

APPENDIX D

CARDIOVASCULAR DISCIPLINE - SUPPORTING MATERIAL

D-1 - Cardiovascular Discipline Report of Countermeasures

Impact of Spaceflight on Cardiovascular Operational Functions

Reduced Orthostatic Function. Predisposition to hypotension and syncopal symptoms during standing, head-up tilt, or lower body negative pressure (LBNP) is well-documented in astronauts following spaceflight [6,8,12,15,23,57,61,74,83,95]. Orthostatic hypotension has been associated with numerous alterations in cardiovascular function (see below). An important operational concern is the postflight presence of orthostatic intolerance with frank syncope in 30-40% of Shuttle crews when not protected by a G-suit and fluid loading [8,9] and 6-9% who are unable to affect immediate egress from the vehicle [77].

Physical deconditioning associated with exposure to microgravity may contribute to reduced effectiveness of blood pressure control during orthostatic challenges following spaceflight because exposure to groundbased simulations can induce higher incidence of syncope in exercise-conditioned subjects compared to their sedentary counterparts [23,81]. This observation provides a basis for the contention that cardiovascular adaptation associated with physical stress may prove to be effective in protecting underlying mechanisms of postflight orthostatic hypotension.

Reduced Physical Work Performance. In the absence of countermeasures, post-flight maximal oxygen uptake (Vo_{2max}) can be decreased by approximately 20% following only 9 to 14 days [68]. Reduced stroke volume and cardiac output are the primary factors contributing to lower aerobic capacity [58,68,81]. In addition to reduced cardiac output, there are also reductions in skeletal muscle blood flow [40] and aerobic pathway enzymes [37,56] which could contribute to limit oxygen delivery and utilization. Vo_{2max} actually increased over the course of the spaceflight in the Skylab 4 crew [15,71]. This was associated with an intensive daily inflight exercise program and indicated that a training effect took place. The commander of Skylab 4, who undertook the least extensive exercise training program both before and during flight compared to other two crewmembers, showed the smallest decrement in Vo_{2max} . This may indicate that intensive exercise may not always be necessary for all individuals during spaceflight. Identification of the minimal amount of exercise needed to maintain pre-flight fitness levels has received little attention to date or whether it is indeed necessary to maintain pre-flight fitness throughout long flights.

Changes in Cardiac Structure and Function

In the absence of some intrinsic disease state, the primary determinants of cardiac structure, mechanical and electrical function and vascular performance include: a) autonomic nervous system function; b) extrinsic cardiac and vascular mechanical loading; c) nutrition and d) drugs and other toxins. There are few data that define if and how these factors may be altered during long duration space missions, with the potential of compromising cardiac structure and function.

Current data suggest that highly trained, well-conditioned healthy young and middle-aged individuals who undertake a relatively active life style in microgravity, with at least moderate exercise, can survive and perform useful work for at least 180 days (and perhaps at least 270 days) with no major overt health problems. At the end of this period, such individuals can return to earth and, though they may require weeks to readapt and function normally, they appear to recover without sequelae manifest within 5-10 years. Remaining unknowns include: a) capacity of such people to function adequately in emergency setting upon reentry; b) capacity to function in microgravity, and upon reentry, during microgravity exposures longer than 6 months; c) deleterious effects of microgravity exposure which become apparent more than 10 years after reentry; and d) impact of microgravity environment on individuals who are older, less well conditioned or who differ in other important ways from the well circumscribed population thus far exposed to microgravity.

Data which have already been analyzed (a small fraction of the total available database) suggest that no major irreversible cardiovascular changes, involving either the heart itself or the vasculature, occur in response to microgravity exposure as defined above. Although few data are available specifically defining the response to microgravity of cardiac structure and performance or intrinsic myocardial function, echocardiographic data provide evidence that cardiac chamber size is reduced in microgravity [3,10,73]. New data using MRI technology provides evidence that this change may represent cardiac muscle atrophy (Blomqvist, unpublished data). This cardiac mass reduction could result from reduced vascular volume and/or interstitial space fluid in the heart. However, dramatic reductions in baseline [10,21,42], orthostatic [6,21,42] and exercise [3,15,68] stroke volumes appear to be primarily the result of lower blood volume since indices of ventricular function (e.g., ejection fraction, aortic pulse wave velocity) are not altered or may actually increase [3,15, 23,73].

Groundbased experiments have demonstrated increases in b₁-adrenergic responsiveness following 16 days of head-down tilt [22]. A given adrenergic discharge would be expected to lead to excessive tachycardia with such alterations, a well-documented phenomenon associated with postflight standing. Therefore, increased responsiveness of cardiac b₁-adrenergic receptors represents a mechanism that may contribute to orthostatically-induced tachycardia following exposure to low gravity.

Small data sets of rhythm recordings suggest the likelihood of ventricular dysrhythmic activity may be related to the duration of microgravity exposure. Arrhythmias observed have included non-sustained ventricular tachycardia. Similar data sets indicate that,

during exposure to microgravity, both heart rate and blood pressure are lower than on earth. Although the incidence of cardiac dysrhythmias has not increased during space missions of duration less than 10 days [48], they have been reported during both spaceflight and groundbased analogues of microgravity with exposures of longer than two weeks. Pre-ventricular atrial contractions (PACs), supraventricular and ventricular contractions, and nodal bigeminy were reported in Apollo 15 crew members who had not experienced such dysrhythmias before flight [54]. During provocative adrenergic agonist testing, increased occurrence of junctional or nodal arrhythmias was observed following head-down bedrest [22]. This is particularly intriguing in light of observations that altered autonomic function was postulated as a possible mechanism underlying changes in junctional rhythm frequently observed in astronauts during the U.S. Skylab missions [86]. There were no junctional rhythms in 8 subjects during adrenergic agonist infusion tests conducted before head-down bedrest. However, following 14 days of exposure to low gravity, isoproterenol induced junctional rhythms in three subjects, with pre-ventricular contractions (PVC's) occurring in one those subjects and pre-atrial contractions (PAC's) occurring in another. Phenylephrine infusion was associated with junctional rhythm for 2 minutes with 1 interpolated beat in one subject, junctional rhythm and PVCs in one subject, bradycardia of 35 bpm with erratic rhythm with escape beats in one subject, and PACs in one subject. These observations indicate that exposure and adaptation to microgravity may increase risk of cardiac arrhythmias.

Structural and Functional Changes of the Vasculature

Changes in Venous Vasculature. There is compelling evidence based on occlusion plethysmography of the legs that venous compliance of the legs (calf) is increased by exposure to microgravity [14,91]. Reduction of leg muscle size in humans with the use of a low gravity model (head-down tilt) increased venous compliance, supporting a causal relationship that a loss in the muscle compartment surrounding the large veins will increase their compliance. Muscle mass causes mechanical compression on the veins that can act to resist venous stretching and consequently reduce blood volume accumulation under a given change in hydrostatic pressure. Leg compliance appears to be less when there is a large muscle mass providing mechanical resistance to limit expansion of the veins. Therefore, an increase in venous compliance in low gravity seems reasonable since a loss of muscle mass in the legs due to disuse in microgravity and bedrest is well established [37,56,91]. Attenuation of autonomically activated vascular smooth muscle, baseline contractile activity or skeletal muscle and venosomatic reflexes [90], and factors other than muscle structure, such as vascular wall structure and fluid shifts from the legs to the circulation, can also contribute to the overall state of venous compliance. Although not yet demonstrated, the possibility that low gravity may induce physiologically significant alterations in one or more of these other determinants of limb compliance cannot be ruled out. However, relationships derived from previous investigations [13,14] suggest that muscle size alone is the primary contributor to elevated limb compliance in subjects exposed to low gravity. Although increased venous compliance would enhance

blood pooling in the lower extremities during orthostasis, there is little evidence that pooling of fluid in the legs is increased following actual or simulated microgravity [6,42].

Changes in Arterial Vasculature. Numerous investigators have reported that exposure to low gravity reduced baseline blood flow [5,21,28,49] and maximal conductance [40] in the vasculature of the arms and legs, suggesting that spaceflight may alter arterial structure and function. Reduction in maximal conductance was associated with greater muscle fatigability [40]. Excessive sympathetic discharge following exposure to actual or simulated microgravity, as evidenced by large elevations in plasma catecholamines during standing [94,98] and increases in urinary noradrenaline and its metabolites [64,67], probably represent the primary mechanism of vasoconstriction and reduced blood flow. Increased vasoconstrictive state appears to be coupled to lower plasma volume since replacement of vascular volume lowers forearm vascular resistance following exposure to head-down tilt [94].

Autonomic and Baroreflex Regulatory Function

Altered Autonomic Balance. Power spectral and time series analyses of baseline R-R intervals from subjects exposed to groundbased analogues of microgravity indicate reductions in high frequency (0.25 Hz) spectrum and standard deviations of R-R intervals, suggesting a reduction in parasympathetic activity [30]. Reduction in diurnal variabilities of heart rate and systolic and diastolic pressures [48] in astronauts during spaceflight supports the notion that parasympathetic activity is reduced.

Although direct measurements of sympathetic nerve activity have not been conducted on individuals exposed to low gravity, reduction in plasma catecholamines during groundbased analogues [21,22,50] and spaceflight [65,80] support the hypothesis that reduced sympathetic stimulation and discharge might be expected with exposure to low gravity environments. However, excessive sympathetic discharge following exposure to actual or simulated microgravity is evidenced by large elevations in plasma catecholamines during standing [94,98] and exercise [41] with concomitant cardioacceleration. Such increases would be expected under conditions of hypovolemia and orthostatic hypotension.

Enhanced Aortic-Cardiac Baroreflex Responsiveness. Although the ability to investigate aortic-cardiac baroreflex function in humans is limited by the anatomical location of baroreceptors, the isolation of aortic baroreceptors has been attempted with the application of neck chambers and lower body negative pressure devices designed to 'clamp' carotid and cardiopulmonary baroreceptor activity during selective pharmacological stimulation [27,29]. When these procedures are applied, it is clear that the heart rate response to aortic baroreceptor stimulation is enhanced following exposure to low gravity [29]. Although this enhanced baroreflex responsiveness may reflect alteration in autonomic function, it appears that a primary underlying mechanism is the hypovolemia associated with low gravity exposure since normovolemia reverses the

heightened response [27]. Thus, restoration of plasma volume should alleviate the primary change in aortic-cardiac baroreflex response.

Impaired Carotid-Cardiac Baroreflex Function. Despite greater standing tachycardia after spaceflight, standing heart rates were lower in syncopal compared to non-syncopal subjects following head-down tilt [16] and began to decline as the duration of spaceflight became longer than 10 to 12 days [74]. These observations raised the possibility that low gravity causes impairment of cardioacceleratory reflexes elicited by carotid baroreceptors since aortic baroreceptor stimulation was associated with enhanced chronotropic response (see above). Impairment of this vagally-mediated carotid-cardiac baroreflex has subsequently been demonstrated after groundbased analogs [16,36] and actual spaceflight [46,74] and its magnitude of attenuation correlated positively with development of orthostatic hypotension and instability (syncope) immediately upon standing [16].

A prominent feature of the change in carotid-cardiac baroreflex adaptation to low gravity is a shift of the stimulus-response relationship downward and to the right, producing a lower gain (less maximum response slope). This indicates that for a given reduction in arterial pressure, there will be a smaller compensatory increase in heart rate after adaptation to low gravity. Since there is little change in baseline mean arterial pressure, elevation in baseline heart rate places the operational point at a lower position near the threshold on the response curve. This relocation of operational point on a less responsive part of the stimulus-response relationship (near threshold in the hypotension range) further compromises the capacity of this reflex to increase heart rate in the face of an orthostatic challenge such as simple standing. Acute alterations in plasma volume do not affect carotid-cardiac baroreflex response [89] and the time course of changes in baroreflex function during bedrest do not parallel that of plasma volume [16]. These data suggest that, unlike aortic-cardiac baroreflex function, impaired carotid-cardiac baroreflex function occurs during low gravity independent of plasma volume reduction and probably cannot be countered with treatments that address the mechanism(s) that control fluid homeostasis.

These alterations in carotid-cardiac baroreflex provide mechanisms that can explain several clinical observations regarding the development of orthostatic hypotension and intolerance following long-term exposure to low gravity. The increase in standing heart rate following spaceflight can be explained by hypovolemia that elicits an exaggerated cardiac response from aortic baroreceptor stimulation. However, some individuals with pronounced orthostatic hypotension after extended exposure to head-down tilt demonstrated less tachycardia during standing than subjects who maintained blood pressure [165], and orthostatic instability after spaceflight was associated with a lower operational setpoint [47]. The observation that reduced maximum gain and lower operational point of the carotid-cardiac baroreflex stimulus-response relationship were associated with orthostatic intolerance [16,47,69] supports the notion that impairment of this reflex function may represent a major autonomic disorder associated with low gravity.

Reduced Vasoconstrictive Reserve. Numerous investigators have reported that exposure to low gravity increased baseline peripheral vascular resistance [21,30,49]. Reflex peripheral vasoconstriction induced by activation of cardiopulmonary baroreceptors in response to a reduction in central venous pressure (CVP) is a basic mechanism for elevating systemic vascular resistance and defending arterial blood pressure during an orthostatic challenge. When hypovolemia is induced in ambulatory subjects, forearm vascular resistance (FVR) is elevated with an upward shift of the stimulus-response curve compared to a normovolemic baseline state [89]. Since the vascular system has a finite vasoconstrictive capacity, it is reasonable to interpret elevated FVR during hypovolemia as representing a reduction in the reserve capacity for further vasoconstriction. The increased slope, or gain, of the cardiopulmonary baroreflex response induced by hypovolemia demonstrates a more responsive peripheral vasoconstriction in a volume-depleted state compared with normovolemia. This appears to be an appropriate adjustment to defend arterial blood pressure. However, the increased cardiopulmonary baroreflex gain represents utilization of vasoconstrictive reserve which, depending on the degree of hypovolemia, could significantly compromise the capacity to provide adequate vascular resistance during orthostatism. Since hypovolemia occurs in low gravity, inadequate elevation of peripheral vascular resistance and maintenance of arterial pressure during standing immediately after exposure to groundbased analogues or actual spaceflight can limit orthostatic function.

Reduction in Central Venous Pressure. Recent spaceflight data indicate that central venous pressure (CVP) is reduced immediately upon entry into orbit [7]. Although the mechanism(s) is unclear, increased cardiac compliance has been proposed with the observation that stroke volume is maintained despite reduced filling pressure [96]. Beyond the acute phase of spaceflight, there is a chronic reduction CVP associated with low gravity [20,61] that may represent an alteration in autonomic functions associated with feedback regulation of blood volume [26]. There is compelling evidence that the reduction in CVP observed during long duration exposure to low gravity represents a 'resetting' of CVP to a lower operating point. Evidence to support this hypothesis includes failure of fluid input to effectively expand plasma volume [94], similar volumes of fluid infusion induce similar volumes of urine excretion despite lower plasma volume in low gravity compared to normal gravity [33], and exposure to head-down tilt 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 CVPs [21,26]. Physiologically, these observations suggest that low gravity causes a resetting of volume control mechanism(s) to a lower operational range for CVP. Clinically, this adaptation will limit the capacity for replacement of plasma volume by simple drinking techniques.

Autonomic resetting of low-pressure baroreceptors to a lower operating range of CVP has two potentially compromising consequences. First, there is less vasoconstriction at the same level of hypovolemia and CVP following exposure to low gravity compared to that of ambulatory hypovolemia. Therefore, less vascular resistance can be developed in the face of low plasma volume and blood pressure after exposure to low gravity. Second,

lower CVP during orthostatic challenge during low gravity is associated with lower cardiac filling and stroke volume, factors that will also limit appropriate blood pressure regulation. Therefore, the adaptation of the cardiopulmonary baroreflex to low gravity can compromise the capacity to increase both cardiac output and peripheral vascular resistance, the two factors that dictate maintenance of arterial pressure during standing.

Finally, the integration of various baroreflex systems should be appreciated. There is evidence that cardiopulmonary baroreceptor unloading results in elevated sensitivity of aortic baroreceptors [4]. Since low gravity reduces blood volume and CVP, reduced tonic inhibition of aortic baroreceptors associated with cardiopulmonary baroreceptor unloading may represent a primary mechanism that contributes to the accentuation of aortic-cardiac baroreflex gain observed with low gravity.

Adrenoreceptor Hypersensitivity. It has been postulated that orthostatic hypotension associated with exposure to low gravity may be partly attributable to adrenergic receptor hypersensitivity in the face of excessively high sympathetic activation [80].

b₂ adrenergic responsiveness was increased in subjects exposed to 16 days of a groundbase analogue of microgravity without affecting α₁-vascular responses [22]. Because vascular b₂-adrenoreceptors elicit vasodilation compared to vascular constriction mediated by α₁-adrenoreceptors, the overall effect of greater b₂ responsiveness in the absence of changes in α₁ responses could produce a lesser vasoconstrictive effect, especially under a condition of increased sympathetic discharge during standing after exposure to low gravity. This hypothesis is supported by the observations that maximal contractile tension in isolated rat aorta evoked by norepinephrine, phenylephrine and vasopressin was diminished by 14 days of head-down tilt [32] and that normal reductions in blood flow to inactive muscle and visceral tissue during exercise did not occur in rats exposed to head-down tilt [70]. The potential to limit orthostatically-induced elevations in peripheral resistance could compromise the capacity of the cardiovascular system to maintain adequate arterial blood pressure and cerebral perfusion during standing. This is consistent with the observation that astronauts who could not complete a 10-min stand test following spaceflight as a result of severe presyncopal symptoms had significantly less elevation in their peripheral resistance compared to that of astronauts who successfully completed the stand test [6].

Especially in the setting of hypovolemia, excessive adrenergic discharge observed upon standing after exposure to low gravity might be ineffective in maintaining upright blood pressure, and baroreceptor-mediated elevations in heart rate might be further enhanced. Since excess tachycardia and contraction against a nearly empty ventricular chamber is known to trigger the Bezold-Jarisch response [85], increased cardiac b-adrenoreceptor hypersensitivity may be an underlying mechanism for orthostatic hypotension and vasovagal syncope associated with low gravity. Although speculative, this possibility has practical implication for development of possible treatments. For example, the use of a b-blocker prior to reambulation might reduce the potential for a vasovagal event. Also, regular exercise has been associated with reduced b-

adrenoreceptor hypersensitivity [11]. Combined with treatment to diminish volume losses, exercise and pharmacological countermeasures might improve orthostatic stability at critical times following reentry.

Role of Skeletal Muscle in Neural Control of Blood Pressure. Neural activity which is responsible for recruitment of motor units in the cerebral cortex and stimulation of mechanoreceptors and metaboreceptors in the contracting muscle reflexively activate cardiovascular control areas in the ventrolateral medulla [35,72]. These central command mechanisms therefore link skeletal muscle activity to autonomic efferent control of the heart and blood vessels. Since there is significant atrophy of skeletal muscle [37] and reduction in skeletal muscle blood flow (see above) during spaceflight, it is possible that the interaction between muscle afferent neural input and central command may be altered. Likewise, it is possible that specific exercise countermeasures may be designed that can enhance the gain between muscle afferent neural input and central command so with muscle movement during standing following spaceflight, there is increased MSNA to the heart and blood vessels, acting to elevated cardiac output and vascular resistance to defend against development of orthostatic hypotension.

Changes in Vascular Volume

As much as 20% reductions in plasma and blood volume are induced by spaceflight [1,2,26], occurring in the initial 24 h of the mission followed by a new equilibrium at a lower volume which is maintained for the remainder of the flight [1,2,26]. Reduction in total circulating blood volume is related to greater tachycardia during standing after spaceflight [9,16,57], suggesting that vascular volume can be an important contributing factor to post-spaceflight orthostatic hypotension and instability. Although the mechanisms are unclear, normal urine output and renal function in the presence of normal fluid intake throughout exposure to low gravity suggest that plasma volume reduction and failure for its maintenance at 1G levels during low gravity is not associated with clinical renal dysfunction [25,26]. A rapid diuresis occurs within the initial 24-48 h of exposure to groundbased analogs of microgravity [26], with a magnitude that can account for the amount of plasma volume reduction. The diuresis may be partly explained by stimulation of mechanoreceptors that leads to a release of atrial natriuretic peptide [51] and a fall in ADH, renin and aldosterone [31].

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 (restoration) during attempts to increase fluid intake [26,33]. In groundbase and spaceflight 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 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 [18,84], has been effective in expanding

plasma volume when combined with adequate dietary intake of fluid and electrolytes [26]. Therefore, there is adequate justification for the use of exercise in restoring or maintaining plasma volume following adaptation to spaceflight.

Because reduction of blood volume during spaceflight is related to orthostatic instability, it seems reasonable that exercise regimens designed to promote hypervolemia might prove effective against orthostatic hypotension. However, data from both spaceflight and ground experiments do not necessarily support this hypothesis. Despite extensive exercise training which increased $\text{Vo}_{2\text{max}}$ by 8%, the three astronauts who completed the 84-day Skylab 4 mission experienced 16% plasma volume reduction, increased venous compliance, and orthostatic instability postflight [15]. Conversely, in a groundbase experiment [52] with intensive cycle exercise training performed for two 30-min periods per day for five days per week during HDT, $\text{Vo}_{2\text{max}}$ and plasma volume were maintained at pre-HDT levels, while groups who performed resistance or no exercise experienced significant reductions in these parameters. However, tolerance time during head-up tilt were significantly reduced in all three groups with no difference between them. Because blood volume was maintained in the cycle-trained subjects, physiological mechanisms in addition to hypovolemia must contribute to orthostatic intolerance. These results from spaceflight and ground studies suggest that repeated exercise training regimens, designed to defend physical fitness, require more specificity to provide appropriate stimuli to the mechanism(s) that control orthostatic stability.

Alterations in autonomic function during exposure to low gravity may have direct effects on blood volume regulation. It has been postulated that lower sympathetic stimulation and discharge in low gravity may contribute to hypovolemia and anemia that accompany spaceflight [80]. Renal denervation substantially increases renal sodium loss. Patients with the Bradbury-Eggleston syndrome, who suffer from the degeneration of peripheral autonomic nerves, particularly illustrate this natriuretic effect while kidney production of dopamine is relatively normal [79]. The expected effects of this neurohumoral alteration would fit the observed reduction in circulating plasma volume and sodium observed in spaceflight and at bedrest that is accompanied by a reduction in plasma renin activity [31]. Therefore, it is possible that a reduction in sympathetic activation and circulating norepinephrine in low gravity could result in increased renal sodium loss because the natriuretic effect of dopamine would be unopposed. This could contribute to the reduction in plasma volume that occurs in the course of the first day of spaceflight. While the central fluid shift seen with low gravity may have the most consequential effect on reduced plasma volume, the specific role of renal sympathetic activity deserves further investigation.

In addition to a loss in plasma volume, the hypovolemia induced by prolonged exposure to low gravity can be contributed to by a more gradual reduction in red cell mass [34,60,66], probably due to a fall in erythropoietin levels [1,2,66]. An association between the sympathetic nervous system and erythropoiesis has been supported by the observation that the reticulocyte response to acute bloodletting was greatly diminished after renal denervation [87]. Intravenous administration of the b-adrenergic receptor

agonist salbutamol increased serum erythropoietin [43] while b-blockers blunted the erythropoietin response to hypoxia [44]. These experimental results provide compelling evidence that sympathetic stimulation, acting through b2-adrenoreceptors, may modulated erythropoiesis through increased erythropoietin production. Thus, reduced sympathetic activity and reduced circulating norepinephrine associated with low gravity could represent an underlying mechanism for the anemia observed with space travel and bedrest.

Following space missions of less than 7 days duration, ingestion of approximately one liter of isotonic saline reduced the heart rate response and maintained blood pressure in astronauts during post-spaceflight stand tests. This observation supported the hypothesis that body fluid loss was a primary mechanism of orthostatic compromise following spaceflight [10,97]. However, when stand test experiments were conducted on bedrested subjects or astronauts who had been exposed to low gravity for durations at or beyond one week, it became apparent that hypovolemia alone could not explain orthostatic compromise since heart rate and blood pressure responses during standing were similar in individuals who did and did not undergo fluid loading procedures [94,97]. It has become apparent that alterations in autonomic functions associated with blood volume and pressure regulation are induced by exposure to low gravity.

References

1. Alfrey, C., M.M. Udden, C.L. Huntoon, T. Driscoll, M.H. Pickett. Control of red blood cell mass in spaceflight. *J. Appl. Physiol.* 81:98-104, 1996.
2. Alfrey, C., M.M. Udden, C.L. Huntoon, and T. Driscoll. Destruction of newly released red blood cells in spaceflight. *Med. Sci. Sports Exerc.* 28:S42-S44, 1996.
3. Atkov, O.Yu., V.S. Bednenko, and G.A. Fomina. Ultrasound techniques in space medicine. *Aviat. Space Environ. Med.* 58(suppl 9):A69-A73, 1987.
4. Bishop, V.S., A. Malliani, and P. Thoren. Cardiac Mechanoreceptors. In: *Handbook of Physiology: The Cardiovascular System. Section 2, Vol. III*, edited by J.T. Shepherd and F.M. Abboud. Bethesda: American Physiological Society, 1983, p. 497-555.
5. Blamick, C.A., D.J. Goldwater, and V.A. Convertino. Leg vascular responsiveness during acute orthostasis following simulated weightlessness. *Aviat. Space Environ. Med.* 59:40-43, 1988.
6. Buckey, J.C., Jr., L.D. Lane, B.D. Levine, D.E. Watenpaugh, S.J. Wright, W.E. Moore, F.A. Gaffney, and C.G. Blomqvist. Orthostatic intolerance after spaceflight. *J. Appl. Physiol.* 81:7-18, 1996.

7. Buckey, J.C., Jr., F.A. Gaffney, L.D. Lane, B.D. Levine, D.E. Watenpaugh, S.J. Wright, C.W. Yancy, D. Meyer, and C.G. Blomqvist. Central venous pressure in space. *J. Appl. Physiol.* 81:19-25, 1996.
8. Bungo, M.W., and P.C. Johnson, Jr. Cardiovascular examinations and observations of deconditioning during the space shuttle orbital flight test program. *Aviat. Space Environ. Med.* 54:1001-1004, 1983.
9. Bungo, M.W., J.B. Charles, and P.C. Johnson. Cardiovascular deconditioning during space flight and the use of saline as a countermeasure to orthostatic intolerance. *Aviat. Space Environ. Med.* 56:985-990, 1985.
10. Bungo, M.W., D.J. Goldwater, R.L. Popp, and H. Sandler. Echocardiographic evaluation of space shuttle crewmembers. *J. Appl. Physiol.* 62:278-283, 1987.
11. Butler, J., M. O'Brien, K. O'Malley, and J.G. Kelly. Relationship of β -adrenoreceptor density to fitness in athletes. *Nature* 298:60-62, 1982.
12. Charles, J.B., and C.M. Lathers. Summary of lower body negative pressure experiments during space flight. *J. Clin. Pharmacol.* 34:571-583, 1994.
13. Convertino, V.A., D.F. Doerr, J.F. Flores, G.W. Hoffler, and P. Buchanan. Leg size and muscle functions associated with leg compliance. *J. Appl. Physiol.* 64:1017-1021, 1988.
14. Convertino, V.A., D.F. Doerr, and S.L. Stein. Changes in size and compliance of the calf following 30 days of simulated microgravity. *J. Appl. Physiol.* 66:1509-1512, 1989.
15. Convertino, V.A. Physiological adaptations to weightlessness: effects on exercise and work performance. *Exer. Sports Sci. Rev.* 18:119-165, 1990.
16. Convertino, V.A., D.F. Doerr, D.L. Eckberg, J.M. Fritsch, and J. Vernikos-Danellis. Head-down bedrest impairs vagal baroreflex responses and provokes orthostatic hypotension. *J. Appl. Physiol.* 68:1458-1464, 1990.
17. Convertino, V.A. Blood volume: its adaptation to endurance training. *Med. Sci. Sports Exerc.* 23:1338-1348, 1991.
18. Convertino, V.A., G.W. Mack, and E.R. Nadel. Elevated venous pressure: a consequence of exercise training-induced hypervolemia? *Am. J. Physiol. (Regulatory Integrative Comp. Physiol.)* 260:R273-R277, 1991.

19. Convertino, V.A. Carotid-cardiac baroreflex: relation with orthostatic hypotension following simulated microgravity and implications for development of countermeasures. *Acta Astronautica* 23:9-17, 1991.
20. Convertino, V.A. Effects of exercise and inactivity on intravascular volume and cardiovascular control mechanisms. *Acta Astronautica* 27:123-129, 1992.
21. Convertino, V.A., D.F. Doerr, D.A. Ludwig, and J. Vernikos. Effect of simulated microgravity on cardiopulmonary baroreflex control of forearm vascular resistance. *Am. J. Physiol. (Regulatory Integrative Comp. Physiol.)* 266:R1962-R1969, 1994.
22. Convertino, V.A., J.L. Polet, K.A. Engelke, G.W. Hoffler, L.D. Lane, and C.G. Blomqvist. Increased b-adrenergic responsiveness induced by 14 days exposure to simulated microgravity. *J. Gravitational Physiol.* 2:P66-P67, 1995.
23. Convertino, V.A. Exercise and Adaptation to Microgravity Environments. In: *Handbook of Physiology: Environmental Physiology. III. The Gravitational Environment.* M.J. Fregly & C.M. Blatteis (eds). New York, NY:Oxford University Press. Section 1, Chapter 36, 1995, p. 815-843.
24. Convertino, V.A. Exercise as a countermeasure for physiological adaptation to prolonged spaceflight. *Med. Sci. Sports Exerc.* 28:999-1014, 1996.
25. Convertino, V.A., K.A. Engelke, D.A. Ludwig, and D.F. Doerr. Restoration of plasma volume after 16 days of head-down tilt induced by a single bout of maximal exercise. *Am. J. Physiol. (Regulatory Integrative Comp. Physiol.)* 270:R3-R10, 1996.
26. Convertino, V.A. Clinical aspects of the control of plasma volume at microgravity and during return to one gravity. *Med. Sci. Sports Exerc.* 81:S45-S52, 1996.
27. Convertino, V.A. Effects of hypovolemia on the aortic-cardiac baroreflex response. *Aviat. Space Environ. Med.* 1997 (in press).
28. Crandall, C.G., J.M. Johnson, V.A. Convertino, P.B. Raven, and K.A. Engelke. Altered thermo-regulatory responses after 15 days of head-down tilt. *J. Appl. Physiol.* 77:1863-1867, 1994.
29. Crandall, C.G., K.A. Engelke, V.A. Convertino, and P.B. Raven. Aortic baroreflex control of heart rate following 15 days of simulated microgravity exposure. *J. Appl. Physiol.* 77:2134-2139, 1994.
30. Crandall, C.G., K.A. Engelke, J.A. Pawelczyk, P.B. Raven, and V.A. Convertino. Power spectral and time based analysis of heart rate variability following 15 days

simulated microgravity exposure in humans. *Aviat. Space Environ. Med.* 65:1105-1109, 1994.

31. Dallman, M.F., J. Vernikos, L.C. Keil, D. O'Hara, and V.A. Convertino. Hormonal, fluid and electrolyte responses to 6° antiorthostatic bed rest in healthy male subjects. In: *Stress: Role of Catecholamines and Other Neurotransmitters*. New York: Gordon and Breach Sci. Publ. Inc., 1984, p. 1057-1077.
32. Delp, M.D., T. Holder-Brinkley, M.H. Laughlin, and E.M. Hasser. Vasoconstrictor properties of rat aorta are diminished by hindlimb unweighting. *J. Appl. Physiol.* 75:2620-2628, 1993.
33. Drummer, C., M. Heer, F. Baisch, C.G. Blomqvist, R.E. Lang, H. Maass, and R. Gerzer. Diuresis and natriuresis following isotonic saline infusion in healthy young volunteers before, during and after HDT. *Acta Physiol. Scand.* 144:101-111, 1992.
34. Dunn, C.D.R., R.D. Lange, S.L. Kimzey, P.C. Johnson, and C.S. Leach. Serum erythropoietin titers during prolonged bedrest: relevance to the "anemia" of spaceflight. *Eur. J. Appl. Physiol.* 52:178-182, 1984.
35. Ebel, D., and K. Baum. Influence of gravity on cardiovascular reflexes from skeletal muscle receptors. *Med. Sci. Sports Exerc.* 81:S23-S28, 1996.
36. Eckberg, D.L., and J.M. Fritsch. Influence of ten day head-down bedrest on human carotid baroreceptor-cardiac reflex function. *Acta Physiol. Scand.* 144:69-76, 1992.
37. Edgerton, V.R., M.-Y. Zhou, Y. Ohira, H. Klitgaard, B. Jiang, G. Bell, B. Harris, B. Saltin, P.D. Gollnick, R.R. Roy, M.K. Day, and M. Greenisen. Human fiber size and enzymatic properties after 5 and 11 days of spaceflight. *J. Appl. Physiol.* 78:1733-1739, 1995.
38. Engelke, K.A., J.D. Shea, D.F. Doerr, and V.A. Convertino. Autonomic functions and orthostatic responses 24 hours after acute intense exercise in paraplegic subjects. *Am. J. Physiol. (Regulatory Integrative Comp. Physiol.)* 266:R1189-R1196, 1994.
39. Engelke, K.A., D.F. Doerr, and V.A. Convertino. A single bout of exhaustive exercise affects integrated baroreflex function after 16 days of head-down tilt. *Am. J. Physiol. (Regulatory Integrative Comp. Physiol.)* 269:R614-R620, 1995.
40. Engelke, K.A., B. Levine, and V.A. Convertino. Effects of acute maximal exercise on maximal leg conductance following exposure to 16 days of simulated microgravity. *Med. Sci. Sports Exerc.* 27:S187, 1995.

41. Engelke, K.A., and V.A. Convertino. Catecholamine response to maximal exercise following 16 days of simulated microgravity. *Aviat. Space Environ. Med.* 67:243-247, 1996.
42. Engelke, K.A., D.F. Doerr, and V.A. Convertino. Application of acute maximal exercise to protect orthostatic tolerance after simulated microgravity. *Am. J. Physiol. (Regulatory Integrative Comp. Physiol.)* 271:R837-R847, 1996.
43. Fink, G.D., and J.W. Fisher. Stimulation of erythropoiesis beta adrenergic agonists. II. Mechanisms of action. *J. Pharmacol. Exp. Ther.* 202:199-207, 1977.
44. Fink, G.D., L.G. Paulo, and J.W. Fisher. Effects of beta adrenergic blocking agents on erythropoietin production in rabbits exposed to hypoxia. *J. Pharmacol. Exp. Ther.* 193:176-181, 1975.
45. Fortney, S.M. Development of lower body negative pressure as a countermeasure for orthostatic intolerance. *J. Clin. Pharmacol.* 31:888-892, 1991.
46. Fritsch, J.M., J.B. Charles, B.S. Bennett, M.M. Jones, and D.L. Wood. Short-duration spaceflight impairs human carotid baroreceptor-cardiac reflex responses. *J. Appl. Physiol.* 73:664-671, 1992.
47. Fritsch-Yelle, J.M., J.B. Charles, M.M. Jones, L.A. Beightol, and D.L. Eckberg. Spaceflight alters autonomic regulation of arterial pressure in humans. *J. Appl. Physiol.* 77:1776-1783, 1994.
48. Fritsch-Yelle, J.M., J.B. Charles, M.M. Jones, and M.L. Wood. Microgravity decreases heart rate and arterial pressure in humans. *J. Appl. Physiol.* 80:910-914, 1996.
49. Gabrielsen, A., P. Norsk, R. Videraek, and O. Hendriksen. Effect of microgravity on forearm subcutaneous vascular resistance in humans. *J. Appl. Physiol.* 79:434-438, 1995.
50. Goldstein, D.S., J. Vernikos, C. Holmes, and V.A. Convertino. Catecholaminergic effects of prolonged head-down bed rest. *J. Appl. Physiol.* 78:1023-1029, 1995.
51. Graham, R.M., and J.B. Zisfein. Atrial natriuretic factor regulation and control in circulatory homeostasis. In: *The Heart and Cardiovascular System*. Scientific Foundation, Fozzard, H.A., E. Haber, R.B. Jennings, A.M. Katz, and H.E. Morgan (eds). New York:Raven Press, 1986, p. 1559-1572.
52. Greenleaf, J.E., C.E. Wade, and G. Leftheriotis. Orthostatic responses following 30-day bed rest deconditioning with isotonic and isokinetic exercise training. *Aviat. Space Environ. Med.* 60:537-542, 1989.

53. Guell, A. Lower body negative pressure as a countermeasure for long term spaceflight. *Acta Astronautica* 35:271-280, 1995.
54. Hawkins, W.R., and J.F. Zieglschmid. Clinical aspects of crew health. In: *Biomedical Results of Apollo*, edited by R.S. Johnston, L.F. Dietlein, and C.A. Berry. Wash., DC: BioTechnology, 1975, p. 43-81.
55. Heer, M., A. Zittermann, and D. Hoetzel. Role of nutrition during long-term spaceflight. *Acta Astronautica* 35:297-312, 1995.
56. Hikida, R.S., P.D. Gollnick, G.A. Dudley, V.A. Convertino, and P. Buchanan. Structural and metabolic characteristics of human skeletal muscle following 30 days of simulated microgravity. *Aviat. Space Environ. Med.* 60:664-670, 1989.
57. Hoffler, G.W. Cardiovascular studies of U.S. space crews: an overview and perspective. In: *Cardiovascular Flow Dynamics and Measurements*, edited by Hwang, N.H.C. and Normann, N.A. University Park Press, Baltimore, 1977, pp. 335-363.
58. Hung, J., D. Goldwater, V.A. Convertino, J.H. McKillop, M.L. Goris, and R.F. DeBusk. Mechanisms for decreased exercise capacity following bedrest in normal middle-aged men. *Am. J. Cardiol.* 51:344-348, 1983.
59. Hyatt, K. H., and D.A. West. Reversal of bedrest-induced orthostatic intolerance by lower body negative pressure and saline. *Aviat. Space Environ. Med.* 48:120-124, 1977.
60. Johnson, P.C., T.B. Drscoll, and A.D. LeBlanc. Blood volume changes. In: *Biomedical Results from Skylab*, edited by R.S. Johnston and L.F. Dietlein. Washington, DC: NASA, 1977, p. 235-241 (NASA Spec. Rep. SP-377).
61. Johnson, R.L., G.W. Hoffler, A.E. Nicogossian, S.A. Bergman, Jr., and M.M. Jackson. Lower body negative pressure: third manned Skylab mission. In: *Biomedical Results from Skylab*, edited by R.S. Johnston and L.F. Dietlein. Washington, DC: NASA, 1977, p. 284-312 (NASA Spec. Rep. SP-377).
62. Kirsch, K.A., L. Rocker, O.H. Gauer, R. Krause. Venous pressure in man during weightlessness. *Science* 225:218-219, 1984.
63. Krutz, R.W., C.F. Sawin, B.J. Stegmann, and R.R. Burton. Preinflation before acceleration on tolerance to simulated space shuttle reentry G profiles in dehydrated subjects. *J. Clin. Pharmacol.* 34:480-483, 1994.

64. Kvetnansky, R., V.B. Noskov, P. Blazicek, C. Gharib, I.A. Popova, G. Gauquelin, et al. Activity of the sympathoadrenal system in cosmonauts during 25-day space flight on station Mir. *Acta Astronautica* 23:109-116, 1991.
65. Leach, C.S., S.I. Altchuler, and N.M. Cintron-Trevino. The endocrine and metabolic responses to space flight. *Med. Sci. Sports Exerc.* 15:432-440, 1983.
66. Leach, C.S., and P.C. Johnson. Influence of spaceflight on erythrokinetics in man. *Science* 225:216-218, 1984.
67. Leach, C.S., and P.C. Rambaut. Endocrine responses in long-duration manned space flight. *Acta Astronautica* 2:115-127, 1975.
68. Levine, B.D., L.D. Lane, D.E. Watenpaugh, F.A. Gaffney, J.C. Buckey, and C.G. Blomqvist. Maximal exercise performance after adaptation to microgravity. *J. Appl. Physiol.* 81:686-694, 1996.
69. Ludwig, D.A., and V.A. Convertino. Predicting orthostatic intolerance: physics or physiology? *Aviat. Space Environ. Med.* 65:404-411, 1994.
70. McDonald, K.S., M.D. Delp, and R.H. Fitts. Effect of hindlimb unweighting on tissue blood flow in the rat. *J. Appl. Physiol.* 72:2210-2218, 1992.
71. Michael, E.L., J.A. Rummel, C.F. Sawin, M.C. Buderer, and J.D. Lem. Results of Skylab medical experiment M171 - metabolic activity. In: *Biomedical Results of Skylab*, R.S. Johnston and L.F. Dietlein (eds). Wash, DC: US Government Printing Office, 1977, p. 372-387 (NASA SP-377).
72. Mitchell, J.H., R.G. Victor. Neural control of the cardiovascular system: insights from muscle sympathetic nerve recordings in humans. *Med. Sci. Sports Exerc.* 81:S60-S69, 1996.
73. Mulvagh, S.L., J.B. Charles, J.M. Riddle, T.L. Rehbein, and M.W. Bungo. Echocardiographic evaluation of the cardiovascular effects of short-duration spaceflight. *J. Clin. Pharmacol.* 31:1024-1026, 1991.
74. Nicogossian, A.E., C.B. Charles, M.W. Bungo, and C.S. Leach-Huntoon. Cardiovascular function in space flight. *Acta Astronautica* 24:323-328, 1991.
75. Pavy-Le Traon, A., P. Vasseur, P. Arbeille, A. Guell, A. Bes, and C. Gharib. Effects of 28-day head-down tilt with and without countermeasures on lower body negative pressure responses. *Aviat. Space Environ. Med.* 66:982-991, 1995.

76. Ploutz, L.L., D.L. Tatro, G.A. Dudley, and V.A. Convertino. Changes in plasma volume and baroreflex function following resistance exercise. *Clin. Physiol.* 13:429-438, 1993.
77. Pool, S.L., J.B. Charles, and B. Beck. Physiologic deconditioning subsequent to short spaceflights (abstract). *Proc. 9th IAA Man in Space Symposium*, Cologne, Germany, June 1991, p. 85.
78. Prystowsky, E.N., and G.J. Klein. Cardiac arrest. In: *Cardiac Arrhythmias*. Prystowsky, E.N., and G.J. Klein (eds). New York: McGraw-Hill, 1994, pp. 273-286.
79. Robertson, D., S.E. Perry, A.S. Hollister, R.M. Robertson, and I. Biaggioni. Dopamine-b-hydroxylase deficiency: a genetic disorder of cardiovascular regulation. *Hypertension* 18:1-8, 1991.
80. Robertson, D., V.A. Convertino, and J. Vernikos. The sympathetic nervous system and the physiologic consequences of spaceflight: a hypothesis. *Am. J. Med. Sci.* 308:126-132, 1994.
81. Saltin, B., C.G. Blomqvist, J.H. Mitchell, R.L. Johnson, Jr, K. Wildenthal, and C.B. Chapman. Response to exercise after bed rest and training. *Circulation* 39(suppl 7):1-78, 1968.
82. Sandler, H. Artificial gravity. *Acta Astronautica* 35:363-372, 1995.
83. Sawin, C.F., E. Baker, and F.O. Black. Medical investigations and resulting countermeasures in support of 16-day Space Shuttle Missions. *J. Gravitational Physiol.* (in press).
84. Shi, X., J.M. Andresen, J.T. Potts, B.H. Foresman, S.A. Stern, and P.B. Raven. Aortic baroreflex control of heart rate during hypertensive stimuli: effect of fitness. *J. Appl. Physiol.* 74:1555-1562, 1993.
85. Smith, M. Mechanisms of vasovagal syncope: relevance to postflight orthostatic intolerance. *J. Clin. Pharmacol.* 34:460-465, 1994.
86. Smith, R.F., K. Stanton, D. Stoop, W. Janusz, and P. King. Quantitative electrocardiography during extended spaceflight: the second Skylab mission. *Aviat. Space Environ. Med.* 47:353-359, 1976
87. Takaru, F., K. Hirashima, and S. Okinaka. Effect of bilateral section of the splanchnic nerve on erythropoiesis. *Nature* 191:500-501, 1961.

88. Tatro, D.L., G.A. Dudley, and V.A. Convertino. Carotid-cardiac baroreflex response and LBNP tolerance following resistance training. *Med. Sci. Sports Exer.* 24:789-796, 1992.
89. Thompson, C.A., D.L. Tatro, D.A. Ludwig, and V.A. Convertino. Baroreflex responses to acute changes in blood volume in man. *Am. J. Physiol. (Regulatory Integrative Comp. Physiol.)* 259:R792-R798, 1990.
90. Thompson, F.J., B.J. Yates, O. Franzen, and J.R. Wald. Lumbar spinal cord responses to limb vein distention. *J. Autonomic Nervous System* 9:531-546, 1983.
91. Thornton, W.E., and G.W. Hoffler. Hemodynamic studies of the legs under weightlessness. In: *Biomedical Results from Skylab*, edited by Johnson, R.S. and Dietlein, L.F. NASA SP-377, 1977, pp. 324-329.
92. Vernikos, J. Pharmacological approaches. *Acta Astronautica* 35:281-296, 1995.
93. Vernikos, J., D.A. Ludwig, A.C. Ertl, C.E. Wade, L. Keil, and D. O'Hara. Effect of standing or walking on physiological changes induced by head-down bed rest: Implications for spaceflight. *Aviat. Space Environ. Med.* 67:1069-1079, 1996.
94. Vernikos, J., and V.A. Convertino. Advantages and disadvantages of fludrocortisone or saline load in preventing post-spaceflight orthostatic hypotension. *Acta Astronautica* 33:259-266, 1994.
95. Watenpaugh, D.E., and A.R. Hargens. The cardiovascular system in microgravity. In: *Handbook of Physiology: Environmental Physiology. III. The Gravitational Environment*. M.J. Fregly & C.M. Blatteis (eds). New York, NY:Oxford University Press. Section 1, Chapter 29, 1995, p. 631-674.
96. West, J.B., H.J.B. Guy, A.R. Elliott, and G.K. Prisk. Respiratory system in microgravity. In: *Handbook of Physiology: Environmental Physiology. III. The Gravitational Environment*. M.J. Fregly & C.M. Blatteis (eds). New York, NY:Oxford University Press. Section 1, Chapter 30, 1995, p. 675-689.
97. White, R.J., J.I. Leonard, R.S. Srinivasan, and J.B. Charles. Mathematical modeling of acute and chronic cardiovascular changes during extended duration orbitator (EDO) flights. *Acta Astronautica* 23:41-51, 1991.
98. Whitson, P.A., J.B. Charles, W.J. Williams, and N.M. Cintron. Changes in sympathoadrenal response to standing in humans after spaceflight. *J. Appl. Physiol.* 79:428-433, 1995.

**D-2 CARDIOVASCULAR COUNTERMEASURES SUMMARY
CHARTS**

TRIED AND/OR ACCEPTED COUNTERMEASURES

CM #1. Fluid Loading: Astronauts consume a isotonic saline 'load' consisting of 8 salt tablets (1 g NaCl per tablet) with about 960 ml fluid approximately 2 hours before re-entry.

Rationale:	<ul style="list-style-type: none"> • Hypovolemia induced by spaceflight can contribute to the observed orthostatic hypotension
Supporting Research:	<ul style="list-style-type: none"> • Acute replacement of vascular volume in groundbase experiments was associated with lower orthostatic heart rate and more stable blood pressure (ref 59) • Initial spaceflight data demonstrated that astronauts who fluid-loaded demonstrated lower heart rate and more stable blood pressure during postflight standing than crew that did not take the countermeasure (ref 9)
Risk/Benefit Ratio:	<ul style="list-style-type: none"> • Low absolute risk for potential benefit
Efficacy:	<ul style="list-style-type: none"> • May provide partial protection primarily for missions of less than 6-7 days duration (ref 9) • Orthostatic protection subsides with mission duration greater than 7 days (ref 97) • The capacity to replace vascular volume with fluid loading may be physiologically limited by resetting of central venous pressure to a lower operational setpoint (ref 26)
Cost effectiveness:	<ul style="list-style-type: none"> • Inexpensive but not totally effective
Operational ease of use:	<ul style="list-style-type: none"> • Simple technique • Time loss on orbit is minimal
Interference with other countermeasures:	<ul style="list-style-type: none"> • No known interferences except for possibility of induced vomiting

Recommendations: Research must focus on identifying countermeasure procedures designed to acutely increase central venous pressure operational setpoint. Fluid loading should be combined with such countermeasure techniques. Acute exercise designed to elicit maximal aerobic effort has proven effective in restoring plasma volume in subjects exposed to groundbased analogs of microgravity; the combination of fluid loading and acute maximal exercise should be considered for spaceflight application to enhance restoration of vascular volume.

TRIED AND/OR ACCEPTED COUNTERMEASURES

CM #2. Dynamic Exercise: Physical exercise has been performed during spaceflight using cycle ergometer, rower, and treadmill devices. There is no set prescription and the amount of exercise (frequency, duration, intensity) is variable.

Rationale:	<ul style="list-style-type: none"> • Reduced physical stress and activity in microgravity can contribute to the observed reduction in aerobic fitness • Reduced fitness may contribute to observed postflight orthostatic compromise
Supporting Research:	<ul style="list-style-type: none"> • Dynamic exercise increases or maintains aerobic capacity in microgravity (ref 15, 24, 52, 71) • Acute maximal aerobic exercise increases baroreflex responsiveness (ref 19, 20, 23, 38, 39, 42) • Exercise expands plasma volume (ref 17, 18, 25) • Resistive exercise promotes muscle hypertrophy which is associated with lower venous compliance (ref 13, 14)
Risk/Benefit Ratio:	<ul style="list-style-type: none"> • Benefit high for maintaining physical and orthostatic performance • Low absolute risk if exercise intensity remains at submaximal levels • Risk of maximal exercise during spaceflight is unknown
Efficacy:	<ul style="list-style-type: none"> • Has proven effective for maintaining aerobic capacity in flight and groundbase experiments • Has proven partially effective for orthostatic losses in groundbase experiments
Cost effectiveness:	<ul style="list-style-type: none"> • Depending on the criteria, relatively inexpensive
Operational ease of use:	<ul style="list-style-type: none"> • Cycle ergometer and rower are simple to use compared to treadmill technique • Resistive exercise devices have not been extensively examined • Time loss on orbit is approximately one hour per day.
Interference with other mission operations:	<ul style="list-style-type: none"> • Vibration and noise caused by exercise could interfere with microgravity experiments, sleep, etc.

Recommendations: Continue research to identify the optimal exercise prescription(s) (i.e., minimal amount of exercise intensity, duration, frequency, and mode) required to produce the greatest cardiovascular benefits associated with physical and orthostatic functions. Also need to identify at what point in mission exercise countermeasures can be applied.

TRIED AND/OR ACCEPTED COUNTERMEASURES

CM #3. LBNP/Saline 'Soak': Astronauts are exposed to 4 hours of lower body negative pressure (LBNP) at 30mmHg decompression with consumption of the standard oral fluid load during the early part of the exposure. The 'Soak' is performed 24 hours before landing.

Rationale:	<ul style="list-style-type: none"> • Replace 1-g stimulus for fluid retention and to fill extravascular fluid space
Supporting Research:	<ul style="list-style-type: none"> • LBNP application during exposure to groundbase analogues of microgravity provides some protection against orthostatic intolerance (ref 53, 75) • Groundbase experiments demonstrated that combining fluid loading with LBNP provided greater orthostatic protection after exposure to bedrest than fluid loading alone (ref 45, 59) • This added protective effect subsided within 18 hours (ref 59) • Has not proven effective during spaceflight (ref 12, 83)
Risk/Benefit Ratio:	<ul style="list-style-type: none"> • Minimum risk with no apparent benefit
Efficacy:	<ul style="list-style-type: none"> • Has not proven effective in spaceflight
Cost effectiveness:	<ul style="list-style-type: none"> • Not applicable
Operational ease of use:	<ul style="list-style-type: none"> • Significant impact on mission schedules with minimum of 5 hours for each crewmember 24 hours before landing
Interference with other mission operations:	<ul style="list-style-type: none"> • Large time commitment can interfere with prelanding schedules

Recommendations: Discontinue as countermeasure, but continue use of LBNP for evaluation of other cardiovascular countermeasures and functions.

TRIED AND/OR ACCEPTED COUNTERMEASURES

CM #4. Re-entry Anti-G Suit (REAGS): A single-bladder G-suit that provides protection against blood pooling in the lower extremities without covering the abdominal area, knees, or the buttock, is inflated to approximately 1 psi (?) during re-entry.

Rationale:	<ul style="list-style-type: none"> • Blood pooling in the lower body contributes to orthostatic hypotension
Supporting Research:	<ul style="list-style-type: none"> • Effective in maintaining blood pressure during and immediately after reentry profiles in groundbased experiments (ref 63, 83) • Leg compression by anti-G suit enhances carotid-cardiac baroreflex responses (Convertino, unpublished data)
Risk/Benefit Ratio:	<ul style="list-style-type: none"> • Minimum risk with good benefit
Efficacy:	<ul style="list-style-type: none"> • Probably effective in defending orthostatic function during and immediately after reentry • No impact on longterm postflight cardiovascular structural or functional reconditioning
Cost effectiveness:	<ul style="list-style-type: none"> • Not applicable
Operational ease of use:	<ul style="list-style-type: none"> • Easy
Interference with other mission operations:	<ul style="list-style-type: none"> • Probably enhances astronaut performance and safety by minimizing orthostatic impact on postflight egress • Could interfere with postflight experiments designed to examine orthostatic performance

Recommendations: Continue operational application as countermeasure, but continue research to determine appropriate amount of time that G-suit should be worn following landing.

TRIED AND/OR ACCEPTED COUNTERMEASURES

CM #5. Liquid Cooling Garment (LCG): A specially-designed full coverage garment with a network of plastic tubing allows for the circulation of water across the body surface to provide conductive cooling of the astronaut.

Rationale:	<ul style="list-style-type: none"> • Incidence of orthostatic hypotension following spaceflight has doubled since the implementation of the post-Challenger accident Launch-Entry Suit (LES) • Increased sweating and decreased vascular resistance associated with LES-induced hyperthermia contributes to loss of body water and orthostatic hypotension
Supporting Research:	<ul style="list-style-type: none"> • Groundbased experiments indicated that the LCG prevented hyperthermia, reduced sweat and insensible weight loss, and increased comfort and orthostatic tolerance compared to conventional air cooling system (Waligora, unpublished data) • Spaceflight data indicate that, compared to the LES alone, the LCG worn in the LES reduced orthostatic symptoms (from 17% to 5%), nausea (from 17% to 9%), and body weight loss (3.75 vs 5.37 kg) (Sawin, unpublished data)
Risk/Benefit Ratio:	<ul style="list-style-type: none"> • Minimum risk with good benefit
Efficacy:	<ul style="list-style-type: none"> • Prevents increase in body temperature, reduced sweat and insensible weight loss, improved comfort and orthostatic tolerance. • Spacecraft electrical power limitations may limit the degree of cooling for the circulating water
Cost effectiveness:	<ul style="list-style-type: none"> • Not applicable
Operational ease of use:	<ul style="list-style-type: none"> • Easy to use
Interference with other mission operations:	<ul style="list-style-type: none"> • Full coverage garment (including legs) increases bulkiness of the protective ensemble and is compressed beneath the REAGS, potentially compromising their effectiveness

Recommendations: Continue to develop as countermeasure, but continue development and testing of a upper torso LCG designed with greater cooling tube density to provide adequate total cooling capacity. Also, continue research to determine appropriate amount of time that LCG should be worn following landing, with and without the use of REAGS.

TRIED AND/OR ACCEPTED COUNTERMEASURES

CM #6. Supine Reentry: The use of a reconfigured middeck has been used to provide the capability of crewmembers to lie supine during reentry from orbit.

Rationale:	<ul style="list-style-type: none">• +Gz acceleration during reentry contributes to orthostatic compromise
Supporting Research:	<ul style="list-style-type: none">• None
Risk/Benefit Ratio:	<ul style="list-style-type: none">• Minimum risk with potentially protective benefit
Efficacy:	<ul style="list-style-type: none">• Minimizes possibility of developing hypotension by preventing orthostatic posture.
Cost effectiveness:	<ul style="list-style-type: none">• Requires reconfiguration of orbiter seating
Operational ease of use:	<ul style="list-style-type: none">• Easy
Interference with other mission operations:	<ul style="list-style-type: none">• Physical layout of orbiter middeck may compromise egress of vehicle• Potentially could minimize interference with physiological experiments by eliminating early 1-g recovery

Recommendations: Continue to develop as countermeasure, but continue research to determine if supine reentry is necessary for longterm spaceflight.

POTENTIAL COUNTERMEASURES

CM #1. Penguin Suit: Elasticized garment with rubber bands woven into the fabric, extending from the shoulders to the waist and from the waist to the lower extremities, providing continuous tension on antigravity muscles.

Rationale:	<ul style="list-style-type: none">• Prevent requirement for increased motor unit recruitment due to loss of muscle strength which stimulates autonomic responses• May enhance muscular support of venous function
Supporting Research:	<ul style="list-style-type: none">• Only anecdotal observational non-quantitative data exists
Risk/Benefit Ratio:	<ul style="list-style-type: none">• Minimal risk for potential cardiovascular benefits
Efficacy:	<ul style="list-style-type: none">• Not yet evaluated
Operational ease of use:	<ul style="list-style-type: none">• Easy use
Interference with other mission operations:	<ul style="list-style-type: none">• None apparent

Recommendations: Future experiments are required to investigate the possible interactions between and benefits of resistance exercise to autonomic function.

POTENTIAL COUNTERMEASURES

CM #2. Resistive Exercise

Rationale:	<ul style="list-style-type: none"> • Prevent alterations in muscle strength and motor unit recruitment • Prevent muscle atrophy
Supporting Research:	<ul style="list-style-type: none"> • Alterations in motor unit recruitment of skeletal muscle can impact autonomic responses (ref 35, 72) • Muscle atrophy is associated with increased venous compliance in the lower extremities (ref 13, 14, 91) • Groundbased experiments indicate that resistance exercise training does not maintain blood volume or ameliorate orthostatic intolerance after prolonged exposure to simulated microgravity (ref 52) • Neither acute or chronic resistance exercise affects carotid-cardiac baroreflex function (ref 76, 88)
Risk/Benefit Ratio:	<ul style="list-style-type: none"> • Risk of cardiovascular events associated with acute hypertension will increase with increased loading
Efficacy:	<ul style="list-style-type: none"> • Not yet evaluated
Operational ease of use:	<ul style="list-style-type: none"> • Dependent on the exercise equipment required
Interference with other mission operations:	<ul style="list-style-type: none"> • None apparent

Recommendations: Future experiments are required to investigate the possible interactions between and benefits of resistance exercise to autonomic function and orthostatic performance.

POTENTIAL COUNTERMEASURES

CM #3. Carotid Stimulation: Application of negative pressure to the carotid baroreceptors with the use of a neck pressure chamber would provide a pressure loading stimulus.

Rationale:	<ul style="list-style-type: none">• Prolonged exposure to actual or simulated microgravity attenuates the carotid-cardiac baroreflex response (ref 16, 19, 20, 36, 42, 46, 74)• Attenuation of carotid-cardiac baroreflex response is associated with orthostatic hypotension (ref 16, 19, 42, 47)
Supporting Research:	<ul style="list-style-type: none">• Increased blood pressure (loading) increases the responsiveness of the carotid-cardiac baroreflex (ref 20)
Risk/Benefit Ratio:	<ul style="list-style-type: none">• Unknown
Efficacy:	<ul style="list-style-type: none">• Not yet evaluated
Operational ease of use:	<ul style="list-style-type: none">• Could allow performance of mission tasks simultaneously with application of countermeasure
Interference with other mission operations:	<ul style="list-style-type: none">• None apparent

Recommendations: Worthy of future experiments to define effectiveness in enhancing baroreflex and orthostatic functions and dose-response relationships.

POTENTIAL COUNTERMEASURES

CM #4. Pharmacological Countermeasures: Various adrenergic agonists and antagonists might prove effective in enhancement of autonomic responses to orthostatic challenges postflight.

Rationale:	<ul style="list-style-type: none">• Variations in autonomic nervous activity impact importantly on cardiovascular function, particularly reflex autonomic responses to orthostatic challenges
Supporting Research:	<ul style="list-style-type: none">• There is evidence of up-regulation in beta adrenoreceptor responsiveness in humans following exposure to groundbase analogs of microgravity (ref 22)
Risk/Benefit Ratio:	<ul style="list-style-type: none">• Unknown
Efficacy:	<ul style="list-style-type: none">• Not yet evaluated
Operational ease of use:	<ul style="list-style-type: none">• Easy
Interference with other mission operations:	<ul style="list-style-type: none">• None apparent

Recommendations: Worthy of future experiments to define effectiveness in enhancing baroreflex functions and dose-response relationships.

POTENTIAL COUNTERMEASURES

CM #5. Human-Powered Centrifuge: A countermeasure designed to simultaneously apply cycle exercise (endurance) with head-to-foot gravity (+Gz) acceleration by using a short-arm (<3 m), dual cycle, human-powered centrifuge.

Rationale:	<ul style="list-style-type: none"> • Presence of gravity may potentiate the beneficial effects of exercise and other countermeasures on cardiovascular function after return from spaceflight (ref 82)
Supporting Research:	<ul style="list-style-type: none"> • Groundbased experiments have demonstrated that 2-4 hours a day of standing can ameliorate orthostatic compromise caused by exposure to simulated microgravity while 2-4 hours of walking reduced physical deconditioning (ref 93)
Risk/Benefit Ratio:	<ul style="list-style-type: none"> • Minimal physical risk • Possibility of motion sickness
Efficacy:	<ul style="list-style-type: none"> • Not yet evaluated
Operational ease of use:	<ul style="list-style-type: none"> • Unknown • No spacecraft power requirements • Space requirement is relatively large
Interference with other mission operations:	<ul style="list-style-type: none"> • Unknown

Recommendations: Worthy of future experiments to define effectiveness in enhancing cardiovascular function.

POTENTIAL COUNTERMEASURES

CM #6. Nutrition

Rationale:	<ul style="list-style-type: none">• Variations in fluid-electrolyte balance and plasma proteins can impact importantly on cardiovascular function• Specifically, concern has been expressed about the possibility that potassium deficiency during spaceflight may increase the risk for arrhythmias (ref 55, 92)
Supporting Research:	<ul style="list-style-type: none">• Potassium and other electrolyte deficiencies have been associated with cardiac arrhythmias (ref 78)• Limited Skylab data indicated that isolated cardiac arrhythmias were associated with hypokalemia (Sawin, personal communication)
Risk/Benefit Ratio:	Unknown
Efficacy:	Not yet evaluated
Operational ease of use:	Unknown
Interference with other mission operations:	None apparent

Recommendations: Worthy of future experiments to define impacts of diet on cardiovascular function during spaceflight.

POTENTIAL COUNTERMEASURES

CM #7. Acute Maximal Exercise: Graded cycle exercise protocol designed to elicit maximal effort (maximal oxygen uptake) within 24 hours of reentry from orbit.

Rationale:	<ul style="list-style-type: none"> • Reduced physical stress and activity in microgravity may contribute to observed postflight orthostatic compromise
Supporting Research:	<ul style="list-style-type: none"> • In ambulatory subjects, acute maximal exercise: <ul style="list-style-type: none"> - increased baroreflex function (ref 20) - expanded plasma volume (ref 17) • In groundbased studies that exposed subjects to analogs of microgravity, acute maximal exercise: <ul style="list-style-type: none"> - increased baroreflex control of heart rate (ref 39, 42) - increased capacity for elevation of vascular resistance (ref 39, 42) - expanded plasma volume (ref 25) - protected orthostatic tolerance (ref 42)
Risk/Benefit Ratio:	<ul style="list-style-type: none"> • Unknown risk of cardiovascular events associated with maximal exercise during spaceflight
Efficacy:	<ul style="list-style-type: none"> • Has been used without any apparent problems during spaceflight
Operational ease of use:	<ul style="list-style-type: none"> • Simple equipment requirement • Can be applied anytime during 18-24 hours prior to reentry
Interference with other mission operations:	<ul style="list-style-type: none"> • None apparent • Minimal impact on life support requirements

Recommendations: Extensive groundbased experiments have demonstrated the efficacy and effectiveness of this countermeasure for protecting orthostatic performance. This approach should be seriously considered for future inflight testing. It must be appreciated that assessment of its effectiveness will require more sophisticated tests than the currently used "stand test".