
[b] Control = no positive pressure.
[c] n = (number of subjects) x (number of observations per subject).

not confounded by presyncopal episodes). Data from the control of Study 2 have been excluded to avoid possible confounding effects of combining nonindependent means. The large standard errors reflect the fact that the supine data from Study 1 are combined with the standing data from Study 2, and the change in posture affected BP, fH, PRA, and PVP. Even so, these combined data are consistent with the results of the separate studies presented in Tables I and II, and in Figs. 1 and 2.

DISCUSSION

The presyncopal signs and symptoms exhibited by the INT subjects were typically very rapid in onset. When coincident with fH and BP measurements, bradycardia and hypotension were consistently observed. Otherwise, however, these measures were poor predictors of an impending presyncopal episode.

It is important to appreciate that before undertaking these studies the INT subjects did not regard themselves

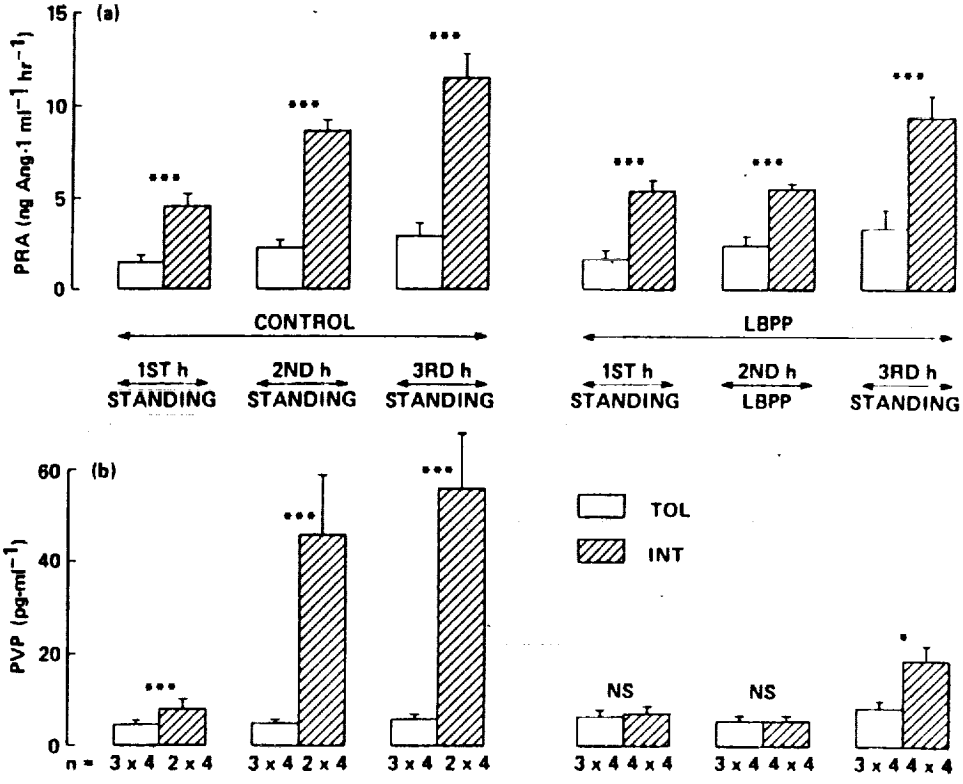

Fig. 2. Comparison of (a), plasma renin activity (PRA), and (b), plasma vasopressin (PVP), in orthostatically tolerant (TOL) and orthostatically intolerant (INT) subjects during 3 consecutive hours of free standing (control), and during 3 h of standing with lower body positive pressure (LBPP) during the second hour. All subjects had undergone 24 h dehydration. Vertical bars represent standard errors. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$. n = (number of subjects) × (number of observations per subject).

TABLE III. COMBINED HEMODYNAMIC AND ENDOCRINE DATA FOR SUPINE DEHYDRATED HEAD-UP TILT, AND FIRST HOUR OF STANDING BEFORE APPLICATION OF LOWER-BODY POSITIVE PRESSURE. Mean ± SEM (n_{TOL} = 6; n_{INT} = 7).

Group	SP	DP	PP	fH	PRA	PVP
TOL	126±3	83±2	43±3	65±7	1.0±0.5	4.5±1.5
INT	106±5	75±2	31±4	72±6	3.7±0.9	4.7±1.2
p<	0.05	0.05	NS	NS	0.05	NS

PRA = plasma renin activity, ng·ml·h^{-1} of angiotensin I.
PVP = plasma vasopressin, pg·ml^{-1}.
For key to other symbols, see Table I.

as being especially prone to postural hypotension; they exhibited no overt clinical signs of orthostatic intolerance. Like the TOL subjects, they were familiar and comfortable with invasive procedures. While the phlebotomy may have contributed towards orthostatic intolerance, within each study the same volume of blood was removed from all the subjects. The signs and symptoms became manifest only following dehydration, the underlying purpose of which was not to provoke postural hypotension, but, as with the supplementary salt during the 26 h of fluid deprivation, was to raise PVP to detectable levels. Since no measurements were made of BP before dehydration, the enhanced intolerance cannot be ascribed with certainty to that dehydration. Yet, in Study 1 rehydration virtually eliminated presyncopal symptoms. Also, values for PRA were obtained after 45-min supine before dehydration, and these were similar for TOL and INT subjects. Finally, as Beetham and Buskirk (2) demonstrated, dehydration does reduce orthostatic tolerance.

According to Bergenwald *et al.* (3), the interindividual variability in susceptibility to fainting is largely unexplained. However, they did observe that fainters consistently had lower blood volumes in relation to body height, and higher orthostatic heart rates, than nonfainters. In Study 1, the INT group had lower blood volumes (52, 63 and 75 ml·kg^{-1}) in relation to body weight than the TOL group (88, 82, and 82 ml·kg^{-1}) but not in relation to body height. Orthostatic fH was greater during dehydrated HUT in the INT group (Table I). Corresponding data were not obtained during Study 2.

Rushmer (17) has pointed out that orthostatic hypotension is commonly experienced by many people with blood pressures "below the normal range." Stevens (20) observed that baseline recumbent systolic pressures were lower in fainters than nonfainters; during HUT the fainters still had lower systolic pressures, and a greater narrowing of the pulse pressure, than did the nonfainters. In both studies reported here, the INT subjects were hypotensive compared to the TOL subjects with respect to systolic and diastolic blood pressures, although after the first hour of Study 2 in the absence of LBPP, and after the second hour with LBPP, blood pressures were undoubtedly influenced by the presyncopal episodes. Nevertheless, as in the study of Stevens (20), systolic pressures were significantly lower in the INT group while supine prior to HUT (Table I) and also significantly lower during the first hour of standing (Table II), when no overt orthostatic symptoms were observed. Thus, resting systolic blood pressure may be a useful predictor of orthostatic intolerance. Diastolic pressure (Table III) may also be a good predictor, even though this was not consistently lower in the INT subjects in Study 2 (Table II). Pulse pressure may be less reliable, reflecting the variability within both systolic and diastolic BP measurements.

As a component of the renin-angiotensin-aldosterone system, renin is an important factor in the regulation of BP (21). By acting to conserve water and electrolytes, an increased secretion of renin is an appropriate response to hypotension (8). The present finding of a consistently higher PRA in the INT subjects is, therefore, consistent with expectation (Figs. 1a, 2a). However, Shvartz *et al.* (19) observed a lower PRA in fainters compared to nonfainters during HUT, which they explained in terms of lower sympathetic activity. Certainly the sympathetic nervous system is involved in the regulation of renin secretion (5,15). Apart from the fact that our subjects were dehydrated, we can presently offer no explanation for these divergent observations. A more definitive study is required with simultaneous determinations of PRA and plasma norepinephrine.

Vasopressin has also been implicated in the regulation of BP (6). However, in Study 1 rehydration greatly attenuated the PVP response to HUT in both the INT ($p < 0.001$) and TOL ($p < 0.05$) subjects. Although PVP increased in both groups during dehydrated HUT, the increase was greater in the INT groups ($p < 0.05$; Fig. 1b). In Study 2, for both control and LBPP, PVP in the TOL subjects did not differ significantly between hours 1, 2, and 3. In the two INT subjects of the control experiment, PVP was greater in hour 2 than in hour 1 ($p < 0.05$), although it did not increase further in hour 3; it was also greater in hour 3 compared with hour 2 following release of LBPP ($p < 0.005$). Taken together, these observations suggest that the increase in PVP generally observed in dehydrated subjects following assumption of an upright posture (1,7,11) is related more to the severity of presyncopal symptoms of orthostatic hypotension than to the changes in BP induced by HUT (1).

Although there was no significant difference between PVP levels in TOL and INT subjects during either rehydrated HUT (Fig. 1b), or during the first 2 h

of standing in the LBPP experiment (Fig. 2b), PRA was consistently greater in the INT subjects. There is, therefore, a dissociation between the responses of plasma PVP and PRA, with only the latter being related to orthostatic intolerance.

Hitherto, dehydration *per se* does not appear to have been considered either as a possible model for elucidating the causes of orthostatic intolerance, or as a means of discriminating between INT and TOL individuals. Beetham and Buskirk (2) assumed that dehydration reduced orthostatic tolerance by reducing blood volume, and although this still has to be proven, clearly some aspect of BP control is compromised by the fluid deficit incurred during dehydration. Similarly, the cardiovascular deconditioning and orthostatic intolerance of simulated weightlessness, as in water immersion and bedrest, and true weightlessness, appear to be related to fluid loss and hypovolemia (18). Therefore, it seems that there may be some justification for hypothesizing a common physiological basis for orthostatic intolerance, whether induced by weightlessness, simulated weightlessness, or dehydration.

In conclusion, we suggest that dehydration may provide a means of identifying individuals who are susceptible to orthostatic hypotension. Following dehydration, individuals who become orthostatically INT have a lower systolic BP and an elevated PRA compared to those who do not become orthostatically INT. Additionally, pulse and diastolic pressures may also be lower. Since these differences can be detected before orthostasis is induced, it may be possible to predict orthostatic intolerance.

ACKNOWLEDGMENT

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Paper VIII

Inhibition of plasma vasopressin after drinking in dehydrated humans

A85-28021

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GEELEN, GHISLAINE, L. C. KEIL, S. E. KRAVIK, C. E. WADE, T. N. THRASHER, P. R. BARNES, GISELA PYKA, CYNTHIA NESVIG, AND J. E. GREENLEAF. *Inhibition of plasma vasopressin after drinking in dehydrated humans.* Am. J. Physiol. 247 (Regulatory Integrative Comp. Physiol. 16): R968–R971, 1984.—To study the effects of nonosmotic and nonvolumetric factors that may influence secretion of vasopressin, serum Na^+, K^+, and osmolality (Osm), hemoglobin, hematocrit, plasma arginine vasopressin (AVP), aldosterone (PA), and renin activity (PRA) were measured in five men and three women (26–50 yr, 73 ± 4 kg) before and after 24 h of mild dehydration (food but no fluid) and seven times during the 1st h after rehydration with 10 ml/kg of tap water (17.5 ± 0.5°C) consumed in 105 s (range 35–240 s). Dehydration increased mean serum Na^+ 3.7 ± 0.7 meq/l ($P < 0.05$), osmolality 9.1 ± 1.1 mosmol/kg ($P < 0.05$), and AVP from a hydrated level of 1.7 ± 0.2 to 3.3 ± 0.5 pg/ml ($\Delta = 1.6$ pg/ml, $P < 0.05$). After rehydration AVP fell to 2.4 ± 0.3 pg/ml ($P < 0.05$) within 3 min and reached the water-replete level of 1.8 ± 0.3 pg/ml 9 min after drinking started. Serum Na^+ and Osm did not change until 30–60 min after drinking. No significant changes occurred in PRA, hemoglobin, hematocrit, or calculated Δ in plasma volume, but PA increased from 11.1 ± 1.5 ng/dl after dehydration to 15.6 ± 2.6 ng/dl ($P < 0.05$) between 30 and 60 min after drinking. The rapid fall in plasma AVP after rehydration took place in the absence of the expected changes in the primary regulators of plasma AVP (i.e., osmolality and plasma volume), with no change in blood pressure. The results suggest that oropharyngeal factors, alone or combined with gastric stimuli, are implicated.

thirst; serum sodium; serum osmolality; serum potassium; plasma volume; antidiuretic hormone

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CHRONIC LOSS OF BODY WATER induced by dehydration increases plasma osmolality and reduces the volume of the extracellular fluid compartment. The subsequent intracellular dehydration and hypovolemia induce thirst and drinking for the correction of the volume deficit and stimulate the release of arginine vasopressin (AVP), which reduces renal water loss (14, 15). Although this sequence of events is well established, the nature and time course of the stimuli that decrease AVP secretion when rehydration occurs need to be determined more precisely. After intracerebroventricular injection of angiotensin II in the unanesthetized monkey, the normal significant rise in plasma AVP, which occurs without drinking, is severely attenuated after drinking (20). Oropharyngeal stimulation, by the act of drinking in dehydrated dogs, induces a rapid decline in plasma AVP that precedes postabsorptive changes in plasma volume or osmolality (21).

The purpose of this study was to determine whether a similar inhibition of AVP secretion occurs in water-deprived humans immediately after rehydration and to investigate the effect of this rapid rehydration or renin, angiotensin, and aldosterone levels.

METHODS

Subjects. Five men and three women 26–50 yr old, weighing 61.9–86.6 kg [mean 72.9 ± 3.7 (SE) kg] volunteered as test subjects. None were engaged in extensive physical activity, and all would be considered in a normal state of hydration.

Dehydration, rehydration, and blood sampling procedure. On *day 1* the subjects were instructed to eat their normal breakfast and report to the laboratory. Immediately before the dehydration period, a blood sample (water-replete control) was drawn from an antecubital vein of the seated subject. The subjects were then water deprived and restricted to a dry diet (4 plain hamburgers) supplemented with 4 g NaCl (total NaCl ~6 g) to increase the osmotic load. Results from a preliminary experiment had shown that merely depriving subjects of food and water for 24 h did not cause a significant increase in serum osmolality.

Twenty-four hours after starting dehydration (*day 2*) subjects returned to the laboratory, and a Teflon catheter (Vicra Quick-Cath) was inserted into an antecubital vein; subjects remained seated quietly for the duration of the experiment.

After the subjects had been seated 25 min, blood samples were drawn at −30, −9, and −3 min before starting rehydration; the mean of these samples was the dehydration control sample. At *time 0* rehydration began; the subjects drank 10 ml/kg tap water (620–870 ml) at 17.5 ± 0.5°C in 105 s (range 35–240 s). Blood samples (17 ml) were drawn 3, 6, 9, 12, 15, 30, and 60 min after drinking

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began. Three milliliters of blood were processed for measurement of serum sodium, potassium, and osmolality, and 3 ml of blood were collected for immediate analysis of hemoglobin (Hb) and microhematocrit (Hct). Four milliliters of blood were collected in chilled tubes containing dry heparin for determination of plasma aldosterone and the remaining 7 ml in chilled tubes containing EDTA for determination of AVP and plasma renin activity (PRA). After centrifugation at 4°C, aliquots of plasma were frozen and stored at −20°C until the hormone and enzyme analyses were performed.

Analyses. Serum sodium and potassium concentrations were measured with an Instrumentation Laboratory Autocal flame photometer (model 643), and serum osmolality was determined by freezing point depression with an Advanced Instruments digimatic osmometer (model 3DII). Quadruplicate Hcts were spun at 11,500 rpm for 3 min and measured on an International microcapillary reader (model CR). Blood hemoglobin was determined with the cyanomethemoglobin method with a Coulter Hb analyzer. Percent change in plasma volume (%ΔPV) was calculated from changes in Hb and Hct with an equation (7) modified from that of Elkinton et al. (4). Hormones were measured by radioimmunoassay: PRA with a New England Nuclear kit, plasma AVP in plasma extracts according to Keil and Severs (9), and aldosterone with a Diagnostic Products kit.

Statistical analyses. Data from the water-replete control samples were compared with those of the dehydration control samples with a paired *t* test. After rehydration the data were analyzed with a one-way analysis of variance for repeated measures (23). Significant differences between the dehydration control data and those at various times after starting rehydration were determined with the Neuman-Keuls multiple-range test. Values are means ± SE.

RESULTS

Effects of dehydration. The 24-h period of water deprivation induced significant ($P < 0.05$) increases in mean ± SE serum Na^+, osmolality, and plasma AVP of 3.7 ± 0.7 meq/l, 9.1 ± 1.1 mosmol/kg, and 1.6 ± 0.6 pg/ml, respectively (Fig. 1). No significant changes were observed in Hct, Hb, serum K^+, or in %ΔPV. At the end of the dehydration period PRA and plasma aldosterone concentrations were 0.7 ± 0.2 ng Ang $1 \cdot ml^{-1} \cdot h^{-1}$ and 11.1 ± 1.5 ng/dl, respectively.

Effects of drinking water. Plasma AVP decreased from 3.3 ± 0.5 to 2.4 ± 0.3 pg/ml ($P < 0.05$) within 3 min after rehydration, continued to fall, and reached water-replete levels (1.8 ± 0.3 pg/ml) by 9 min (Fig. 1). However, changes in blood composition did not follow the same time course. After rehydration serum osmolality was unchanged, and sodium decreased ($P < 0.05$) only between 30 and 60 min. No significant changes occurred in blood Hct, Hb, or, therefore, in PV. Serum potassium concentration increased ($P < 0.05$) at 9 and 12 min after rehydration. Neither the act of drinking nor the apparent absorption of water had any effects on PRA levels that remained constant throughout the experiment. However, the plasma aldosterone level, which was 11.1 ± 1.5 ng/dl after the 24-h water deprivation, remained unchanged until 30 min after drinking, when it rose to 15.6 ± 2.6 ng/dl at 30 min ($P < 0.05$) and remained elevated at 14.0 ± 2.2 ng/dl ($P < 0.05$) after 60 min (Fig. 1).

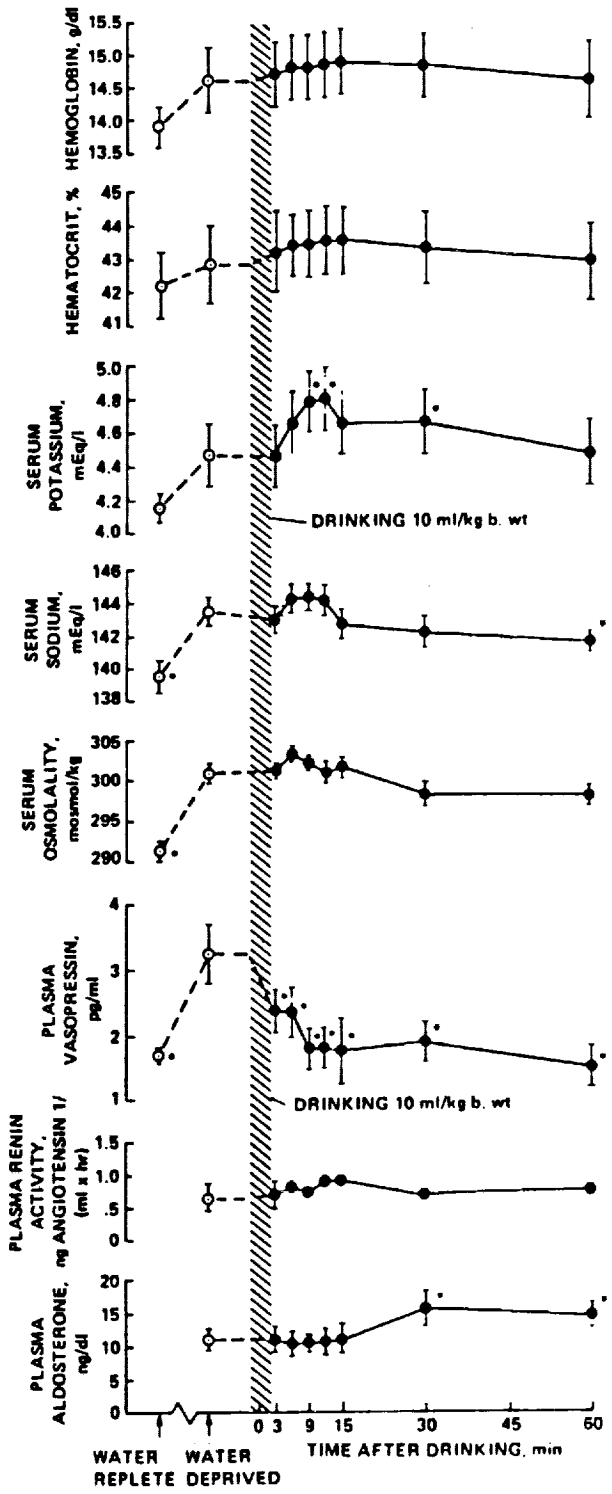

FIG. 1. Effect of 24-h water deprivation and rehydration in 5 men and 3 women (±SE). * $P < 0.05$ from water-deprived value.

DISCUSSION

The role of peripheral factors, such as oropharyngeal and gastric stimuli, in the control of drinking and satia-

tion of thirst has been documented in many species (1, 5, 6, 10, 12, 13), but little is known about the role of such factors in humans. After water loss the slower rate of drinking in humans is similar to that in rats and monkeys but different from the faster rate in dogs and camels (6, 8, 17). Nicolaïdis (11) observed anticipatory poto-diuretic reflexes in the rat immediately (<1 min) after oral and/or gastric receptors were stimulated by water. Little is known of the extent to which these factors may affect vasopressin secretion. Restoration of the extracellular fluid (ECF) volume deficit and the subsequent decrease in ECF osmolality, induced by drinking and gastrointestinal absorption, have been considered to be responsible for the fall in plasma AVP after rehydration. Results from dehydrated dogs (21) and monkeys (2) suggest that oropharyngeal factors alone, and not stimuli from gastric distension or hepatoportal osmoreceptors, may account for temporary satiety and the extremely rapid inhibition of AVP secretion after drinking in these dehydrated animals. These findings prompted us to determine if plasma AVP in dehydrated humans would respond to drinking in a similar manner.

When our subjects underwent 24-h water deprivation associated with a standard dry diet supplemented with 4 g NaCl, serum sodium, osmotic, and plasma AVP concentrations were raised significantly, whereas serum potassium, hematocrit, hemoglobin, and plasma volume were unchanged. Plasma AVP concentration fell significantly within 3 min after drinking, followed by a further decrease such that AVP reached water-replete levels only 9 min after drinking began. At the same time serum osmolality, hematocrit, hemoglobin, and %ΔPV were unchanged, whereas serum sodium concentration decreased significantly only between 30 and 60 min after drinking. These unchanged or delayed responses suggested a delay in water absorption from the gut. The early and rapid fall in plasma AVP concentration after rehydration occurred in the absence of expected changes in the primary regulators of plasma AVP—osmolality and plasma volume—with essentially no change in blood pressure.

These results confirm those of Thrasher et al. (21), who, by using dehydrated dogs with chronic gastric fistulas, concluded that oropharyngeal stimuli are important for the inhibition of drinking and that such stimuli appear to be sufficient to initiate the decrease in AVP secretion after drinking. The drinking-induced depression of AVP in their dogs occurred within 3 min, but depression of plasma osmolality began 15 min after drinking. Such was not the case with our subjects because the elevated serum osmolality was unchanged throughout 1 h after drinking. In a similar study in which AVP was not measured, Rolls et al. (18) allowed their mildly dehydrated subjects free access to water for 1 h, and 65% of the total hourly intake was consumed during the first 2.5 min; this was 9 ml/kg water in 2.5 min, close to the required 10 ml/kg drunk by our subjects in 1.8 min. So, with a similar rate of water intake, we demonstrated a rapid fall in plasma AVP after drinking. In both former studies (18, 21) plasma dilution after rehydration occurred earlier than in the present study, but access to water after dehydration was unrestricted and probably led to absorption of a greater amount of water: 30 ml/kg in 3 min in dogs (21) and 15 ml/kg in 60 min in humans (18). Thus the more rapid drinking in dogs compared with humans appears to be related to faster absorption of water from the gut and more rapid hemodilution, not to differential responses of AVP.

In the present study rapid inhibition (<3 min) of AVP secretion after drinking, in the absence of changes in serum Na^+, osmolality, or plasma volume, aldosterone, or renin activity, also suggests the action of an oropharyngeal neural mechanism mediated by the central nervous system but does not eliminate possible gastric neuroendocrine activity stimulated by distension. Drinking by mildly dehydrated monkeys causes variations in the firing rates of osmosensitive cells in the supraoptic nucleus (SON) (22), whereas water consumption by monkeys deprived of water for 5–6 days was accompanied by both an abrupt fall in plasma AVP and a decrease in the firing rate of the SON neurons with no change in plasma osmolality (2). Because local changes in tonicity and mechanical stimulation of the oropharynx and stomach activate neurons in the lateral preoptic (LPO) area, and these LPO neurons appear to play a role in the modulation of thirst behavior (19), neuronal activity may also act to modulate the rate of vasopressin secretion during and after drinking.

Another explanation for the early decrease in plasma AVP, which precedes changes in Na^+, osmolality, or plasma volume, would be the participation of putative hepatoportal osmoreceptors. However, they may be only a "subsystem," and their function may be detected only under special experimental conditions, thus minimizing the importance of their functional role in the normal regulation of body fluid composition (3, 16). Thrasher et al. (21) observed a rapid decrease in plasma AVP concentration in the dehydrated dog after oral rehydration with a solution of artificial extracellular fluid that should not have changed hepatoportal osmolality. No change in plasma AVP occurred after direct gastric administration of water, which should have lowered hepatoportal osmolality before lowering systemic osmolality. Thus hepatic osmoreceptors do not appear to play a major role for inhibition of plasma AVP after drinking in the dog.

Inhibition of plasma AVP, after drinking in dehydrated humans, as a stimulus for diuresis would be an inappropriate response for water conservation, assuming that a decrease in AVP from 3.2 pg/ml to a normal level of 1.5 pg/ml would cause a diuresis. That the equilibrium attenuated level of AVP does not fall below 1.5 pg/ml in humans (present study) and dogs (21), or below the control level of 4–5 pg/ml in monkeys (2, 20), suggests that sufficient AVP remains in the plasma to forestall significant diuresis. The decrease in AVP is perhaps more likely a signal to stop drinking than a stimulus for excretion.

The rapid fall in AVP after drinking was dissociated from PRA and aldosterone. PRA was unchanged from the water-deprived level, and PA did not increase significantly until 15–30 min after drinking. The transient rise in serum potassium 9–12 min after drinking may have contributed to the rise in PA.

The rapid decrease in plasma AVP concentration after

copious drinking in dehydrated humans suggests inhibition of AVP secretion. The dissociation between the AVP response and the unchanged plasma volume, PRA, or serum sodium, osmotic, or aldosterone concentrations suggests that oropharyngeal-gastric stimuli mediated by the central nervous system are most likely responsible for the depressed AVP. But the action of other factors that mediate fluid-electrolyte homeostasis, e.g., the natriuretic and diuretic hormones, have not been eliminated.

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Paper IX

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Effect of Longitudinal Physical Training and Water Immersion on Orthostatic Tolerance in Men

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To test the hypothesis that moderately intense physical training has no effect on orthostasis, orthostatic and fluid-electrolyte-endocrine responses to 60° head-up tilt were compared before and after 6 h of water immersion (34.5 ± 0.1°C) up to the neck following 6 months of exercise training. During the tilt test the five male subjects (27–42 years) each wore a lower-body positive-pressure suit (MAST-111A antishock trousers). The tilt procedure consisted of a 40-min supine control period (suit deflated), followed by a maximum 90-min tilt period (suit inflated to 50 ± 5 mm Hg for 30 min, then deflated for 60 min or until presyncope). The mean ±S.E. pretraining cycle ergometer peak $\dot{V}o_2$ was 3.20 ± 0.14 L·min^{-1} (39 ± 2 ml·min^{-1}·kg^{-1}), 3.36 ± 0.27 L·min^{-1} (42 ± 4 ml·min^{-1}·kg^{-1}) after 3 months (N.S.), and increased by 18% to 3.78 ± 0.36 L·min^{-1} (48 ± 5 ml·min^{-1}·kg^{-1}, +22%, $p < 0.05$) posttraining. During pretraining, water immersion tilt tolerance decreased from 74 ± 16 min before to 34 ± 9 min (Δ = 40 min, $p < 0.05$) after immersion. During posttraining, water immersion tilt tolerance decreased similarly from 74 ± 16 min preimmersion to 44 ± 13 min (Δ = 30 min, $p < 0.05$) postimmersion (74 vs. 74 min, N.S.; 34 vs. 44 min, N.S.). Fluid-electrolyte-endocrine responses were essentially the same during all four tilts: plasma volume decreased by 9.0 to 12.6% (all $p < 0.05$); plasma sodium and osmotic concentrations were unchanged, while serum protein and plasma renin activity increased ($p < 0.05$) Plasma vasopressin concentration increased significantly only in both postimmersion tilt tests, to 75–85 pg·ml^{-1} ($p < 0.05$). None of the subjects fainted. We conclude that 6 months of moderately intense physical training has no significant effect on 60° head-up tilt tolerance.

FOLLOWING SPACE MISSIONS of at least several days' duration, enhanced postural hypotension (orthostasis) is invariably present in astronauts and cosmonauts (39). One major component of the mechanism of orthostatic intolerance is the absolute levels and relative distribution of the body fluid volumes (3,10,22). It is well established that body hypohydration greater than 2–3% of the body weight results in lower orthostatic tolerance (2,18,49). Consequently, oral fluid loading before reentry and after landing, as well as G-suit inflation during reentry, are used routinely to ameliorate reentry and postlanding hypotension.

It has been suggested that the physiological responses to physical exercise training and the level of physical fitness would modify the deconditioning-induced postural hypotensive syndrome. A single period of exercise induces significant intercompartmental fluid shifts (8,9,22) whereas an extended period of exercise training can result in an absolute increase in the extracellular (plasma and interstitial) fluid volume (7,8,40). From these observations a logical deduction is that long-term exercise training would increase orthostatic tolerance and, therefore, astronauts should maintain high levels of physical fitness.

Conclusions from cross-sectional investigations of tilt-table and lower body negative pressure tolerances in trained athletes and untrained subjects do not consistently support this view. Rather, they indicate that trained athletes have lower (16,20,32,36,38,49), higher (11,23,43), or unchanged (2,12,20,28,29,47) tolerances. Some investigators have suggested that endurance exercise training is responsible for reduced orthostatic tolerance and have recommended that endurance exercise should not be performed by astronauts (29,36). This recommendation is unjustified as it was based upon results of cross-sectional studies which may be influenced by other factors, especially genetic factors. Results from most longitudinal training studies indicate improvements in tilt tolerance (10,20,44–46), although two studies have reported decreased tolerance after 8 d of exercise with

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heat acclimation (17,18). The periods of training used in these longitudinal studies (10,17,18,20,44–46) varied from 8 d (17,18) to 3 months (45) and may have been too short to have significantly influenced orthostatic blood pressure control. However, the practical question in terms of astronaut performance involves the effect of training on orthostatic tolerance following weightlessness deconditioning.

The purpose of the present study was to determine the effect of 6 months of moderately intense aerobic training on tilt-table tolerance before and after 6 h of water-immersion deconditioning.

MATERIALS AND METHODS

Peak oxygen uptake, 60° head-up tilt-tolerance and various fluid-electrolyte-endocrine responses were measured in five untrained healthy men: aged 27–42 years, height 178 ± 6 cm, weight 81.8 ± 8.8 kg, and having a body surface area of 2.00 ± 0.12 m^2. They were nonsmokers and not taking inappropriate medications; they were requested to live their normal lives and to observe reasonable personal health practices. Tilt tolerance was measured before (control) and after 6 h of water immersion (34.5°C) preceding and following 6 months of supervised exercise training (Fig. 1).

Exercise training: The training was conducted at the Movements Unlimited Fitness Center in San Mateo, CA by an instructor certified by the American College of Sports Medicine. The men were trained mainly in group sessions; the exercise consisted of calisthenics, rope-jumping, stationary cycling, and weight lifting. The group-session-exercise intensity was increased gradually; during the first 3 months the sessions lasted 1 $h \cdot d^{-1}$ for 2 $d \cdot week^{-1}$. During the second period of 3 months, the frequency of the 1-h sessions was increased to 3 $d \cdot week^{-1}$. In addition, the subjects were encouraged to walk/run unsupervised for 15 $min \cdot d^{-1}$, 2 $d \cdot week^{-1}$. During each session the intensity was increased progressively so that near-peak levels were attained for 3–4 min near the end of the workout. Appropriate warm-up and cool-down exercises were employed. The number of training sessions attended by each subject were: CAR-24, CLA-73, LAL-56, LON-42, and VAS-32 ($\bar{X}$ = 45).

Water immersion: The day before immersion the subjects were requested to refrain from eating and drinking after 2300 hours. The following day, between 0700 and 0800 hours, the subjects were given 850 ml of water to drink; then they urinated, were weighed, and then immersed to the neck in the sitting position in thermoneutral tap water: mean ±S.E. pretraining water temperature was 35.5 ± 0.1°C and posttraining temperature was 35.4 ± 0.1°C. The subjects were allowed to change their position in the tank. Nothing was consumed nor were blood samples taken during immersion; the subject stood briefly to urinate as necessary. Body weight (±5 g) was measured dry following the final (6 h) micturition. Thus, weight loss during immersion represented net respiratory and renal fluid losses.

Peak oxygen uptake: Oxygen uptake was determined with a Quinton electronic ergometer (model 845). The subjects warmed up at a load of 400–500 $kg\text{-}m \cdot min^{-1}$ and then started the test at a load estimated to be 400 $kg\text{-}m \cdot min^{-1}$ below peak load. The load was then increased by 100 $kg\text{-}m \cdot min^{-1}$ each 2 min until the subject reported exhaustion. Peak oxygen uptake ($\dot{V}O_2$ peak) was measured during the final minute of exercise with standard expired-air techniques: the Otis-McKerrow respiratory valve, a calibrated Pneumoscan (model S-3000) electronic spirometer, and Applied Electrochemistry oxygen (model S-3A) and carbon dioxide (model CD-3A) analyzers. The composition of the standard calibration gases was determined with the Scholander technique.

Orthostasis: After a 40-min supine control period, the subjects were tilted head-up to 60° from the horizontal for up to 90 min (Fig. 2) on a motor-driven table with a footrest. The feet rested on a soft cushion to minimize proprioceptive cues. Footrest load was 60–70% of the subject's weight. The subjects wore a lower-body positive-pressure suit (MAST-IIIA medical anti-shock trousers, David Clark Co.) which covered the legs, thighs, and abdomen and was inflated to 50 ± 5 mm Hg (33) during the first 30 min of the 90-min tilt period (Fig. 2). The suit was deflated during the last 60 min of tilt or until presyncopal signs and symptoms occurred. The purpose of the suit was to decrease tolerance in a consistent manner via the sudden deflation so more of the subjects would reach tolerance within the 90-min period. None of the subjects fainted.

Heart rate was determined from an ECG record and indirect blood pressure was measured with a sphygmomanometer.

A short nylon catheter (Quick-Cath, Travenol Lab) was inserted 3 cm into an antecubital vein 30 min before the tilt. The catheterized arm was supported comfortably in a neutral, horizontal position throughout tilt. After 2 ml of blood were withdrawn and discarded, then 18 ml of blood were taken for the two supine control (−10 min, −5 min) blood draws (Fig. 2). The same procedure was followed for the six tilt blood-draws at +1, +6, +29, +31, +36, and +90 min (or at the point of presyncope). Thus, 160 ml of blood were withdrawn from each subject during each tilt procedure.

Blood analyses: Plasma sodium and potassium were measured by flame photometry (Instrumentation Laboratory Auto Cal, model C43) and osmolality by freezing point depression (Advanced Digimatic Osmometer, model 3D II). Serum total protein was measured with the Biuret method (35). Plasma vasopressin (PVP) and plasma renin activity

Fig. 1. Experimental protocol.

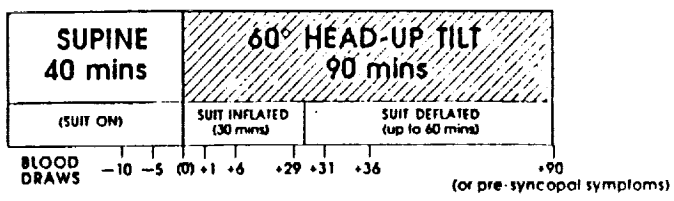

Fig. 2. Tilting protocol and timing of blood draws.

(PRA) were measured by radioimmunoassay: PRA with a New England Nuclear Kit and PVP with the method of Keil and Severs (27). Blood for PRA and PVP determinations was collected and chilled in tubes containing EDTA and centrifuged at +4°C; aliquots of plasma were frozen and stored at −20°C to await analysis. Plasma volume was measured with Evans blue dye from one 10-min postinjection blood sample (21) with a method modified from that of Campbell *et al.* (5). Percent change in PV was calculated from the hemoglobin (Hb) and hematocrit (Hct) (21) with an equation modified from Elkinton *et al.* (15). Blood Hb was analyzed with the cyanomethemoglobin method on a Coulter Hemoglobinometer. Microhematocrits were measured in quadruplicate and spun at 11,500 rpm for 10 min and measured on a modified International microcapillary reader (model CR). Raw Hct values were corrected for trapped plasma and whole-body Hct by multiplication with the factors 0.96 and 0.91 (0.874), respectively.

Statistical analyses: Data were analyzed with Student's paired *t*-test, analysis of variance, and the Spearman rank correlation-coefficient. The null hypothesis was rejected when $p < 0.05$, and nonsignificant differences are denoted by N.S.

RESULTS

Peak exercise: There was a significant increase in peak oxygen uptake and a significant decrease in resting heart rate after 6 months of training although not after 3 months (Table I). Peak oxygen uptake was 3.20 ± 0.14 L•min^{-1} pretraining, 3.36 ± 0.27 L•min^{-1} ($\Delta = +5\%$, N.S.) midtraining, and increased to 3.78 ± 0.36 L•min^{-1} ($\Delta = +18\%$, $p < 0.05$) after training. Resting heart rate decreased from 67 to 62 beats•min^{-1} ($p < 0.05$) after 6 months. Peak heart rates ranged from 184 to 188 beats•min^{-1} (N.S.). Both exercise load and peak ventilation tended to increase (N.S.) during training. Resting PV was unchanged by training.

Orthostatic tolerance: There was no significant change in pre-immersion (control) tilt tolerance after training (Fig. 3); pretraining control tolerance was 73.8 ± 16.2 min and posttraining control tolerance was 74.0 ± 16.0 min (Table II, Fig. 3). In both cases, four subjects had tolerances of 90 min, whereas one subject had tolerances of 9.0 and 10.0 min, respectively. Postimmersion tolerance was 33.6 ± 9.1 min pretraining, and 44.3 ± 13.1 min posttraining. Both postimmersion values were lower ($p < 0.05$) than their respective control tolerances, but were not significantly different from each other (Table II). There was no significant correlation between peak $\dot{V}O_2$ and tilt tolerance. The word "tolerance" should be understood to mean that the tilt test was terminated at 90 min unless presyncopal signs and symptoms intervened.

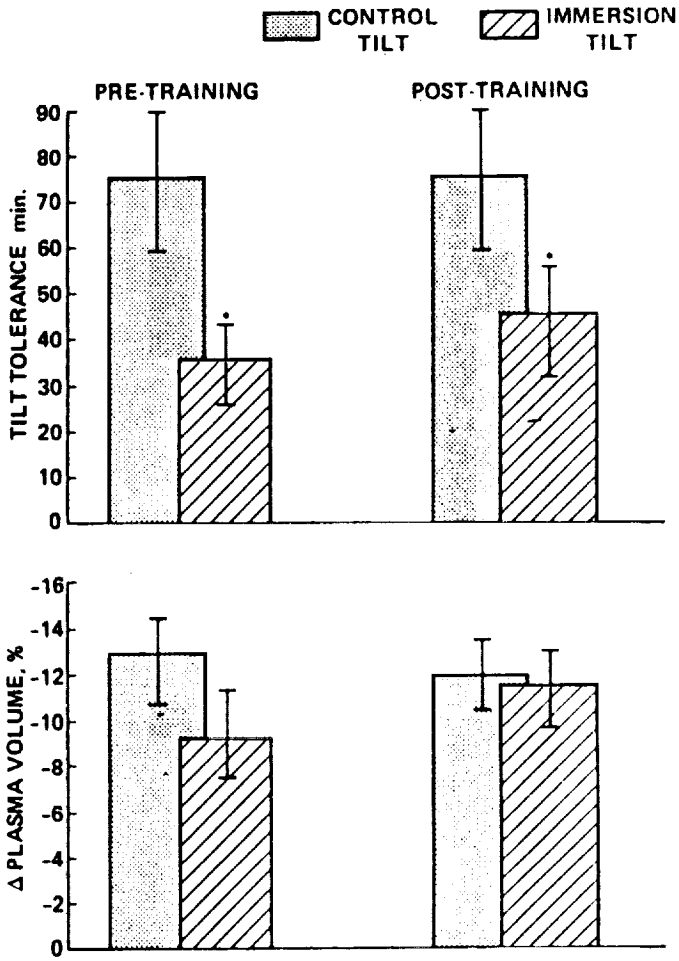

Fig. 3. Mean (±S.E.) tilt-tolerance and change in plasma volume before (control) and after immersion in the pre- and posttraining experiments. *$p < 0.05$ from the corresponding control value.

TABLE I. PEAK EXERCISE PARAMETERS BEFORE, DURING, AND AFTER 6 MONTHS OF AEROBIC EXERCISE TRAINING.

	Peak O_2 Uptake		Body Weight, kg	Heart Rate		$\dot{V}_{E_{BTPS}}$, L•min^{-1}	Load, kg-m•min^{-1}	Plasma Volume, ml
	L•min^{-1}	ml•min^{-1}•kg^{-1}		Rest, bpm	Peak, bpm			
Pretraining								
Mean	3.20	39.3	81.8	67	188	107.9	1197	3555
±S.E.	0.14	1.8	3.9	3	2	9.1	43	222
Midtraining								
Mean	3.36	42.1	80.6	61	184	116.7	1440	—
±S.E.	0.27	4.0	4.2	3	3	7.9	93	—
Posttraining								
Mean	3.78*	47.8*	80.1	62*	187	126.6	1480	3185
±S.E.	0.36	5.2	4.6	3	1	9.3	92	71

* $p < 0.05$ from pretraining value.

TABLE II. MEAN (±S.E.) INDIVIDUAL DATA FOR TILT-TOLERANCE AND PLASMA VASOPRESSIN (PVP) AND RENIN ACTIVITY (PRA) LEVELS AT THE POINT OF TOLERANCE IN FIVE MEN BEFORE AND AFTER TRAINING.

Subject	Pretraining						Posttraining					
	Preimmersion			Postimmersion			Preimmersion			Postimmersion		
	Tol, min	PVP, pg·ml^{-1}	PRA, ngAngI	Tol, min	PVP, pg·ml^{-1}	PRA, ngAngI	Tol, min	PVP, pg·ml^{-1}	PRA, ngAngI	Tol, min	PVP, pg·ml^{-1}	PRA, ngAngI
CAR	90.0	3.8	3.20	37.0	>104.0	3.02	90.0	4.4	3.58	90.0	3.0	3.53
CLA	9.0	82.7	1.61	2.7	50.1	5.88	10.0	31.2	1.70	8.4	21.0	1.38
LAL	90.0	1.5	5.35	35.0	87.4	5.47	90.0	4.4	9.77	40.9	>400.0	5.92
LON	90.0	2.2	5.73	60.1	16.4	11.65	90.0	32.0	5.23	—	—	—
VAS	90.0	0.1	5.26	33.0	>115.0	3.42	90.0	0.8	3.38	38.0	38.1	2.34
$\bar{X}$	73.8	18.1	4.23*	33.6*	>74.6†	5.89*	74.0	14.6	4.73	44.3*	>115.5†	3.29
±S.E.	16.2	16.2	0.79	9.1	18.2	1.54	16.0	7.0	1.38	13.1	95.1	0.98

* $p < 0.05$ from corresponding prevalue.
† $p < 0.05$ from zero.

At 90 min or at the point of tolerance for the four tilts, PV had decreased by 12.6, 9.0, 11.8, and 11.4% (Fig. 3). These were all significant ($p < 0.05$) reductions from supine control levels, but they were not significantly different from each other despite the significant differences in the tilt tolerances. Thus, the reduced tolerances after immersion were not due to the magnitude of the relative shifts in PV during tilt.

Water immersion: Body weight (urine and respiratory) decreased during 6 h of immersion from 83.55 ± 3.86 to 82.43 ± 3.93 kg (Δ = 1.12 kg, $p < 0.05$) pretraining, and from 81.47 ± 4.55 to 79.73 ± 4.64 kg (Δ = 1.74 kg, $p < 0.05$) after training. The posttraining loss of 1.74 kg was greater ($p < 0.05$) than the pretraining loss of 1.12 kg. Thus, the somewhat greater diuresis during posttraining immersion was not associated with lower orthostatic tolerance (Fig. 3).

Orthostatic fluid-electrolyte-endocrine responses: The time courses of these responses during the control and postimmersion tilts both before and after training are presented in Fig. 4 and 5, respectively. In all experiments PV decreased progressively during tilt with suit inflation; there was a linear, precipitous decrease for at least the first 6 min with some leveling off by min 29. When the suit was deflated, PV decreased further and, except during the pretraining postimmersion tilt, continued to decline throughout the tilt period reaching levels between −9.0 to −12.6% ($p < 0.05$).

In general, in both pre- and posttraining, the plasma Na^+, K^+, and osmotic concentrations and the PRA and PVP responses remained essentially unchanged from the supine position levels throughout the 30 min of control or postimmersion tilt with suit inflation (Fig. 4 and 5). Following deflation, most electrolyte and osmotic concentrations remained similar to their preceding inflation levels. The progressive decrease in PV was reflected in the significantly increasing serum protein concentrations (Fig. 4 and 5), the Hct and the Hb concentrations (Table III).

The PVP concentrations were unchanged from supine levels during tilt with inflation in all four tilt conditions and for 6 min after deflation (Fig. 4 and 5). The PVP showed a tendency to rise to 15–18 pg·ml^{-1} (N.S.) at the end of nearly 90 min of tilting (i.e., after 60 min of deflation) in both preimmersion tilts. The subjects exhibited few presyncopal signs or symptoms. On the other hand, the PVP response was drastically amplified during the postimmersion tilts

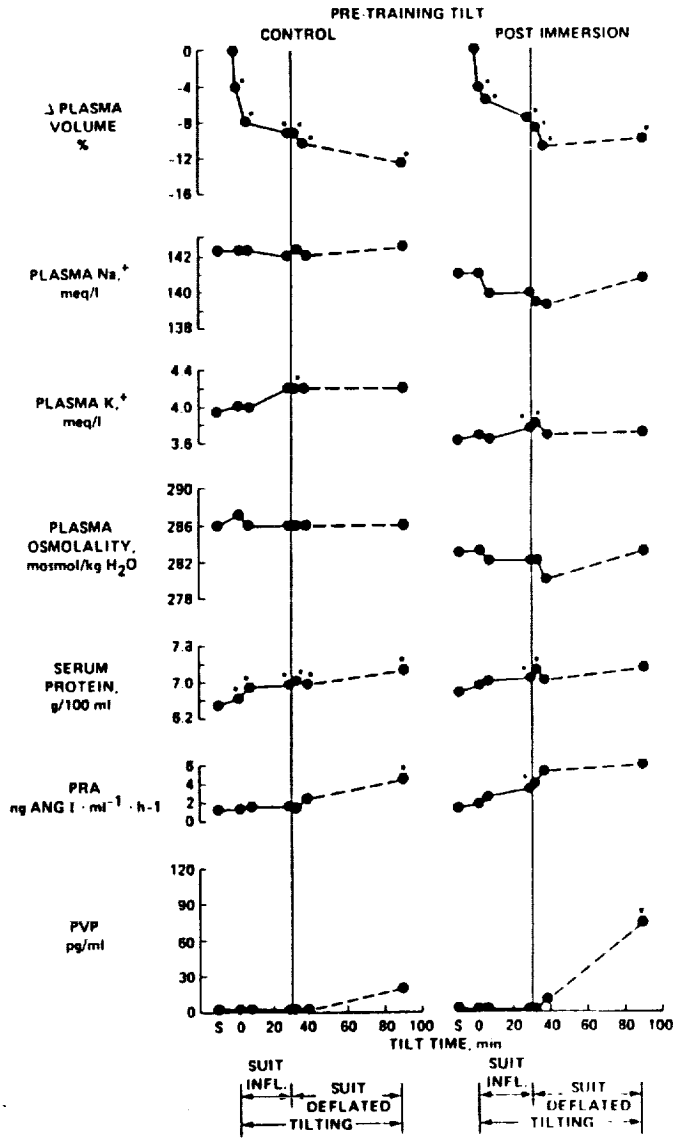

Fig. 4. Mean change in plasma volume, plasma electrolytes, osmolality, serum protein concentration, plasma renin activity (PRA), and plasma vasopressin (PVP) concentration during the *pretraining* (control and postimmersion) tilt experiment. The 90-min values were taken at the point of intolerance, hence the dashed line. *p < 0.05 from corresponding supine control (S) value.

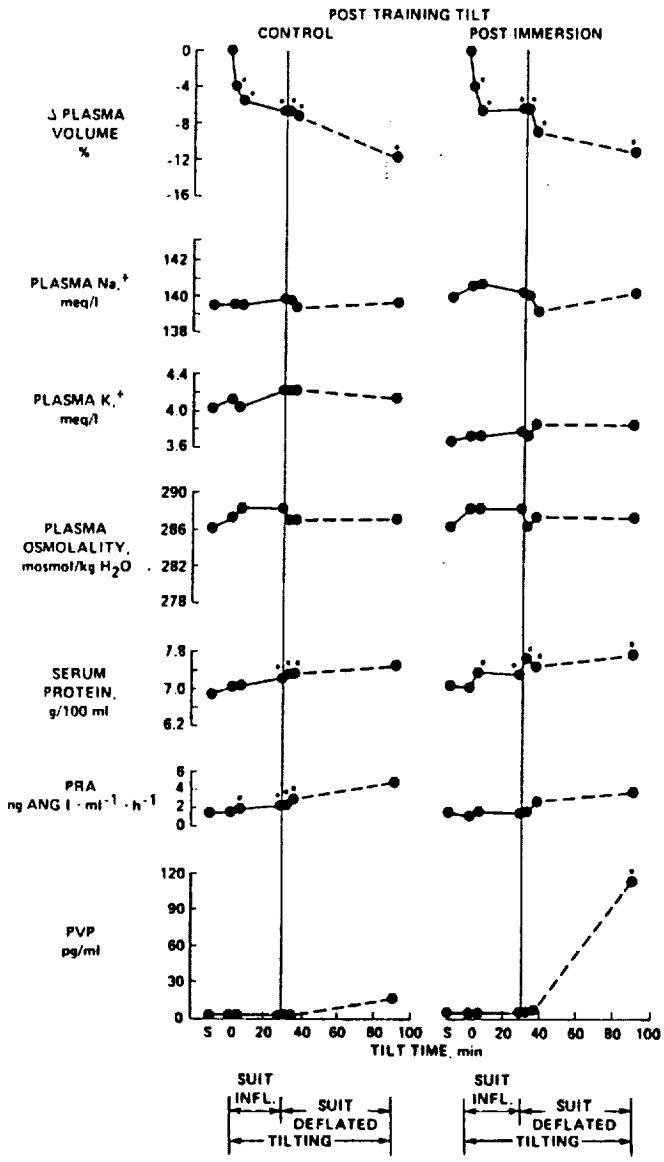

Fig. 5. Mean change in plasma volume, plasma electrolytes, osmolality, serum protein concentration, plasma renin activity (PRA), and plasma vasopressin (PVP) concentration during the *posttraining* (control and postimmersion) tilt experiment. The 90-min values were taken at the point of intolerance, hence the dashed line. *$p < 0.05$ from corresponding supine control (S) value.

both before and after training. In only one of the postimmersion tilts did a subject tolerate the full 90 min; the others had to be returned to the horizontal position because of the onset of presyncopal signs and symptoms. Both before and after training, the postimmersion-tilt PVP levels rose after suit deflation to between 75 and 85 pg·ml^{-1} ($p < 0.05$). None of the subjects fainted, but in some cases PVP rose to extremely high levels: >104, >115, and >400 pg·ml^{-1} (Table II). There was no significant relationship between PVP levels at the end of tilting and the state of training. The magnitude of the PVP concentrations appeared to reflect the severity of the presyncopal signs and symptoms.

On the other hand, the PRA was elevated significantly only after the two pretraining tilts and exhibited a much more consistent response (Table II). The range of PRA at tolerance was 3.29 to 5.89 ngAngI·ml^{-1}·h^{-1}.

DISCUSSION

Ground-based physical exercise training and in-flight exercise have been an integral part of the astronaut preparation program since its inception. The question of the type and intensity of exercise that will result in optimal performance and well-being of astronauts continues to be investigated. The old cliche, "If a little exercise is good, more is better," must be viewed with caution because, when compared with untrained subjects, some trained athletes exhibit significantly lower tolerances to tilting and application of lower body negative pressure (32,36,38,49). These findings have led to the unwarranted conclusion that the reduced orthostasis was due to the exercise training per se. This hypothesis has been investigated recently using short-term training (heat-exercise acclimation) and there was no significant reduction in tilt (20) or in +G_z-acceleration (19,20) tolerance. The training periods used in these studies may have been too short (8–12 d) to have induced adaptive responses that would have influenced blood pressure control. The question of whether exercise training per se reduces tilt tolerance remains unresolved. The present study was designed to determine the effect of 6 months of moderately intense training on tilt-table (orthostatic) responses before and after 6 h of water-immersion deconditioning.

With both pre- and posttraining, there was a significant decrease in tilt tolerance after immersion. However, despite the significant increase in peak oxygen uptake, there were no significant changes in control or postimmersion tilt tolerances measured after training. This finding suggests that the use of venous catheters had no significant effect on the results. The lower orthostatic tolerance found in some endurance-trained athletes has been associated with their state of aerobic fitness, as represented by the level of their peak oxygen uptake. Results from the present study suggest that this association may be spurious; the variations in the tilt tolerance may simply reflect genetic differences in the blood-pressure-control system.

The magnitude of the differences in peak oxygen uptake reported from cross-sectional studies in the literature to support the causal association between peak $\dot{V}O_2$ and tilt tolerance is not directly comparable to the longitudinal increases in peak $\dot{V}O_2$ reported in the present study. In normal ambulatory subjects, training-induced increases in peak $\dot{V}O_2$ can range from 15%–25% (13). In the present study, 6 months of moderately intense exercise training resulted in an 18% (L·min^{-1}) or 22% (ml·min^{-1}·kg^{-1}) increase in peak $\dot{V}O_2$. After bedrest deconditioning, the magnitude of the increase in peak $\dot{V}O_2$ after prolonged intensive training can reach 61% (42). When comparing moderately trained athletes with trained subjects, the difference in peak $\dot{V}O_2$ is about 50%, and can rise to over 100% in highly trained Olympic athletes (16,30,36–38,42). It is unlikely that this large difference in peak $\dot{V}O_2$ between trained and untrained people is due only to their training regimes. It seems that 75%–85% of a person's peak $\dot{V}O_2$ is determined by genetic factors (31,41); that leaves 15–25% for training, as noted above. Thus, results from the present study do not necessarily conflict with observations that some athletes have lower tilt tolerance than some nonathletes.

TABLE III. MEAN (±S.E.) HEMOGLOBIN ($g \cdot dl^{-1}$) AND HEMATOCRIT (vol %) VALUES BEFORE (−10 AND −5 min) AND DURING TILTING (+1 TO +90 OR FINAL min) FOR THE FOUR EXPERIMENTS.

min	−10	−5	+1	+6	+29	+31	+36	+90 or final min
Pretrainining—Preimmersion								
Hb	14.5	14.5	14.9	15.3	15.3	15.3	15.4	15.8*
±S.E.	0.9	0.7	0.8	0.9	1.0	0.8	1.1	1.1
Hct	37.1	37.0	37.9	38.9	38.8	38.8	38.8	39.9*
±S.E.	0.8	0.7	0.8	1.0	1.2	1.0	1.0	0.7
Pretraining—Postimmersion								
Hb	14.7	14.6	15.1	15.2	15.4	15.5	15.6	15.6*
±S.E.	0.2	0.2	0.2	0.2	0.2	0.2	0.4	0.2
Hct	38.3	38.1	38.9	38.9	39.4	39.6	39.7	40.1*
±S.E.	1.0	0.9	0.9	1.0	0.9	0.9	1.1	0.8
Posttraining—Preimmersion								
Hb	14.6	14.5	15.0	15.1	15.3	15.2	15.2	15.8*
±S.E.	0.3	0.3	0.3	0.2	0.4	0.3	0.3	0.5
Hct	37.1	37.1	37.9	38.3	38.4	38.6	39.0	39.9*
±S.E.	0.7	0.7	0.8	0.8	0.9	0.9	0.8	0.9
Posttraining—Postimmersion								
Hb	14.6	14.6	15.0	15.5	15.2	15.2	15.4	15.9*
±S.E.	0.2	0.2	0.3	0.4	0.2	0.3	0.2	0.3
Hct	37.1	37.2	37.8	38.3	38.1	38.2	38.5	39.4*
±S.E.	0.8	0.8	0.9	1.1	0.7	0.6	0.7	0.5

* $p < 0.05$ from corresponding −5 min value.

Perhaps for individuals to manifest lower orthostatic tolerance, they must first be highly trainable, and not merely be more highly trained than a more sedentary nonathletic person. The expression of genetic factors which may incidentally be associated with high aerobic "trainability" may be confounded by other more subtle elements involved in the process of exercise training which may not be revealed in studies concentrating on differences in oxygen uptake. The length of time that individuals have participated in exercise training and the mode, frequency, and intensity of their training is generally unknown. Differences in tolerance between those trained aerobically and anaerobically have been reported (36,44,45); tolerance may be affected even more by training posture, i.e., erect weight-bearing (running, jumping) vs. erect partial-weight-bearing (cycling) or horizontal nonweight-bearing (swimming).

Inclusion of genetic factors, other than those involved in limiting aerobic capacity, in determining an individual's orthostatic tolerance also helps to resolve the paradox implied by the finding of an *inverse* relationship between peak oxygen uptake and tolerance; i.e., if a high peak $\dot{V}O_2$ predicts low tolerance, then how do deconditioning procedures such as bed-rest, water immersion, and weightlessness (which reduce peak $\dot{V}O_2$) also reduce orthostatic tolerance? The results from the present study refute the first element of this paradox; an increased aerobic capacity did not lower tolerance. One subject was much more intolerant that the others in both the pretraining control and postimmersion tilts; he also had the highest peak $\dot{V}O_2$. Although, after 6 months of training, the other subjects' peak $\dot{V}O_2$ levels were higher than his pretraining level, their control tolerances were unchanged, and their postimmersion tolerances actually tended to increase (N.S.). The responses of the intolerant subjects were similar to those of the other subjects.

Thus, we still have not answered the question of what physiologic mechanism is responsible for the orthostatic intolerance of some individuals and the greater tolerance of others. More plausible mechanisms include decreased sensitivity of the high-pressure (carotid) baroreceptors (48), reduced vascular sympathetic activity (14) accompanied by increased vagal inhibition, increased beta-adrenergic receptor sensitivity, and greater arteriolar dilation with exercise training (50). These responses are all associated with high aerobic fitness and chronically lower blood pressure.

The level of PV seems to be intimately associated with orthostatic tolerance, especially with the decreased tolerance following water immersion. Prolonged water immersion for 6 h reduces PV by 8%–10% (4,34). Thus, at the beginning of each preimmersion tilt, the subjects should have had a greater absolute PV than at the beginning of each postimmersion tilt. Since the percent PV loss during both preimmersion and postimmersion tilts was not different, the absolute PV loss for the preimmersion tilt must have been greater than for the postimmersion tilt, yet postimmersion tolerance was significantly less. Thus, a smaller absolute PV loss was associated with a lower tolerance postimmersion. Therefore, changes in tolerance cannot be attributed to the level of absolute PV loss during tilting. However, the mechanism of intolerance seems to respond to the percent or relative loss of PV regardless of the initial absolute volume. Since immersion diuresis can result in an 8%–10% loss of PV, the additional 10%–12% shift of PV during tilt results in a total PV loss of 20%, the point of intolerance (25). The reason four of our five subjects did not reach presyncope during the control tilts was that PV decreased in toto by only 11.8% and 12.6% at the end of the 90-min tilt periods. The same studies which reported that trained athletes had lower orthostatic tolerances than untrained subjects also showed that the untrained subjects had earlier onset and greater diuresis during water immersion (4,49). This in-

crease in diuresis and urinary sodium excretion during immersion in untrained men was confirmed recently by Claybaugh *et al.* (6). Contrary to these results, our subjects had significantly *greater* diuresis after training. These divergent findings suggest that trained endurance athletes have different fluid-electrolyte responses compared to recently trained people who were previously untrained.

Except for PVP concentrations, the fluid, electrolyte, protein, and PRA patterns in control and postimmersion tilts were generally unchanged following training (Fig. 4 and 5). The PRA increased with the severity (length) of the tilt in all four experiments. Results from recent studies in our laboratory have suggested that the levels of PRA in supine, dehydrated subjects might be a predictor of orthostatic intolerance (26). If training caused decreased tolerance, we would have expected a greater increase in posttraining postimmersion PRA. In fact we found essentially no difference in supine PRA and a tendency (N.S.) for posttraining postimmersion PRA at tolerance (3.29 ± 0.98 ngAngI•ml^{-1}•h^{-1}) to be lower than the comparable pretraining postimmersion value of 5.89 ± 1.54 ngAngI•ml^{-1}•h^{-1}. But the increases in PRA preceded the increases in PVP, even during tilting with the suit inflated. The pre- and posttraining PVP concentration at the point of tolerance increased significantly during postimmersion tilting, but was unchanged at the point of intolerance during both preimmersion tilts. Since plasma osmolality was essentially constant, these differing PVP responses were most likely caused by the absolute shifts of PV (33); i.e., about 20% after immersion vs. 9%–11% after the preimmersion tilts. Thus, the very great increases in PVP concentrations during postimmersion tilt are probably manifestations of the severity of the presyncopal symptoms, as suggested by others (1,24,25) rather than a factor affecting tolerance.

The present study was designed to mimic the type of exercise training program that astronauts may undertake. The peak oxygen uptake of the astronaut corps is about 42 ± 8 ml•min^{-1}•kg^{-1} (39) similar to the 40 ± 2 (pretraining) and 48 ± 5 ml•min^{-1}•kg^{-1} (posttraining) levels in the present study. Results from this and the other longitudinal training studies (10,20,44–46) mentioned in the Introduction indicate no change or a tendency to increase orthostatic tolerance after training. Indeed, anaerobic training (heavy weight-lifting) with gain in abdominal strength has been associated with increased tolerance (43). Thus, initiation or continuation of a moderately intensive and comprehensive exercise training program would not seem to be a disadvantage for the maintenance of orthostatic tolerance in astronauts with normal levels (40–50 ml•min^{-1}•kg^{-1}) of peak oxygen uptake.

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7.0. CONCLUSION

That our findings demonstrate man's unique and complete adjustment to his bipedalism should come as no surprise to anyone. However, the human ability to stand and walk on two limbs rather than four is not the result of man's ultimate "conquest and triumph" over the force of gravity. Our studies remind us that man's erect posture is extremely vulnerable and requires from birth to death a moment-to-moment struggle against this unremitting and ubiquitous force. Nevertheless, since a normal healthy human spends about two-thirds of his entire life on his feet or haunches, the upright position can hardly be considered nonphysiological. On the contrary some recognized physiologists have suggested the erect posture is more basic to the nature of man and should be regarded his "resting physiologic position" (Gauer and Thron, 1965; Greenleaf, 1984).

Notwithstanding, man has paid a high price for this distinct old habit of rising on his hind limbs at any time and walking around. When the human body stands up, about 70-75% of the blood volume is contained below the heart, whereas in our animal friends the same share of blood is accumulated above the heart (Rowell, 1983). This fact implies that for a steady state of blood flow to be accessible for the human brain during orthostasis, a number of intricate mechanisms have been developed throughout our evolutionary process (section 2.6.). Yet, even in healthy man a continuous cerebral blood flow is hard to maintain when standing still for a long period of time, or during an experimental HUT position. As a matter of fact, during passive standing or HUT without using the leg muscles ("the muscle pump") man will eventually succumb to gravity and fall. Prevention of this fall is lethal (section 5.4.D.).

When upright, man is continuously trembling on the brink of circulatory collapse, and even small perturbations in the regulatory mechanisms required to maintain homeostasis during erect posture may lead to significant morbidity (section 5.4.D.a.).

Gauer and Thron (1965) repeatedly emphasized the importance of continued orthostatic stress to assert adequate blood volume and immunity from circulatory failure. Without even being aware of it, we stress the circulation every day simply by standing up in the morning and maintaining the upright posture throughout most of the day. Forced BR or weightlessness undoubtedly leads to orthostatic intolerance and postural hypotension upon return to a +1 Gz position. While man seems to adapt readily to inactivity, immobilization, and weightlessness, readaptation to a head-to-foot direction of inertial force (+Gz) is truly much more troublesome (section 3.3.).

LBNP and physical activity are under intense investigations as possible countermeasures to reduce or prevent some of the undesirable deconditioning effects of weightlessness (Wolthuis et al., 1974; Greenleaf, 1984; PAPER IX). At the present time we simply do not know what kind of countermeasure, or combinations of countermeasures, are needed to assure nonreversible changes of the cardiovascular system, bone, and muscles following long-duration exposure to weightlessness.

There is no doubt man will find a solution to the many biomedical problems currently facing the human presence in space. On the other hand, answers to these questions are of paramount importance before a manned mission to Mars can be undertaken. A round-trip to Mars will last at least 2 yr, and the crew must work effectively during their short stay on the surface of the planet.

Exposure to fractional or continuous artificial G-forces (use of an on-board centrifuge or slow rotation of the spacecraft) instead of a weightless trip to Mars is also being evaluated. Such a solution is feasible, but would add immensely to the cost of a Mars mission.

Physiologists are devoting thousands of hours of research to better understand biomedical problems of man's responses to weightlessness. Results of these investigations will further benefit persons who must be inactive for several years, such as paralyzed trauma victims or stroke patients, or even sedentary and old people.

We have shown that in humans WI diuresis is not dependent on the Henry-Gauer reflex (PAPER III). The newly discovered natriuretic peptide may play an important role in the fluid and electrolyte response during WI (section 4.4.E.c.).

By utilizing LBPP we are in the process of studying the significance of a contribution by high-pressure receptors for water and salt regulation in man (PAPERS IV, V, VI, and VII).

Our data indicate that oropharyngeal and gastric receptors are important sites for control of vasopressin secretion independent of changes in blood pressure (high-pressure receptors), blood volume (low-pressure receptors), and plasma osmolality (PAPER VIII).

In the course of our studies we have added an alternative tool and have developed a protocol to help elucidate human reactions to gravity and weightlessness. Applying LBPP by an antigravity suit represents a new noninvasive, nonpharmacological, and inexpensive method for studying physiological characteristics of man's circulatory, renal, electrolyte, and hormonal systems (section 5.0.; PAPERS IV, V, VI, and VII). Furthermore, the quickly controlled translocation of body fluids from the lower to the upper portions of the organism by external counterpressure is a very effective principle to improve cerebral perfusion during increased +Gz acceleration (section 5.4.E.) to prevent postural hypotension (PAPER II) and to treat shock and intractable abdominal bleeding (Pelligra and Sandberg, 1979; sections 5.4.A. and 5.4.B.a.; PAPER I).

8.0. ABBREVIATIONS

AGARD	Advisory Group for Aerospace Research and Development
ADH	Antidiuretic Hormone
ANF	Atrial Natriuretic Factor
ANP	Atrial Natriuretic Peptide
AVP	Arginine Vasopressin
BR	Bed Rest
CBV	Central Blood Volume
CID	Cardiovascular Index of Deconditioning
CNS	Central Nervous System
CO	Cardiac Output
COP	Colloid Osmotic Pressure
CPC	Circumferential Pneumatic Counterpressure
CSF	Cerebrospinal Fluid
CVP	Central Venous Pressure
CW	Cardiac Work
DBP	Diastolic Blood Pressure
ESA	European Space Agency
EVA	Extravehicular Activity
GLOC	G-induced Loss of Consciousness
HDT	Head Down Tilt
HIP	Hydrostatic Indifferent Point
HOI	Head Out Immersion

HR	Heart Rate
HUT	Head Up Tilt
LBNP	Lower Body Negative Pressure
LBPP	Lower Body Positive Pressure
MAP	Mean Arterial Pressure
MAST	Medical Antishock Trouser
NI	Neck Immersion
PASG	Pneumatic Antishock Garment
PP	Pulse Pressure
PRA	Plasma Renin Activity
PV	Plasma Volume
PVP	Plasma Vasopressin
SBP	Systolic Blood Pressure
SMS	Space Motion Sickness
SV	Stroke Volume
TPR	Total Peripheral Resistance
WI	Water Immersion

9.0. REFERENCES

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16. Abstract

Because of their erect posture, humans are more vulnerable to gravitational changes than any other animal. During standing or walking man must constantly use his antigravity muscles and his two columns—the legs—to balance against the force of gravity. At the same time, blood is surging downward to the dependent portions of the body, draining blood away from the brain and heart, and requiring a series of complex cardiovascular adjustments to maintain the human in a bipedal position.

It was not until April 12, 1961, when Yuri Gagarin became the first human being to orbit Earth, that we could confirm man's ability to maintain vital functions in space—at least for 90 min. Nevertheless, man's adaptation to weightlessness entails the deconditioning of various organs in the body. Muscles atrophy, and calcium loss leads to loss of bone strength as the demands on the musculoskeletal system are almost nonexistent in weightlessness. Because of the lack of hydrostatic pressures in space, blood rushes to the upper portions of the body, initiating a complex series of cardioregulatory responses.

Deconditioning during spaceflight, however, first becomes a potentially serious problem in humans returning to Earth, when the cardiovascular system, muscles and bones are suddenly exposed to the demanding counterforce of gravity—weight.

One of the main purposes of our studies was to test the feasibility of using Lower Body Positive Pressure, applied with an antigravity suit, as a new and alternative technique to bed rest and water immersion for studying cardioregulatory, renal, electrolyte, and hormonal changes in humans. The results suggest that Lower Body Positive Pressure can be used as an analog of microgravity-induced physiological responses in humans.

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