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Clinical aspects of the control of plasma volume at microgravity and during return to one gravity

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ABSTRACT

CONVERTINO, V. A. Clinical aspects of the control of plasma volume at microgravity and during return to one gravity. *Med. Sci. Sports Exerc.*, Vol. 28, No. 10, Suppl., pp. S45-S52, 1996. Plasma volume is reduced by 10-20% within 24-48 h of exposure to simulated or actual microgravity. The clinical importance of microgravity-induced hypovolemia is manifested by its relationship with orthostatic intolerance and reduced maximal oxygen uptake ($\dot{V}O_{2max}$) after return to one gravity (1G). Since there is no evidence to suggest that plasma volume reduction during microgravity is associated with thirst or renal dysfunctions, a diuresis induced by an immediate blood volume shift to the central circulation appears responsible for microgravity-induced hypovolemia. Since most astronauts choose to restrict their fluid intake before a space mission, absence of increased urine output during actual space flight may be explained by low central venous pressure (CVP) which accompanies dehydration. Compelling evidence suggests that prolonged reduction in CVP during exposure to microgravity reflects a "resetting" to a lower operating point, which acts to limit plasma volume expansion during attempts to increase fluid intake. In ground-based and space flight experiments, successful restoration and maintenance of plasma volume prior to returning to an upright posture may depend upon development of treatments that can return CVP to its baseline 1G operating point. Fluid-loading and lower body negative pressure (LBNP) have not proved completely effective in restoring plasma volume, suggesting that they may not provide the stimulus to elevate the CVP operating point. On the other hand, exercise, which can chronically increase CVP, has been effective in expanding plasma volume when combined with adequate dietary intake of fluid and electrolytes. The success of designing experiments to understand the physiological mechanisms of and development of effective countermeasures for the control of plasma volume in microgravity and during return to 1G will depend upon testing that can be conducted under standardized controlled baseline conditions during both ground-based and space flight investigations.

SPACEFLIGHT, CENTRAL VENOUS PRESSURE, $\dot{V}O_{2max}$, ORTHOSTATISM, RENAL FUNCTION, BLOOD VOLUME, HYDRATION

The reduction of plasma volume during exposure to space flight and its ground-based analogs of microgravity is well established (8-13,16,18-22,25,27,28,31,34,43). Cross-sectional data from space flight and longitudinal

data from ground-based experiments demonstrate that the time-course of the microgravity-induced hypovolemia follows a rapid reduction of 10-20% in the initial 24-48 h, followed by a new equilibrium (Fig. 1). The similarity of timecourse and magnitude between space flight and ground-based data suggests that ground-based experiments produce effective simulations and may provide appropriate controlled experimental conditions to investigate the mechanisms associated with reduced plasma volume in microgravity. With this background, the purpose of this paper is: 1) to review the results from several controlled experiments from ground-based analogs of microgravity in an attempt to provide working hypotheses for the underlying mechanisms of the regulation of plasma volume during space flight; and 2) to provide a physiological basis for development of clinical countermeasures for restoration of plasma volume prior to return to the one-gravity (1G) environment of Earth.

CLINICAL EFFECTS OF MICROGRAVITY-INDUCED HYPOVOLEMIA

Microgravity-induced hypovolemia has clinical implications for normal physiological function upon return to Earth. Cross-sectional data obtained from subjects during exposure to ground-based analogs of microgravity clearly demonstrate a positive correlation between the percent decrease in maximal oxygen uptake ($\dot{V}O_{2max}$) and the percent reduction in plasma volume (9). Since aerobic capacity in athletes is associated with large blood volumes compared with more sedentary subjects (7,14), the comparison of changes in $\dot{V}O_{2max}$ and plasma volume induced by microgravity in individuals of high physical fitness to subjects with low fitness provides a unique model to examine the relationship between plasma volume and aerobic capacity. When such an experiment was conducted, 10 physically fit individuals demonstrated an average 16% reduction in both $\dot{V}O_{2max}$ and plasma volume compared with only a 6% reduction in both $\dot{V}O_{2max}$ and plasma volume in 10 unfit subjects, with a correlation coefficient of 0.84 across all 20 subjects (9). These data suggest that plasma volume contributes to the reduction

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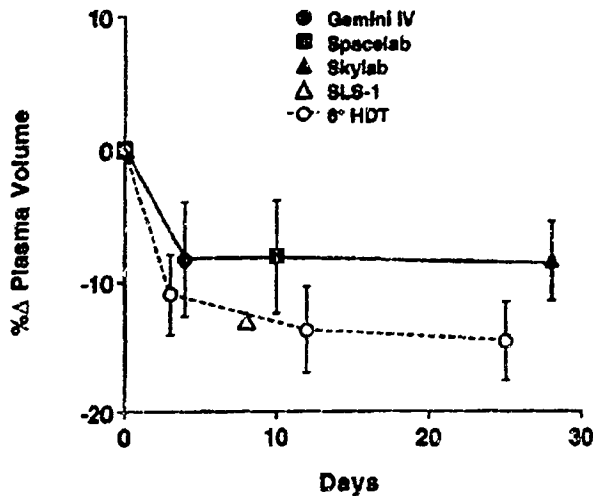


Figure 1—Comparison of time courses of percent change (%Δ) in plasma volume during adaptation to actual space flight (closed symbols and solid line; Δ) and ground-based analog using 6° head down tilt (HDT) (open circles and broken line). Spaceflight data from Gemini IV (Fischer et al., Red blood cell and plasma volume changes in manned space flight. *J.A.M.A.* 200:579-583, 1967), Spacelab (Leach and Johnson, Influence of space flight on erythrokinetics in man. *Science* 225: 216-218, 1984), Skylab IV (Johnson et al., Blood volume changes. In: *Biomedical Results from Skylab*, R. S. Johnston and L. F. Dietlein (Eds.), Washington, DC: National Aeronautics and Space Administration, 1977, pp. 235-241 (NASA SP-377)), and SLS-1 (Alfrey, Regulation of red cell volume at microgravity. *Med. Sci. Sports Exerc.* 28(Suppl.):S42-S44, 1996). HDT data from Convertino et al. (Head-down bedrest impairs vagal baroreflex responses and provokes orthostatic hypotension. *J. Appl. Physiol.* 68:1458-1464, 1990). Modified from Convertino. Exercise and adaptation to microgravity environments. In: *Handbook of Physiology: Environmental Physiology. III. The Gravitational Environment*, M. J. Fregley and C. M. Blatteis (Eds.). New York: Oxford University Press, 1995, pp. 815-843.

in $\dot{V}O_{2max}$ observed following exposure to microgravity and that individuals who have higher fitness and blood volume are predisposed to greater reduction in plasma volume and physical conditioning when exposed to microgravity environments unless effective treatments (countermeasures) are implemented to ameliorate the magnitude of hypovolemia.

In addition to the relationship between plasma volume and aerobic capacity, the hypovolemia induced by exposure to microgravity is inversely related to the magnitude of orthostatically induced tachycardia, indicating that the larger decrease in blood volume is related to greater cardiovascular compromise during an orthostatic challenge (24). The observation that plasma volume alone is not a reliable predictor of orthostatic tolerance after space flight (5) probably reflects the multifactorial etiology of post-space flight orthostatic hypotension. However, it is clear that reduction in intravascular volume does contribute to orthostatic problems. Therefore, emphasis should be placed on the development of countermeasures designed to restore plasma volume during microgravity just prior to return to 1G for the clinical treatment of post-space

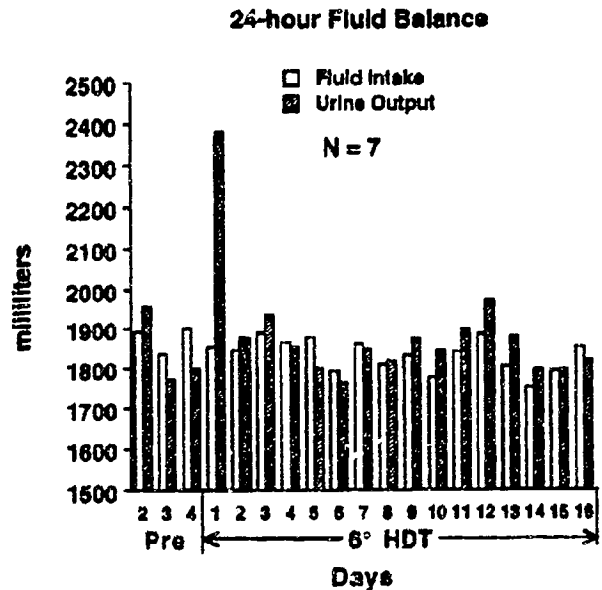


Figure 2—24-h fluid intake (open bars) and urine outputs (lined bars) before (Pre) and during 16 d of 6° HDT in seven subjects. Each bar represents the average of all subjects. Modified from Convertino et al., Restoration of plasma volume after 16 d of HDT induced by a single bout of maximal exercise. *Am. J. Physiol. (Regulatory Integrative Comp. Physiol.)* 270:R3-R10, 1996.

flight compromise to orthostatic competence and physical work performance.

MECHANISMS OF MICROGRAVITY-INDUCED HYPOVOLEMIA

Reduction in and inability to maintain plasma volume during exposure to microgravity may represent clinical dysfunction of mechanisms associated with fluid intake or renal function. Contrary to this notion, when subjects are allowed to drink ad libitum under experimental conditions controlled for dietary intake of sodium and calories, their fluid intakes match their urine outputs with the same magnitude as pre-exposure (Fig. 2). In addition, sodium, osmotic, and free water renal clearances are similar during exposure to actual and simulated microgravity compared with ambulatory function (13,16,23,32,33,37,38). Thus, with normal balance in fluid intake and output and normal renal function throughout exposure to simulated microgravity, there is no evidence to suggest that plasma volume reduction and failure for its maintenance at 1G levels during microgravity exposure is associated with clinical dysfunction.

One of the basic mechanisms proposed to explain the reduction in plasma volume during space flight is a pronounced diuresis. It is clear from ground-based experiments that a rapid diuresis occurs within the initial 24-48 h of exposure (13,15,16,19,22) and that the magnitude of this diuresis can account for the amount of

plasma volume reduction (13; Fig. 2). Discrepancy concerning this explanation for plasma volume reduction has evolved from the failure of an observable diuresis during actual space flight, a finding that has challenged the validity of ground-based models as being appropriate analogs to investigate the mechanisms underlying microgravity-induced hypovolemia. However, dramatic differences between the response of central venous pressure (CVP) during ground-based experiments and space flight may provide a reasonable explanation for the discrepancies in diuretic response.

Acute alterations in CVP can act as a stimulus to alter the rate of urine output. An immediate elevation in CVP induced by ground-based simulations of microgravity is associated with diuresis (39,42) while the lack of any consistent diuresis during actual space flight occurs in the presence of an immediate reduction in CVP (3). One possible explanation for the discrepancy in CVP and diuretic responses between exposure to actual and simulated microgravity is that the ground-based model does not accurately produce the physiological stimulus induced by actual space flight. However, the observation that hypovolemia, as well as numerous other physiological responses, occurs with similar magnitude under both space flight and simulated conditions (9) is not consistent with this hypothesis. An alternative explanation is that discrepancies in CVP and diuretic responses between exposure to actual and simulated microgravity reflect a difference in baseline hydration (volemic) state of astronauts. Recent experiments conducted on nonhuman primates during transient exposures to microgravity induced by parabolic flight in a KC-135 aircraft provided new insight into physiological mechanisms that may be involved in dictating the magnitude of transient changes in CVP during exposure to microgravity. In these experiments, five baboons underwent their exposures to microgravity under three volume states: euvolemic, volume depleted (furosemide and water restriction for 24 h), and volume expanded (osmotic expander). Recordings of right atrial pressure indicated that CVP increased by 4.2 ± 2.9 mm Hg during volume expansion, did not change in the euvolemic state, and decreased by 3.2 ± 2.2 mm Hg during volume depletion (30). It therefore appears that the initial hydration state may be critical in determining the change in CVP and subsequently the stimulus for diuresis during the initial period of exposure to microgravity. Compelling evidence exists that crew members undergo voluntary dehydration prior to launch in addition to reduced drinking during the initial 48 h of a mission due to space motion sickness, which can account for a reduced urine output during the initial week of space flight (31). Although unsubstantiated by blood volume measurements, it is probable under these conditions that astronauts enter their missions in a volume-depleted state that would attenuate initial elevations in CVP consistent with space flight measurements (3) and

eliminate the stimulus for early diuresis. It is therefore reasonable to hypothesize that an initial elevation in CVP leading to diuresis is a primary mechanism underlying microgravity-induced hypovolemia and that increased CVP and urine output during actual space flight will not be evident until normal hydration and fluid intake can be maintained in astronauts immediately prior to and during the initial period of a mission. The apparent dependence of the initial CVP and renal response on the hydration state of astronauts underscores the importance of designing space flight experiments that provide for a controlled baseline condition. Without such controlled baseline conditions, it will be difficult to compare the accuracy by which ground-based analogs simulate the physiological responses associated with actual space flight and therefore greatly limit our capabilities to investigate mechanisms underlying the regulation of plasma volume in microgravity and during return to earth (2).

MECHANISMS OF PLASMA RESTORATION DURING RETURN TO 1G

Relationships between circulating intravascular volume and operational functions of standing and performing physical work suggest that maintenance or replacement of plasma volume should provide clinical treatment for orthostatic incompetence and reduced $\dot{V}O_{2max}$. Early space flight experiments demonstrated that both supine and standing heart rates measured immediately after space flight were significantly lower in astronauts who drank approximately 1 l of isotonic saline within 2 h of reentry from space flight compared with crew members who did not take the fluid-loading countermeasure (4). These data clearly supported the contention that body fluids (plasma volume) contribute to orthostatic compromise following space flight and that fluid replacement can ameliorate space flight effects. However, data from extended space flight experiments indicated that as the duration of space flight increases beyond 7-10 d, fluid-loading becomes less effective for ameliorating orthostatic compromise following the mission (44). The ineffectiveness of fluid-loading to protect orthostatic competence with increased duration of exposure to microgravity may reflect delayed adaptations of autonomic functions associated with blood pressure regulation (10-12). In addition, however, data from a ground-based experiment demonstrated that a fluid-loading prescription identical to that implemented by astronauts failed to restore a 15% plasma volume deficit induced by 7 d of head-down tilt (HDT)(43). Taken together, data from ground-based and space flight experiments suggest that the failure to maintain or replace plasma volume during exposure to microgravity is not limited by fluid-electrolyte intake, but may be dependent upon mechanisms associated with regulation of plasma volume.

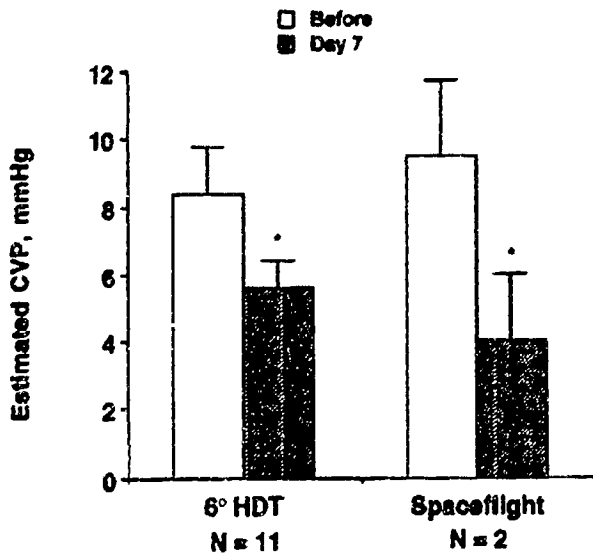


Figure 3—Estimated central venous pressure (CVP) before (open bars) and after (lined bars) 7 d of exposure to 6° head down tilt (HDT) (Convertino et al., Effect of simulated microgravity on cardiopulmonary baroreflex control of forearm vascular resistance. *Am. J. Physiol.* 266:R1962-R1969, 1994) and actual space flight (Kirisch et al., Venous pressure in man during weightlessness. *Science* 225:218-219, 1984). Values represent mean \pm SE. Asterisks indicate that all subjects decreased CVP in the microgravity condition.

Indirect measurements of CVP during ground-based simulations and actual space flight support the notion that CVP is chronically reduced in a similar manner in both conditions of microgravity (Fig. 3). With regard to long-term plasma volume regulation during exposures to microgravity and restoration of intravascular volume at the end of space missions, this observation may be more significant than the transient decrease that occurs upon entry into orbit (3). If reduced CVP is merely a reflection of lower plasma volume, then increasing fluid input should be effective in expanding plasma volume to the point where CVP has regained its baseline level. On the other hand, if the reduction in venous pressure observed during long duration exposure to microgravity represents a "resetting" to a lower operating point, then similar volumes of fluid intake should induce similar volumes of urine excretion.

The concept of a lower operating point is supported by the results of a ground-based experiment (17) where subjects who received intravenous infusion of isotonic saline solution ($22 \text{ ml}\cdot\text{kg}^{-1}$ body weight) showed similar urine outputs before compared to the 6th day of HDT (Fig. 4). This hypothesis is further supported by the observation that exposure to 7 d of HDT caused the cardiopulmonary baroreflex stimulus-response relationship to shift to the left so that the response for peripheral vascular resistance occurred in a lower range of central venous pressures (11). Figure 5 illustrates the cardiopulmonary baroreflex stimulus-response relationships under

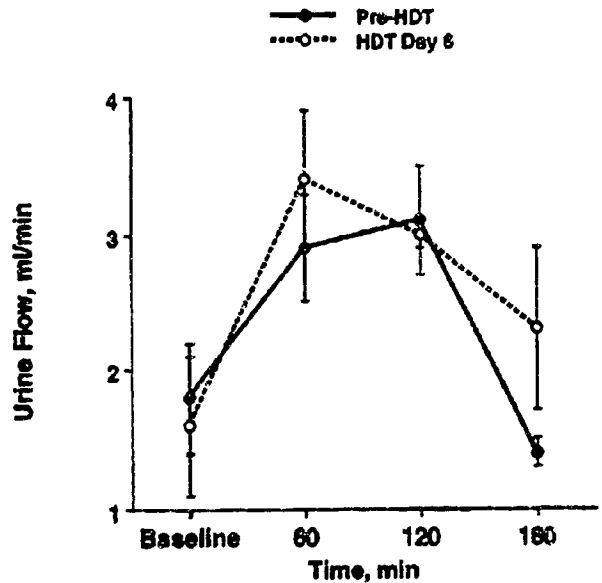


Figure 4—Mean (\pm SE) urine flow rates of six subjects at baseline (Pre) and at 60, 120, and 180 min after intravenous infusion of $22 \text{ ml}\cdot\text{kg}^{-1}$ of 0.9% saline before (solid circles and solid line) and on day 6 (open circles and broken line) of 6° HDT. Modified from Drummer et al., Diuretics and natriuretics following isotonic saline infusion in healthy young volunteers before, during and after HDT. *Acta Physiol. Scand.* 144:101-111, 1992.

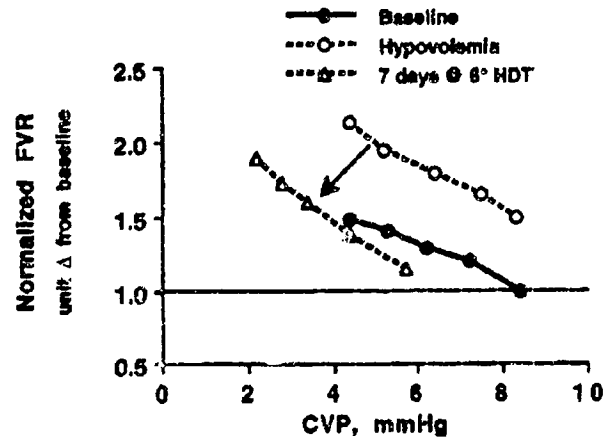


Figure 5—Relationship between forearm vascular resistance (FVR) and central venous pressure (CVP) during ambulatory hypovolemia (O, broken line), and 7 d of 6° HDT (Δ , broken line) compared with and expressed as unit changes (Δ) from baseline control (\odot , solid line). Values are normalized to multiples of baseline FVR with normovolemia (=1.0) and represent average of 8 subjects (hypovolemia) and 10 (HDT) subjects. Modified from Convertino et al., Effect of simulated microgravity on cardiopulmonary baroreflex control of forearm vascular resistance. *Am. J. Physiol.* 266:R1962-R1969, 1994.

normovolemic baseline state compared with those associated with hypovolemia alone and with hypovolemia associated with exposure to a ground-based analog of microgravity. Similar increase in slope of the cardiopulmonary baroreflex relationship for hypovolemic and HDT subjects was associated with similar degrees of

CVP Setpoint Hypothesis

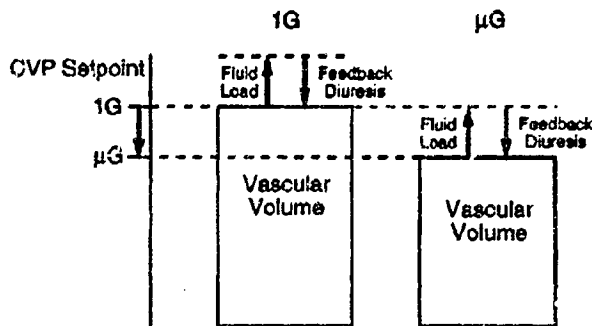


Figure 6—Illustration of a setpoint hypothesis to explain the change in central venous pressure (CVP) caused by exposure to microgravity (μG). Modified from Convertino, *Countermeasures against cardiovascular deconditioning*, *J. Gravitational Physiol.* 1:P125-P128, 1994.

plasma volume reduction (16% vs 13%, respectively) while chronic exposure to HDT induced a shift to the left along the CVP axis. Further evidence of resetting is provided by the observation that acute pharmacological (fludrocortisone) restoration of plasma volume following 7 d of exposure to a ground-based analog of microgravity reduced the slope of the cardiopulmonary baroreflex stimulus-response relationship to preexposure level, but failed to return the operating range of CVP (43). Taken together, these comparable data suggest that increased responsiveness of the baroreflex relationship following adaptation to microgravity can be primarily explained by hypovolemia while its shift may represent a resetting of the cardiopulmonary baroreflex response to a lower operational range for CVP.

Despite the evidence from stimulus-response experiments, a physiologic mechanism for explaining the longitudinal "resetting" of the CVP operational point during microgravity remains unknown. Numerous brain nuclei and neural pathways have been identified as integrators for processing information from systemic receptors for controlling plasma and blood volume. One possible hypothesis is that extended exposure to microgravity induces long-term adaptation of this "visceral neuroaxis" so that the same level of CVP (input) from cardiopulmonary receptors produces a greater renal excretion of water and electrolytes (output), thus changing the processing function of the CNS integrator (26). This hypothesis will remain speculative until future experiments are designed to investigate the neural plasticity of peripheral and central nervous system mechanisms associated with blood volume regulation.

CLINICAL IMPLICATION OF CVP RESETTING ON FLUID REPLACEMENT

A hypothesis for CVP resetting is illustrated in Figure 6. The box on the left represents a state of normovolemia

under 1G conditions. Elevated CVP resulting from fluid loading will initiate a feedback diuresis to return CVP to its setpoint. The assumption that fluid loading following space flight can successfully restore plasma volume must be based on the assumption that the preflight CVP setpoint has remained intact. However, similar urine volume rates during saline infusion (17) and failure to chronically restore and maintain plasma volume during saline loading (25,43) observed in human subjects during exposure to ground-based analogs of microgravity support the notion that the chronic reduction in CVP reflects a change to a lower operating point and that elevated CVP resulting from fluid loading will initiate a feedback diuresis to return CVP so that plasma volume will remain contracted (the box on the right). Therefore, the attempt to use fluid loading as a countermeasure appears to require an additional stimulus that could reset the CVP operating point to preflight levels.

BASIS FOR DEVELOPMENT OF CLINICAL COUNTERMEASURES

LBNP. The application of lower body negative pressure (LBNP) with fluid loading has been proposed as a means of enhancing plasma volume expansion and retention on the basis that LBNP induces fluid shifts toward the lower extremities in a similar manner to standing in Earth's 1G environment, which in turn reduces CVP and stimulates neuroendocrine secretions associated with fluid and electrolyte retention. In a ground-based experiment, six subjects ingested approximately 1 l of either isotonic saline alone or ingested the saline after receiving a 4-h exposure to 30 mm Hg of LBNP at the end of 7 d of bed rest (25). Two hours following the fluid loading regimens, plasma volume and heart rate and systolic blood pressure responses during a LBNP exposure at 50 mm Hg was measured in each subject. The plasma volume increase from the end of bed rest to the end of fluid loading was greater with the combination of saline load with LBNP (from 2.80 ± 0.18 to 3.24 ± 0.31 l) compared with saline alone (from 2.81 ± 0.33 to 3.02 ± 0.43 l). Likewise, average systolic blood pressure during exposure to 50 mm Hg LBNP was maintained at a higher level with the combination of saline load with LBNP compared with saline load (109 ± 9 mm Hg vs 101 ± 11 mm Hg) with a lower average heart rate response (89 ± 19 bpm vs 100 ± 17 bpm). These results alone provided compelling evidence that LBNP could significantly enhance the replacement and retention of plasma volume and its clinical impact on orthostatic stability following exposure to space flight. However, a seldom discussed observation presented in this investigation was the observation that when three of the six subjects were retested with exposure to 50 mm Hg LBNP after being returned to bed rest for an additional 18 h, average plasma volume (2.94 ± 0.19 l) and heart rate response had returned to

levels measured at the end of 7 d of bed rest before any saline loading. These results suggest that plasma volume expansion induced by combinations of saline loading and LBNP and its protective effects on orthostatic performance are transient and fail to provide effectiveness as a long-term countermeasure treatment. This relationship has been further supported by a recent ground-based experiment that demonstrated no protective effects on orthostatic performance following 28 d of HDT in subjects who underwent daily exposure to 15 min of -30 mm Hg LBNP once every other day during the 3rd week and daily during the 4th week of HDT compared with subjects who received no treatment (40). The failure of LBNP to chronically restore and maintain plasma volume following exposure to microgravity may be consistent with the CVP operational point hypothesis since there is no evidence that such exposure induces chronic elevations in CVP.

Exercise. The effectiveness of exercise to enhance plasma volume expansion and retention in the 1G environment of earth is well established (7). In ground-based experiments assessing the effects of simulated microgravity, both chronic and acute exercise on a cycle ergometer completely protected or restored plasma volume with exposure of 16–28 d to HDT compared with subjects who did not exercise (13,20,22), suggesting that exercise may represent an effective treatment for protection of plasma volume during space flight. If the CVP operating point hypothesis is correct (Fig. 6), then any attempt to apply a countermeasure for prolonged plasma volume expansion in a microgravity environment will require a stimulus that can reset the CVP operating point to preflight levels. It is possible that exercise provides such a stimulus since exercise-induced hypervolemia is associated with sustained elevation in CVP (14,41). Resetting of CVP by exercise to a higher operating point that allows plasma volume expansion is further supported by the observations that endurance exercise training chronically increased CVP without inhibiting hormones associated with regulation of vascular volume (14) and shifted the cardiopulmonary baroreflex stimulus-response relationship to the right so that the response for peripheral vascular resistance occurred in a higher range of central venous pressures (35,36). If a primary mechanism for plasma volume expansion by exercise is elevation of the CVP operating point, then exercise may represent an effective countermeasure treatment to chronically expand and protect plasma volume prior to return to earth from space flight.

The effectiveness of exercise to maintain or restore plasma volume during actual space flight is challenged by the observation that plasma volume is reduced even though astronauts routinely exercise (6,27,28). One conclusion that might be drawn from these space flight results is that in the absence of an exercise countermea-

sure in microgravity, hypovolemia would be greater than that observed in astronauts who exercise. This notion is supported by the data presented in Figure 1, which demonstrates that the magnitude of plasma volume reduction in astronauts who exercised during space flight (27) is less than that reported from a ground-based experiment where subjects did not exercise (10). The inability of current inflight exercise countermeasures to completely restore or defend plasma volume similar to that observed in ground-based experiments may be associated with the failure to enhance exercise-induced hypervolemia with adequate fluid and dietary intake. Thus, efforts to increase fluid and electrolyte intake following exercise may optimize plasma volume expansion during space flight in crew members.

SUMMARY

A pronounced 10–20% reduction in plasma volume is induced within 24–48 h of exposure to microgravity. The clinical importance of microgravity-induced hypovolemia is manifested by the relationships between the magnitude of plasma volume reductions and orthostatic intolerance and reduced $\dot{V}O_{2max}$ after return to one gravity. A primary mechanism underlying microgravity-induced hypovolemia can be explained by an immediate diuresis. Since astronauts choose to restrict their fluid intake immediately before a space mission, the absence of increased urine output during actual space flight may be explained by a reduction in CVP, which accompanies dehydration despite an immediate blood volume shift to the central circulation. There is no evidence to suggest that plasma volume reduction during exposure to microgravity is associated with dysfunction of mechanisms controlling thirst and renal function. Compelling evidence suggests that prolonged reduction in CVP during exposure to microgravity reflects a "resetting" to a lower operating point, which acts to limit plasma volume expansion during attempts to increase fluid intake. Successful restoration and maintenance of plasma volume prior to returning to the 1G environment of earth may depend upon the development of countermeasure treatments that can return CVP to its baseline operating point. Exercise appears to represent such a countermeasure when combined with adequate dietary intake of fluid and electrolytes. Although generally comparable results suggest that ground-based analogs can be used to investigate physiological effects of space flight, several important differences in responses have been consistently reported. Unfortunately, the inability to systematically control baseline conditions before and during space flight experiments makes it difficult to verify ground-based models. Therefore, the success of designing experiments to un-

derstand the physiological mechanisms of the control of plasma volume in microgravity and during return to one gravity will depend upon testing that can be conducted under standardized controlled baseline conditions during both ground-based and space flight investigations.

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