Fluid volume control during short-term space flight and implications for human performance

Donald E. Watenpaugh*

Department of Integrative Physiology, and Cardiovascular Research Institute, University of North Texas Health Science Center, Fort Worth, TX 76107, USA

*Present address: Naval Submarine Medical Research Laboratory, Box 900, Groton, CT 06349-5900, USA
(e-mail: watenpaugh@nsmrl.navy.mil)

Summary

Space flight exerts substantial effects on fluid volume control in humans. Cardiac distension occurs during the first 1–2 days of space flight relative to supine and especially upright $1g$ conditions. Plasma volume contraction occurs quickly in microgravity, probably as a result of transcapillary fluid filtration into upper-body interstitial spaces. No natriuresis or diuresis has been observed in microgravity, such that diuresis cannot explain microgravity-induced hypovolemia. Reduction of fluid intake occurs irrespective of space motion sickness and leads to hypovolemia. The fourfold elevation of urinary antidiuretic hormone (ADH) levels on flight day 1 probably results from acceleration exposures and other stresses of launch. Nevertheless, it is fascinating that elevated ADH levels and reduced fluid intake occur simultaneously early in flight. Extracellular fluid volume decreases by 10–15 % in microgravity, and intracellular fluid volume appears to increase. Total red blood cell mass decreases by approximately 10 % within 1 week in space. Inflight Na$^+$ and volume excretory responses to saline infusion are approximately half those seen in pre-flight supine conditions. Fluid volume acclimation to microgravity sets the central circulation to homeostatic conditions similar to those found in an upright sitting posture on Earth. Fluid loss in space contributes to reduced exercise performance upon return to $1g$, although not necessarily in flight. In-flight exercise training may help prevent microgravity-induced losses of fluid and, therefore, preserve the capacity for upright exercise post-flight. Protection of orthostatic tolerance during space flight probably requires stimulation of orthostatic blood pressure control systems in addition to fluid maintenance or replacement.

Key words: microgravity, human, central venous pressure, plasma volume, extracellular fluid volume, intracellular fluid volume, antidiuretic hormone, thirst.

Introduction

Space flight exerts substantial effects on vertebrate fluid volume control. The physiological mechanisms of these effects remain inadequately understood, but recent progress is substantial. Most work to date has been descriptive studies of humans, largely because of the limited opportunities for and limitations of in-flight research. Fluid volume effects in space result largely from the weightless environment of space flight, yet the chronobiological environment may also contribute. This brief review serves as an update to past reviews covering this topic (Fortney et al., 1996; Norsk and Epstein, 1991; Watenpaugh and Hargens, 1996). Smith and colleagues (Smith et al., 1997) and Leach Huntoon and colleagues (Leach Huntoon et al., 1998) offer two particularly comprehensive and recent reviews.

The hypothetical foundation

Gravity pulls blood downwards in upright humans, away from the central circulation. Therefore, the traditional view of human fluid regulatory acclimation to $0g$ holds that removal of gravity's influence leads to central fluid redistribution, which in turn activates Henry–Gauer and related reflexes (Watenpaugh and Hargens, 1996). The headward fluid redistribution distends the heart and stimulates baroreceptors, such that renal sympathetic nerve activity, antidiuretic hormone (ADH) secretion and renin–angiotensin–aldosterone system activity decrease, while atrial natriuretic peptide secretion increases. These collective neurohumoral responses elicit natriuresis and diuresis, and the resulting reduction in blood volume renders central circulatory homeostasis appropriate for existence in microgravity. It is now well established that existence in microgravity leads to a 10–15 % reduction in plasma and blood volume. However, results from flight experiments reveal that fluid regulatory acclimation to microgravity is very different from and more complicated than the straightforward process described above.

Recent developments

Central circulatory stimuli for fluid volume regulation in microgravity

Three recent articles report surprising results concerning how microgravity affects the central circulation and, thus, the nature of one putative stimulus to volume-regulating mechanisms. Buckey and co-workers (Buckey et al., 1996a; $N=3$) and Foldager and co-workers (Foldager et al., 1996; $N=1$) each directly measured central venous pressure (P_{cv}) before and during Shuttle launch and insertion to orbit ($0g$). In ground-based conditions, P_{cv} is a reliable indicator of cardiac filling pressure. Both groups found that P_{cv} did not increase in microgravity. Instead, P_{cv} decreased below pre-flight supine values and sometimes below upright levels immediately upon insertion to orbit, and remained at these unexpectedly low levels. At the same time, Buckey and co-workers (Buckey et al., 1996a) found increased cardiac chamber volumes relative to supine $1g$ conditions.

In a subsequent study, Videbaek and Norsk (Videbaek and Norsk, 1997) discovered how simultaneous cardiac expansion and P_{cv} reduction occur in microgravity. They measured atrial diameter, P_{cv} and pressure outside the heart (esophageal pressure, a measure of intrathoracic pressure) in supine subjects during parabolic flight, which produces short periods of micro- and hypergravity. They confirmed that P_{cv} decreases in microgravity relative to supine $1g$ conditions, and they further found that intrathoracic pressure decreases with reduced G_x substantially more than P_{cv}, such that cardiac transmural pressure increases in microgravity (G_x is ventral to dorsal acceleration; Fig. 1). Increased cardiac transmural
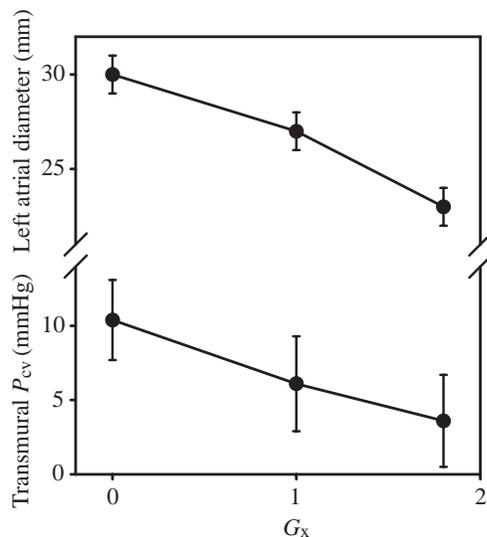

Fig. 1. Left atrial diameter and transmural central venous pressure (P_{cv}) in supine subjects during parabolic flight ($N=4$; means ± S.E.M.). Data from Videbaek and Norsk (Videbaek and Norsk, 1997). Linear regression of the transmural P_{cv} means *versus* acceleration in the ventral to dorsal direction (G_x) yielded the relationship: transmural $P_{cv}=-3.8G_x+10.2$ (Watenpaugh and Smith, 1998). 1 mmHg=0.133 kPa.

pressure in $0g$ corresponded to increased atrial diameter. It appears that removal of gravitational compression expands the thorax and thereby decreases pressure inside it (and inside the abdomen; Estenne et al., 1992) such that effective cardiac filling pressure increases in acute microgravity (Watenpaugh and Smith, 1998; White and Blomqvist, 1998).

Therefore, taking this recent evidence together with earlier findings (summarized in Watenpaugh and Hargens, 1996), it seems clear that cardiac distension occurs during the first 1–2 days of space flight relative to the supine position in $1g$ and especially to upright $1g$ conditions. It is also probable that arterial baroreceptors are relatively stimulated during this time and that intracranial pressure is abnormally increased (Draeger et al., 1995). What then happens to fluid volume regulation?

Fluid volume acclimation to and homeostasis in chronic microgravity

Leach, Alfrey and co-workers (Leach et al., 1996; Alfrey et al., 1996b) recently provided the most comprehensive and best-controlled description to date of fluid regulatory acclimation to space flight. Their data from seven Spacelab Life Sciences (SLS) astronaut subjects yielded key new findings and confirmed some older results that had been tentative (Leach et al., 1983). They collected pre- and post-flight data with subjects in the supine position.

They found a 9 % increase in plasma protein concentration on flight day 1, and a 17 % reduction in plasma volume by 22 h of flight. This agrees with the early in-flight hemoconcentration seen by others (Kirsch et al., 1984) and establishes that plasma volume contraction occurs quickly in microgravity. This hemoconcentration probably results from increased upper-body vascular pressures in microgravity (Parazynski et al., 1991) and perhaps reduced interstitial pressures (Estenne et al., 1992); both factors would encourage transcapillary fluid filtration into upper-body interstitial spaces, and substantial filtration can occur in minutes (Watenpaugh et al., 1992). The early hemoconcentration is all the more notable given the probable concomitant tissue fluid reabsorption from the legs into the circulation (Thornton et al., 1992). Although some protein may leave the circulation early in flight, the increased plasma protein concentration on flight day 1 does not support extravasation of protein as a primary mechanism for early in-flight net capillary filtration and plasma volume contraction. Increased plasma protein concentration increases plasma colloid osmotic pressure and, therefore, opposes capillary filtration.

In agreement with earlier reports (Drummer et al., 1993; Leach, 1987; Leach et al., 1983), the SLS results revealed no natriuresis or diuresis in microgravity, so diuresis cannot explain microgravity-induced hypovolemia. Leach and co-workers (Leach et al., 1996) confirmed that both fluid intake and urine output decrease significantly on the first day in flight and remain relatively low during space flight (Fig. 2). The reductions in thirst and fluid intake occur regardless of space motion sickness. For example, none of the four studied SLS-2 crew members experienced motion sickness.
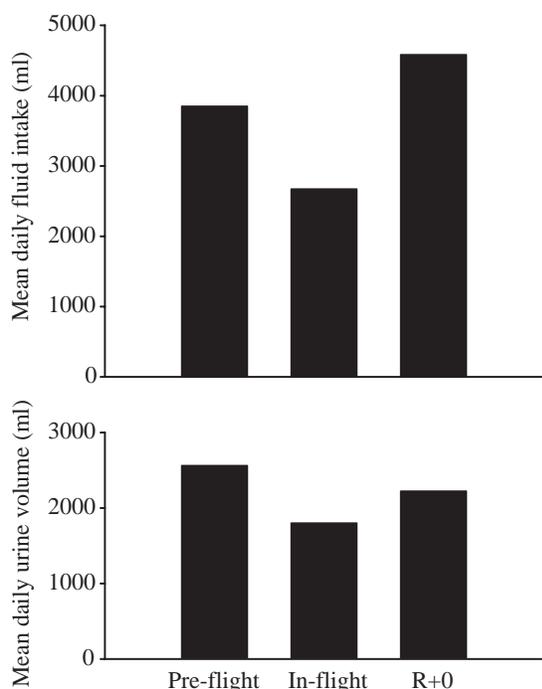
Fig. 2. Mean daily fluid intake and urine output compiled from Spacelab Life Sciences data as reported by Leach and colleagues (Leach et al., 1996) (N=6–7). In-flight data are for flight days 1–9. R+0 represents landing day.

The reduction in urine flow occurs in spite of an approximately 19 % elevation of glomerular filtration rate in microgravity (Leach et al., 1996). Distal tubule/collecting duct actions of ADH probably contribute to the reduction of urine flow early in flight. Leach and colleagues (Leach et al., 1996) observed a fourfold elevation of urinary ADH levels on flight day 1, in agreement with earlier reports (summarized by Smith et al., 1997). The investigators caution that acceleration exposures and other stresses of launch and re-entry probably contribute to ADH (and cortisol) elevation at those times, and these stress reactions almost certainly color responses to microgravity *per se*. Atrial distension would be expected to reduce ADH levels during this time (Guyton, 1991). It remains possible (probable?) that natriuresis and diuresis occur if a subject goes directly and immediately from an upright 1g existence into sustained 0g, and with no concurrent stressful stimuli, but no means currently exist to perform this experiment.

It is striking that fluid intake decreases by 41 % on flight day 1 while ADH levels are so markedly elevated. Normally, ADH secretion and thirst correlate strongly, which is logical (Guyton, 1991). The same stimuli (hyperosmolarity, reduced blood volume and blood pressure) and hypothalamic regions regulate ADH secretion and thirst, and they each act to preserve or increase fluid volume and decrease osmolarity (Jurzak and Schmid, 1998; McKinley et al., 1999). Serum osmolarity remained unchanged by space flight (Leach et al., 1996), so hypo-osmolarity does not reduce thirst in space.

Central volume expansion reduces thirst, even in subjects made hyperosmotic by dehydration (Wada et al., 1995), so central volume expansion probably contributes to the reduction in thirst in microgravity. If stress-induced ADH elevation and central blood volume expansion compete in central nervous control of thirst and in control of diuresis, then central blood volume expansion clearly wins control of thirst, whereas ADH wins control of renal water excretion, at least in the circumstances of early acclimation to microgravity.

Reduced angiotensin II levels early in flight may also decrease fluid intake at that time. Angiotensin II is a physiologically important mediator of thirst and drinking (Guyton and Hall, 1997). On flight day 1, Leach and co-workers (Leach et al., 1996) reported that plasma renin activity declined to half the value seen pre-flight. A decline in plasma renin levels would lead to a reduced level of plasma angiotensin. Evaporative (insensible) loss of fluid decreases somewhat in microgravity (Leach et al., 1978) which, in turn, reduces the need to drink.

ADH decreases back to pre-flight levels by the second day in flight, so persistent in-flight antidiuresis must result from mechanisms other than ADH. Renin–angiotensin may contribute because plasma renin activity is commonly elevated after a few days in space (Smith et al., 1997). However, aldosterone levels usually remain stable or decrease in microgravity (Leach et al., 1996), and such uncoupling between renin–angiotensin and aldosterone also occurs during bed rest (Fortney et al., 1996). Atrial natriuretic peptide (ANP) levels usually tend to decrease during space flight (Leach et al., 1996; Smith et al., 1997), and reduced ANP levels could decrease urine production. Reduced urine flow in space may simply result from the decreased thirst and fluid intake; the mechanism for the latter may be the indirect cause of the former.
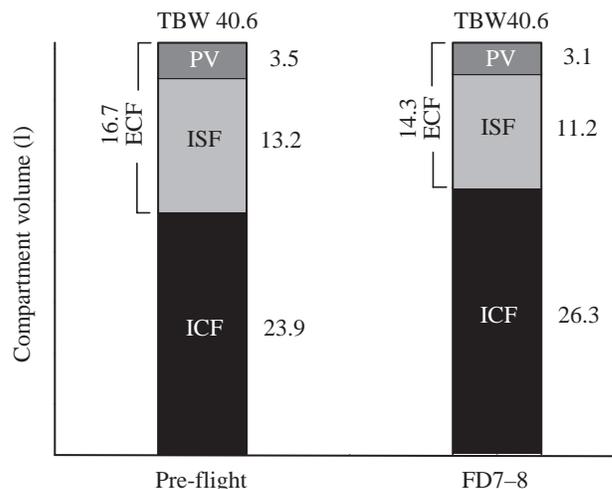

Fig. 3. Mean fluid compartment volumes before and during space flight. Data from Leach and colleagues (Leach et al., 1996) (N=6). TBW, total body water; ECF, extracellular fluid; PV, plasma volume; ISF, interstitial fluid; ICF, intracellular fluid; FD7–8, flight days 7–8.
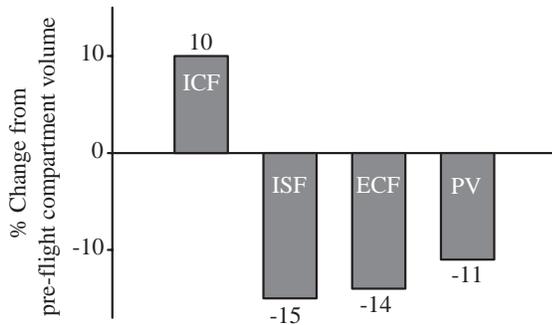
Fig. 4. Mean percentage change in fluid compartment volumes from pre-flight to flight days 7–8. Data from Leach and colleagues (Leach et al., 1996) ($N=6$). ICF, intracellular fluid; ISF, interstitial fluid; ECF, extracellular fluid; PV, plasma volume.
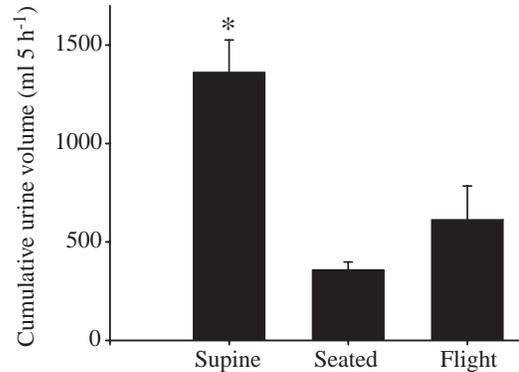

Fig. 5. Cumulative urine volumetric responses (over 5 h) to infusion of 2 % body mass of isotonic saline in pre-flight supine and seated conditions and during flight (flight days 4–6). Data from Norsk and colleagues (Norsk et al., 1995) ($N=4$; means + S.E.M.). *Significantly greater than seated and flight values ($P<0.05$).

Leach and colleagues (Leach et al., 1996) found that extracellular fluid volume decreased in microgravity (by approximately 10 % by flight day 2 and approximately 14 % by flight day 7/8), yet they also found that total body water content remained unchanged in flight, such that calculated intracellular fluid volume tended to increase (Fig. 3, Fig. 4). Given that K^+ is the primary intracellular cation, upregulation of intracellular volume in flight agrees with the trend towards reduced K^+ excretion observed during the first 2 days in flight. Na^+ excretion did not change in microgravity. By the second day in flight, plasma protein concentration decreased back to pre-flight levels, probably as a result of hepatic catabolism of plasma albumin in response to elevated flight day 1 plasma protein levels.

In contrast to the apparent overall intracellular volume elevation, mean erythrocyte volume may decrease somewhat in flight (Alfrey et al., 1996b). Total red blood cell mass decreases by approximately 10 % within 1 week of space flight and may decrease slightly more thereafter (Alfrey et al., 1996b). Alfrey and co-workers (Alfrey et al., 1996a; Alfrey et al., 1996b) explained that the reduction of mean erythrocyte volume may result from preferential destruction in microgravity of younger erythrocytes, which are larger than older erythrocytes. They noted reduced serum erythropoietin levels on flight days 2–4. Microgravity-induced reduction of red blood cell mass follows reduction of plasma volume and is quantitatively similar to, and physiologically appropriate for, the reduced plasma volume. Human fluid metabolism appears to stabilize after the first few days of these relatively short space flights, but during flights lasting months, longer-term acclimation processes may well occur.

In-flight response to isotonic volume expansion

In the first in-flight study of fluid volume regulation employing an experimental intervention, Norsk and co-workers (Norsk et al., 1995) investigated how endocrine and renal responses to an acute isotonic volume stimulus in microgravity compared with those responses in $1\,g$. They assessed the responses of four astronauts to 2 % body mass of isotonic saline (approximately 1.8 l) infused intravenously over 20–22 min in supine and seated postures before flight and in microgravity on flight days 4–6 of the Spacelab D-2 mission.

Norsk and co-workers (Norsk et al., 1995) found that in-flight Na^+ and volume excretory responses to saline infusion were approximately half of those seen in pre-flight supine conditions (Fig. 5), and in-flight responses were somewhat delayed relative to pre-flight supine responses. In-flight responses slightly exceeded those seen in pre-flight seated conditions. They noted that their flight results differed from findings in a ground-based flight simulation employing head-down bed rest: after 6 days of bed rest, Drummer and colleagues (Drummer et al., 1992) observed responses to saline infusion that were similar to pre-bed-rest supine responses.

The flight study also reported plasma norepinephrine and renin concentrations, which approximated or exceeded pre-flight seated levels and which significantly exceeded pre-flight supine levels (Norsk et al., 1995). In-flight aldosterone levels appeared to be intermediate between pre-flight supine and upright values. Other reported catecholamine responses to space flight vary widely (Smith et al., 1997).

Norsk and co-workers (Norsk et al., 1995) stated that microgravity-induced extracellular fluid volume contraction probably led to attenuation of in-flight renal responses to infusion relative to pre-flight supine responses. With the extracellular fluid compartment 10–15 % less than 'full' in microgravity, an infused volume challenge may be temporarily 'stored' more easily in that compartment, thereby allaying renal responses. They further postulated that early in-flight reduction of fluid and Na^+ intake contributes to the extracellular hypovolemia. Finally, their data confirm that fluid volume acclimation to microgravity sets the central circulation to homeostatic conditions similar to those found in an upright sitting posture on Earth (Watenpaugh and Hargens, 1996).

Predictable post-flight fluid regulatory events

After return to Earth, the anomalies seen in microgravity

disappear, and relatively predictable fluid volume regulatory events ensue. As the hypovolemic astronauts again assume an upright posture in gravity, cardiac stroke volume and arterial pressure fall below pre-flight upright levels (Buckey et al., 1996b), and fluid-retaining systems become activated. Relative to pre-flight levels, landing day urinary ADH levels increase almost threefold, plasma renin activity increases almost fourfold, plasma aldosterone levels increase by 50 % and plasma atrial natriuretic peptide levels decrease by 33 % (Leach et al., 1996). Fluid intake is relatively high on landing day, and urine volume is reduced compared with pre-flight values, although above in-flight levels (Fig. 2). Fluid metabolism appears to normalize well within 1 week after returning from 9–14 days in space (Leach et al., 1996). Longer-duration space flights may require longer recovery periods.

The context of limits to human performance

Aerobic exercise training increases blood volume, which then contributes to increased exercise performance by increasing the capacity for oxygen delivery (Sawka et al., 2000). Therefore, does microgravity-induced downregulation of blood and extracellular fluid volumes decrease human exercise performance? If one remains in microgravity, the answer may be 'no'. During Skylab (Michel et al., 1977) and more recently (Levine et al., 1996), investigators saw no significant reduction of peak oxygen consumption or workload during in-flight cycle ergometry. Both these studies involved significant in-flight exercise not directly associated with the peak oxygen consumption testing. Therefore, it remains possible that extracellular hypovolemia and reduced red cell mass could decrease exercise performance in chronic microgravity without maintenance exercise, especially given the neuromuscular deconditioning associated with prolonged existence in microgravity (Edgerton and Roy, 1996). However, Levine and co-workers (Levine et al., 1996) noted that, without gravity pulling the blood down into the lower-body venous circulation during exercise, cardiac filling and muscle perfusion appear to be well maintained during exercise in microgravity, in spite of reduced blood volume. Extravehicular activity imposes additional challenges of low atmospheric (suit) pressure (approximately 34 kPa; Webb et al., 1996) and potential thermoregulatory limitations (Watenpaugh and Hargens, 1996) which, when combined with microgravity-induced hypovolemia, may well reduce exercise performance.

Fluid loss in space most definitely contributes to reduced performance upon return to $1\,g$. Post-flight hypovolemia and relative anemia constitute probably the most important mechanisms for post-flight reduction of orthostatic tolerance and upright exercise capacity (Buckey et al., 1996b; Levine et al., 1996; Michel et al., 1977; Watenpaugh and Hargens, 1996). Compromised cerebral perfusion in upright posture after flight may also reduce mental performance. The hypovolemia results in a reduced stroke volume during orthostasis and exercise which, in turn, decreases cardiac output at a given heart rate and, therefore, decreases the heart rate reserve and peak cardiac output available to compensate for these stresses. Reduced red cell mass decreases exercise performance by decreasing the capacity for oxygen delivery.

Fluid volume regulation and countermeasures to deconditioning in microgravity

Astronauts currently consume 1 l of isotonic drink or water plus salt tablets shortly before re-entry from space to replace some of the fluids lost in flight. On the basis of the results of Norsk and co-workers (Norsk et al., 1995) discussed above, this fluid should be retained longer than if it were ingested in supine $1\,g$ conditions. During post-flight standing tests, the fluid countermeasure partially reverses the commonly observed tachycardia and hypotension (Bungo et al., 1985), but it does not restore responses to pre-flight levels and it may not substantially improve post-flight orthostatic tolerance (Buckey et al., 1996b). No studies exist concerning the effects of late-flight fluid replacement on post-flight exercise performance. One might expect the strategy to offer limited help, given the marginal improvements in orthostatic responses and the fact that fluid replacement does not restore, but instead dilutes, red cell mass. Although probably not practical, it would be interesting to perform late-flight infusion of enough whole blood and saline to replace lost blood volume and interstitial fluid, respectively, and then see to what degree orthostatic and exercise functions were restored.

As noted above, exercise training expands blood volume (Sawka et al., 2000). Therefore, some have postulated that in-flight exercise training may help prevent microgravity-induced losses of fluid and thereby protect orthostatic tolerance and upright exercise capacity (Convertino, 1987; Watenpaugh, 2000). The strategy seems to work for protection of blood volume and exercise capacity during simulated space flight (bed rest), but not necessarily for orthostatic tolerance (Fortney et al., 1997; Watenpaugh et al., 1994). Protection of orthostatic tolerance during space flight probably requires stimulation of orthostatic blood pressure control systems in addition to fluid maintenance or replacement. Exercise may solve the fluid problem, but does not challenge the circulation to maintain cerebral perfusion, as does orthostasis.

However, from a broader perspective, a collection of separate countermeasures against specific single components of microgravity-induced deconditioning (fluid loss, vascular atrophy, cardiac remodeling, skeletal muscle atrophy, bone demineralization, vestibular dysfunction, etc.) is probably not the most efficient way to protect overall astronaut $1\,g$ performance. The body functions as an integrated system so, to be most time- and energy-efficient, countermeasures against $0\,g$ should exploit and stimulate integrated functional adaptations to gravity as much as possible.

Possible future research directions

The substantial recent progress concerning fluid metabolism during space flight naturally leads to new questions. For

example, how does microgravity lead to a reduction in fluid intake? Are the neural and/or humoral consequences of central volume expansion the primary mechanism? The early in-flight ADH/fluid intake anomaly requires explanation. Also, why does microgravity not elicit the predicted natriuresis and diuresis? Do stress-induced ADH secretion and its effects countermand other factors that should favor increased urine flow early in flight?

Interesting discrepancies exist between microgravity and its ground-based simulations such as bed rest and water immersion. The simulations elicit the expected natriuresis and diuresis (Fortney et al., 1996; Norsk and Epstein, 1991), whereas space flight does not. Confounding complications surrounding the early phase of space flight (pre-launch posture, acceleration of launch, stress, space motion sickness, etc.) may partly explain this discrepancy, but other more fundamental differences may also be important.

The effects of microgravity on cell volume and its regulation deserve further attention. It is probable that gravitational force exerts tissue- and cellular-level effects, such that removal of gravitational force leads to reduced tissue pressures (Estenne et al., 1992; Videbaek and Norsk, 1997) and cytoskeletal effects (Guignandon et al., 1995; Skagen, 1998), which could increase cell volumes, for example. The effects of microgravity on cell volume may be linked to neuroendocrine responses to microgravity (Hussy et al., 2000). Given that K^+ is the primary intracellular cation and given the trend for early in-flight reduction of K^+ excretion (Leach et al., 1996), regulation of K^+ levels may prove interesting to study in space.

A recumbent posture during waking hours shifts fluid centrally and thereby activates Henry–Gauer and related reflexes to increase urine flow (Vagnucci et al., 1969). However, at night, renal responses to such fluid shifts are suppressed (Krishna and Danovitch, 1983; Shiraki et al., 1986). No postural fluid shifts occur in space, yet circadian rhythmicity in renal function may or may not persist. The implications of such rhythmicity for fluid metabolism in microgravity remain unknown.

References

Alfrey, C. P., Udden, M. M., Huntoon, C. L. and Driscoll, T. (1996a). Destruction of newly released red blood cells in space flight. *Med. Sci. Sports Exerc.* **28**, S42–S44.

Alfrey, C. P., Udden, M. M., Leach-Huntoon, C., Driscoll, T. and Pickett, M. H. (1996b). Control of red blood cell mass in spaceflight. *J. Appl. Physiol.* **81**, 98–104.

Buckey, J. C., Jr, Gaffney, F. A., Lane, L. D., Levine, B. D., Watenpaugh, D. E., Wright, S. J., Yancy, C. W., Jr, Meyer, D. M. and Blomqvist, C. G. (1996a). Central venous pressure in space. *J. Appl. Physiol.* **81**, 19–25.

Buckey, J. C., Jr, Lane, L. D., Levine, B. D., Watenpaugh, D. E., Wright, S. J., Moore, W. E., Gaffney, F. A. and Blomqvist, C. G. (1996b). Orthostatic intolerance after spaceflight. *J. Appl. Physiol.* **81**, 7–18.

Bungo, M. W., Charles, J. B. and Johnson, P. C., Jr (1985). Cardiovascular deconditioning during space flight and the use of saline as a countermeasure to orthostatic intolerance. *Aviat. Space Env. Med.* **56**, 985–990.

Convertino, V. A. (1987). Potential benefits of maximal exercise just prior to return from weightlessness. *Aviat. Space Environ. Med.* **58**, 568–572.

Draeger, J., Schwartz, R., Groenhoff, S. and Stern, C. (1995). Self-tonometry under microgravity conditions. *Aviat. Space Env. Med.* **66**, 568–570.

Drummer, C., Heer, M., Baisch, F., Blomqvist, C. G., Lang, R. E., Maass, H. and Gerzer, R. (1992). Diuresis and natriuresis following isotonic saline infusion in healthy young volunteers before, during and after HDT. *Acta Physiol. Scand.* **(Suppl.) 604**, 101–111.

Drummer, C., Heer, M., Dressendorfer, R. A., Strasburger, C. J. and Gerzer, R. (1993). Reduced natriuresis during weightlessness. *Clin. Invest.* **71**, 678–686.

Edgerton, R. V. and Roy, R. R. (1996). Neuromuscular adaptations to actual and simulated spaceflight. In *Handbook of Physiology: Environmental Physiology*, vol. I (ed. M. J. Fregly and C. M. Blatteis), pp. 721–763. New York: Oxford University Press.

Estenne, M., Gorini, M., Van Muylem, A., Ninane, V. and Paiva, M. (1992). Rib cage shape and motion in microgravity. *J. Appl. Physiol.* **73**, 946–954.

Foldager, N., Andersen, T. A., Jessen, F. B., Ellegaard, P., Stadeager, C., Videbaek, R. and Norsk, P. (1996). Central venous pressure in humans during microgravity. *J. Appl. Physiol.* **81**, 408–412.

Fortney, S. M., Greenleaf, J. E. and Schneider, V. S. (1996). The physiology of bed rest. In *Handbook of Physiology: Environmental Physiology*, vol. II (ed. M. J. Fregly and C. M. Blatteis), pp. 889–939. New York: Oxford University Press.

Fortney, S. M., Watenpaugh, D. E., Ballard, R. E., Williams, W. J., Lee, S. M. C., Ueno, T., Ertl, A. C. and Hargens, A. R. (1997). Daily supine LBNP exercise during 14-day bedrest does not maintain LBNP-simulated orthostatic tolerance. *Aviat. Space Env. Med.* **68**, 638 (Abstract).

Guignandon, A., Vico, L., Alexandre, C. and Lafage-Proust, M. H. (1995). Shape changes of osteoblastic cells under gravitational variations during parabolic flight – relationship with PGE2 synthesis. *Cell Struct. Funct.* **20**, 369–375.

Guyton, A. C. (1991). *Textbook of Medical Physiology*. Philadelphia: W. B. Saunders Co. 1014pp.

Guyton, A. C. and Hall, J. E. (1997). *Human Physiology and Mechanisms of Disease*. Philadelphia: W. B. Saunders Co. 737pp.

Hussy, N., Deleuze, C., Desarmenien, M. G. and Moos, F. C. (2000). Osmotic regulation of neuronal activity: a new role for taurine and glial cells in a hypothalamic neuroendocrine structure. *Prog. Neurobiol.* **62**, 113–134.

Jurzak, M. and Schmid, H. A. (1998). Vasopressin and sensory circumventricular organs. *Prog. Brain Res.* **119**, 221–245.

Kirsch, K. A., Rocker, L., Gauer, O. H., Krause, R., Leach, C., Wicke, H. J. and Landry, R. (1984). Venous pressure in man during weightlessness. *Science* **225**, 218–219.

Krishna, G. G. and Danovitch, G. M. (1983). Renal response to central volume expansion in humans is attenuated at night. *Am. J. Physiol.* **244**, R481–R486.

Leach, C. S. (1987). Fluid control mechanisms in weightlessness. *Aviat. Space Env. Med.* **58**, A74–A79.

Leach, C. S., Alfrey, C. P., Suki, W. N., Leonard, J. I., Rambaut, P. C., Inners, L. D., Smith, S. M., Lane, H. W. and Krauhs, J. M. (1996). Regulation of body fluid compartments during short-term spaceflight. *J. Appl. Physiol.* **81**, 105–116.

Leach, C. S., Altchuler, S. I. and Cintron-Trevino, N. M. (1983). The endocrine and metabolic responses to space flight. *Med. Sci. Sports Exerc.* **15**, 432–440.

Leach, C. S., Leonard, J. I., Rambaut, P. C. and Johnson, P. C. (1978). Evaporative water loss in man in a gravity-free environment. *J. Appl. Physiol.* **45**, 430–436.

Leach Huntoon, C. S., Grigoriev, A. I. and Natochin, Y. V. (1998). Fluid and electrolyte regulation in spaceflight. In *Science and Technology Series*, vol. 94, 238p. San Diego: Univelt Inc.

Levine, B. D., Lane, L. D., Watenpaugh, D. E., Gaffney, F. A., Buckey, J. C. and Blomqvist, C. G. (1996). Maximal exercise performance after adaptation to microgravity. *J. Appl. Physiol.* **81**, 686–694.

McKinley, M. J., Gerstberger, R., Mathai, M. L., Oldfield, B. J. and Schmid, H. (1999). The lamina terminalis and its role in fluid and electrolyte homeostasis. *J. Clin. Neurosci.* **6**, 289–301.

Michel, E. L., Rummel, J. A., Sawin, C. F., Buderer, M. C. and Lem, J. D. (1977). Results of Skylab Medical Experiment M171 – Metabolic

Activity. In *Biomedical Results from Skylab*, vol. SP-377 (ed. R. S. Johnston and L. F. Dietlein), pp. 372–387. Washington, DC: NASA.

Norsk, P., Drummer, C., Rocker, L., Strollo, F., Christensen, N. J., Warberg, J., Bie, P., Stadeager, C., Johansen, L. B., Heer, M., Gunga, H.-C. and Gerzer, R. (1995). Renal and endocrine responses in humans to isotonic saline infusion during microgravity. *J. Appl. Physiol.* **78**, 2253–2259.

Norsk, P. and Epstein, M. (1991). Manned space flight and the kidney [editorial]. *Am. J. Nephrol.* **11**, 81–97.

Parazynski, S. E., Hargens, A. R., Tucker, B., Aratow, M., Styf, J. and Crenshaw, A. (1991). Transcapillary fluid shifts in tissues of the head and neck during and after simulated microgravity. *J. Appl. Physiol.* **71**, 2469–2475.

Sawka, M. N., Convertino, V. A., Eichner, E. R., Schnieder, S. M. and Young, A. J. (2000). Blood volume: importance and adaptations to exercise training, environmental stresses and trauma/sickness. *Med. Sci. Sports Exerc.* **32**, 332–348.

Shiraki, K., Konda, N., Sagawa, S., Claybaugh, J. R. and Hong, S. K. (1986). Cardiorenal–endocrine responses to head-out immersion at night. *J. Appl. Physiol.* **60**, 176–183.

Skagen, E. B. (1998). Cortical microtubule reorganization in protoplasts isolated from *Brassica napus* hypocotyl is affected by gravity. *J. Gravitat. Physiol.* **5**, P117–P120.

Smith, S. M., Krauhs, J. M. and Leach, C. S. (1997). Regulation of body fluid volume and electrolyte concentrations in spaceflight. *Adv. Space Biol. Med.* **6**, 123–165.

Thornton, W. E., Hedge, V., Coleman, E., Uri, J. J. and Moore, T. P. (1992). Changes in leg volume during microgravity simulation. *Aviat. Space Env. Med.* **63**, 789–794.

Vagnucci, A. H., Shapiro, A. P. and McDonald, R. H., Jr (1969). Effects of upright posture on renal electrolyte cycles. *J. Appl. Physiol.* **26**, 720–731.

Videbaek, R. and Norsk, P. (1997). Atrial distension in humans during microgravity induced by parabolic flights. *J. Appl. Physiol.* **83**, 1862–1866.

Wada, F., Sagawa, S., Miki, K., Nagaya, K., Nakamitsu, S., Shiraki, K. and Greenleaf, J. E. (1995). Mechanism of thirst attenuation during head-out water immersion in men. *Am. J. Physiol.* **268**, R583–R589.

Watenpaugh, D. E., Ballard, R. E., Schneider, S. M., Lee, S. M. C., Ertl, A. C., William, J. M., Boda, W. L., Hutchinson, K. J. and Hargens, A. R. (2000). Supine lower body negative pressure exercise during bed rest maintains upright exercise capacity. *J. Appl. Physiol.* **89**, 218–227.

Watenpaugh, D. E., Fortney, S. M., Ballard, R. E., Lee, S. M. C., Bennett, B. S., Murthy, G., Kramer, G. C. and Hargens, A. R. (1994). Lower body negative pressure exercise during bed rest maintains orthostatic tolerance. *FASEB J.* **8**, A261 (Abstract).

Watenpaugh, D. E. and Hargens, A. R. (1996). The cardiovascular system in microgravity. In *Handbook of Physiology: Environmental Physiology*, vol. I (ed. M. J. Fregly and C. M. Blatteis), pp. 631–674. New York: Oxford University Press.

Watenpaugh, D. E. and Smith, M. L. (1998). Human cardiovascular acclimation to microgravity. *J. Gravitat. Physiol.* **5**, P15–P18.

Watenpaugh, D. E., Yancy, C. W., Buckey, J. C., Lane, L. D., Hargens, A. R. and Blomqvist, C. G. (1992). Role of atrial natriuretic peptide in systemic responses to acute isotonic volume expansion. *J. Appl. Physiol.* **73**, 1218–1226.

Webb, J. T., Fischer, M. D., Heaps, C. L. and Pilmanis, A. A. (1996). Exercise-enhanced preoxygenation increases protection from decompression sickness. *Aviat. Space Env. Med.* **67**, 618–624.

White, R. J. and Blomqvist, C. G. (1998). Central venous pressure and cardiac function during spaceflight. *J. Appl. Physiol.* **85**, 738–746.