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SUMMARY

A large number of animal and human flight and ground-based studies have been conducted to uncover the cardiovascular effects of weightlessness. Findings indicate changes in cardiovascular function during simulations and with spaceflight that lead to compromised function on reambulation and/or return to Earth. This altered state termed "cardiovascular deconditioning" is most clearly manifest when in an erect body position. Hemodynamic parameters (compared to predeconditioned state) indicate the presence of an excessive tachycardia, hypotension (leading to presyncope in one-third subjects), decreased heart volume, decreased plasma and circulating blood volumes and loss of skeletal muscle mass, particularly in the lower limbs. No clinically harmful effects have been observed to date, but in-depth follow-ups have been limited, as has available physiologic information. Available data concerning the causes for the observed changes indicate significant roles for mechanisms involved with body fluid-volume regulation, altered cardiac function and the neurohumoral control of the control of the peripheral circulation. Satisfactory countermeasures have not yet been found. Hemodynamic changes in the immediate postflight period have been best handled by lower body counter pressure (anti-gravity suits). Return to preflight state has been variable (weeks to months) and only slightly dependent on flight duration. Animal flight studies have concentrated on uncovering operant mechanisms. Future progress awaits availability of flight durations longer than several weeks.

INTRODUCTION

The U.S. and Soviet space programs have documented that exposure to weightlessness--even for short periods--induces significant changes in the cardiovascular system (refs. 1-3). A loss of adaptive capacity, termed deconditioning, can be shown to occur during flight with provocative testing and becomes clearly apparent and troublesome with return to Earth. Returning cosmonauts and astronauts have consistently exhibited significant orthostatic hypotension, loss of exercise capacity, and difficulty in readapting to normal activity (refs. 4-8). Deconditioning has persisted in some crewmembers for periods lasting from several hours to several months, and this has no relation to mission duration (refs. 3,4,8-10). This paper will review the data obtained to date and discuss our understanding of the processes which cause the observed changes. Information is still quite limited, and have been provided by sporadic observations of selected crewmembers during and/or following space flight and through a much larger number of ground-based studies using bed rest, water immersion, and immobilization to simulate the weightless state. Much remains to be learned about the operant mechanisms of weightlessness, and will

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require carefully planned space experiments, as well as additional ground-based studies.

THE ROLE OF GRAVITY

Gravity has a profound effect on all life forms on Earth. Gravity influences human and animal cardiovascular function by exercising a hydrostatic effect on the circulation. Gravity, together with bodily position and the functional responses of the peripheral circulation, governs how intravascular volume is distributed and, as a result, controls cardiac pump function. In the standing position, the body must compensate for changes in gravitational pull to maintain blood flow to the head and to ensure adequate distribution of blood to other critical organs such as the heart. During postural changes, muscle propioreceptors, semicircular canals, otho-liths, and mechanoreceptors (baroreceptors and volume receptors) provide the necessary input to register gravitational field magnitude, or a change in its orientation to the body. Humans, as opposed to other animals, are particularly affected by gravitational changes because of their normal sitting or upright stance, and also because of their large body mass and blood volume below the level of the heart. Although the effects of gravity on the human cardiovascular system have been of interest to physiologists for decades, there is a renewed emphasis with the Space Age and our entry into a weightless environment.

The hydrostatic pressure created by gravity is a static force, functioning perpendicular to the Earth's surface, and the greater the force, the larger the resultant counterpressure must be to equal or offset gravitational effects. In reacting to hydrostatic pressure, the cardiovascular system is governed by: 1) the magnitude of the gravity field which is static on Earth when the body is in a stable position; 2) the elastic properties of blood vessels, particularly the pressure/volume relationships of veins; and 3) the pressure and flow generated by the heart, which is a dynamic function.

With postural changes on Earth, body fluids are redistributed, and secondary changes occur in ventricular filling (atrial pressure) and stroke volume, as shown in figure 1. Despite the fluid shift during a change from a supine (0°) to a standing or sitting (+90°) position, blood pressure is maintained at, or slightly above, supine values. The intrathoracic volume shifts are associated with the significant decreases in heart size and circulating blood volume (refs. 2,9,11-13). Secondary decreases in coronary flow and myocardial oxygen consumption also occur (ref. 14). Although redistribution of intravascular volume during postural changes is governed primarily by hydrostatic pressure, its magnitude is strongly influenced by pressure/volume differences in various systemic tissues. Venous volume of the legs increases by about 500 ml (ref. 15), with most of the volume transmitted to the deep intra- and intermuscular leg veins (ref. 16) and about 200-300 ml to the pelvic and gluteous maximus areas. Studies by de Marees and Pixberg (ref. 17), and Montgomery and associates (refs. 18-20) indicate that the spanchnic area also plays an important role. Under normal conditions, about 70% of total blood volume resides in the

systemic veins and the remainder in the heart and lungs (15%), systemic arteries (10%), and capillaries (5%) (refs. 15,16). As much as 20% of normal plasma volume may be lost to extravascular spaces after 20 min of quiet standing (ref. 13) and the contraction of limb muscles also affects venous volume and pressure (refs. 21,22). The process can be modified by changes in compliance of perivascular tissues, altered tissue pressure, or myogenic and neurogenic effects on venous tone and vasomotor activity (refs. 16,23,24).

When the force of gravity is removed during weightlessness, or is reduced during ground-based simulations, significant hemodynamic changes occur as the body attempts to adapt. Immediate changes, as shown in figure 2, are very similar to those that occur when changing from sitting or standing (+90°) to a supine (0°) body position, and include a headward shift of fluid from the legs and pelvis, increased central blood volume, increased stimulation of central low-pressure mechanorecep-tors, and increased preload and stroke volume for the heart. Careful analysis of flight data and testing postflight revealed that a slight head-down position (-4° to -8°) best approximated the flight conditions back on Earth (refs. 25,26).

Although the body is surprisingly capable of adapting to weightlessness or ground-based simulations, the adaptive changes reduce the ability to readapt to Earth gravity after space flight, or to upright posture after simulation. This response has been termed "cardiovascular deconditioning," and is manifested by orthostatic intolerance, rapid heart rate, and significantly reduced tolerance to exercise stress (refs. 2,3).

During weightlessness, the body floats freely in space with no apparent weight or mass. Hydrostatic pressure is eliminated, and fluids that are normally located in the lower regions of the body when standing are displaced to the upper regions. As a result, individuals exposed to weightlessness experience head fullness and facial puffiness. In-flight measurements of lower-leg girth have indicated that as much as 1,000-1,500 ml of fluid may shift to the upper body in weightlessness, as compared with a 500-600-ml shift when changing position on Earth (refs. 3,27). These immediate or short-term fluid shifts trigger neurohumoral responses resulting in fluid and electrolyte changes as shown in figure 2. Subsequent long-term adjustments to these fluid shifts during weightlessness are believed to be the cause of orthostatic intolerance and cardiovascular deconditioning observed after all space flights and ground-based simulations.

Short-term effects of weightlessness were first observed during aircraft power dives in the first and second world wars. After World War II, this brief exposure to weightlessness, induced by parabolic flight (Keplerian trajectory), began to be used to study motion sickness, select space crews, and test countermeasures. But these maneuvers provided exposure to weightlessness lasting 45-60 sec at best, thus severely limiting the period of observation. As the possibility of manned space flight became a reality, techniques were needed for Earth-based simulation that would allow days or months for observation. Water, or bouyant, immersion was the first such technique to be developed and has proved to be an excellent tool for studying short-term effects (refs. 3,11). Long-term studies using this technique have been difficult, however, because of problems of maintaining appropriate fluid

temperature and personal hygiene and avoiding skin maceration of subjects when immersion lasts longer than 12 hr. Recently, Soviet investigators have attempted to remedy problems with long-term immersion by having subjects lie on a thin sheet of plastic which separates them from the immersion medium (refs. 28,29). Other methods have also been developed and widely used including chair rest, bed rest, and immobilization of animals.

None of these ground-based techniques, however, precisely duplicates the weightless environment because gravity is not entirely eliminated. Nonetheless, ground-based studies have provided important information on how the body adapts to inactivity and long-term fluid shifts, how long adverse effects may persist, and the feasibility of various countermeasures. This information has been critical to U.S. and Soviet manned space programs, and also has produced clinical applications for use on Earth. Many questions still remain to be answered, including the long-term effects of exposure to weightlessness over months or years, the physiological effects on males versus females and the effects of age or disease conditions.

MISSION EXPERIENCE

U.S. and Soviet Animal Space Flights

A history of major animal space flights is given in table 1. Successful animal flights proved that humans could travel in space without serious effects from acceleration, radiation, or weightlessness. The last U.S. large-animal flight occurred in 1969, and carried a pig-tail monkey into orbit (ref. 30). The flight lasted 8.8 days, but the heavily instrumented animal died shortly after recovery, having lost 20% of its body weight during flight. Although the outcome raised many questions and considerable controversy, the most plausible answer was that the animal was too heavily instrumented as a result of an effort to obtain as much physiological data as possible during the costly flight. Most recently, two uninstrumented squirrel monkeys and 24 rats (five instrumented) were successfully flown aboard a 7-day Shuttle mission (Spacelab 3) to test animal-holding capability for future use of these animal models in upcoming space-flight experiments.

Soviet investigators began launching animal flights in 1949 and used dogs as primary test subjects until 1966. The last Soviet dog flight (Cosmos 110) remained in orbit for 22 days and was successfully recovered (refs. 31,32). The two dogs on board were monitored for ECG, phonocardiograms, and noninvasive carotid artery tracings. Both dogs exhibited decreases in cardiac output and stroke volume; attempts to withdraw blood and measure intravascular arterial pressure during flight were unsuccessful. The animals also showed evidence of severe dehydration and weight loss (26.3% and 28.9%, respectively). This occurred despite use of semisolid food bars, gels, and/or feeding by gastrostomy. Since dogs drink primarily by lapping, oral intake of fluid became difficult to nearly impossible during flight, thus contributing to, or causing the significant weight loss. Since that time, Soviet investigators have launched a series of five animal flights lasting from

18 to 22 days with rats as the primary payload (refs. 31,33). Animals were studied before and immediately after flight. A major finding was the arrest of bone growth, which was determined by tetracyline labeling (ref. 34). Changes have occurred in almost all body systems (ref. 35) and have included both ultrastructural and biochemical changes in the myocardium (refs. 36,37). Mitochondrial changes could best be explained by a decrease in coronary perfusion during flight. Norepinephrine levels were increased for the cardiac ventricles and decreased for the atria (refs. 36,38). One flight (Cosmos 936) contained a centrifuge which exposed 10 rats to +1 G_z throughout the mission. Exposure to centrifugation diminished, but did not prevent weightlessness changes. U.S. investigators have participated in the Cosmos program starting with the second (Cosmos 605) flight.

In December 1983, Soviet investigators successfully orbited two chronically instrumented Rhesus monkeys and 10 Wistar rats for 5 days in an unmanned biosatellite. The monkeys were variously monitored before, during, and after flight for central nervous system responses (primarily vestibular nuclei), EGC, limb EMGs, respiration, blood pressure, cardiac output, blood flow to the head, daily rhythm changes of heart rate and body temperature, and metabolic changes, including changes of bone calcium (refs. 39,40). Results from measurement of common carotid pressure and flow (doppler transducer) in one animal so instrumented demonstrated a significant increase in pressure on insertion into orbit and a slight decrease in flow (refs. 40,41). Pressure showed expected daily variations with a tendency for gradual fall of levels as the flight increased. In contrast, flow velocity during flight was elevated and tended to remain elevated compared to preflight control levels. These findings are consistent with expected changes in hemodynamics associated with a significant fluid shift to the head. Postflight measurements are not obtained in the hemodynamically instrumented animal because of its demise 69 hr postflight caused by an ileal volvulus. Pregnant rats were used to study effects of weightlessness on birthing and development biology. Results in these latter rat studies have failed to reveal significant weightlessness effects (ref. 40). U.S. investigators participated in this flight as in the previous Soviet biosatellite programs (refs. 39,40).

A 7-day reflight of this experiment (Cosmos 1667) was successfully accomplished from July 10-17, 1985. Findings were identical to those obtained during the previous Cosmos 1514 flight. Pregnant rats were not flown. U.S. involvement was limited to cardiovascular measurements of pressure and flow obtained from chronic instrumentation of the left common carotid artery in one of the two rhesus monkeys flown. Both animals tolerated the flight without incident and had no difficulties in the postflight period. Data obtained during flight (animal chronically chaired) was compared with results from a synchronous ground-based control experiment with the animal placed in the flight capsule and all conditions identical, except for the presence of weightlessness, one month later (15-22 August 1985) (ref. 42). Average heart rate decreased over the course of the flight (142 ±3.2 bpm on days 1-116 ±7 bpm on day 6), this did not occur during the control experiment (daily means ranged from 131 to 143 bpm). Mean blood pressure during flight and ground-based control were not significantly different, but showed a tendency to rise during the flight. Mean blood flow velocity during flight was significantly lower

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(p < 0.01) than during the control experiment (32 ±2 cm/sec versus 43 ±1 cm/sec). The conclusions drawn with regards to weightlessness effects on cardiovascular function were: 1) Headward shift of fluid during space flight can be demonstrated to result in altered hemodynamics for the vascular bed associated with the common carotid artery, 2) Space flight is associated with an 18% decrease in blood flow velocity. Since this was associated with little change in arterial pressure, the associated increase in peripheral vascular resistance was primarily due to a decrease in blood flow, 3) Adaptive responses were evidenced, but not complete over the short duration of the 7-day space flight exposure. The most recent 2-wk flight containing primates (Cosmos 1887) was accomplished in August 1987. Data has not as yet been reported from this effort.

Manned Space Flights

Both U.S. and Soviet manned space programs have been unequivocally successful, with only a limited number of difficulties that would be expected from such a large undertaking. As of January 1988, 51 missions have been launched by the United States and 62 by the Soviet Union, placing more than 160 people (nine women) into orbit, some as many as five times. Cardiovascular deconditioning has been observed consistently in both programs during and after flight as noted in table 2 for the United States and in table 3 for the Soviet Union. Postflight changes are of interest since they have occurred despite the heavy use of countermeasures in the programs of both countries.

U.S. Manned Space Flight

Cardiovascular deconditioning was first manifested by orthostatic intolerance following the Mercury missions. Crewmembers exhibited a decrease in systolic pressure, a narrowing in pulse pressure, and a substantial increase in heart rate (ref. 3). These symptoms were again present in returning Gemini crewmembers and were accompanied by a moderate loss of exercise capacity (refs. 4,43). During flight, however, there were no significant changes in blood pressure, ECG, or measurement of systolic time intervals. Apollo crewmembers again exhibited orthostatic intolerance following flight, as well as a loss of red blood cell mass and decrements in postflight exercise capacity, including a 25% decrease in submaximal oxygen uptake (ref. 44). The crew of Apollo 15, moreover, experienced episodes of bigeminy and bradycardia during flight which were attributed to potassium loss resulting from strenuous preflight activity in excessive heat (ref. 3).

Cardiovascular changes were documented for the first time in flight during Skylab missions (ref. 6). These flights were considerably longer than previous missions, lasting 28, 59, and 84 days. Lower-body negative pressure (LBNP) tests proved to be a greater physiological stress in space than on Earth beginning with mission days 4-6. The greatest loss in LBNP tolerance occurred during the first 3 wk of flight and showed no evidence of progressive change after 50-60 days. Crewmembers of Skylab 3 (59 days) and 4 (84 days) also exhibited elevated mean resting

heart rates and increased numbers of premature ventricular contractions during exercise (ref. 45). Altered in-flight cardiovascular function was evidenced at rest as early as the second day of a 1982 7-day Soviet mission by French investigators who demonstrated significant 20-40% increases in resting cardiac output, and transient 10% increases in left ventricular volume by using echocardiography and Doppler ultrasound flowmetry (ref. 46). Similar findings have been reported for in-flight echocardiographic measurements for four crewmembers of STS 51-D (April 1985) (ref. 47). However, in-flight values were closer to those when standing, than when supine (ref. 48).

Delayed effects also occur (ref. 49). These include adaptations to restore fluid redistribution. Altered neuro-humoral responses to stress and moderate losses of calcium, phosphorus and nitrogen also occur as shown in figure 2. Calcium losses, for example, have amounted to 0.5%/mo of total body calcium and have continued unabated throughout all flights in which measurements have been made (refs. 50,51). Loss of muscle mass in the lower extremities has also been a regular finding for longer-duration flights and has occurred despite use of in-flight leg exercise (refs. 52,53). Weight loss ranging from 1 to 12 Kg has also been a feature of most flights and has not correlated with flight duration (refs. 7,8,10,54-56). The average loss for the nine crewmembers aboard the Skylab mission was 3 Kg, weight gains of 1-2 Kg have been reported after long-term Soviet missions (ref. 8). Leach (ref. 57) has noted that at least half of the weight loss has been regained within the first 24-48 hr following flights and, therefore, has been attributed to negative fluid balance.

Upon return from flights, all cosmonauts and astronauts have exhibited decrements in orthostatic tolerance (70° tilt, LBNP, stand tests) and exercise capacity (tables 2 and 3). Changes have been present irrespective of flight duration and have persisted despite use of countermeasures, with the latter having some effect on the severity of postflight reactions and shortening recovery time in some instances (refs. 3,53,54,58). Postflight exercise tolerance measured as submaximal oxygen uptake has shown 25-50% losses, and was first measured after the Apollo missions (ref. 45). Similar findings occurred with Skylab, yet submaximal tolerance (75% max) was not decreased during flight (ref. 59). Postflight studies have also indicated that all crewmembers experience fluid losses, decreases in circulating blood volume and decreased heart size (refs. 60-66).

In April 1981, the Space Shuttle or Space Transportation System (STS) was implemented as the first reusable space vehicle capable of airplane-type reentry. In this mode, passengers receive reentry stress in the $+G_z$ (heat-to-foot) direction, which may last for considerable periods (up to 20 min) and reach levels of 1.6 to 1.8 times the force of normal gravity. Twenty-three flights have been accomplished so far lasting from 54 hr to 10 days. Aside from the Challenger accident in January 1986, no serious medical problems have occurred, but all astronauts have been provided with gravity-suit (G-suit) protection because of concern for decreased orthostatic tolerance following exposure to weightlessness. The major medical problem has been space motion sickness, lasting over the first 3-5 days of flight, and manifested in most individuals as a loss of appetite, stomach awareness,

headache, occasionally progressing to nausea and vomiting (20-25% of individuals). Again, similar findings have occurred for Soviet crews. Figure 3 shows recent findings for end-diastolic volume (EDV) measured by echocardiography in four Shuttle crews (refs. 49,60). End-diastolic volume showed an immediate 22% decrease consistent with a loss of plasma volume; however, full recovery was still not present one to two weeks following flight and may be due to the high level of physical conditioning present in the various crewmembers. Cardiovascular deconditioning has also been present postflight and significant in 30% of Shuttle passengers and crew (ref. 58).

Soviet Manned Spaceflight

Soviet investigators have consistently observed the same cardiovascular changes with space flight reported by investigators in the U.S., including postflight ortho-static intolerance and decreased exercise tolerance (refs. 7,8,10,54,55,67-70). Since the 84-day Skylab flight in 1974, the Soviets have accomplished seven longer missions lasting 96, 140, 150, 175, 185, 211, and 237 days, the latter ending on October 2, 1984. On February 20, 1986 the Soviets launched their new space station "Mir" which has been almost continuously occupied by various crews visiting it and their previous Salyut-7 space complex which is still in orbit (refs. 71,72).

On December 28, 1987 a new record for space endurance was set by cosmonaut Yuri Romanenko who lived aboard the "Mir" Space Station for 324 days. A large number of physiologic tests have been performed periodically during these flights, including collection of urine and blood samples (finger punctures). Cardiovascular tests have included measurements of ECG and associated systolic time intervals, blood pressure by cuff and microphone, apexcardiography, impedance plethysmography, occlusion plethysmography of the arm and leg, noninvasive measurement of jugular venous pres-sure, and LBNP and exercise stress testing. In-flight cardiovascular changes, as noted in table 3, have been similar to those observed in the U.S. program. Occlu-sion plethysmography indicated a decrease in venous tone of the legs (refs. 7,8,68,73), while impedance plethysmography showed increased flow and filling of cerebral vessels which returned toward preflight levels in some crew members after 3-4 mo of flight (refs. 8,68). An increase in PVCs and sinus arrhythmias was observed in some crewmembers. As with the Skylab experience, LBNP tests were more stressful during flight, even at lower levels of suction (-20 to -30 mm Hg). Nonin-vasive measurement of jugular venous diameter documented a significant and persis-tent headward shift of fluid regardless of flight duration. Apexcardiography indi-cated increased stroke volume and cardiac output early in flight. These changes correlated closely with already mentioned more recent echocardiography measurements showing an early increase in ventricular volume and resting output (ref. 46). Atkov and associates (refs. 74,75), however, failed to find evidence of sustained changes during his 237-day mission. To date, all crews have been able to perform in-flight tasks without limitations from cardiovascular deconditioning. In addition to Romanenko, one cosmonaut, Vaberic Ryuman, has spent almost a year (360 days) in space as a result of serving aboard the 175-day and 185-day missions, having a 6-mo recovery period between flights. Subsequently, Leonid Kezim has been in space for

373 days (3 flights) and Vladimir Solovyov for 262 days (2 missions). There has been no reported evidence for clinical or physiologic harm from these exposures.

To avoid deconditioning during long-term flights, all Soviet crewmembers wear load suits during waking hours which contain elastic cords attached to the arms and legs to supply resistance to motion. Countermeasures prior to flight include intensive physical training and one week of sleeping in a head-down (-6° to -12°) position. During flight, extensive bicycle or treadmill exercises are used (up to 2-2.5 hr daily), incremental LBNP is experienced for 5-7 days before reentry and ingestion of salt/water additives is made just before entry. Similar fluid loading just prior to reentry is used in recent U.S. Shuttle flights (ref. 58). These countermeasures have not been entirely successful, as cosmonauts continue to experience significant postflight cardiovascular deconditioning as gaged by heart rate response to a 20-min tilt test (70° back angle) (refs. 69,70,73,76). Figure 4 illustrates flight-induced changes of EDV in Soviet crews participating in the 96-, 140-, and 175-day flights, as determined by echocardiography (ref. 77). Eight to 50% decreases were present and agree in general with findings following Skylab and Shuttle flights (refs. 60,61). It is believed that the major cause for these changes is a significant flight-related loss of intravascular volume (refs. 62,64,78).

GROUND-BASED SIMULATIONS OF WEIGHTLESSNESS

Comprehensive research on physiological responses could not be conducted in space during the early phases of manned flight because of engineering and performance requirements, the small number of subjects participating during each flight, and the high cost of flight experiments. Ground-based simulations were required and gradually developed. The first technique used was water immersion, followed shortly by chair rest and bed rest, isolation, experimentation with altered gravitational environments, and immobilization of animals. These methods, of course, have not precisely duplicated conditions during weightlessness because none entirely eliminates the effects of gravity. However, responses during and after exposure closely mimic those measured after spaceflight and they have provided a wealth of information on physiological responses to inactivity for both astronautical and clinical purposes.

Human Studies

Water immersion- A large number of water immersion studies have now been accomplished in normal healthy individuals to simulate weightless conditions and to study the body mechanisms responsible for long-term fluid and electrolyte control. These aspects have been the subject of a number of excellent reviews (refs. 11,79-81). Immersion of a subject in a fluid medium parallels exposure to weightlessness by producing a prompt headward shift of body fluids, brisk involuntary diuresis, and loss of body and plasma fluids (refs. 11,15,81-83) resulting in cardiovascular

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deconditioning and orthostatic intolerance following exposure. Immersion differs from weightlessness in two respects; first, the hydrostatic forces exerted on the body by the immersion fluid result in negative pressure breathing, which in itself causes blood to shift to the thorax. Second, gravity effects are not eliminated even though bodily movements require less effort in the immersion medium. Few long-term studies (24 hr or longer) have been reported because of limitations inherent in maintaining proper thermoregulation. Shulzenko and associates (ref. 84) have attempted to solve some of these problems by separating subjects from water with a thin sheet of plastic and placing them in a horizontal position while immersed to the neck. Although hygiene remains a major problem, subjects have been able to tolerate such exposures for up to 56 days without ill effects (ref. 29). The resultant data have been comparable to horizontal or head-down bed rest.

During immersion (see fig. 1) investigators have observed a decrease or little change in heart rate and slight decreases in systolic and diastolic blood pressures (refs. 82,83,85-87). A diuresis occurs early (free water) and is associated with the known shift of blood centrally, which results in cardiac enlargement (refs. 88,89) and persistent and significant increases (from 10-14 mm Hg) in venous pressure (refs. 27,90-94) (see fig. 5). Plasma volume loss after 6-8 hr of immersion has averaged 10% (range 4-16%) (refs. 9,11,15,95,96) and have generally correlated with a fall in plasma antidiuretic hormone (ADH) levels (refs. 11,94). Orthostatic intolerance, a primary indicator of cardiovascular deconditioning, has been observed consistently after immersion (refs. 15,82,83,90,97-99). Using tilt or centrifugation it can be shown that significant cardiovascular deconditioning occurs after 2-6 hr of immersion, and exacerbates if continued for 12-24 hr (refs. 83,100). The exact mechanisms responsible for these latter changes still remain unclear, and may be associated with altered sympathetic nervous system activity caused by stimulation of both high as well as low-pressure baroreceptors (refs. 101-104). This is supported by findings of significant (50% or greater) decreases in plasma epinephrine and/or norepinephrine levels in several studies which persist during the course of immersion (refs. 85,91,105), although Epstein and associates found no change in one study (ref. 106).

Horizontal bed rest- As with immersion, bed-rest simulation of weightlessness does not completely eliminate the hydrostatic effects of gravity. However, the hydrostatic intra- and extravascular pressure gradients that exist during standing are eliminated or minimized, causing a significant central or cephalad fluid shift. The body readily adapts to bed rest, as it does to weightlessness, but when exposed once again to normal gravitational forces, symptoms of cardiovascular deconditioning are universally exhibited. By far, the greatest number of simulation studies have employed the bed-rest technique. Consequently, much more information is available on bed-rest responses than other simulation methods.

Since the first study in 1921, well over 150 individual horizontal bed-rest studies have been conducted by U.S., Soviet, and other European investigators to measure cardiovascular changes (ref. 107). Over 1,500 normal subjects have now been studied. A detailed listing of individual horizontal bed-rest studies has been published in several previous reviews (refs. 3,108-110) and is summarized in

table 4. Study durations have ranged from several hours to over 7 mo, with the majority of subjects being males aged 19-35 yr, but more recently normal older individuals to 65 yr have also been tested and have included females as well as males (refs. 3,66,111-116).

Early bed-rest investigations were concerned with evaluating the metabolic effects of immobilization. The earliest of these studies demonstrated that nitrogen excretion increased with bed rest (ref. 107) and a bed-rest-related loss of calcium was also documented (ref. 117). In the 1940s, observations were extended and investigators identified the involvement of other body systems, including a loss of glucose tolerance (refs. 118,119), loss of muscle mass and strength, a decrease in cardiovascular deconditioning (refs. 120-122), and an increased risk of venous thromboembolism (refs. 66,123-125). Findings during this early period are summarized in a monograph written by Browse (ref. 126). With the beginning of the Space Age and the realization that bed rest could be used to simulate weightlessness, the number of bed-rest studies proliferated in preparation for manned space flight and utilized completely normal and healthy individuals as opposed to previous studies conducted in subjects with known clinical illness (ref. 66). Table 4 shows that the majority of these studies lasted 7-21 days, which covered the duration of early manned flights (tables 2 and 3). As Soviet investigators have moved to place humans in orbit for longer periods (175 days, 185 days, and 211 days), they have preceded these flight with bed-rest studies of similar duration. Results have clearly shown that bed rest for periods longer than 3-5 days leads to clear-cut manifestation of deconditioning and the potential for any or all of the previously discussed complications.

Subjects consistently exhibit a diuresis and a rapid 8-10% loss of plasma volume over the first few days which continues to decrease at a slower pace to 20% by day 30 of bed rest (refs. 79,80,127-129). Bed-rest studies lasting 100-200 days have registered 30% losses in plasma volume (refs. 78,80,128). These changes are summarized in figure 6. Concurrent with loss of plasma volume is an increase in hematocrit and when exposures continue longer than 2 wk there is a decrease in red cell mass and slight reticulocytes (refs. 130-132). These changes have leveled off after 60 days of bed rest, remaining stable, but depressed, for the remainder of the bed-rest period (ref. 130). The stabilizing influence is probably an increase in bone marrow activity, but the exact causes are still unknown. Similar findings have occurred with space flight (refs. 133-135). Yet, recent measurements in shorter-term Shuttle flights (ref. 135) have failed to show a reticulocytosis or provide an explanation for the red cell losses. X-ray and echocardiographic measurements of heart size have correlated with plasma volume decreases and state of athletic conditioning of subjects. End-diastolic volume after 2 wk of horizontal bed rest in seven athletically trained male subjects aged 19-25 yr fell 11% (p < 0.01) from 70 ±2 ml/M^2 to 62 ±3 ml/M^2. In seven similarly aged nonathletic males EDV changed 6% from 62 ±3 ml/M^2 to 58 ±3 ml/M^2 (refs. 66,136). A 12% decrease has been observed in nonathletic females (ref. 137). A 23% loss in EDV has recently been reported in 8- to 10-day Shuttle flights (ref. 60) and 8 to 50% losses in 96- to 185-day Soviet flights (refs. 8,77).

Resting stroke volume and cardiac output have also fallen as would be predicted from the decrease in heart size and lowered metabolic demand associated with inactivity and loss of muscle mass. In the previous athletic and nonathletic males, stroke volume fell 3 and 9%, respectively, and cardiac output 6 and 13%. Respective changes for females were 25 and 21%.

Bed-rest exposures up to 6 mo have demonstrated that resting systolic and diastolic blood pressures generally remain within normal limits, with some tendency toward elevation of diastolic values in many studies (refs. 3,120,129,138-141). During bed rest, resting pulse rate and systolic time intervals have varied, although resting heart rate usually has increased as bed-rest duration lengthens (refs. 121,127,129,138,139,142-145). Taylor and associates (ref. 122) first pointed out that heart rate increased by 0.5 bpm with each day of bed rest, and this rule is generally observed today. Bed-rest studies up to 10 days in duration have reported heart rate increases (from baseline values) up to 12-32 bpm; 30-day studies up to 26 bpm; 62-day studies up to 25 bpm; and 70- to 120-day studies, increases of 1-5 bpm per week of study. Some investigators, however, have reported little or no changes (ref. 146) or even a decrease (ref. 147) in heart rate.

Electrocardiographic findings have been variable. Slight, but significant, changes in T-waves have been noted in standard limb leads and by vector cardiography in subjects bed rested for 10 wk and monitored weekly (refs. 148,149). Over time T-wave amplitudes increased in standard limb leads; U-waves of increasing amplitude were detected in precordial leads and became significant by the second or third week of bed rest. Changes were postulated to result from altered blood and tissue levels of potassium and calcium induced by bed rest, but blood levels of these ions were not measured over the course of the study. During manned flight, Soviet cosmonauts have exhibited similar T-wave responses (ref. 3). But Hyatt and associates (ref. 150), in studying changes with potassium ingestion during 2 wk of bed rest, found no significant ECG changes. In the Skylab missions, VCG tracings showed slight, but significant, changes in QRS and T-wave amplitudes (ref. 45). Increases in the QRS complex amplitude and decreases in the T-wave amplitude were also seen following 6 mo of bed rest in a study by Turbasov (ref. 151). Tkachev and Kul'kov (ref. 152), in a 49-day bed rest study, noted that subjects exhibited more and more significant increases in heart rate and decreases in registered T-wave either in anticipation of, or during, venipuncture. However, anxiety over venipuncture may not be the only explanation for wave form changes. It is known that heart size decreases during bed rest (ref. 137, 153-155) and space flight (refs. 8,61,71); there is also a regular decrease in red cell mass (refs. 132-135,156). Such changes in heart size, or a shift in heart location within the chest, as well as change in hematocrit are known to be capable of inducing ECG changes in themselves (ref. 157).

Resting levels of blood glucose and plasma insulin have been found to be unaltered with short-term bed rest, but to become variable and tend to decrease with studies up to 2 mo in duration (refs. 118,119,158,159). During bed rest challenge by an oral glucose load has resulted in an inappropriately high (2-4 times greater) insulin response (refs. 158,160,161). Dolkas and Greenleaf (ref. 158) found that the intensity of the glucose-insulin response was inversely proportional to the

total energy expended daily during bed rest. Those who did not exercise showed the greatest change. It was estimated that at least 1020 kcal/day of supplemental exercise was needed to restore the hyperinsulinemia to control values.

Head-down bed rest- Recently head-down bed rest has also been used to provide information on cardiovascular changes that occur with inactivity and weightlessness. This technique was originally introduced by Soviet investigators following reports from their cosmonauts that the head-down position postflight best reproduced the symptoms of head fullness and awareness felt during flight (ref. 26). The first study conducted in 1969 (ref. 162) consisted of a 30-day comparison of horizontal (0°) and head-down tilt (-4°). A large number of subsequent studies have now been completed and are summarized in table 5. Body positions have varied from -2° to -15° with durations from 24 hr to 182 days. Most head-down studies have used angles of -4° to -6° (table 5), because post-bed-rest heart rate responses to 70° passive head-up tilt seem to best imitate findings following weightlessness (ref. 26). Subjective feelings have included complaints of blood rushing to the head, heaviness of the head and palpitations in the temples. Objective findings have included neck vein engorgement, increased distention of the retinal veins (refs. 163-166), and increased central and jugular venous pressures (refs. 26,111,167-175). Most signs and symptoms reach maximum intensity within 3 hr after beginning an experiment and closely mimic those experienced during the first few hours of space flight. With head-down bed rest, subjective and objective findings have been increasingly severe with greater angulation. Recently Katkov and associates (refs. 170,171,183) have reported on a series of bed-rest studies using a -15° head-down position as a means of studying a worse-case response.

A significant number of invasive and noninvasive studies have been completed to understand the hemodynamic changes that occur with head-down as opposed to supine and upright body positions (refs. 2,54,127,144,169-173,176-186). With head-up tilt, both jugular and right atrial pressures drop significantly to levels ranging from -1 to -2 mm Hg, with similar changes occurring in left-ventricular filling pressure, since such values parallel right-sided measurements. With head-down tilt, the reverse occurs, with central venous pressure (CVP) rising by approximately 9 mm Hg and jugular pressure to over 30 mm Hg. These pressures represent a change of more than 10 mm Hg in ventricular preload (CVP) and 25 mm Hg in jugular vein pressure when moving from +70° (head-up) to -70° (head-down).

In comparison to seated head-out immersion (fig. 5) head-down body positions of -5° to -20° result in only one-half to one-fourth the CVP levels (ref. 187). In addition, figure 5 shows that elevated pressure levels with bed rest are not sustained and tend to normalize rapidly. During a 24 hr -5° head-down bed-rest study in five subjects (20- to 30-yr-old males), Nixon and associates (ref. 175) observed a sharp 50% increase in CVP over the first 40 min of observation, with a return to baseline levels within 90 min and a continually gradual decline which was significantly below baseline levels by 12-16 hr of the study. Blomqvist and associates (ref. 111) in more recent studies of older males (40-48 yr) found similar initial CVP increases (fig. 5) with delays of up to 24 hr for return to baseline. On the other hand, Katkov and associates (ref. 170) measured mean right atrial pressure

hourly over the first 7 hr of a 7-day, -15° head-down bed-rest study which showed no significant change from baseline levels of 4.3 mm Hg for eight subjects. Central venous pressure was 2.5 mm Hg on Day 2 of bed rest and continued dropping to levels of 0.9 mm Hg by Day 5 and persisted at such levels to the end of the study. The previously described sharp increases reported by Nixon and associates (ref. 175) could have been missed in this latter study since only hourly values were reported. Yet, mean pulmonary artery pressure gradually increased over the first 7 hr (9.6-11.9 mm Hg) and then gradually decreased to 7.4 mm Hg by Day 3 of the study. The disparity of right atrial and pulmonary pressure changes is of interest occurring as it did during the period of bed-rest-induced diuresis, and remains unexplained. Heart rate, cardiac output (thermodilution), and stroke volume did not change significantly over the course of the -15° head-down study. Of interest are recent peripheral venous pressure measurements obtained during spaceflight by Kirsch and associates (refs. 188,189) which closely parallel head-down bed rest findings. Values obtained by the first or second day of flight were below initial ground-based levels and tended to fall over the course of the flight. One exception to these findings has been the sustained 4 mm Hg increases in mean right atrial pressure found by Lollogen and associates (ref. 174) over the course of a 2-hr -6° head-down study (fig. 5). These results agree more closely with changes occurring during water immersion and presently remain unexplained.

Most hemodynamic responses during and after head-down bed rest have paralleled or exceeded horizontal results, but findings have been variable. Kakurin (ref. 26) found exaggerated head-down heart rate response during 70° tilt. Convertino (ref. 190) found in-flight exercise response was better matched after -6° bed rest, than when horizontal. Katkovskiy and associates (ref. 191) found a greater decrease in exercise capacity head-down for subjects after 30 days bed rest. Using LBNP after 7 days bed rest, Goldwater and associates (ref. 192) found a significantly (p < 0.05) greater (39%) decrease in cardiac output in -6° subjects (compared to 4% for 0°); greater decrease in left-ventricular diastolic volume (58% vs 37%) and increased blood pooling in the legs and pelvis (impedance plethysmography). In contrast, Hyatt and West (ref. 193) reported no evidence of significant physiological change in eight male subjects exposed to 7 days of 0° and -5° bed rest. In this regard, resting hemodynamic changes (heart rate, cardiac output, stroke volume) during 7 days of -15° bed rest (ref. 170) failed to show significant changes over the course of the study. Absolute values showed little difference from the original (control) 0° position.

Soviet investigators have failed to note regular increases in resting heart rate during the first month of head-down bed rest, but significant increases have occurred thereafter (refs. 194,195). Therefore, associated increases observed in cardiac output have been attributed to increases in stroke volume. Changes were usually most prominent by the sixth to ninth day of bed rest and returned to baseline levels by the 15th to 20th day. Such changes have occurred in both horizontal and head-down positions, but were earlier and more pronounced in head-down subjects. The reported accuracy of these latter cardiac output measurements must be questioned, however, since they were determined noninvasively using CO_2 rebreathing techniques (ref. 196) or mechanocardiography (ref. 197) and differ from those

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reported by Katkov (ref. 170) using indicator dilution techniques. Changes in blood redistribution with significantly greater headward shifts of volume were also documented in the head-down body position; these shifts persisted throughout the bed-rest period. Changes were measured using radioactive iodinated serum albumin (RISA) (refs. 26,168) and impedance plethysmography (ref. 20). However, the quantitative accuracy of both methods has been questioned (refs. 198,199).

Head-down bed rest has been used extensively by Russian investigators to study various countermeasures. Particular attention has been paid to the use of physical exercise, exposure to LBNP and muscle electrostimulation (refs. 76,146,184, 200-209). In preparation for projected long-term flights, Soviet investigators exposed 18 male subjects (31-40 yr of age) to 182 days of -4° head-down bed rest (ref. 76). The subjects were divided into three groups: controls; those receiving daily, or weekly, exercise (simulated bicycle riding, rowing and impact loading to simulate walking, running, and jumping); and muscle electrostimulation. Twenty-minute passive stand tests (75° back angle) were done 11 times during the study (three during control, five during bed rest, and three post-bed-rest). Results are shown in figure 7 for the muscle stimulation subjects and compared with identical postflight tests after various Salyut 6 long-term space missions. The bed-rest and flight findings are similar. During these tests, the subjects in the two treated groups exhibited presyncopal symptoms only twice during 22 tests, whereas the untreated controls had five episodes of presyncope. Systolic time intervals for the untreated group exhibited prolonged isometric contractions (PEP) and shorter left ventricle ejection times, as have been previously reported after Skylab (refs. 210-212).

To date, there have been far fewer studies using head-down bed rest than horizontal bed rest. From the information obtained, however, it appears that head-down bed rest offers a strong potential for simulating the cardiovascular changes that occur early in spaceflight. However, this hypothesis can be proved only by definitive physiological measurements conducted in the actual state of weightlessness.

Other techniques for simulating weightlessness- A number of techniques other than bed rest and immersion have been used to simulate the weightless condition on Earth, including chair rest, confinement, and partial-body support systems. Findings have varied and point to the multifactoral nature of the adaptive process which may be evidenced to a greater or lesser extent by a specific simulation method.

Chair rest has been one of the first used of these techniques (refs. 195, 213,214). In these studies, cardiovascular deconditioning has occurred despite the presence of a gravity vector along the long axis of the body and its concommitant hydrostatic influence. Lamb and associates (refs. 213,214) conducted a number of chair-rest studies lasting 4, 6, 8, and 10 days. After 10 days of chair rest, total blood volume and red cell mass decreased to an extent observed after an identical number of days of bed rest. Orthostatic tolerance and exercise capacity tolerance decreased progressively as the duration of chair rest lengthened (ref. 214). After as little as 4 days of chair rest, subjects exhibited symptoms of orthostatic intolerance, ranging from presyncope to frank syncope (ref. 213). Soviet investigators have found similar responses with chair rest (refs. 195,215).

Deconditioning has also been documented after confinement in small chambers used to simulate space cabin environments (refs. 216-219). In a group of 36 confined subjects Lamb and associates (ref. 220) found decreases in blood volume, hemoglobin, exercise tolerance, and orthostatic tolerance; changes were of a magnitude seen after bed rest. One-fourth of the subjects exhibited postconfinement syncopal episodes during tilt-table tests and the remainder exhibited increases in heart rate and decreases in pulse pressure and systolic pressure. Yet, all of these subjects had spent significant periods of the day (up to 12 hr) in the upright position. Similar findings have been reported by Panferova and associates (ref. 195) who confined 58 subjects for 3-72 days in small chambers ranging in size from 20-200 m^3. Subjects were both chair rested and permitted to move about and undertake exercise regimens. Subjects confined for 20-24 days in the 20 m^3 chamber demonstrated average pulse rate rises of 31-102 bpm with isometric (hand grip) testing, compared with changes of 20-34 bpm before confinement (ref. 195). Maximal changes were seen on Day 14 of confinement. In an analogous test of cosmonauts during space flight (Soyuz 9), Soviet investigators (refs. 219,221) found similar pulse rate changes with testing. Recovery to pretest levels was significantly shorter for the cosmonauts than for the confined subjects (ref. 195). Finally, weight losses similar to those seen in space crews have been observed during confinement experiments (ref. 195).

Body support systems which reduce gravitational load and direction along the long axis of the body were developed to train astronauts to move on the lunar surface and have been applied to study the effects of reduced gravitation in animals. For the lunar expeditions, Hewes and associates (ref. 222) developed a suspension system attached to a small overhead trolley and aligned subjects at an angle of 9.5° from the horizontal. Cables supported each subject's head, chest, hips and buttocks, and the calf of each leg at the desired angulation. When suspended, subjects experienced 1/6 g and could move freely, but their rate of movement was reduced by 40%. Soviet investigators adapted this system for animal experimentation (ref. 223). The equipment consists of a cone (4-m high) with walls at the same angulation used in human studies. Rhesus monkeys dressed in special suits have been suspended inside the cone from three days to two months. Findings have shown that motor activity, particularly posture and kinematics, have been altered in much the same way as in human subjects. Similarly, the animals have also exhibited an early diuresis, decreased erythropiesis (determined from bone marrow samples), ECG findings indicative of electrolyte changes, loss of 12-30% of body weight and posttest orthostatic intolerance.

A partial body-support system has also been developed for studying rat responses to reduced gravitation (ref. 224). The system suspends the animals by tail in a -15° head-down position to induce headward fluid shifts, permits normal use of limbs and some weight-bearing, and effectively unloads the rear limbs without nerve or spinal cord section, or the use of casts. Using this system, Popovic (ref. 225) found changes similar to that observed with human head-down bed rest. Right atrial pressure rose from 0 to +5 mm Hg during the first day and returned to baseline levels by Day 2. Heart rate increased slightly initially, while mean arterial pressure decreased. Both values returned to baseline (presuspension)

levels by the second to third day. Cardiac output and stroke volume also increased slightly during the first several days and then returned to baseline levels. During recovery from 7 days suspension, animals demonstrated elevated heart rates for 7-14 days. Cardiac output recovered after 3 days.

Use of an antigravity (anti-G) suit has also allowed for headward shift of fluid from the lower body to the upper half of the body by direct mechanical compression of body tissue. Worn either as a tight-fitting leotard alone, or as pants with inflatable air or liquid bladders, the resulting counterpressure opposes any fluid displacement and pooling of blood to the legs, abdomen and/or pelvis. For over 80 yr these suits have been used in surgery to control bleeding and to maintain blood pressure postsurgery or trauma (ref. 226). Anti-G suits have also been used for nearly 45 yr to counteract increased gravitational forces as might be encountered in aircraft or in a human centrifuge (ref. 227). Physiological studies at rest have shown similarities with bed rest or immersion (ref. 228). As with bed rest, initial CVP increases have not been maintained (ref. 11,229), and long-term inflation may lead to pooling and eventual decreased venous return (ref. 11). Air pressure along over the lower half of the body (without use of a suit) has also been used to induce headward fluid shifts. By placing the lower body in a tightly sealed box, Moore-Ede and Kass (ref. 230) have been able to obtain fluid and electrolyte changes in squirrel monkeys by simulating head-down tilt and immersion.

In general, ability to induce evidence of varying degrees of cardiovascular deconditioning by these differing methods point to the conclusion that both induced shifts of fluid load and inactivity play key roles in producing the resultant physiological effects.

Responses to Orthostatic Stress Testing Following Bed Rest

Investigators have used various forms of stress testing to determine orthostatic intolerance following bed rest. The three methods used have been passive standing, 70° head-up tilt, and LBNP. Comparison of heart rate changes during these forms of testing have failed to show significant differences (refs. 198,231). Each test has been used to assess blood pressure maintenance in the face of a standard footward shift of body fluid allowing for quantitation of the various system responses shown in figure 1, including measurements of blood pooling in the lower half of the body, heart size, cardiac output, and blood flow distribution, in addition to the regular determination of heart rate changes. Head-up tilt at 70° is the oldest of the three techniques. With progressive shift from the supine to upright position, blood pressure tends to remain stable or increase, heart rate increases, and stroke volume and cardiac output falls (refs. 2,127,144,180,232). During 70° tilt, maximal heart rate has shown increases of 15-35 bpm before, and 20-60 bpm following bed rest (refs. 127,233-237).

Over the past decade, LBNP has been used widely, since it can be applied during flight, to induce a shift of body fluids similar to that occurring with change in body position on Earth (ref. 198). Lower-body negative pressure at -40 or -50 mm Hg

results in changes in heart rate and blood pressure, similar to those occurring during passive standing and 70° tilt (ref. 198,238). During ground-based testing LBNP allows subjects to be stressed in the supine position so that other physiological measurements, such as echocardiography, can be accomplished more easily. Recently, stepwise increases in suction up to -100 mm Hg have been used to determine maximal physiological capacity in both males and females (refs. 239,240). Derived data permit far better quantification of orthostatic loss, since at least 80-90% of the adult population (male and female) can tolerate 15 min of 70° tilt or -50 mm Hg LBNP before bed rest without loss of consciousness. As a rule, 50% decrements in capacity have followed bed rest (refs. 115,129,137,144,192,241-243).

Lower-body negative pressure has proved to be a greater stress during flight in both the U.S. and Soviet space programs as evidenced by an excessive tachycardia and an inability to control blood pressure upon pressurization (refs. 6,209,244). Such changes have persisted during flight but were not progressive beyond 50-60 days on the 84-day Skylab flight which is the longest U.S. flight of record. Changes have been of a lesser magnitude in Soviet flights and have been attributed to the heavy use of in-flight countermeasures, particularly exercise (refs. 8,10,54,244).

Orthostatic intolerance has been observed consistently with provocative testing after only three days of bed rest (6-12 hr of immersion). An increase in heart rate has been the earliest and most consistent finding, with the increase ranging to over 100% after bed rest in many individuals (refs. 83,127,243,145-248). The exact mechanisms still remain unclear and one reason may be the stimulation of low, as well as high-pressure baroreceptors by attendant footward fluid shifts (refs. 16, 101,104,249-254). Involvement of low-pressure receptors have been shown during LBNP studies in which splanchnic and forearm blood flow show significant change well in advance of change in pulse pressure (refs. 101,104,249,253,255). Lastly, heart rate responses during LBNP have been shown to be slightly different for male and female subjects before and after bed rest and this is associated with differences in redistribution of blood flow (refs. 3,19,20,137).

Operational medicine personnel, both here and in the Soviet Union, have used stand tests because of its ease of application to simplify such testing during the evaluation of flight crews particularly at remote recovery sites. Heart rate changes with such stand tests have averaged 35 bpm before and 60 bpm after bed rest (ref. 231).

Response to Acceleration

In comparison to standing or upright tilt which exposes the circulation to Earth's normal +1 G_z (head-to-foot) acceleration, riding in a human centrifuge permits measurement of response to multiples of such factors. Exposure to +G_z acceleration augments the fluid shifts from the head to the feet, particularly from intrathoracic compartment to the legs. Recent interest by U.S. investigators has been prompted by the +G_z reentry mode of Shuttle vehicles. Although these vehicles are launched in the classic +G_x mode, they land like airplanes with crew and

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passengers in a seated position, receiving gradually building exposures which may reach +2.0 G_z in magnitude and have overall durations lasting 20 min or more (refs. 71,256).

As would be expected, subsequent studies of pilots (ref. 257), younger males (ref. 258), and older males and females (refs. 66,114,259-261) following 1-2 wk of bed-rest and ranges of +1.5 G_z to +4 G_z have shown decreased tolerances of up to 50% or more at higher +G_z levels. Leverett and associates (ref. 262) showed that significant changes occur rapidly. They studied nine experienced male centrifuge riders (age 20-36 yr) after sequential bed-rest periods of 24 hr and 7 days. Acceleration exposures consisted of consecutive +G_z profiles at +2.5, +3.0, +3.5, and +4.0 G_z with rapid onset rates (ROR) of 1 g/min and the peak held for 270 sec. Exaggerated heart rates were noted in all subjects after the first exposure (24 hr); 20% of the group developed visual symptoms or blackout at +2.5 G_z and 40% showed similar responses at +3.0 G_z.

Gravity suits (G-suits) afford subjective and objective physiological benefits in almost all cases before and after bed rest using Shuttle reentry profiles and/or levels up to +4.0 G_z (refs. 260,261). Use of G-suits, which consist of tight-fitting trousers containing air-inflatable leg and abdominal bladders was postulated on its proven ability to maintain ventricular filling by preventing fluid shift to the lower body which might be aggravated by the consistent diuresis and decrease in plasma volume regularly seen with spaceflight, inactivity, and bed rest (refs. 227, 257,263-265).

There have been notable exceptions to the findings of significantly decreased +G_z tolerance after bed rest and findings remain unexplained. In an early study, Mehan and Jacobs (ref. 266) found no change in acceleration tolerance time for six subjects exposed to ROR of 1 g/sec after 30 days of bed rest, despite 25.4% decreases in total blood volume. Miller and Leverett (ref. 264) again found no significant losses with ROR and gradual onset acceleration (GOR) of 0.1 g/sec after 4 wk of bed rest. Jacobson and associates (ref. 258) found only two of six male subjects to have decreased tolerance time at maximal +3.0 G_z acceleration following 2 wk of bed rest. These findings occurred despite cardiovascular deconditioning as evidenced by higher heart rates and lower mean blood pressure during LBNP and acceleration.

Acceleration stress has also induced a variety of neurohumoral and fluid and electrolyte changes, many of which become magnified following bed rest. These include marked increases in plasma ACTH, plasma fibrinogen, plasma renin, plasma ADH, and urinary cortisol (refs. 137,159,267-272). These may represent nonspecific responses to the stress of centrifugation, particularly the increased cortisol excretion and increase in plasma ACTH and ADH. However, in most cases a significantly greater response was found after bed rest. ACTH in female subjects following +3.0 G_z increased 215% from resting levels before bed rest and 360% after. Since a reaction did occur, such evidence of increased pituitary responsiveness may reflect a change in end-organ sensitivity and will need further study. +G_z evoked extremely large changes in ADH (ref. 268). Prior to bed rest, +3.0 G_z caused ADH to increase from 2.5 ±0.6 (SE) to 52.4 ±18.9 pg/ml (p < 0.05, 2000% change); following bed-rest

values increased from 1.8 ±0.4 to 15.1 ±4.0 pg/ml (p < 0.02, 740% change). Plasma renin activity (PRA) did not change significantly with acceleration increasing 47% from resting levels of 0.75 ±0.09 ng Ang 1/ml/hr before bed rest and 17% from baseline levels of 1.49 ±0.06 ng Ang 1/ml/hr. Bed rest, however, did cause a significant (p < 0.05) doubling in resting values. Similar general changes in response to bed rest and/or acceleration have been seen in both male and female subjects up to age 65 yr. Overall system responsiveness has been noted to decrease for older subjects. Last, acceleration provoked significant increase in blood fibrinolytic activity which was considerably increased after bed rest and was greater for females than males (ref. 269). An adequate explanation for these latter changes is still lacking. Vascular endothelium is a known reservoir for the precursor plasminogen necessary for this response and may be released secondary to hypoxia. Post-bed-rest acceleration increases may be an indicator of greater tissue hypoxia or lower-body pooling. Similar increases in fibrinolytic activity have been found by Soviet investigators with bed rest or immersion (ref. 156).

Exercise--Athletes Versus Nonathletes

Exercise on treadmills or bicycle ergometers has been used extensively to determine what happens to work capacity following space flight and bed rest. Exercise tolerance (maximal or submaximal) has decreased a significant 12-25% (submaximal) following space flight (refs. 59,67,68,273-275) and 17-28% (maximal) after bed rest (refs. 112,113,190,276-281), although one group found no change (ref. 80). Five males exposed to 20 days of bed rest showed a 28% decrease in exercise tolerance when both supine and upright (ref. 154). Since this decrease could not be attributed to impaired venous return during exercise, it was suggested that a primary decrease in myocardial function had been induced by bed rest. More recent studies with middle-aged men, however, have failed to support this conclusion since a significantly greater decline in $\dot{V}O_2$ max (17% decrease) occurred when upright compared with 7% when supine (ref. 277).

The impaired work capacity seen after space flight (or bed rest) may very likely stem from physical inactivity, which results in the loss of skeletal muscle strength, loss of pumping effectiveness of lower-limb skeletal muscles, and reduction in muscle metabolism (refs. 279,282,283). But these factors have not been thoroughly investigated to date. Although it has been suggested that exercise during immobilization can reduce the dependent cyanosis associated with bed rest (ref. 284), it has not eliminated orthostatic intolerance or prevented loss of acceleration tolerance, although it has lessened the problem somewhat (ref. 285). It has been difficult to compare the results of the many exercise studies because of differences in study durations and exercise testing methods. This is particularly the case during flight where individual astronauts have followed highly individualistic training programs, both before and during flight.

Athletic conditioning and maintenance of high fitness levels have been emphasized in both the U.S. and Soviet space programs and exercise testing plays a large role in initial selection for flight training, annual physical examinations, and

postflight evaluations (refs. 286-288). In addition, in-flight aerobic exercise--ergometer or "treadmill"--has been used extensively as a countermeasure for deconditioning in the Soyuz/Salyut program and throughout the Skylab flights and recent Shuttle flights (refs. 45,256,275). Both new and veteran astronauts voluntarily adhere to a vigorous self-supervised aerobic conditioning program which is monitored yearly (ref. 286). This fact has recently been confirmed from yearly physical examinations of the astronaut corps where lipid profile data suggest that the HDL, LDL, and VLDL lipid fraction levels compare favorably with those of joggers running at least 2 miles three times per week (ref. 286). The $\dot{V}O_2$ max of older (mean age 46 ±4.1) previously selected astronauts of 41.7 ml/kg/min and that of newly selected younger (age 33 ±3) astronauts of 47.5 ml/kg/min are much higher than those of the general U.S. age-matched population (ref. 289). The age-adjusted mean for percentage body fat of the older astronauts was only 12.7%, much lower than the norm of 25% for their age and even lower than the age-adjusted mean of new astronauts, suggesting a sustained training effect from the many years in this program. However, total cholesterol levels were slightly higher than age-matched controls, although the cholesterol/HDL ratio was lower, suggesting reduced cardiovascular risk (ref. 290).

Recently, Klein and associates (ref. 291) reviewed evidence suggesting that heavy aerobic conditioning may be counterproductive as a countermeasure to deconditioning. Several studies have indicated that physically well-conditioned individuals become deconditioned more rapidly than more sedentary individuals, losing a higher proportion of exercise capacity ($\dot{V}O_2$ max) when exposed to high altitudes (ref. 291), immersion (ref. 99), and bed rest (refs. 192,292). Mangseth and Bernauer (ref. 293) presented evidence of poor orthostatic tolerance in four endurance-trained athletes ($\dot{V}O_2$ max 66 ml/kg·min) who fainted after an average of 17 min of passive upright tilt. In contrast, four "fit" nonathletes ($\dot{V}O_2$ max 52 ml/kg·min) were able to tolerate a full 30 min of tilt without fainting. The mean $\dot{V}O_2$'s for both groups were considerably higher than those of individuals participating in recent flights, or ground-based studies. Luft and associates conducted LBNP studies of five runners ($\dot{V}O_2$ max 45 ml/kg·min) and five nonrunners ($\dot{V}O_2$ max 34 ml/kg·min) before and after acute dehydration (water restriction and work performed at high ambient temperatures (refs. 294,295). Resultant plasma volume losses were similar to those seen with bed rest: runners and nonrunners showed 14 and 12% decreases in plasma volume, respectively. Baseline LBNP tolerance for the runners was 42% less than for the nonrunners, and the gap widened after dehydration, with a further decrease of 41% for the runners, but only 26% for the nonrunners. The degree of fluid shift or pooling into the legs (Whitney strain gages) was greatest in the runners and considered responsible for their lower tolerance to LBNP. In another study, Luft used Lasix (average dose, 0.86 mg/kg orally) to induce about a 10% decrease in intravascular volume, demonstrating that athletic subjects had a significantly lower tolerance to LBNP after Lasix dehydration (ref. 295-297). Finally, these investigators demonstrated significantly greater specific losses in LBNP tolerance for runners than for other types of athletes (refs. 294,297). LBNP tolerance time of 11.5 ±5.5 (SD) min for 13 endurance runners (mean age, 30; $\dot{V}O_2$ max, 51.4 ml/kg·min), was significantly lower (p < 0.01) than 15.7 ±2.5 min for 12 weight lifters and body builders (mean age, 29; $\dot{V}O_2$ max, 38.7 ml/kg·min) and

15.7 ±2.0 min for 12 swimmers (mean age, 47; $\dot{V}O_2$ max, 35.2 ml/kg·min). LBNP tolerance of 12 nonathletes (mean age, 29; $\dot{V}O_2$ max, 34.9 ml/kg·min) was 15.8 ±1.6 min. During LBNP, runners had the largest leg compliance (with weightlifters second) and lowest increases in heart rate (swimmers were second). The swimmers on the average, were 17 yr older than subjects in the other groups, which may explain their greater LBNP tolerance compared with runners; weight differences also may have contributed. The $\dot{V}O_2$ max level of current age-matched astronauts (mean age, 33; $\dot{V}O_2$ max 47.5 ml/kg·min) indicates that their aerobic capacity is closer to that of the runners in the foregoing study (refs. 286,287).

Athletes have also been shown to lose a higher proportion of their $\dot{V}O_2$ max following the deconditioning of altitude and water immersion simulation of weightlessness (ref. 291). Lower orthostatic tolerance also occurred in athletes following the deconditioning from water immersion (ref. 98,99), but not during $+G_z$ acceleration (12 athletes and 12 nonathletes) in the absence of any deconditioning exposure. However, the level of acceleration ($+6.8 G_z$) was attained rapidly (0.07 g/sec), may have masked subtle differences between the two groups. In our laboratory, difference between athletic and sedentary individuals have been accentuated following bed-rest deconditioning (refs. 241,279). Exercise in-flight, or during water immersion deconditioning may be more effective in sedentary people or those with lower $\dot{V}O_2$'s (refs. 98,291). It is well known that the improvement of exercise capacity after a given amount of training is much greater for those starting at a sedentary level (ref. 154). For example, in Skylab 4, the scientist pilot and pilot had high levels of aerobic conditioning preflight. In flight they exercised up to 2 hr/day, yet they had a higher frequency of syncope and presyncope during LBNP and a greater loss of orthostatic tolerance and exercise capacity postflight than the more sedentary commander of that flight who had performed less in-flight exercise than the others (refs. 6,275). The scientist pilot and pilot also had greater leg compliance and leg blood pooling during in-flight LBNP than the commander (ref. 6), although weightlessness increased compliance in all three Skylab 4 astronauts (ref. 235). In addition, the athletic scientist pilot and pilot had significant decreases in echocardiographically determined EDV, stroke volume, and left ventricular mass postflight in contrast to the commander (ref. 61). From an adaptation standpoint, it makes little sense for individuals to spend a large amount of time exercising preflight to build up high levels of aerobic fitness which can only be maintained by larger amounts of time-consuming in-flight exercise, when the net result postflight is a greater loss of exercise capacity and orthostatic tolerance than in the sedentary person.

Beneficial in-flight effects of isotonic exercise, including a feeling of enhanced well-being (refs. 8,244), have been reported. Recovery of cardiovascular performance during LBNP exercise tests following Skylab or recent long-term Soyuz flights has been more rapid than following previous shorter flights; an effect which has been attributed to more in-flight exercise. Some weightlessness simulation studies have indicated that isotonic exercise can decrease the degree of cardiovascular deconditioning which would normally occur (refs. 206,279), others, however, have not confirmed this finding (refs. 136,285,298). The issue is far from

being resolved since the differences between flight and ground-based studies regarding duration, intensity, and type of exercise are large.

Despite the numerous studies that have been conducted, the mechanisms underlying the loss of $\dot{V}O_2$ max with bed rest or inactivity remain unexplained. Significant reductions in physical activity have been shown to lead to losses in lean muscle mass (refs. 276,279), as well as increases in body fat content which, in turn, is associated with an absolute decrease in muscle blood flow and possible decreases in muscle capillary density (ref. 282). Such changes are sufficient in themselves to explain a decrease in $\dot{V}O_2$ max. Other important factors are the marked reduction in oxidation potential associated with decreased work capacity and loss of blood and plasma volume regularly seen with bed rest, which limits maximal cardiac stretch and ultimately the maximal realizable flow. Study of athletes, particularly runners, provides yet another insight related to enhanced vagal tone. Inactivity in such individuals may foster maldistribution of flow, limiting flexibility and the ability to withstand orthostatic stress.

Age and Sex Differences

Bed-rest or immersion data from females or subjects 50 yr or older has been quite limited compared to males aged 20-40 yr (table 4). In addition, only nine female astronauts have flown in the U.S. program compared to 113 males, with two female cosmonauts versus 98 males in the Soviet program. Physiological changes have been similar for the most part, but sex-related differences have been present. As expected, females have had lower resting levels of stroke volume, EDV and cardiac output as compared to males due to their greater lower-body surface area; their body fat content is also greater. Slightly greater losses in females have occurred with bed rest as compared to nonathletic males (refs. 3,66,137). Loss of LBNP tolerance after 2 wk of bed rest was greater in females, and heart rate response was more exaggerated than for males (ref. 66). Such findings are probably due to smaller initial EDVs in these areas, resulting in comparatively smaller ventricular volumes at each stage of orthostatic stress. The menstrual cycle could not be demonstrated to have a major effect on LBNP or acceleration tolerance (ref. 137).

Body fluid and electrolyte changes caused by bed rest have shown similar changes in males and females (refs. 137,299,300). However, notable differences have occurred in greater total-protein increases in males (expected with plasma volume losses) and significantly greater increases in plasma fibrinogen (at rest and with stress (refs. 83,300). Blood hormonal responses (renin, aldosterone, cortisol, norepinephrine, epinephrine, and 17 OHCS) to 6-hr bed rest and water immersion have shown greater changes generally for males, except for urinary excretion of norepinephrine and 17 OHCS during LBNP (refs. 299,301).

In preparation for the Space Shuttle program, with plans to allow participation of older and sedentary subjects, men and women from 35-65 yr of age were studied for physiological changes after 10 days of strict bed rest (simulating 7-10 day Shuttle flights). Age did not appear to be a factor in cardiovascular deconditioning

following bed rest and, in fact, older individuals showed smaller post-bed-rest losses of LBNP and acceleration tolerances (refs. 114,261). In addition, older men lost only 8.4% of their $\dot{V}O_2$ max, while younger men showed a 9.3% reduction (ref. 112).

Comparison of work capacity in men and women, 45-55 yr (refs. 113,279), showed little reduction (-0.8%) in the men, and a small, but significant, 4.7% loss in the women. After bed rest, both the men and women were able to reach their maximal workloads, but the women had a shorter tolerance time than before bed rest, while the men showed no change in tolerance time. The larger decrease in muscle mass (lean body weight) in the women (-5.1%) compared with the men (-1.9%) may have contributed to the difference. Moreover, the efficiency of oxygen transport, transfer, and utilization by muscle tissue was slightly reduced in the women, but not in the men.

Animal Studies

Animals have not only preceded man in flight (ref. 32), they have also provided extensive information through ground-based studies of the physiological effects of weightlessness. Animals have been immobilized (whole body or limbs) for varying lengths of time, and have included observations in rabbits, rats, dogs, and monkeys. Although findings have varied by species in many cases, most subjects have exhibited the same physiological responses of body fluid shifts and orthostatic intolerance seen in humans following space flight, or ground-based simulations.

Data have been collected from more than 350 rabbits immobilized in tight-fitting cages over periods from 1-2 wk to 7-1/2 mo (refs. 302-305). Immobilization for 1-3 wk has resulted in severe generalized atherosclerotic disease affecting the heart and its peripheral tissues (refs. 3,304-307). Only two of 21 controls, fed a similar normal colony diet and living in standard vivarium cages, demonstrated findings of a similar nature, but these were of far less severity. After one month, biochemical changes in the myocardial and central nervous systems of immobilization showed a persistent 50% decrease of myocardial norepinephrine content (from 0.88 ±0.06 ug/g to 0.44 ±0.06 ug/g [wet tissue]) after the first 2 wk; hypothalamic norepinephrine content showed a similar 60% decrease (0.2 ±0.02 ug/g control to 0.08 ±0.016 ug/g) (refs. 147,302,308). Further, adrenal function and levels of plasma 11-oxycorticosteroids also significantly decreased two- to threefold. Electron micrographs after 12, 14, and 30 days of immobilization revealed mitochondrial changes and capillary morphology. Decrease in central nervous system catechol content was felt to indicate a primary loss of sympathetic nervous system control. This conclusion was supported by increases in thresholds for hypothalmic electro-stimulation which did not return to normal levels until 3 wk after immobilization.

Immobilized rats have also exhibited decreases in myocardial contractility and diminished cardiovascular response to hypoxic stress. Pulse rate increased from 358 ±4 bpm to 378 ±8 bpm (p < 0.05) after 2 wk of immobilization (ref. 269). Baranski and associates (refs. 147,309) noted an accelerated heart rate with stress

(swimming) for male Wistar rats immobilized for 6-7 mo. During such stress, both S-T segment depression and T-wave inversion occurred. Animals restrained for up to 100 days and studied by brief periods of aortic occlusion have revealed temporal decreases in myocardial contractile function (maximal pressure developed, PEP, dp/dt) (refs. 147,310). Electron microscopy of myocardial muscle showed changes similar to those found in rabbits, but of less severity and degree (refs. 311-314). Biochemical changes revealed evidence of decreased oxidative phosphorylation (refs. 147,315). Decreases of catecholamine content in specific brain stem areas have also occurred in immobilized rats (ref. 316).

Dogs immobilized for 2 wk in body casts have shown significant decreases in resting cardiac output and blood pressure (ref. 317). Other investigators, however, have not consistently found evidence of orthostatic intolerance or decrements in acceleration tolerance in dogs body-casted for a similar period of time (ref. 318). Krasnykh (ref. 153), in a 90-day study of 40 immobilized dogs, found significant decreases in heart silhouette areas using teleroentgenography. Decreases in end-diastolic areas were greater than end-systolic areas. Kymographic wave forms, representing contraction patterns, showed evidence of decreased myocardial function. Dogs immobilized for 6 mo have shown distinct postmortem evidence of a loss of skeletal and cardiac muscle mass and changes in microvascular structure of most tissues (refs. 319,320). The animals continued to show hind-limb small-vessel changes (hard and soft tissues) 1 mo after immobilization. Similar changes have been found 3 wk after immobilization in rats and 4-8 wk after in rabbits (ref. 147). Other investigators have also found that immobilized dogs demonstrate disorders in bone metabolism (refs. 317,321).

Recently an increasing number of immobilization studies have been conducted with nonhuman primates (refs. 223,322-330). These studies have been justified on the physiologic similarity of this animal model to humans and the fact that nonhuman primates, like humans, spend considerable time in an upright position. Following 14-18 days of horizontal immobilization (body cast from axilla to ankles) rhesus monkeys have demonstrated significant decrease in blood volume (12.7% and 19.2%, respectively) which is due primarily to losses in plasma volume (12.9% and 23.0%, respectively) (ref. 326). Red cell mass decreases also were present (12.4% and 11.4%, respectively). Response to 90° upright tilt demonstrated greater heart rate increases and blood pressures fall after casting (ref. 326). Acceleration ($+G_z$) tolerance was also significantly reduced in all animals (ref. 326). Peak tolerance fell 50% (+6 G_z to +3 G_z) after casting and time at +3 G_z fell 75%. Use of a G-suit (inflated abdominal air bladder, 50 mm Hg/g) significantly improved post-immobilization tolerance in all cases, but did not return values to control levels. Total body water (tritiated water) was found to decrease 18% over the course of 2 wk in a -6° head-down position, with 11% loss occurring during the first 7 days (ref. 328). These changes were accompanied by expected changes in plasma electrolytes and hematocrit. Similar findings have been reported in all of the above categories after human bed rest (refs. 3,64,66).

Use of nonhuman primate models has also allowed for direct biochemical and morphological study of body tissues which have shown significant change of cardiac

as well as central nervous system structures (refs. 91,324) and will be discussed in detail in the material that follows.

Findings from animal studies to date indicate that significant cardiovascular changes occur in all animal species with immobilization. Rabbits are the most severely affected by such changes and rats are the most resistant. Similarly, during animal flight studies, rats to date have shown minimal cardiovascular changes. The monkey appears to be the most promising animal model for simulating humans in future space flight and ground-based studies, not only because of its phylogenetic similarity to humans, but also because of exhibited parallel cardiovascular changes with immobilization. Verification of the validity of cardiovascular findings of immobilized animals to humans must await quantitative physiological measurements made in the space environment which are planned for future animal flight projects.

ROLE OF VARIOUS MECHANISMS

Fluid-Volume Changes

Whether with spaceflight, bed rest, or immersion there is a headward redistribution of blood volume accompanied by compensatory loss of water, potassium, and sodium, while hormonal mechanisms are activated to restore a sensed increased vascular volume to normal limits. As shown in figure 2, these shifts are accompanied by changes in ADH, aldosterone, plasma renin activity (PRA), and a probable release of an atrial natriuretic factor (ANF) (refs. 11,15,250,331-333). Based on extensive work using water immersion, it has long been felt that physiological changes are initiated by a stretch of central cardiac mechanoreceptors residing primarily in the atrial walls (refs. 12,102,250,331,334). The end result is an 8-10% loss of plasma volume, starting within the first few hours of immersion, or the first 24-48 hr of bed rest, as shown in figure 6, and continues more slowly thereafter. Early plasma volume losses during ground-based studies, with few exceptions, have been associated with a decrease in serum ADH, although urinary levels have been variable (refs. 128,335-337). Limited post-space-flight measurements have shown increases in both serum and urine ADH (refs. 56,78,335). These latter changes undoubtably reflect physiological reaction to a volume-depleted state and the stresses of reentry.

Recent work on human and nonhuman primates casts doubt on the acceptance of atrial stretch as the only explanation for observed changes. Diuresis has occurred in monkeys during immersion or fluid loading following vagotomy or cardiac denervation, which should have interrupted the main neural afferent pathways from cardiac mechanoreceptors (refs. 338-340). Similar findings have been found in dogs (refs. 341,342). In addition, a fall in plasma ADH has been documented with head-down tilt in subjects after heart or heart/lung transplantation, conditions where again afferent input to the central nervous system from cardiac stretch receptors has been interrupted, or significantly decreased (ref. 343). These findings point

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to reduced cardiopulmonary receptor sensitivity in monkeys and humans, and possibly greater reliance on high-pressure baroreceptor response for control of ADH and PRA. This is supported by work from a number of investigators who have demonstrated that nonhypotensive hemorrhaging, or a graded decrease in central blood volume, do not lead to increase in ADH or renin release until there is an actual fall in blood pressure (refs. 27,344-347). Additional evidence for high-pressure baroreceptor involvement under these conditions is provided by findings of changes in blood catecholamine levels (refs. 15,85,105,106,249,346,348,349) and efferent renal nerve activity (refs. 339,350-354). Plasma renin levels also decrease (refs. 342, 355-359). Finally, there may be still other factors operating. Davis and Dubois (ref. 341) found an occasional immersion diuresis in dogs despite cervical vagotomy. Such findings could be best explained by a hemodilution caused by an early intravascular shift of extravascular fluid and thus supports conclusions by a number of investigators (refs. 360-363) that there may be a volumetric, as well as osmotic, control of ADH. In addition, Kravik and associates (ref. 337) recently found that diuresis could be induced during head-out immersion without significant decreases in ADH. Findings in this latter case may rely upon direct central nervous system effects (including high-pressure baroreceptors), or on the release of a still to be identified diuretic factor. Such possibilities are further supported by findings of a fall in ADH levels in dehydrated subjects by just taking water into their mouths (ref. 364).

Data clearly points to the loss of plasma volume as a major contributor to the deconditioning process; yet, hemodynamic responses are clearly disproportionate relative to the magnitude as well as the duration of the induced hypovolemia (refs. 56,64,128,365,366). This is particularly the case for athletes in which altered exercise or orthostatic responses have persisted for weeks, and to months in some cases (refs. 154,210,212). Even in deconditioning studies showing a relationship between decreased plasma volume and decreased orthostatic tolerance, replacement of fluid losses with saline, bouillion, plasma, and blood transfusions has resulted in an inconsistent or only transient improvement of orthostatic tolerance (refs. 294,296,367-370). Anti-G suit inflation restores central blood volume following bed rest, but has not returned acceleration heart rates and blood pressures to presimulation levels (refs. 114,259,260,371). Clearly, factors other than plasma volume loss must also be implicated in these processes.

Conditioning programs have often produced higher plasma volumes (refs. 154, 282,283,372-375). Several studies have documented both a larger baseline plasma volume in athletic subjects, and a greater decrease in orthostatic tolerance (acceleration, tilt, or LBNP), which was directly related to the loss in plasma volume (refs. 114,296). On the other hand, some studies have not shown any significant correlation of plasma volume loss with decreased orthostatic tolerance (refs. 99, 115,241,296,297). Skipka and Schramm (ref. 87), during water immersion found smaller plasma volume and diuretic losses in trained versus untrained subjects; yet all the athletic subjects (10 of 11) either fainted or came near fainting after immersion, while only three of 11 untrained subjects did so. All features of fluid and electrolyte function showed lesser changes in the trained subjects.

To explain these findings, these investigators in subsequent immersion studies (ref. 376) measured urinary excretion of the norepinephrine break-down product vanilyl-mandilic acid (VMA). Vanilyl-mandilic acid increased slightly during immersion and doubled during orthostatic tilt immediately following immersion in nonathletes; VMA only slightly increased, if at all, under identical conditions in athletes. Since VMA excretion under these circumstances serves to gage sympathetic nervous system and adrenal responsiveness, it appears that these systems are less active in athletes and this helps to explain the poor orthostatic response observed in this group. Such results also point to the possibility that athletes may be more dependent on ADH for blood pressure control (refs. 377-379). Decreases in circulating blood volume would leave these individuals particularly vulnerable to syncope if attendant ADH levels were also suppressed (as occurs with water immersion and/or bed rest) in the face of the blunted sympathetic response capability discussed previously.

The plasma volume decreases regularly seen during bed rest would be expected to be directly associated with changes in either extracellular, intracellular fluid volume spaces, or both, because each equilibrates and comes into osmotic balance with the other. Extracellular volume, representing the sum of plasma volume and interstitial fluid (bromide space), has been measured in only a few bed-rest studies and the findings have been highly variable. During the first several weeks of bed rest some investigators have either found no decrease in extracellular fluid, despite a decrease in plasma volume (ref. 64); others a greater decrease than plasma volume (refs. 380,381); others equal decreases for both (refs. 80,121,298); or an actual increase in extracellular volume (ref. 144). These differences may also be explained by known difficulties in making accurate measurements of this fluid space. In contrast, most investigators have shown a tendency for a decrease in total body water (2-5%), but usually changes have not usually been highly significant (refs. 79,80,300,335,365,381,382). During bed rest, a small but regular decrease in body weight is observed, except in those studies in which it has been deliberately controlled by diet (increase in relative calories) to remain constant. Weight loss would be expected to correlate with loss of plasma volume except in these latter instances where fluid volume losses are usually replaced by increased adipose tissue. In several studies (refs. 79,80) in which total body water has decreased and extracellular fluid volume remained normal or unchanged, losses by necessity must come from displacement of intracellular fluid and can be explained only by a decrease in lean body mass, since adipose tissues contain no water. Post-bed-rest measurements have tended to support this position since lean body mass in the few instances in which it has been measured have shown decreases (80,276), yet several studies in older individuals have shown no change (refs. 112, 113,260,383).

Findings following both short- and long-term space flight, as well as bed rest, have shown rapid restoration of plasma volume losses after landing and/or reambulation (usually within 24-48 hr) (refs. 56,338). In longer bed-rest studies or flights, extracellular fluid losses are probably gradually restored, but a total body-water decrease undoubtably occurs because of known loss of muscle mass, particularly of the legs. Lastly, in a 120-day bed-rest study, Pak and associates

(ref. 384) detected a periodicity of diuresis. A negative water balance was present during the first 36 days, which ceased and actually became positive by the 53rd day (sodium was retained and aldosterone activated), and became negative again by the 83rd day (ADH suppressed). These changes were recently reconfirmed by Krotov and associates (refs. 385,386) and point to the dynamic nature of the neurohumoral alterations shown in figure 2.

Compensatory losses of sodium and potassium accompany the diuresis. Urinary sodium losses are marked and significant during the first several days of bed rest, potassium excretion becomes significant only toward the end of the first week and continues thereafter (refs. 128,150,338). These changes are attributed to altered secretion of aldosterone, the salt-retaining hormone of the adrenal cortex. Recent findings of a putative ANF in animals may also explain these changes, but measurements during human bed rest have not been accomplished to date. Serum aldosterone has been observed to decrease with immersion and bed rest, but urinary measurements have been more variable showing increases, slight decreases, or no change (refs. 87,144,233,387). Recently a number of investigators (refs. 175,388,389) have shown prompt and sustained decreases in ADH, PRA, and aldosterone over the first 8 hr of -6° head-down bed rest. PRA reached a nadir at 2 hr and returned to base-line by 24 hr. In contrast, aldosterone, which is now considered to be controlled to a great extent by PRA, did not reach its nadir until 4 hr and was still suppressed at the 24-hr measurement. The exact reasons for these changes are unknown and may represent the result of stimulation of low- and/or high-pressure barorecep-tors and associated altered renal hemodynamics. They may also be caused by release of an ANF. Volicier (ref. 390) found that PRA and plasma aldosterone levels were not significantly different from horizontal findings during the first 6 hr, but were significantly increased by the end of 24 hr at -5°. These results remain unex-plained in the light of recent findings.

In spite of the various changes in electrolyte excretion (particularly sodium and potassium), plasma concentrations of most electrolytes and hormones have shown little change or slight decreases (refs. 127,128,144,159,161,233,336,365,367, 391-393). Many changes with longer-term observations appear related to the known stresses of prolonged immobilization and losses of muscle mass and bone content (refs. 394-398).

Alterations in Cardiac Function

The headward fluid shift with bed rest and immersion creates changes in stroke volume and cardiac output (fig. 1). These changes occur in at least three stages. The first stage results immediately with a change from the upright to supine position, because of a significant headward fluid shift. The enlarged central circulating blood volume leads to an increase in both the ventricular filling pressure and the heart volume. These changes augment stroke volume and cardiac output, as governed by Starling's Law of the heart. A second hemodynamic stage occurs over the next 24-48 hr as low-pressure baro- and volume-receptors react to restore the detected central volume overload. A decrease in cardiac output toward

normal levels during this period is consistent with the ensuing diuresis and concommitant decrease in heart size and EDV. If inactivity and bed rest are continued for longer periods (weeks, months, or years), a third stage of adaptation occurs. During this phase, cardiac output and stroke volume continue to decrease and eventually stabilize at a new and significantly lower level as compared with pre-bed-rest values. This decrease in flow is consistent with the imposed prolonged inactivity, with a resultant decrease in oxygen demand, loss of skeletal muscle mass, decrease in circulating blood volume (loss of plasma and red cell volumes) and decrease in circulation to specific organs and muscle beds. Support for these possibilities were recently provided during human -15° head-down tilt which showed as much as 30-40% decrease in myocardial oxygen consumption over the course of a 7-day study (ref. 183). Coronary flow per se (measured by thermodilution) increased slightly for the first few days then gradually decreased until the fifth day after which it had stabilized (mean 26% decrease).

Resting cardiac output and stroke volume have remained normal (ref. 170) or usually decreased during bed rest (refs. 66,127,154,243), although a few investigators have found an increase (refs. 1,147,168,399). Inconsistencies reported in these hemodynamic findings may have resulted from employed methodologies, which have varied from measurements made at the time of cardiac catheterization using Fick or indicator dilution methods (refs. 127,144,154,170,400) to measurements using echocardiography (refs. 155,175,401); various external mechanical means, including apexcardiography (refs. 211,212,402), mechanocardiography (refs. 402-404), or vibrocardiography (refs. 197,404); and single breath CO_2, or acetylene rebreathing methodologies (refs. 91,405-408). Teleroentgenograms were also used by Krasnykh in several studies (refs. 153,321,409-411). These bed rest changes differ significantly from findings with water immersion in which a sustained increase in CVP and cardiac output occurs with no change or a decrease in heart rate (refs. 11,15,85, 90,92,412).

Krasnykh, in a 30-day (ref. 410) and then 100-day (ref. 411) bed rest study, noted significant 20% decreases in diastolic X-ray heart images and associated stroke volumes for 20 subjects. In the 30-day study, one group of controls was free to move about, but confined in a small chamber and another group performed supine exercise on a treadmill during bed rest. The group performing exercise during bed rest revealed slight and insignificant decreases in X-ray diastolic area and stroke volume. The confined control group exhibited a 10% reduction in heart diastolic size which correlated with previous plasma volume losses reported by Lamb and associates (refs. 213,214) using chair rest and Ioffee (ref. 215) using chair rest and chamber confinement. Such confined subjects have revealed an increased incidence of orthostatic intolerance, despite ability to stand up and move about each. In follow-ups for at least two subjects after bed rest, Krasnykh found that X-ray registered heart size and stroke volume did not completely return to pre-bed-rest levels, even after 60 days of recovery, despite a regular exercise program. These results parallel similar previous original findings reported by Saltin and associates for three athletically conditioned subjects (ref. 154), and more recent findings of post-space-flight effects reported by Bungo (ref. 60) (fig. 4). Delays in readaptation correlate with a delay in the return of other cardiovascular

parameters as well. Systolic time intervals did not return to control levels for 4 wk following the 84-day Skylab flight (ref. 210), or after 28 days of bed rest (refs. 211,212).

Although heart size increases significantly with water immersion and change to a supine body position, echocardiography (single crystal, M mode) has failed to demonstrate evidence of any additional significant increase in left ventricular EDV (compared with horizontal) during the first 24 hr of either horizontal or -5° or -6° head-down bed rest (refs. 27,175,413). Such findings also correlate with known decreases in plasma volume occurring during the first 24-48 hr of bed rest. These changes also parallel venous pressure measurements shown in figure 5. Various investigators have found that heart size may not necessarily increase in the head-down position. Avasthy and Wood (ref. 177), using lateral chest X-rays from intact dogs, showed that overall heart size failed to increase when the animals were acutely placed in the -90° head-down position. Wilkins and associates (ref. 414) also failed to show an increase in human heart size on lateral chest X-rays in a head-down position. Further, Rushmer (ref. 415) found canine left-ventricular dimensions to be maximal when horizontal (0°) compared with either +30° (head-up) or -30° (head-down) body positions. These findings may be due to multiple factors such as a shift of the heart and diaphragm within the chest, change in upper-body vascular compliance, to accommodate the significant headward shift of fluid, or possible shifts in the hydrostatic indifference point for the right-heart circulation (refs. 2,12). These latter mechanisms not only help explain a potential decrease in heart size at rest when head down, but similar otherwise puzzling decreases during foot-to-head ($-G_z$) acceleration originally reported by Jongbloed and Noyons (ref. 416). Nixon and associates (ref. 175) did report some increase in hourly echocardiographic left ventricular dimensions after several hours in a -5° head-down position. This occurred, however, when CVP had decreased and this finding remains unexplained.

Ground-based studies have convincingly shown changes in myocardial morphology and biochemistry across animal species with immobilization (refs. 147,310, 312,313). Rats immobilized for durations of up to 120 days have shown significant decreases in both body and heart weight with the greatest losses occurring in skeletal muscles (refs. 147,311,417). After 20 days of immobilization, heart mass showed a significant 23% decrease (64 ±25 mgm to 493 ±19 mgm), while general body mass decreased 54% (147 ±6.6 g to 79 ±2.5 g); longer-term studies have shown relatively greater losses for body mass (ref. 147). Heart mass loss during a 100-day immobilization was (20% for the left ventricle and 22% for the right ventricle) (ref. 147). At 100 days ventricular dry weight, analyzed to rule out loss of water content by fluid-electrolyte changes, decreased by 24.3% for the left ventricle and 26% for the right ventricle. These decreases were further confirmed by study of protein turnover rates. Left-ventricular incorporation of 35-sulfur labeled methionine tended to decrease over the first 2-5 days of immobilization, but showed significant decreases of 27%, 39%, and 60% at 15, 30, and 100 days, respectively (ref. 147). By 30 days, there was a significant 9% decrease in total myocardial protein, and by 100 days, the loss had doubled to 18%. Using histopathological examinations, Bourne and associates found progressive degenerative changes in the

myocardium of monkeys immobilized from 2-6 mo; these changes were significant after 3 mo of immobilization (refs. 324,325). Early findings have also been present in recent shorter-term head-down studies (refs. 329,418). In general, changes have been similar to those found in rabbits and, to a lesser extent in rats; manifesting as an accumulation of fat droplets, followed by actual muscle fiber degeneration with subsequent round-cell infiltration, and an increase in connective tissue content, as the period of immobilization lengthened. The myocardium from immobilized monkeys demonstrated elevated levels of hydroxyproline in both the right (2.5 mgm/gm [wet tissue] to 4.67 mgm/gm) and left (1.34 mgm/gm [wet tissue] to 1.75 mgm/gm) ventricles, supporting electron and light microscope findings of an increase in fibrous tissue. Lysosomal enzyme activity (both free and total) was also elevated in both ventricles, suggesting an increase in net accumulation of lysosomes, as well as increased degradation. Reduced protein synthesis was indicated by a decrease in ribonucleic acid (2.40 mgm/gm [wet tissue] to 1.58 mgm/gm for the right ventricle; 2.30 mgm/gm to 2.01 mgm/gm for the left). Sarcoplasmic reticulum from animals casted 30 days showed greater than 50% reductions in rates of Ca^{++} binding and uptake compared to controls, suggesting a state of reduced myocardial contractility (ref. 419). A decrease in magnesium-stimulated ATPase activity of the right ventricle was also observed as additional indirect evidence of such a latter state.

Postflight electron microscopy of rats flown aboard the Russian Cosmos series have shown reduced mitochondrial numbers and relative volume of smooth endoplasmic reticulum (refs. 37,309). Myocardial myosin ATPase activity was also reduced and norepinephrine content increased. These morphologic and biochemical changes in flight and immobilized animals appear best explained by a reduction in coronary blood flow and load associated with a hypodynamic state (ref. 417). Although coronary flow per se has not yet been measured in animals under real or simulated flight conditions, expected significant reductions have occurred for man during head-down (-15°) bed rest (ref. 183).

Findings are further supported by slight, but nonsignificant, reductions in echocardiographically derived left-ventricular mass in the three-man 84-day Skylab crew (ref. 61) and similar slight loss of posterior wall thickness for Shuttle crews (ref. 60). Similar findings have occurred for Soviet crews (refs. 8,75). Heart-body ratios have invariably been larger in wild animals as compared with domestic forms of the same animal species (ref. 147). In addition, vigorous exercise has regularly resulted in increased cardiac size and mass (refs. 283,373,420-425), particularly in young animals and younger adults. In these cases exercise hypertrophy is associated with myocardial fiber hyperplasia, fiber hypertrophy, or both. More importantly, the augmented cardiac dimensions and mass rapidly disappear with detraining (refs. 372,421) although some controversy still exists regarding the exact extent and nature of each process (refs. 422,426). It would be expected that the reverse might take place under hypogravic and hypodynamic conditions. However, there is no data to date in the literature on response of cardiac myocyte size to chronically reduced load. Further studies need to focus upon whether the reduction in heart size following space flight or immobilization is due to a general reduction in myocyte diameter, a localized atrophic process or a reduction in the cardiac collagen substructure.

The relationship of ventricular mass to volume may be critical for triggering vasodepressor syncope during orthostatic stress, possibly mediated by the Bezold-Jarish reflex. Unmyelinated vagal afferent receptors, some of which originate in the ventricles, can be excited by certain chemical stimuli or metabolites and by increased intramyocardial pressure caused by contractions in a ventricle with a markedly decreased EDV or end-systolic volume caused by decreased venous return. During LBNP stress in 25-34 yr old women who were not endurance-trained athletes, the onset of vasodepressor syncope was associated with a critical level of ventricular EDV (approximately 30 ml) (ref. 137). Other studies have suggested the importance of a critical volume in other nonathletic subjects who experience syncope during orthostatic stress. Epstein and associates (ref. 427) suggested that vasovagal syncope was facilitated by increased sympathetic activity during ortho-static stress loading to an increased ejection fraction and tachycardia which further lowered ventricular volumes and produced a functional outflow gradient with high left-ventricular wall tension, and prolonged isometric contraction time against falling systemic pressure. The threshold volume for a given individual probably varies with body size and cardiac dimensions, as well as the underlying balance of sympathetic and parasympathetic activity at the time of stress. Aerobically trained athletes may have a higher critical volume than sedentary subjects because they start from a higher point. During orthostatic stress by a given decrease in EDV may lead to a greater systolic mechanoreceptor distortion because of the athlete's greater intrinsic myocardial contractility and/or ventricular hypertrophy. These mechanisms may compensate for the lower position on the Starling curve caused by the fall in EDV so that intraventricular wall tension may be relatively higher, stimu-late a greater number of fibers (due to greater cross-sectional wall area) than in the sedentary subject, or excite mechanoreceptors to a greater degree for a propor-tionately similar fall in EDV. For the athlete, the ratio of filling volume to ventricular mass, rather than absolute EDV may be critical during orthostatic stress in setting the point of vasodepressor syncope. In Skylab 4, the only echocardio-graphic information obtained just prior to syncope was from the pilot during his immediate postflight LBNP test. Preflight, the pilot was the most aerobically conditioned astronaut of this crew with a VO_2 max of 54.2 ml/kg·min. His resting EDV was 175 ml, ventricular mass estimated at 280 g and his EDV dropped to 125 ml during preflight peak LBNP stress without syncope. Postflight, his ventricular mass was estimated at 240 g, his EDV decreased to 70 ml at peak LBNP stress, and the LBNP exposure was terminated early because of impending vasodepressor syncope. In con-trast, the sedentary commander with lower ventricular mass and filling volumes preflight, and EDV and systolic volume during splash down LBNP which were similar to those of the pilot, tolerated the full postflight LBNP without problems. However, it is impossible to generalize from such a small amount of data.

Changes in Venous Compliance or Capacity

Increased venous pooling during tilt or LBNP has been postulated to be an important contributor to loss of tolerance following bed rest. However, findings in general have failed to confirm this hypothesis (refs. 68,428). During in-flight LBNP tests in the Skylab missions, significant increases in relative leg volume

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displacement were observed (refs. 6,235). Although indicating greater leg pooling, the methods used to determine leg volume changes (either capacitance leg band (refs. 6,429) or Whitney strain gage (refs. 245,246,430) have made quantitative interpretation difficult. If the initial dimensions should decrease significantly for any reason (as they do during space flight, because of cephalad shift of blood and muscle atrophy from disuse), the displacement of the same amount of blood into the leg by tilt, or LBNP, would register an apparent increased percentage change in leg volume, even though the absolute volume of displacement to the limb would have been unchanged. In addition, athletic individuals would be expected to lose signif- icant amounts of leg muscle mass with weightlessness-induced disuse. When findings are corrected for these differences, the importance of changes to space-flight- induced venous volume with LBNP is markedly decreased. To overcome these instrumen- tation limitations, Musgrave and associates (ref. 238) developed a water plethysmo- graph for use during LBNP. With their technique, subjects were found to exhibit similar, or smaller increases in leg volume following bed rest (refs. 238,431). These findings were confirmed in a 2-wk study using females (ref. 137). All female subjects showed symptoms of syncope following bed rest. Water plethysmography of both legs during LBNP failed to induce greater increases in leg volume following bed rest. In fact, 10 of 12 subjects showed decreases (ref. 137). Finally, these findings have been supported by other investigators during tilt testing using Whitney strain gages (ref. 245,430) and more recently by impedance plethysmography during LBNP (refs. 18-20,116,259). In addition, Montgomery and associates (ref. 20), using these latter methods in both males and females, documented that increased leg blood pooling did not occur after bed rest during acceleration expo- sures of up to +3 G_z. In fact, decreases in pooling of up to 10-12% were registered as had been the case with LBNP after bed rest. Bed-rest-induced plasma volume decreases may have been a contributing factor in all of the above findings (refs. 115,161,277,300). These results suggest that a significant loss of blood volume to the legs may not be a primary, or even contributory, factor to syncope. Epstein and associates (ref. 427) reached similar conclusions concerning venous pooling while studying vasovagal syncope in otherwise normal subjects. Several groups (refs. 432,433) using forearm venous occlusion plethysmography have found normal or decreased venous distensility after bed rest. These findings undoubtably relate to bed-rest-induced hypovolemia and triggering of low-pressure receptors (refs. 102,249,253,255). Schmid and associates (ref. 433) showed that venous reac- tions to infused tyramine (releases norepinephrine from peripheral sympathetic nerves) were attenuated after 2 wk of bed rest, while reactions to norepinephrine remained unchanged. These findings are best explained by a decreased ability to release norepinephrine or a decrease in synthesis. Neither of these possibilities have been adequately studied to date, although Chobanian and associates (ref. 233) showed that plasma norepinephrine turnover rates were not seriously altered during 3 wk of bed rest.

Considerable attention has also been given to extremity venous pooling as a countermeasure. It was postulated that this approach would improve venomotor tone and decrease CVP and volume. Techniques have ranged from the use of periodically inflated cuffs (refs. 237,247) to the use of reverse gradient garments (refs. 161,278). Cuffs have been placed on the legs alone (refs. 141,237,434,435)

or on both legs and arms (refs. 237,247,436). Early studies of Graveline (ref. 436) and Vogt and Johnson (ref. 237) resulted in favorable findings, but subsequent configurations have neither prevented plasma volume losses nor offset loss of tolerance to LBNP or tilt (refs. 141,237,247,434,437). The use of cuffs curing the Gemini VI and Gemini VII flights failed to alleviate postflight deconditioning in any of the crew members (ref. 438). A reverse gradient garment has been used during bed rest to simulate venous volume fluctuations in the extremities, as occurs during normal daily activity. This countermeasure, however, failed to prevent post-bed rest LBNP changes, or to improve acceleration tolerance to +2.5 and +3.0 G_z (ref. 161). Resultant venous pooling by the garment did improve post-bed-rest loss of exercise capacity (ref. 278). Finally, leg dangling 2-hr each day during a 60 day, -4° head-down bed-rest study failed to improve orthostatic tolerance (ref. 464).

Resting leg volume changes have not been greater in athletes versus nonathletes after bed rest (refs. 432,439). Yet, aerobic training, similar to heat acclimatization does result in increased plasma volume and enhanced cutaneous vasodilation and sweating for a given level of work, and with less of an increase in core (rectal) temperatures than in sedentary people (refs. 297,366,440). Evidence linking the cutaneous vasoconstriction point to 50% of maximal stress (VO_2 max) during exercise supports the idea that athletes may be slower to vasoconstrict than untrained individuals (refs. 440,441). Results from a study of LBNP tolerance in five runners and five nonathletes showed 42% lower tolerance in runners than nonrunners (ref. 297). During LBNP rectal temperatures of runners were consistently lower than sedentary subjects, and heart rates were correlated with rectal temperatures. Sedentary subjects working in the heat (50°C) had higher rectal temperatures and a 54% better LBNP tolerance than runners who had greater leg compliances. Furthermore, runners had more residual extravascular leg pooling (edema) following release of LBNP, suggesting higher transudation from capillaries compared to the sedentary group and is consistent with the finding of higher capillary density in trained muscles (ref. 282).

Impairment of Cardiovascular Reflex Control

In-flight resting heart rates have been variable in U.S. astronauts (ref. 45), but consistently higher in almost all bed-rest studies and in many Soviet cosmonauts (refs. 7,8,10,54,244). Significant decreases in resting EDV and stroke volume found after flight and bed rest may explain such findings (refs. 3,66). Plasma volume losses have been a consistent finding postflight and in most simulation studies as well. Resting catecholamine levels have not changed significantly (refs. 85, 233,349) but increased levels of resting PRA (refs. 144,241,367,388) following bed rest have been taken as an indication of increased B-adrenergic activity. It is postulated that the higher resting PRA levels result from decreased cardiac filling volumes caused by reflex triggering of sympathetic responses from low-pressure cardiopulmonary mechanoreceptors, but high levels of PRA have also been found in subjects whose central blood volume remained unchanged (ref. 233). Post-bed-rest infusion isoproterenol has been shown to significantly increase resting PRA over

that of pre-bed-rest infusion, suggesting heightened post-bed-rest B-adrenergic sensitivity (ref. 144). Thus, B-adrenergic activity in the resting state appears to be as high or higher following bed-rest simulation of weightlessness. However, the response of resting heart rate, cardiac output, mean arterial pressure and systemic vascular resistance to infused isuprel was unchanged after bed rest in at least one study (ref. 144). The elevation of resting mean arterial pressure to infused nore-pinephrine (graded dosages ranging from 0.005-0.160 ug/kg/min) and angiotensin II (0.5-16.0 ug/kg/min) was unchanged after 2-3 wk of bed rest in a group of six healthy men, suggesting no change in resting alpha-adrenergic responsiveness follow-ing bed rest (ref. 233). However, weightlessness simulation studies in primates have produced a lower blood pressure response to intravenous injections of norepine-phrine and phenylephrine (refs. 323,330). Bolus injections of phenylephrine (4.0 ug/kg) and norepinephrine (2.0 ug/kg) before and after immobilization (casting) using the method of Smyth and associates (ref. 442) at 2 wk of casting, which resulted in only 40% and 64%, respectively, of heart rate slowing, and 68% and 63% of diastolic blood pressure elevation; at 4 wk such changes were 43% and 23% of heart rate slowing and 68% and 73% for diastolic pressure rise. Vascular smooth-muscle responses to nitroprusside (2.0 ug/kgm) showed no evidence of change. Heart rate-blood pressure slope (R-R interval response) was significantly reduced within 7 days of horizontal immobilization (4 ug/kg bolus injection of phenylephrine) with changes remaining attenuated throughout 28 days of study (ref. 323). Increase in beta-adrenergic activity as a cause for the higher heart rates was ruled out by propranolol blockade (1.0 mgm/kgm). These changes may have been due to the altered (decreased) central blood volume known to occur in these cases (ref. 326) because baroreceptor reflex control is known to change with interventions which increase central blood volume experimentally (refs. 443-445) or in human subjects with con-gestive heart failure (refs. 357,446). Furthermore, long-term immobilization may induce changes in central neural pathways. Changes at the electron microscopic level have been found in primate hypothalamus and hypophysic after head-down immobi-lization (ref. 322). Healy and associates (ref. 447) have shown that central mona-mine depletions with 6-hydroxydopamine alters cardiovascular regulation. Immobili-zation stress in rats have been shown to reduce monoamine content of hypothalamic and brain stem nuclei (refs. 316,448); the central serotonergic neuronal system may also be involved (ref. 449). Similar changes have been found in rats after space flight (ref. 450). Changes in peripheral vascular components are also possible, but unlikely, based on the results of Chobanian and associates (ref. 233), which demon-strated unaltered pressor responses to epinephrine and angiotensin infusion as well as vasoconstrictor responses to cold pressor tests after bed rest. However, adreno receptor desensitization has been reported with immobilization or with repeated injections of sympathomimetric amines (ref. 451).

Orthostatic stress following weightlessness or bed rest simulation has usually produced increased heart rates, plasma catecholamine and PRA levels, and systemic vascular resistance (refs. 144,233,241). However, subjects who developed vasovagal syncope during post-bed-rest testing have been characterized by lower PRA responses and lower plasma norepinephrine levels (ref. 241). Hartley and associates (ref. 452) found lower baseline and exercise VMA excretion levels in highly condi-tioned athletes, a finding which primarily reflects decreased metabolism of

norepinephrine, and may indicate lower circulating norepinephrine levels following athletic conditioning. In addition, Skipka and associates (refs. 87,376) found lower VMA excretion in subjects with poor tilt tolerance following immersion-induced decreases in plasma volume. Tonic vagal input has been implicated in reflex inhibition of renin release (ref. 453), an effect which may be accentuated in athletes with high vagal tone. This mechanism, however, remains controversial. Suppression of renin was found prior to orthostatic testing and vasovagal syncope in pre-bed-rest subjects who later manifested very low orthostatic tolerance to LBNP (ref. 241). The association of high athletic-conditioning levels with low PRA responsiveness to LBNP in that study needs to be further investigated.

Tachycardia (increased B-1 adrenergic activity) and peripheral vasodilation (increased B-2 adrenergic activity) have been clearly manifest in all subjects during orthostatic stress after bed rest even in subjects with early onset of vasovagal syncope. The importance of these beta-adrenergic mechanisms (excluding renin release) was demonstrated by propranolol infusions by Melada and associates (ref. 144). Propranolol (0.15 to 0.2 mg/kg initially followed by 0.04 mg/kg every 20 min) suppressed PRA but, more importantly, prevented the fall in blood pressure and presyncopal symptoms at the end of the tilt stress. Cardiac catheterization data revealed that the increase in systemic vascular resistance (B-2 blockage or peripheral vasodilation) was primarily responsible for blood pressure maintenance. Heart rate was also significantly lower at the end of the tilt stress and this may have allowed for greater ventricular filling and less distortion of ventricular mechanoreceptors which have been implicated in vasovagal syncope. These benefits of IV propranolol following bed rest have recently been reconfirmed by Sandler and associates (ref. 240) on a group of middle-aged subjects. Other studies on normal nondeconditioned subjects have demonstrated a beneficial effect of propralolol on systemic vascular resistance during upright tilt (ref. 454), but not to LBNP or +3 G_z acceleration (refs. 455,456).

It is postulated that athletes exposed to weightlessness simulation have a condition of high vagal tone in the presence of increased B-adrenergic activity and possibly decreased peripheral alpha-adrenergic effectiveness. This situation leads to decreased orthostatic or acceleration tolerance caused by concomitant peripheral vasodilation, increased leg vessel compliance, and blood pooling (refs. 294, 296,297). This situation may be exacerbated by a general increase in leg compliance reported to occur during weightlessness (refs. 62,235,291). Furthermore, the presence of increased cardiac sympathetic activity has been linked to arrhythmias in athletes with augmented vagotonia and nonathletes following exercise training (refs. 357,457). An increase of sympathetic activity may accentuate vagal cardio-inhibitory effects producing early vasovagal syncope during orthostatic stress, or decreased contractility and decreased sinus and/or AV node conduction. This "accentuated antagonism" phenomenon for athletes may explain the often observed inappropriately slow heart rate response for a given stress, with a greater tendency to develop arrhythmias. Many astronauts and cosmonauts have demonstrated occasional episodes of atrial or ventricular arrhythmias during flight or EVA. Arrhythmias have occurred to degrees slightly greater than could be predicted from ground-based examinations and could possibly be due to the mechanisms described.

The question of lower alpha-adrenergic activity and its relationship to reduced orthostatic tolerance in athletes following weightlessness simulation requires further investigation. Recently a markedly reduced plasma norepinephrine response to standing was shown in subjects who fainted after bed rest (ref. 241). Of interest are findings in horizontally casted primates given bolus injections of norepinephrine and the direct-acting vasoconstrictor phenylephrine which demonstrated reduced alpha-adrenergic responsiveness, possibly a result of decreased alpha-receptor function peripherally, or from the presence of already highly constricted vessels (refs. 323,327,330). All animals had higher diastolic pressures following weightlessness simulation, which supports the latter possibility. It is possible that greater resting vasoconstriction would be necessary to compensate for the significant 20% loss in plasma volume induced during the study. The importance of an effective norepinephrine response to acute postural stress has been previously documented (refs. 104,181,233,458,459).

Heart rate responses to submaximal doses of atropine have been used to quantitate the degree of vagal tone and to distinguish nonathletes from athletes. Maximal doses of atropine were less sensitive, provoking a similar tachycardia in both conditioned and unconditioned subjects. Stegemann and associates (ref. 99) administered two tablets (0.25 mg) of belladona to four endurance-trained athletes prior to the end of water immersion deconditioning. To reduce any psychological effects, the subjects were made unaware of the medication, which was dissolved in grapefruit juice. After atropine, all trained subjects were able to tolerate the full 10 min of tilt in which the previous tilt tolerance averaged only 6 min. Maximal doses of atropine (2 mg) given intravenously either 10 min prior to LBNP or at the onset of vasodepressor syncope have been shown to improve LBNP response (delayed the onset of syncope and prolonged LBNP tolerance time) in four out of six subjects (ref. 460). Once vasodepressor syncope began, late treatment caused tachycardia, but did not reverse low blood pressures. Only two subjects were able to tolerate the post-atropine vasodepressor state for the allotted 4 min interval without loss of consciousness. Chae and Jun (ref. 461) reported on the effects of submaximal doses of atropine (0.01 mg/kg) in anesthetized untrained dogs exposed to postural stress. During 5 min of 90° upright tilt, atropine caused slightly elevated heart rates, significantly elevated mean blood pressures and elevated CVPs as compared to tilt responses with placebo. It was postulated that atropine caused an improved orthostatic tolerance by blocking cholinergic vasovagal reflexes, and by blocking the cholinergic sympathetic vasodilator nerves in skeletal muscles, hence preventing the stress-induced relaxation of peripheral vessels in the gravity-dependent region. The latter mechanism may have accounted for the lower decrease in venous return and CVP during upright tilting after atropine.

COUNTERMEASURES

A variety of countermeasures have been developed and tested to offset the effects of weightlessness, but none have yet to be totally satisfactory.

The use of exercise (both isometric and isotonic (refs. 285,395,462) has already been discussed and has received extensive study and use both in spaceflight (refs. 43,52,53,67,463) and bed rest (refs. 2,202,203,284,394,434,464-467). The use of heavy exercise and physical conditioning is postulated on their ability to increase intravascular volumes and improve general skeletal muscle strength and tone. Although such effects occur during bed rest, various regimens have failed to prevent post-bed-rest orthostatic intolerance (refs. 247,394,395,464) and loss of acceleration tolerance (ref. 285). Bungee cord exercises (mainly isometric) were used during the 8- and 14-day Gemini missions (ref. 4) and during bed rest (refs. 141,237) but did not provide protection in either case. During the longer Skylab and Soyuz missions, crewmen claimed that the heavy in-flight exercise regimens gave them a sense of well-being, but the regimens did not prevent postflight orthostatic intolerance (ref. 6). Further studies are still needed to determine the most optimal exercise regimes during flight, and whether or not it shortens the readaptation period following flight.

During spaceflight, cosmonauts have been required to wear load-suits daily to provide Earth-like resistances to movement during weightlessness. These suits, combined with heavy exercise regimens, have resulted in subjective improvements. But orthostatic intolerance has still occurred both during and after flight (refs. 5,6,54,55,244) and is shown in figure 4, in which heart rate responses in cosmonauts postflight are compared to post-bed-rest findings.

Lower-body negative pressure has offered some promise as a countermeasure because it has improved plasma volume and orthostatic tolerance during bed rest when applied for 4-6 hr/day (refs. 201,203,243,246,370,395,468,469). Such use is impractical for space flights because of the long periods of treatment required to be effective. Soviet investigators have developed an LBNP suit (Chibis) capable of use while in space (ref. 71). The suit consists of pleated trousers held in place by suspenders and connectable to a vacuum source. The suit it is used routinely during the last week of space flight and in conjunction with ingestion of a saline solution (1 liter) just prior to reentry (refs. 7,8,55). This combination has been shown to improve plasma volume loss and orthostatic intolerance in ground-based studies (refs. 206,244,336). Studies in the U.S. have shown similar results (refs. 247, 370,468). Subjects in these latter studies were treated with -30 mm Hg LBNP for 4 hr/day and ingested 1000 ml of beef bouillon containing 154 mEq of sodium. Such regimens, however, have not prevented postflight problems in cosmonauts and astronauts, since orthostatic intolerance has continued to be a consistent and regular finding. Similarly, and as already discussed, induced venous pooling whether by tourniquet, cuffs, leotards, or specially designed reverse gradient garments (RGGs) have failed to provide significant protection for loss of orthostatic tolerance (refs. 141,195,236,381). However, venous pooling did provide some protection against loss of exercise capacity in one study (ref. 278).

Periodic centrifugation has also been used to readapt the cardiovascular system to orthostatic stress following bed rest. White and associates (ref. 470) reported that four daily rides (7.5 min) on a short-radius (7-ft) centrifuge prevented orthostatic syncope after 10 days of bed rest. But the procedure failed to offset other

cardiovascular changes, such as loss of weight, plasma volume and red cell mass. Soviet investigators have reported similar findings (refs. 29,471-474). However, this countermeasure does not appear to be practical for spaceflight even if efficacious because of the cost, weight, power, and volume requirements of onboard installations. Several innovative techniques that do not require a centrifuge to provide acceleration forces have also been tested during bed rest. Periodic bouncing exercises on a railed bed between two trampolines to induce $+G_z$ along the long axis of the body did not prevent orthostatic intolerance after bed rest (ref. 475). Battacharya and associates (ref. 476) induced a programmed level of acceleration by restraining subjects horizontally on a mechanically driven table to receive 20 min of intermittent $+G_z$ acceleration along the spine. Acceleration profiles were similar to those observed during upright jumping on a trampoline or hard surface. Repetition rate of imposed forces was 1 Hz, and peak table acceleration was $+1.5$ G_z. Findings indicated that post-bed-rest syncope and increased heart rate with 70° passive tilt could be prevented or ameliorated by this technique. Dietrich and associates (ref. 120) also demonstrated benefits (cardiovascular and musculoskeletal) from an oscillating bed.

The most effective countermeasure found to date for preventing or reducing postflight or bed-rest-induced orthostatic intolerance has been a counter-pressure garment (anti-G suit) or leotard (refs. 13,247,248,467). Miller and associates (refs. 129,248) successfully protected subjects in this manner in bed rest studies lasting 2-4 wk. G-suits have also been effective in preventing orthostatic intolerance following water immersion (ref. 83). The suits provide external pressure which helps to prevent excessive blood pooling and fluid loss to the lower body and abdomen in the standing position (refs. 227,265). This technique has prevented fainting in individuals suffering from postural hypotension resulting from autonomic insufficiency (ref. 181). A number of additional studies have demonstrated the effectiveness of these suits in reversing post-bed-rest physiological changes in older men and women (refs. 114,242,261).

Water cooling of the lower parts of the body by 10°, administered through specially designed garments has been shown to improve LBNP tolerance (refs. 477,478). The decrease in mean skin temperature increased resting stroke volume by 11% and during LBNP at -50 mm Hg by 35%. Additional benefits were lower heart rates (-8 bpm), higher blood pressure (+8 mm Hg), and increased muscle tone, as manifested by a significant increase in oxygen uptake (+84 ml/min). Leg cooling has also been shown to improve $+G_z$ tolerance (ref. 479). Although this technique is promising, it has not yet been used during space flight, or with bed-rested subjects.

Soviet investigators have suggested that electrostimulation of muscles may be useful for avoiding bone and muscle deconditioning with immobilization (refs. 164, 205,209,311,480,481). Methods for electrostimulation of the lower portions of the body have varied considerably with regard to the number of electrodes used (10-20), amount of current and duration of use (from 15 min to several hours a day). Most often a portable, multichannel electrostimulator has been used. The technique has been applied alone or in conjunction with other methods such as physical training.

Physiological results from the use of such methodology during a 182-day bed rest study are shown in figure 7. Heart rate results during 75° tilt indicate that a deconditioning response is still present. Marked benefit, however, was present in maximal exercise testing. Exercise capacity remained intact in the treated group, while dropping by about 40% in the untreated subjects (refs. 76,206).

The use of most drugs as countermeasures has produced inconclusive results. The daily administration of 2 mg of 9-fluorohydrocortisone given periodically over the course of bed-rest studies of 6, 43, 53, and 74 days returned plasma volume to normal, but did not prevent orthostatic intolerance (refs. 127,482,483). Doses of 0.2 mg of the drug given daily in a 14-day bed-rest study (ref. 127) and 0.4 mg given daily in a 10-day study (refs. 127,482) had identical effects. The drug caused nausea in some subjects and did not prevent orthostatic intolerance (ref. 127). The administration of pitressin during water-immersion and bed-rest studies prevented diuresis and improved plasma volume, but did not prevent orthostatic intolerance (refs. 83,247,484,485). Soviet investigators have also used a variety of other pharmacologic agents including adrenal steroids (deoxycorticosterone) (ref. 485), central nervous system stimulants (amphetamine, caffeine, and strychnine) (refs. 435,486) and androgens (nerobol) (refs. 485,487) and scopalamine (alone or in combination) (ref. 486). These agents have had only partial and incomplete restorative effects on cardiovascular and fluid-electrolyte changes and muscle degeneration. Soviet investigators have also used the calcium blocking agent (isoptin) with limited success (refs. 488,489).

As already discussed, propranolol has provided some benefit during tilting both before (ref. 454) and after bed rest (refs. 144,240), most likely by a blockade of beta-2 mediated vasodilation or a release of epinephrine. These findings stand in contrast to results reported by Bjurstedt who found no benefit from propranolol during LBNP testing or exposure to $+G_z$ (refs. 455,456). Recently, clonidine (a centrally acting alpha nervous system stimulator) has been found to improve orthostatic tolerance in subjects exposed to -6° head-down bed rest (refs. 490-494). Soviet investigators (refs. 495-497) have used a similar psychoanaleptic sydnocarb with positive effects alone or in combination with beta blockers or dihydroergotamine (DHE). Dihydroergotamine has been used because of its known ability to induce peripheral venoconstriction and has been shown to have beneficial effects in improving acceleration tolerance (ref. 498). Side effects (headache, nausea), as with 9-alpha fluorohydrocosterone have limited DHE clinical use. Bonde-Peterson and associates (ref. 499) have also reported on the use of captopril, an angiotensin convertine enzyme inhibitor, during LBNP. Hemodynamic responses worsened, pointing to an important role of the renin-angiotensin system for blood pressure control under these conditions.

Finally, since many of the physiological responses to hypoxia are the reverse of those seen with weightlessness, investigators have exposed various subjects in chambers to altitudes of up to 10,000-20,000 ft (refs. 500-502). The resultant mild hypoxia prevented the loss of red blood cell mass, but did not significantly alter orthostatic intolerance.

SUMMARY

Physiological findings from space flight and ground-based studies have demonstrated that cardiovascular responses to weightlessness and inactivity on Earth are similar. The most striking and well-documented findings are related to the loss of orthostatic tolerance and changes in fluid and electrolyte balance in both cases. The basic causes underlying these observations are related to the withdrawal of normal gravity action along the long column of the body with attendant headward shift of blood and tissue fluid and a decrease in metabolic demand caused by inactivity. Gauer (refs. 12,15) originally demonstrated that these central volume shifts trigger intrathoracic low-pressure mechanoreceptors to alter renal handling of water and electrolytes by inhibiting ADH secretion and by decreasing production of aldosterone. Recent work casts doubt in these shifts as the sole explanation and points to involvement by high-pressure receptors, ANF and the central nervous system. Two areas that need further intensive study are: 1) the metabolism of neurotransmitter substances and their release from nerve endings, and 2) the manner and nature of loss of skeletal and cardiac muscle mass. Significant information concerning the manner and pattern of cardiovascular adaptation has been provided by extensive animal ground-based studies. Suitability of results to man and their simulation of weightlessness must await definitive studies during flight, which are currently being planned by both U.S. and Soviet investigators. To date, rabbits have been found to be most sensitive to cardiovascular change during ground-based simulation studies, rats being the most resistant. Hemodynamic changes in restrained primates have closely paralleled findings in bed-rested humans and have clearly pointed to involvement of the central nervous system as well as peripheral control mechanisms. The inability to use invasive measurements on humans and lack of adequate countermeasures to postflight or bed-rest cardiovascular deconditioning has resulted in the very large number of bed-rest studies conducted to date.

In recent years, both U.S. and Soviet investigators have concentrated on bed rest studies by placing subjects in the head-down position. This approach has resulted from subjective responses of cosmonauts that the head-down position more nearly duplicated the space flight effects of head fullness and awareness and because this position appears to produce cardiovascular results more rapidly. However, to date, the effectiveness, accuracy, and reproducibility of findings with the head-down versus the horizontal technique have not been confirmed. Consequently, many more studies will be needed to compare the two. Such studies must use methods and measurements that can be verified by in-flight findings. Since older and less physically fit individuals will be flying in the future, studies also need be directed at determining whether exposure to weightlessness will accelerate or ameliorate cardiovascular disease. To date, bed-rest studies in older males and females have failed to demonstrate diminished capability. Future emphasis must not only include studies to determine the body's adaptive mechanisms, but also data on slowly developing effects that could alter the ability of humans to remain in space for the very long periods (1 yr or more) planned for the future. The physical condition of all returning space crews and passengers must continue to be carefully and thoroughly evaluated to obtain additional important data. The task has been

difficult at first because only a limited number of individuals (and all of them in prime physical condition) have flown in space, and only a few for long periods. Data will become more readily available, however, as the number and durations of flights increase. This information must be supplemented by carefully planned and executed animal flight experiments.

The development of countermeasures to the effects of weightlessness and ground-based inactivity is a second critical area where research is needed not only for space flight, but also for clinical applications on Earth. To date, no entirely reliable or effective countermeasure has been determined. Soviet use of LBNP suits late in flight, and the ingestion of a saline drink prior to reentry have been partially successful, but cosmonauts returning from the most recent long-term flights again exhibited significant cardiovascular deconditioning. Furthermore, variously used in-flight exercise regimens have contributed to the feeling of well-being in space crews, but have not prevented cardiovascular deconditioning. Both bed-rest and immersion studies offer an excellent ground-based test vehicle for evaluating future appropriate countermeasures before they are used in space. Various pharmacologic measures also hold great promise in these regards.

Finally, the information generated by the next generation of space flights, both animal and human, as well as associated ground-based studies, can provide additional benefits by providing data which will be useful in clinical treatment of subjects with atherosclerotic heart disease and hypertension here on Earth. This has already been the case, since the large number of bed-rest studies in normal healthy individuals have pointed to the problems of immobilization and fostered recent clinical practice of earlier, and earlier ambulation after surgical procedures or myocardial infarction.

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TABLE 1.— SIGNIFICANT U.S. AND SOVIET ANIMAL FLIGHTS

Series Designation	No. of Flights	Flight Duration	Primary Animal	Physiological Measurements Made	Findings
U.S. FLIGHTS					
Mercury	2	To 183 min.	Chimpanzee	ECG, arterial and venous pressure, body temperature, performance testing.	No significant cardiovascular changes in first flight; blood pressure high and occasional extra systoles in second flight.
Biosatellite	1	8.8 days	Pigtail monkey	ECG, EMG, EOG, body temperature, direct measurement of arterial and venous pressure by catheters.	Loss of 20% in body weight with marked dehydration; slight but significant changes in central venous pressure during flight. Pre- and postflight histobiochemical studies showed loss of myocardial function and decreased norepinephrine content.
SPACELAB 3	1	7 days	2 squirrel monkeys 24 rats	5 rats instrumented for temperature and ECG.	Animals survived without harm. Biochemical and histological changes in hind limb skeletal muscle of rats.
SOVIET FLIGHTS					
Sputnik	5	65 min.—25 hr.	Dogs	Pulse and respiration rate, blood pressure, ECG, sphygmograms.	Recovered animals suffered no ill effects from radiation or Zero G and prepared the way for the first manned flight of Yuri Gagarin.
Kosmos 110	1	22 days	Dogs	ECG, pulse rate, blood pressure, respiration rate, seismocardiograms, hematology.	Changes seen in cardiac function during flight, with heart rate lower during second half than preflight measurements. Postflight, animals showed 20% loss of body weight, mostly from fluid losses; increased heart rate at rest; rapid fatigue; as well as calcium depletion and gait changes.
Kosmos 605—1129	5	18.5—21.5 days	Rats	Physiological, morphological, and biochemical examinations. Centrifugation of some animals on one flight (936).	Histo-biochemical changes noted in all body systems. Minimal cardiovascular changes with altered catecholamine content for the heart. EM changes due either to stress or to altered perfusion. Centrifugation during flight ($+ 1\ G_z$) did not prevent calcium losses.
Kosmos 1514 and 1667	2	5 and 7 days	2 rhesus monkeys each flight	Neurophysiological, hemodynamic, and performance changes for both animals on each flight.	Changes in neurophysiological and hemodynamic parameters on insertion into orbit. Rapid adaptation to weightlessness.

SOURCES: Klein, 1981; Nikolaev and Ilyin, 1981; Sandler, 1980.

TABLE 2.- U.S. MANNED SPACE MISSIONS

Variable Measured	MERCURY, 1961–63 4 Flights; 5–35 h	GEMINI, 1965–66 10 Flights; 4 h–13.8 d	APOLLO, 1968–75 12 Flights; 6–12.5 d	SKYLAB, 1973–74 3 Flights; 28, 56, 84 d	SHUTTLE, 1981– 22 Flights; 54 h–10 d
Pulse rate	Resting level elevated postflight (86 vs 76 bpm). Normalized 9–19 h postflight. No arrhythmias.	Resting level 18-62% higher postflight. Peak on re-entry, 180 bpm. Rare premature ventricular contractions.	Resting level elevated in 60% of crew members. Return to normal 30–50 h postflight. Episodic bigeminy in Apollo 15 crew.	Inflight resting levels increased but returned to normal by 4–5 d postflight. Multiple premature ventricular contractions in Skylab 2 crew.	Increased postflight but returned to normal by Day 3 in crews of shorter flights.
Blood pressure	Decreased during flight. Returned to normal 9–19 h postflight.	No significant change.	Labile up to 3 d postflight	LBNP more stressful during and after flight.	Increased until Day 3 postflight in shorter flights.
Orthostatic tolerance	Presyncopal episode with tilt (heart rate, 188 bpm) in MA-9.	Decreased postflight. Heart rate 17–105% higher with tilt.	Decreased postflight with LBNP or stand test.	Loss of tolerance to LBNP 4–6 days in flight. Significantly reduced during first 3 weeks postflight.	·Stand tests showed decrease on Day L+0 but returned to normal by L+3. 22% decrease in end diastolic volume on Day L+0; not reversed by L+7 to L+14.
Exercise tolerance	No significant change.	Decreased postflight.	Significant decrease postflight in 25–30 astronauts; greatest in Apollo 15 crew.	No change during flight at 50% max. Significantly reduced postflight.	Reduced postflight.
Plasma volume and red blood cells	No significant change.	20% decrease in red cell mass in GT-5 crew.	16% loss in red cells in crews of Apollo 14–16. Moderate decrease in serum potassium.	8.4–15.9% decrease in plasma volume. Significant decrease in heart size. 15% loss in red blood cells during first 40 days in orbit.	Decreased plasma volume indicated by slightly elevated BUN and serum proteins in STS-1.

TABLE 3.- SOVIET MANNED SPACE MISSIONS

Variable Measured	VOSTOK, 1961—63 6 Flights; 1.5—119 h	VOSKHOD, 1964—65 2 Flights; 24—26 h	SOYUZ, 1967—70 8 Flights; 27—424 h	SOYUZ/SALYUT 1—5, 1971— 77. 15 Flights; 2—63 d	SOYUZ/SALYUT 6—7, 1977—. 25 Flights; 175—237 d
Pulse rate	Decreased during flight. Returned to normal 4— 9.5 h postflight.	Immediate increase during liftoff; returned to normal 2 h in flight. One vagatonic reaction. Decreased during sleep. Moderate tachycardia in Voskhod 2.	Decreased during flight.	Unchanged during flight; increased postflight. Stroke volume and ejection time decreased postflight.	Pulse rate, stroke volume and cardiac output increased during flight. Prolonged recovery of certain indices, such as systolic time interval, with stress for as long as 4-6 weeks postflight.
Blood pressure	Decreased during flight.	Decreased during flight.	Decreased during flight; increased postflight.	Unchanged during flight; increased postflight.	Decreased systolic pressure during flight; stabilized after 2—3 months in flight.
Orthostatic tolerance	Decreased with standing postflight.	Decreased postflight.	Marked decrease; returned to normal by Day 11 postflight.	Decreased postflight.	Decreased but not as much as in shorter missions. 8— 50% decrease in end diastolic volume.
Exercise tolerance	High during flight in Vostok 5 and 6.	Findings variable during flight. Decreased postflight until Day 3.	Increased during flight; decreased postflight for more than 5 days; normal by Day 8 postflight.	Decreased postflight.	Decreased postflight.
Plasma volume and red blood cells			Decreased plasma volume.	Decreased plasma volume.	Decreased plasma volume during flight, but rapidly restored to normal postflight. Reduced RBC and Hb levels during first 3 months of flight (Hb mass, -18% by end of mission). Elevated reticulocytosis postflight persisted 30 d or more.

TABLE 4.- REPRESENTATIVE HORIZONTAL BED-REST STUDIES

Duration	No. of Studies	No. of Subjects	Representative References
30 min. to 48 hours	15	212 (16 F)	Birkhead, 1964; McCally et al., 1968
3 to 7 days	31	305	Hyatt and West, 1977; Lamb and Stevens, 1965; Melada et al., 1975
8 to 14 days	44	448 (32 F)	Greenleaf et al., 1973, 1975; Hyatt, 1971; Sandler and Winter, 1978.
15 to 21 days	13	261 (8 F)	Saltin et al., 1968; Taylor et al., 1945, 1949
24 to 28 days	13	187 (1 F)	Lynch et al., 1967; Miller et al., 1964
30 to 35 days	10	75	Aleksandrov and Kochetov, 1974; Asyamolov et al., 1973; Morse, 1967; Suvorov, 1974
40 to 49 days	10	151	Cherepakhin et al., 1977; Deitrick et al., 1948
56 to 75 days	6	75	Brannon et al., 1963; Georgiyevskiy and Mikhaylov, 1978; Vernikos-Danellis et al., 1974
84 to 210 days	8	90	Grigor'yev et al., 1976; Krasnyk, 1979; Parin et al., 1970

NOTE: Additional information on horizontal bedrest studies may be found in Greenleaf et al., 1982; Nicogossian et al., 1979; and Sandler, 1980.

TABLE 5.- REPRESENTATIVE HEAD-DOWN BED-REST STUDIES

Duration	No. of Studies	No. of Subjects	Body Position	Representative References
24-60 hr.	4	34	-5°	Nixon et al., 1979; Norsk et al., 1981; Volicier et al., 1976
5 days	2	14	0°, -4°, -8°, -12°	Bascands et al., 1984; Kakurin et al., 1976; Katkov et al., 1979
7 days	11	73	-4°, -5°, -8°, -15°	Guell et al., 1980; Katkov et al., 1982, 1985
10-11 days	4	34	0°, -4°, -6°, -8°, -12°	Polese et al., 1980; Sandler et al., 1985
14 days	2	12	0°, -4°, -5°	Hyatt and West, 1976; Kakurin, 1978; Yegorov et al., 1970
30 days	4	56	-2°, -4°, -6°, +6°	Beregovkin and Kalinichenko, 1974; Genin and Kakurin, 1972
45-49 days	4	45	-4°, -6.5°	Georgiyevskiy et al., 1979; Kakurin et al., 1980; Tkachev and Kul'kov, 1975
60 days	1	6	-4.5°	Anashkin et al., 1979
100 days	1	33	-2°, -6°, +6°	Krotov et al., 1977
182 days	1	12	-6°	Kakurin, 1981

NOTE: Additional information on head-down bedrest may be found in Greenleaf et al., 1982; Nicogossian et al., 1979; and Sandler, 1980.
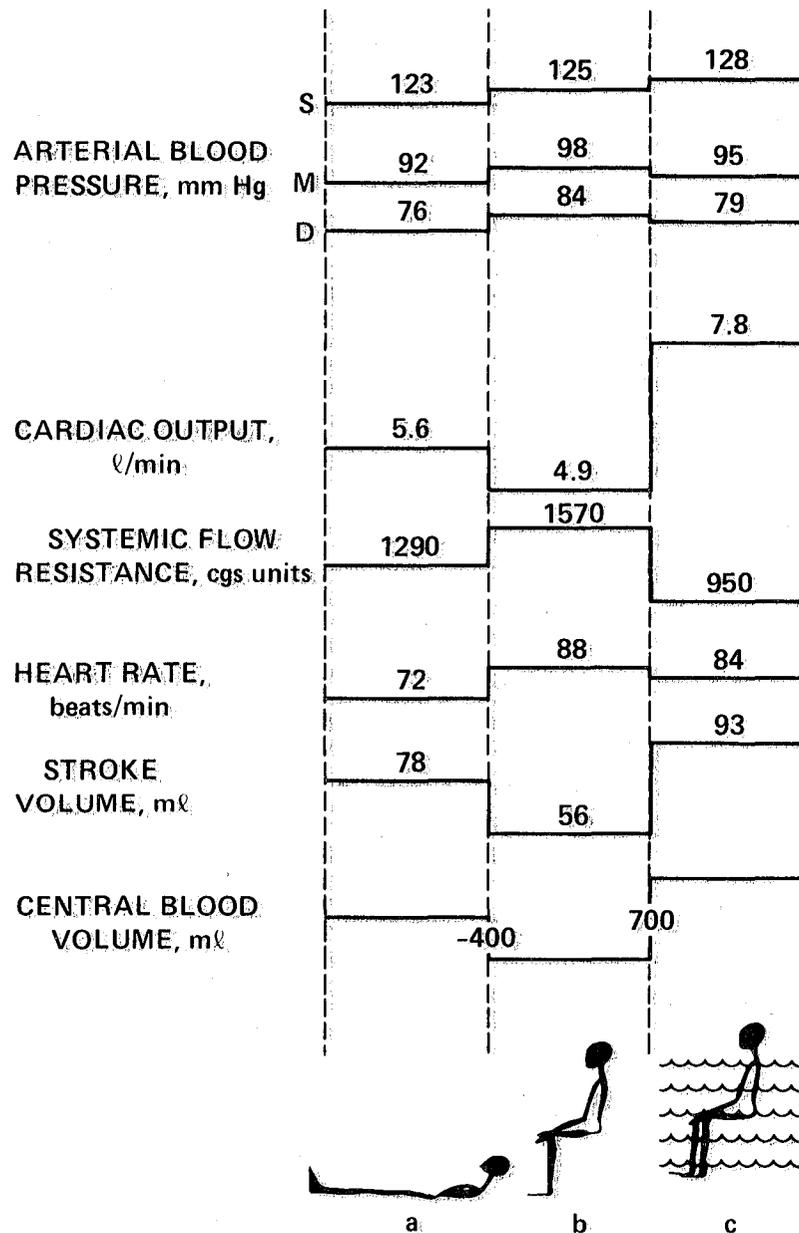
Figure 1.- Hemodynamic changes from (a) supine to (b) upright posture to
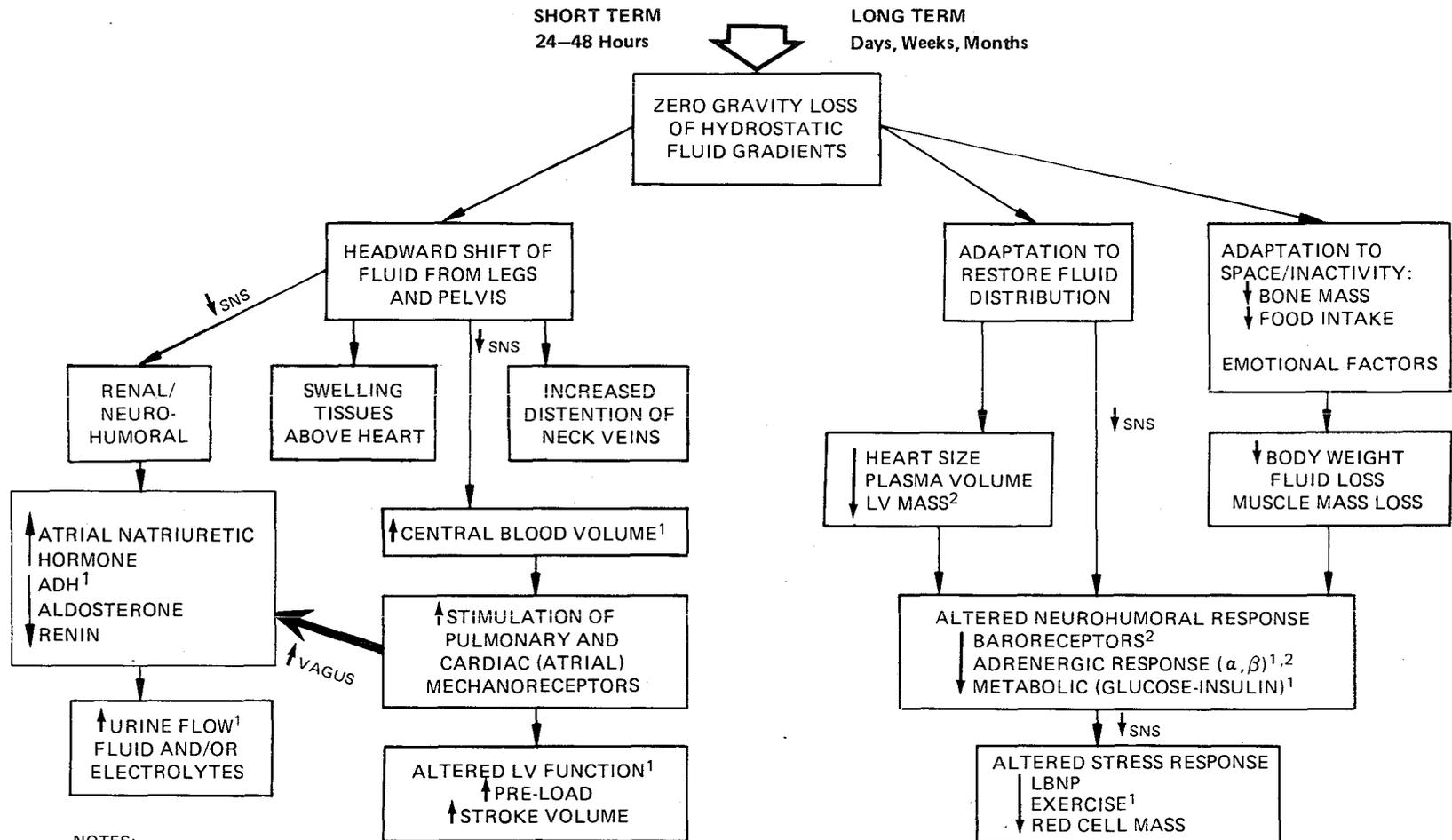head-out immersion.

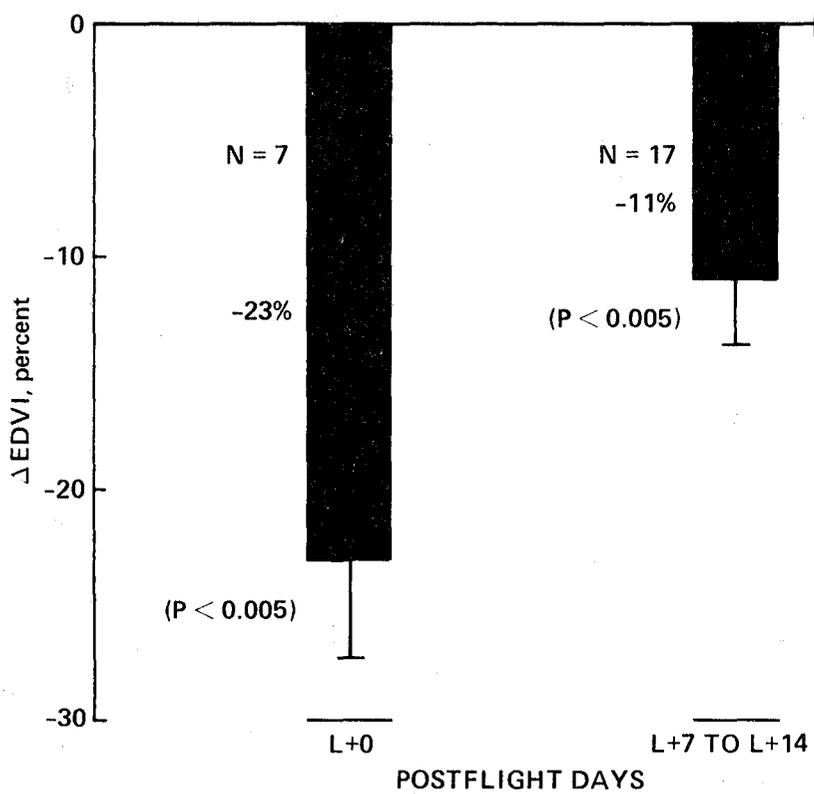Figure 2.- Cardiovascular responses to actual or simulated weightlessness.

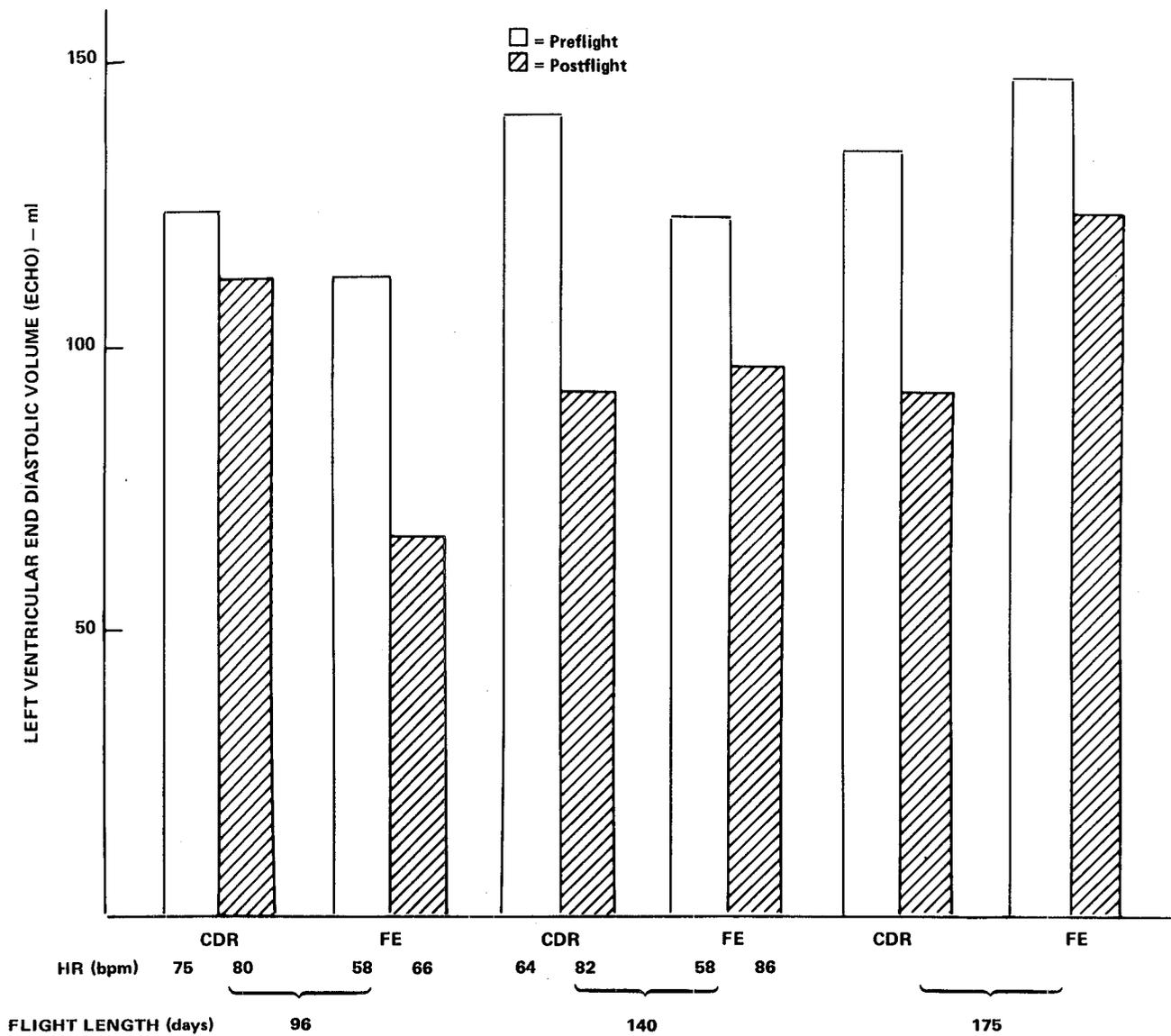Figure 3.- Changes in EDV following space flight.

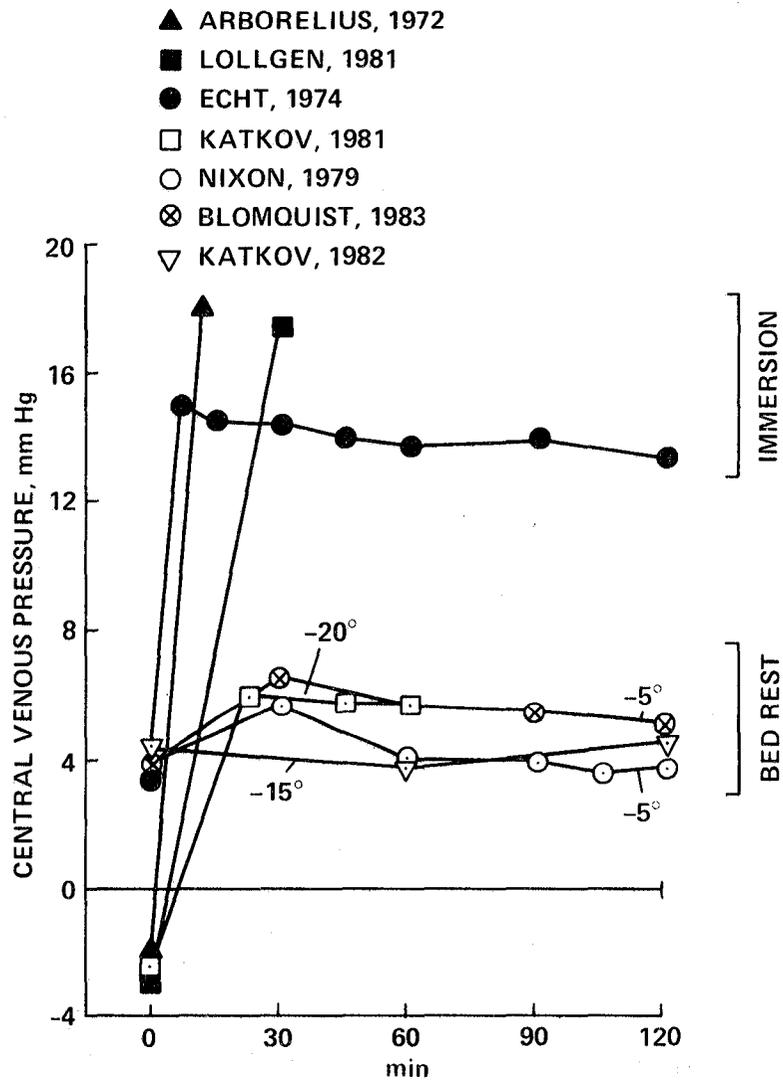Figure 4.- Echocardiographic measurements of heart volume following long-term space flight (96-175 days).

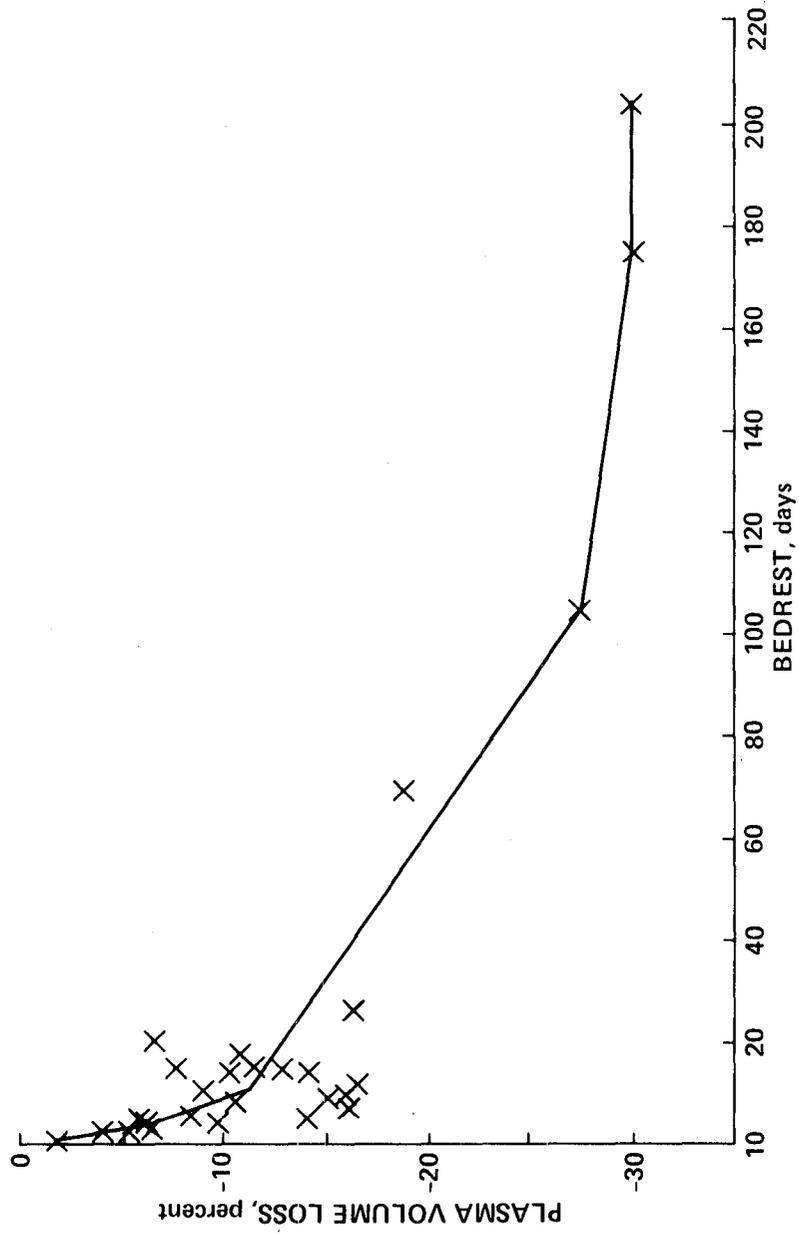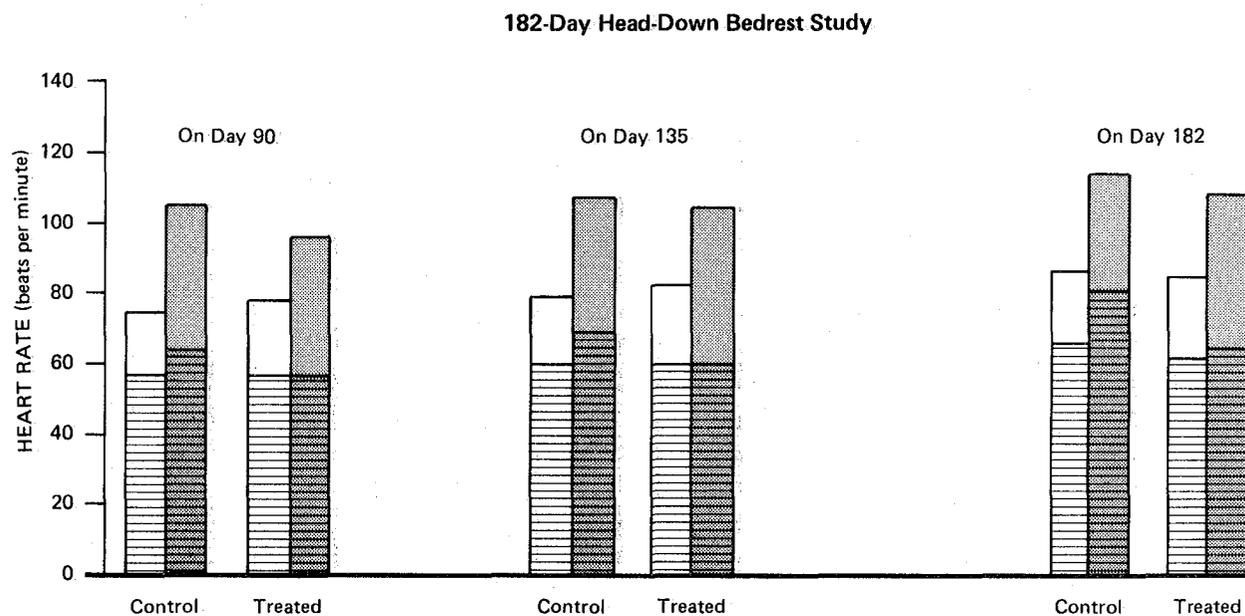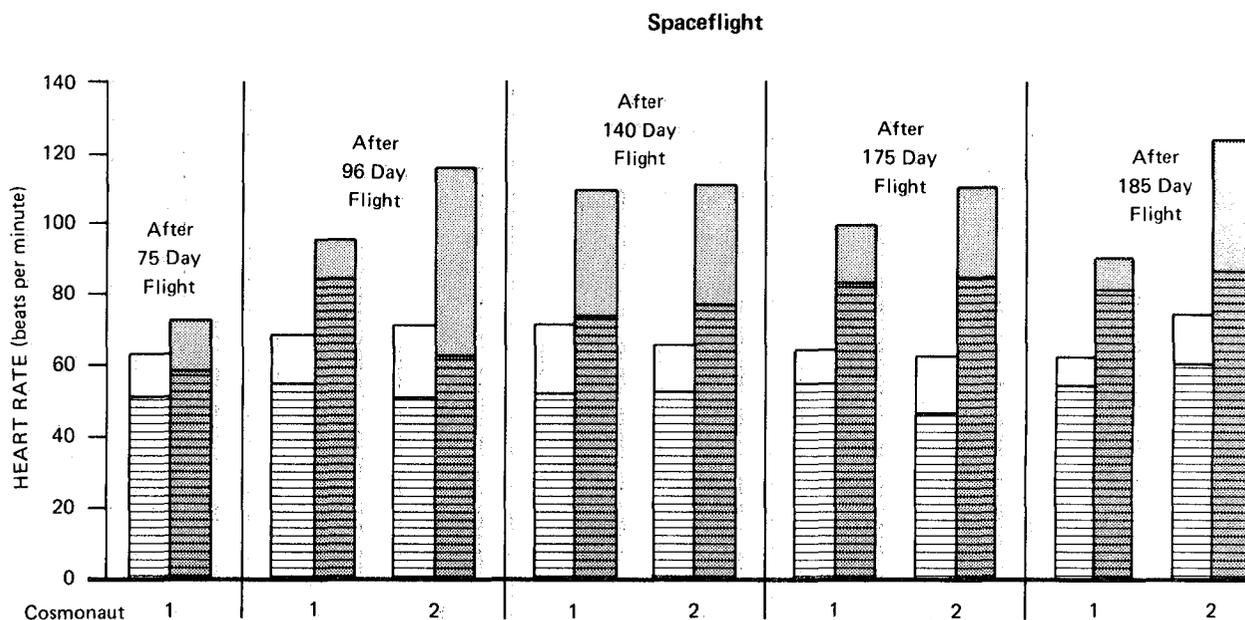Figure 5.- Comparison of changes in CVP with bed rest and immersion.

Figure 6.— Plasma volume loss during bed rest.

Spaceflight

182-Day Head-Down Bedrest Study

NOTE: Treatment consisted of electrical muscle stimulation.

▦ Horizontal

☐ After 70° upright tilt.

▨ After spaceflight and bedrest.

Figure 7.- Changes in heart rate during 70° tilt before and after space flight and head-down bed rest.

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16. Abstract

A large number of animal and human flight and ground-based studies have been conducted to uncover the cardiovascular effects of weightlessness. Findings indicate changes in cardiovascular function during simulations and with spaceflight that lead to compromised function on reambulation and/or return to Earth. This altered state termed "cardiovascular deconditioning" is most clearly manifest when in an erect body position. Hemodynamic parameters (compared to predeconditioned state) indicate the presence of an excessive tachycardia, hypotension (leading to presyncope in one-third subjects), decreased heart volume, decreased plasma and circulating blood volumes and loss of skeletal muscle mass, particularly in the lower limbs. No clinically harmful effects have been observed to date, but in-depth follow-ups have been limited, as has available physiologic information. Available data concerning the causes for the observed changes indicate significant roles for mechanisms involved with body fluid-volume regulation, altered cardiac function and the neurohumoral control of the control of the peripheral circulation. Satisfactory countermeasures have not yet been found. Hemodynamic changes in the immediate postflight period have been best handled by lower body counter pressure (anti-gravity suits). Return to preflight state has been variable (weeks to months) and only slightly dependent on flight duration. Animal flight studies have concentrated on uncovering operant mechanisms. Future progress awaits availability of flight durations longer than several weeks.

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