Section 1

Cardiovascular Deconditioning

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BACKGROUND

Spaceflight causes adaptive changes in cardiovascular function that may deleteriously affect crew health and safety [1, 2, 3, 4, 5]. Over the last three decades, symptoms of cardiovascular changes have ranged from postflight orthostatic tachycardia and decreased exercise capacity to serious cardiac rhythm disturbances during extravehicular activities (EVA). The most documented symptom of cardiovascular dysfunction, postflight orthostatic intolerance, has affected a significant percentage of U.S. Space Shuttle astronauts [6, 7, 8, 9]. Problems of cardiovascular dysfunction associated with spaceflight are a concern to NASA. This has been particularly true during Shuttle flights where the primary concern is the crew's physical health, including the pilot's ability to land the Orbiter, and the crew's ability to quickly egress and move to safety should a dangerous condition arise.

The study of astronauts during Shuttle activities is inherently more difficult than most human research [8]. Changes in diet, sleep patterns, exercise, medications, and fluid intake before and during spaceflight missions are difficult to control. Safety restrictions make many standard research protocols inadvisable. Data collections must occur without disruption of primary mission objectives. Hardware malfunctions during in-flight data collections affect the quantity and/or quality of resulting data. Concurrent investigations may confound interpretation of both studies. Consequently, sample sizes have been small and results have lacked consistency. Before the Extended Duration Orbiter Medical Project (EDOMP), there was a lack of normative data on changes in cardiovascular parameters during and after spaceflight. The EDOMP for the first time allowed studies on a large enough number of subjects to overcome some of these problems.

There were three primary goals of the Cardiovascular EDOMP studies. The first was to establish, through descriptive studies, a normative data base of cardiovascular changes attributable to spaceflight. The second goal was to determine mechanisms of cardiovascular changes resulting from spaceflight (particularly orthostatic hypotension and cardiac rhythm disturbances). The third was to evaluate possible countermeasures. The Cardiovascular EDOMP studies involved parallel descriptive, mechanistic, and countermeasure evaluations (Table 1-1).

GOAL 1 – DESCRIPTIVE STUDIES

Introduction

Before EDOMP, data describing changes in basic cardiovascular parameters during and after spaceflight were sparse and equivocal, and were sometimes only reported as case studies. Because of the competition for in-flight resources, many experiments were often scheduled on the same crew members, even though one study may have interfered with the measurements of another. Because of these limitations, reports were inconsistent, and a good representative data base did not exist. Even such a basic parameter as heart rate had been reported to be increased, decreased, and unchanged during spaceflight. The main objective of the EDOMP cardiovascular descriptive studies was to correct this deficit by collecting data; and by monitoring heart rate, blood pressure, cardiac dysrhythmias, cardiac function, and orthostatic intolerance, consistently and with a large enough number of subjects to make meaningful conclusions.

Methods and Materials

The first descriptive study was conducted as Detailed Supplementary Objective (DSO) number 463. This study employed 24-hour Holter monitor recordings before flight, during flight, and after flight on five crew members to document any occurrence of in-flight cardiac dysrhythmias [10].

The second descriptive study (DSO 602) employed Holter monitors as well as automatic blood pressure devices to monitor heart rate, cardiac arrhythmias, and arterial pressure for 24-hour periods before, during, and after flight [10]. The subjects were 12 astronauts who flew missions lasting from 4 to 14 days. During data collections the electrocardiogram was recorded continuously, using the Holter monitor, and blood pressure was taken automatically every 20 minutes when the subjects were awake,

Table 1-1. Cardiovascular EDOMP studies

Descriptive Studies	*Mechanistic Studies*	*Countermeasure Evaluations*
In-flight Holter Monitoring (463) 5 Subjects PI1	Baroreflex Function (467) 16 Subjects PI1	In-flight Lower Body Negative Pressure (478) 13 Subjects PI1
In-flight Arterial Pressure and Holter Monitoring (602) 12 Subjects PI2	Baroreflex/Autonomic Control of Arterial Pressure (601) 16 Subjects PI2	LBNP Countermeasure (623) 12 Subjects PI1
Cardiac Function (466) 32 Subjects PI1	Neuroendocrine Responses to Standing (613) 24 Subjects PI3	Hyperosmotic Fluid Countermeasure (479) 23 Subjects PI1
Orthostatic Function during Entry, Landing and Egress (603) 34 Subjects PI1	Cardiovascular and Cerebrovascular Responses to Standing (626) 40 Subjects PI2	In-flight Use of Fludrocortisone (621) 16 Subjects PI2

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and every 30 minutes during sleep. Subjects maintained normal routines, both on the ground and in flight.

In the third descriptive study (DSO 466), 32 astronauts on short duration missions (4-5 days in space) were studied with two-dimensionally directed M-mode echocardiography to determine the effects of spaceflight on cardiac volume, cardiac function, and cardiac mass [11]. Heart rate, blood pressure, and echocardiograms were obtained in the supine and standing positions before and after flight. M-mode echocardiograms were interpreted according to American Society of Echocardiography (ASE) measurement conventions [12]. Cardiac volumes and ejection fraction were derived by using the Teichholz formula [13]. Myocardial mass index was subsequently determined from a modification of the ASE basic formula for left ventricular mass. The mean velocity of circumferential fiber shortening was estimated by the method of Cooper et al. [14].

In the fourth descriptive study (DSO 603), the standard Shuttle launch and entry pressure suit (LES) was modified to include a biomedical instrumentation port that would allow physiological signals to be monitored while the LES was being worn. An automatic blood pressure/heart rate monitor was used to measure the electrocardiogram continuously and to determine heart rate and arterial pressure at 2-minute intervals. In most cases, three 1-axis accelerometers were used to provide reference acceleration levels. A fourth accelerometer was attached to the upper torso of the LES to document changes in body posture. The following parameters were derived from the collected data: (1) heart rate, (2) systolic, diastolic, and mean arterial pressure, and (3) pulse pressure. These values were compiled for several time periods during the preflight and in-flight testing period. These were (1) preflight seated and standing values with the g-suit inflated to the expected in-flight level, (2) in flight prior to onset of gravity, (3) at the onset of gravity, (4) at peak gravity during entry, (5) at touchdown, and (6) seated and standing measurements during the first stand [15].

Results

There were several important findings in the first two studies (DSO 463 and 602). First, heart rate, diastolic pressure, and their variabilities were reduced during spaceflight (Figures 1-1 and 1-2). Second, the diurnal variations of both heart rate and diastolic pressure were reduced during spaceflight. Third, monitoring records demonstrated that spaceflight did not increase dysrhythmias (Figure 1-3). These data are unique because they were obtained during normal 24-hour routines, rather than as a part of any in-flight experiment intervention. Therefore, they are important for establishing a normative data base for cardiovascular parameters during short duration spaceflight.

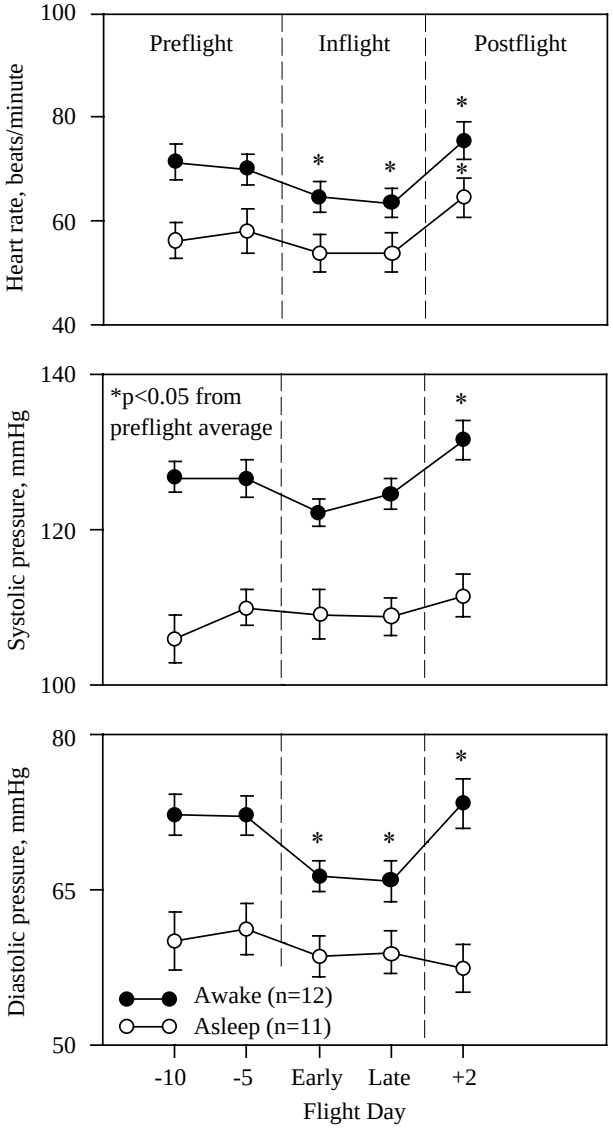


Figure 1-1. Heart rate and arterial pressure before, during, and after flight.

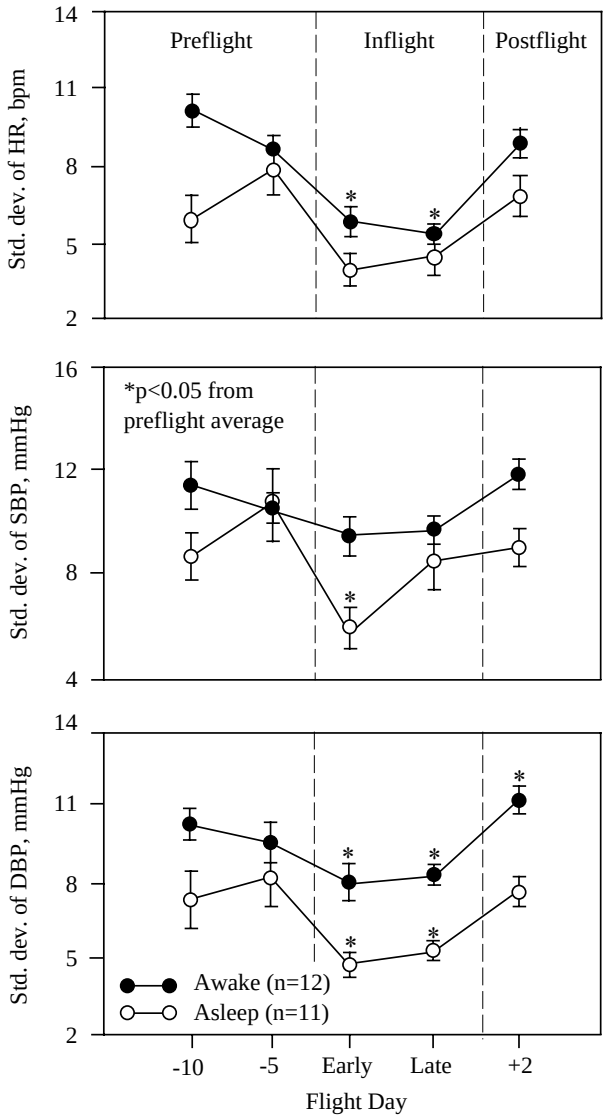


Figure 1-2. Intrasubject standard deviations of heart rate and arterial pressure before, during, and after flight.

In the third study (DSO 466) (Table 1-2), the supine left ventricular end diastolic volume index (EDVI) diminished by 11% (P<0.0006) on landing day when compared with preflight. Similar to EDVI, supine left ventricular stroke volume index (SVI) diminished by 17% (P<0.006) on landing day compared with preflight. Overall standing EDVI was less than supine, but no significant changes occurred between test days. Left ventricular end systolic volume index (ESVI) did not significantly change for position or time. Total peripheral resistance index (TPRI) was significantly greater in the standing position than the supine position on all test days except landing day. Similarly, the TPRI orthostatic response was less on landing day. Ejection fraction and velocity of circumferential fiber shortening did not change significantly, suggesting that spaceflight of this duration has no effect on myocardial contractility. Left ventricular wall thickness and myocardial mass index also showed no significant changes (data not shown).

Arterial pressures and heart rates were monitored in the fourth study (DSO 603) during landing and egress from the Orbiter. Arterial pressure responses are shown in Figure 1-4. During spaceflight, both systolic and diastolic pressure were elevated relative to preflight baseline values throughout the recording period, reaching their highest values at peak gravity during entry, and on touchdown. Standing upright for the first time after landing was associated with a significant decrease, from the seated value, in systolic pressure. In seven cases, the drop was greater than 20 mmHg. This occurred in 22% of the subjects on landing day, but did not occur in any subjects before flight.

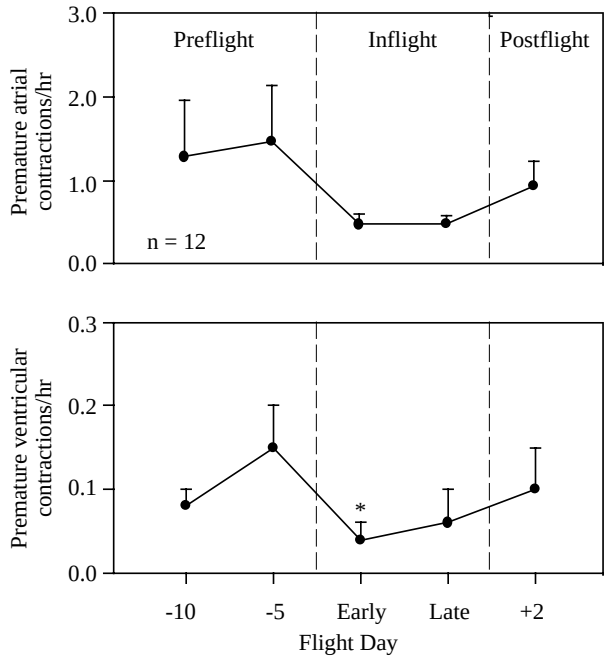


Figure 1-3. Premature atrial and ventricular contractions before, during, and after flight.

When the subjects stood after touchdown, diastolic pressures also decreased relative to values while the subjects were seated. During standing in the laboratory before flight, systolic and diastolic pressures exhibited small increases. There were differences in arterial pressure and heart rate attributable to use of the g-suit when crew members who inflated the g-suit (n=24) were compared with those who did not (n=8). Most notably, diastolic pressure was more adequately maintained in the g-suit-inflated group during the post-touchdown standing maneuver, compared to the non-inflated g-suit group ($P < 0.006$) (data not shown).

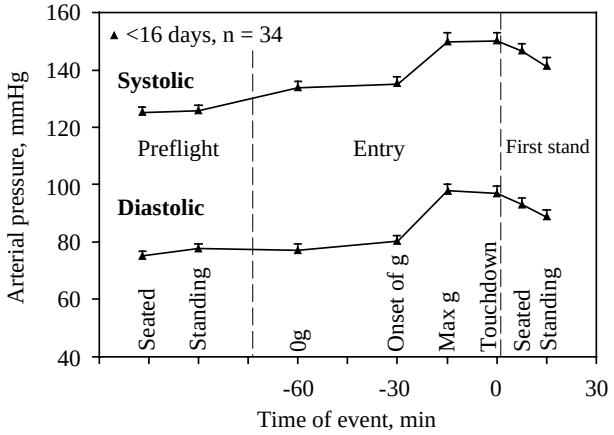


Figure 1-4. Systolic and diastolic pressure response to entry, landing, and egress.

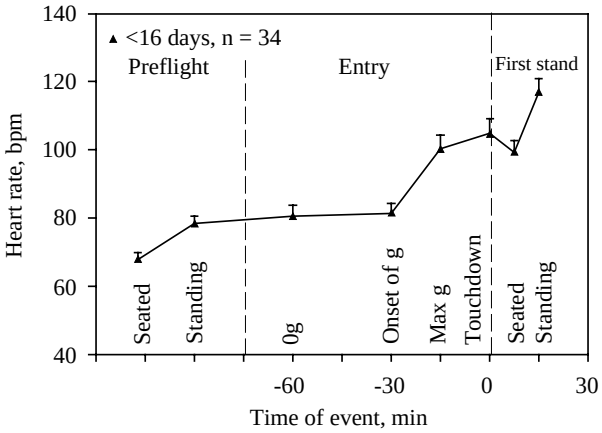


Figure 1-5. Heart rate response to entry and landing.

Heart rate also reached high values at peak gravity and touchdown. The maximum value was obtained during the first stand (Figure 1-5). Although there was large inter-individual variability in seated and standing heart rates, crew members generally showed a substantial increase in heart rate upon standing after touchdown. There was a 70% increase in heart rate upon standing compared to the increase seen before flight. Four crew members had heart rate values on standing that were equal to, or greater than, their maximal heart rate responses during preflight lower body negative pressure tests. The highest heart rate observed for any crew member was 160 bpm. Both systolic pressure and heart rate returned quickly to preflight values during the first hour after landing, although substantial differences frequently remained.

Conclusions

In the first two descriptive studies, the results indicate that heart rate, blood pressure, and cardiac dysrhythmias decreased during spaceflight when compared to preflight norms. This suggests that living in a microgravity environment did not cause a constant stress to the cardiovascular system. However, the adaptive changes that occurred in response to the microgravity environment left the astronauts ill-prepared for the cardiovascular stresses associated with return to Earth.

In the third study, changes in cardiac function occurred after short duration (4 to 5 day) spaceflights. These changes included decreased left ventricular end diastolic volume and decreased stroke volume indices, with compensatory increased heart rate and increased maintenance of cardiac output. In addition, altered total peripheral vascular resistance occurred, with an apparent reduction in the ability to augment peripheral vascular tone on assumption of upright posture. Changes in cardiovascular measurements resolved within 7 days of landing. There were no significant changes in left ventricular contractility or cardiac mass after short

Table 1-2. Cardiovascular measurements (mean ± SEM) before and after short-duration spaceflight

	L–10		*L–5*		*L+0*		*L+(7-10)*	
HR								
Supine	57	(1.8)	58	(2.0)	70*	(2.2)	57	(1.8)
Standing	75	(2.6)	75	(2.7)	101**	(3.6)	78	(2.2)
SBP								
Supine	105	(2.1)	106	(2.2)	109	(2.0)	106	(2.2)
Standing	110	(1.7)	114†	(1.7)	111	(2.2)	112	(2.0)
DBP								
Supine	64	(2.1)	61	(2.1)	68	(2.6)	64	(2.7)
Standing	79	(1.7)	79	(1.3)	81	(1.6)	80	(1.2)
MAP								
Supine	77	(1.9)	76	(2.0)	82	(2.2)	78	(2.4)
Standing	89	(1.5)	91	(1.2)	91	(1.5)	91	(1.3)
PP								
Supine	41	(1.9)	45	(1.5)	41	(2.2)	43	(1.8)
Standing	31	(1.8)	35	(1.7)	31	(2.1)	32	(1.8)
EDVI								
Supine	59.4	(2.7)	56.1	(3.3)	52.6††	(2.7)	56.7	(2.6)
Standing	41.3	(2.4)	42.6	(4.5)	35.8	(2.7)	43.0	(2.4)
ESVI								
Supine	20.9	(1.2)	18.6	(2.0)	20.5	(1.6)	19.6	(1.6)
Standing	17.3	(1.8)	16.2	(3.3)	13.4	(1.6)	17.6	(1.9)
SVI								
Supine	38.5	(1.8)	37.5	(1.9)	32.1	(1.8)	37.1	(1.6)
Standing	24.0	(1.5)	26.4	(1.9)	22.3	(1.5)	25.4	(1.1)
TPRI								
Supine	38.4	(2.2)	38.9	(2.6)	39.7	(2.5)	39.4	(2.5)
Standing	51.7	(3.8)	49.0	(6.7)	41.8	(2.0)	47.0	(2.1)
EF								
Supine	65	(1.3)	68	(2.1)	62	(2.0)	66	(1.6)
Standing	59	(3.3)	64	(5.6)	63	(2.5)	60	(2.2)
LVMI	63.3	(2.5)	59.6	(2.4)	61.1	(2.2)	60.9	(2.1)

**P* 0.0005, cf of L-10 supine ***P* 0.0001, cf of L-10 standing *†P* 0.04, cf of L-10 standing

††P 0.0006, cf of L-10 supine *P* 0.006, cf of L-10 supine

HR = heart rate (bpm)

SBP = systolic blood pressure (mmHg)

DBP = diastolic blood pressure (mmHg)

MAP = mean arterial pressure (mmHg)

PP = pulse pressure (mmHg)

EDVI = left ventricular end-diastolic volume index (ml/m^2)

ESVI = left ventricular end-systolic volume index (ml/m^2)

TPRI = total peripheral vascular resistance index (mmHg, l/min/m^2)

EF = ejection fraction (%)

LVMI = left ventricular mass index (g/m^2)

L– = launch minus

L+ = landing plus

duration spaceflight. Echocardiography provided a useful noninvasive technique for evaluation of cardiovascular physiology after spaceflight.

Analysis of results from the fourth study showed that entry, landing, and seat egress after Shuttle flights were associated with drops in systolic pressure and increases in heart rate. These results describe a cardiovascular system under significant stress during nominal entry, landing, and seat egress, and indicate that the cardiovascular system was performing at or near its maximum capacity in a significant fraction (20%) of the study population. While these crew members were never clinically hypotensive, their swings in arterial pressure and heart rate indicate that they were unable to buffer arterial pressure changes as well as before flight. It is questionable whether sufficient reserve capacity remained to permit unaided emergency egress by these individuals.

GOAL 2 – MECHANISTIC STUDIES

Introduction

The series of EDOMP cardiovascular mechanistic studies was undertaken to test the hypothesis that orthostatic hypotension following spaceflight is due, at least in part, to a disruption of autonomic control of the cardiovascular system. The series consisted of four studies. The first study was a simple evaluation of carotid baroreceptor cardiac reflex function before and after 4 to 5 days in space. The second study tested carotid baroreflex function after 8 to 14 day spaceflights, and added measurements of resting plasma catecholamine levels, Valsalva maneuvers, and spectral analyses of arterial pressure and heart rate. The third study evaluated the relationship between plasma catecholamine levels and total peripheral resistance changes upon standing. The fourth study looked at integrated cardiovascular and cerebrovascular responses to standing, as well as the effect of reduced postflight plasma volume on orthostatic tolerance. All of these studies used data only from crew members who had not taken vasoactive or autonomic medications within 12 hours, or caffeine within 4 hours of the study.

Methods and Materials

The first mechanistic study (DSO 467) tested 16 astronaut subjects before and after 4 to 5 day spaceflight missions [7, 16]. Subjects were studied 10 and 5 days before launch, on landing day, and up to 10 days after landing. The protocol consisted of a 20-minute supine rest period, followed by carotid baroreceptor stimulation. A stepping motor-driven bellows was connected to a neck chamber to deliver stepped pulses of pressure and suction to the neck. During held expiration, the pressure was increased to 40 mmHg and held for 5 seconds. With the next seven heart beats, the pressure stepped down sequentially to 25, 10, -5, -20, -35, -50, and -65 mmHg. R-R intervals were plotted against carotid distending pressure, derived by subtracting the neck chamber pressure from the systolic pressure. The following variables were taken from the stimulus-response relationship: maximum slope, R-R interval range of response, minimum and maximum R-R intervals, and operational point. The operational point was the R-R interval at zero neck pressure which represented the relative hypotensive versus hypertensive buffering capacity of the reflex.

The second mechanistic study (DSO 601) repeated the above measurements before and after spaceflight missions lasting 8 to 14 days [8]. In addition, 5 minutes of continuous ECG data were taken for spectral analyses of R-R intervals, and blood samples were drawn before the neck stimuli for analysis of plasma catecholamine levels. Two Valsalva maneuvers were performed at 30 mmHg expired pressure for 15 seconds, and two were performed at 15 mmHg expired pressure for 15 seconds. Sixteen astronaut subjects participated in this activity, using the same schedule as the previous study.

The third mechanistic study (DSO 613) measured catecholamine levels and cardiovascular responses to standing in 24 astronauts before and after spaceflight [17]. Studies were performed 10 days before launch, on landing day, and 3 days after landing. Arterial pressure, heart rate, and cardiac output were measured. Blood samples, drawn at the end of a 20-minute supine rest period and after 5 minutes of standing, were tested for catecholamines and plasma renin activity.

The fourth mechanistic study (DSO 626) sought to define differences in physiological responses of astronauts who did or did not become presyncopal on landing day [18]. This study was performed on 40 astronauts before and after Shuttle missions of up to 16 days. The protocol consisted of a 20-minute supine rest period, followed by a blood draw for analyses of plasma catecholamine and plasma renin activity. Plasma volume was then measured by the carbon monoxide rebreathing (CORB) technique. An enhanced stand test was then performed, and included the following: (1) echocardiographic measurements to obtain aortic cross sectional area, (2) continuous wave Doppler for aortic flow, and (3) beat-to-beat arterial pressure and ECG. All measurements were continued for 5 more minutes supine and 10 minutes standing. A final blood sample was drawn at the end of standing. This entire protocol was performed 30 and 10 days before launch, on landing day, and 3 and 10 days after landing. Data were analyzed to document differences between presyncopal and non-presyncopal astronauts.

Results

In the first study of short duration flights (DSO 467), the following summary data were obtained on landing

day and compared to the preflight norm (Table 1-3, Figure 1-6): resting R-R intervals and standard deviations; the slope, range, and position of operational points on the carotid distending pressure; and R-R interval response relation. These variables were all reduced on landing day relative to preflight. Stand tests on landing day revealed two separate groups, differentiated by their ability to maintain standing arterial pressure. This maintenance of arterial pressure was determined by evaluating preflight slopes, operational points, and supine and standing R-R intervals, and by preflight-to-postflight changes in standing systolic pressures, body weights, and operational points (Table 1-4, Figures 1-7, 1-8, and 1-9).

In the second study, involving longer duration flights (DSO 601), the following changes between preflight and landing day were found: (1) orthostatic tolerance decreased, (2) R-R interval spectral power in the 0.05 to 0.15-Hz band increased (Figures 1-10 and 1-11), (3) resting plasma norepinephrine and epinephrine levels increased, (4) the slope, range, and operational point of the carotid baroreceptor cardiac reflex response decreased (Table 1-5), and (5) blood pressure and heart rate responses to Valsalva maneuvers were altered (Figures 1-12 and 1-13). Carotid baroreceptor cardiac reflex response changes persisted for several days after landing (Table 1-5).

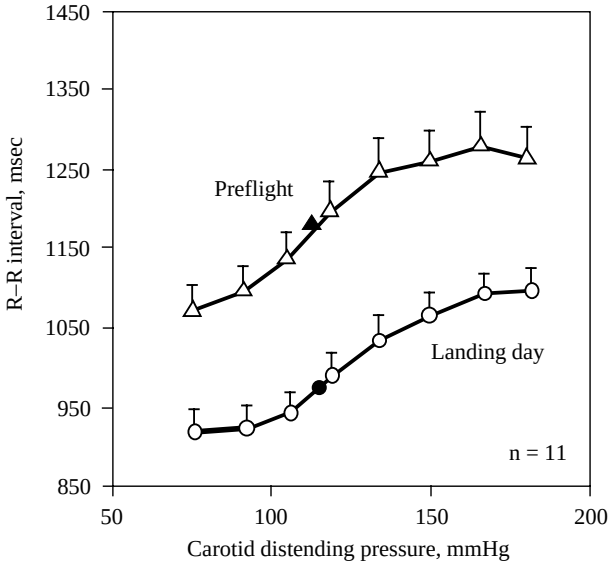


Figure 1-6. Carotid baroreceptor vagal-cardiac reflex responses before flight and on landing day. Closed symbols, position of operational points. Average operational point was reduced significantly on landing day, but slope and range were not.

Table 1-3. Measurements from all subjects on all test days

			Postflight Day		
	Preflight	*Landing Day*	*2*	*3*	*8-10*
Systolic pressure, mmHg	116±2	116±2	117±2	116±2	116±2
Diastolic pressure, mmHg	75±1	73±2	72±2	73±2	74±2
R-R interval, ms	1,123±42	965±25*	1,069±38	1,134±39	1,069±31
Standard deviation of R-R, ms	62±6	40±4*	58±6	55±5	47±5
Body weight, kg	75.6±4.0	74.4±2.4*	75.2±2.4	75.3±2.4	75.4±2.1
Baroreflex measurements					
Maximum slope, ms/mmHg	5.0±1.0	3.4±0.5	3.6±0.6*	3.90±0.6*	3.9±0.6*
Operational point, %	48.9±3.5	29.4±4.2†	39.8±3.6	52.4±4.7	42.4±6.0
R-R interval, ms					
Range	243±47	182±25	177±20*	192±102*	189±27*
Minimum	1,081±43	923±30*	1,036±39	1,084±35	1,037±31
Maximum	1,324±68	1,104±31*	1,213±41*	1,275±43	1,226±38*
Carotid distending pressure, mmHg					
At minimum R-R	80±4	83±4	92±9	82±7	75±2
At maximum R-R	153±8	172±4	160±6	157±7	161±5

Values are means ± SE. All comparisons between landing day and preflight measurements used only 11 subjects; those between landing day and measurements taken 8-10 days after landing used only 12 subjects.
* $P < 0.05$; † $P < 0.01$.

Table 1-4. Subjects grouped according to relative orthostatic tolerance judged by cardiovascular parameters

	10 Days Before Launch		Landing Day	
	More resistant	Less resistant	More resistant	Less resistant
Weight, kg	74.30±3.3	77.20±2.9	73.86±3.3	75.76±2.9
Age, yr	42.1±2.4	43.1±1.8		
		Stand tests		
Systolic pressure, mmHg				
Supine	110.4±3.4	106.4±3.0	110.3±3.7	117.9±3.9
Standing	121.4±3.4	118.9±2.0	124.3±4.0	114.0±2.9
Diastolic pressure, mmHg				
Supine	66.0±3.0	68.6±3.2	71.8±3.8	80.9±3.8
Standing	81.0±2.6	84.7±2.0	87.7±3.4	87.7±9.1
Heart rate, beats/min				
Supine	58.6±2.3	51.3±2.6	67.0±2.4	66.7±2.6
Standing	76.9±3.0	66.9±3.0*	98.3±3.7	104.4±4.2
R-R interval, m				
Supine	1,032±10	1,205±11*	901±9	931±10
Standing	791±10	912±11*	640±9	613±12
		Baroreflex measurements		
Maximum slope, ms/mmHg	3.7±1.5	5.9±2.3*	3.2±1.2	5.0±2.0*
R-R range, ms	194±9	232±13	177±8	225±12
Operational point, %	45.8±3.3	54.4±3.4*	32.4±3.3	27.7±4.1

Values are means ± SE for 11 subjects. *$P \leq 0.05$ between groups.

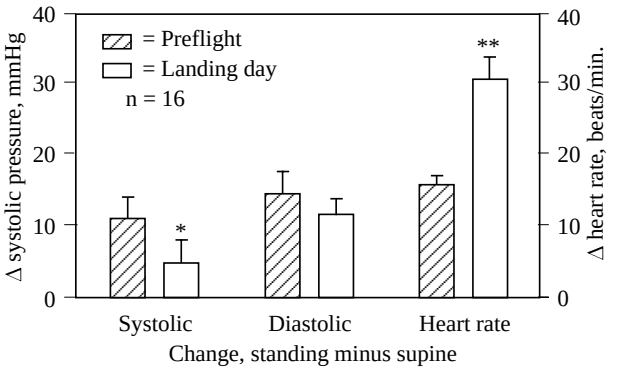


Figure 1-7. Preflight and landing day differences between standing and supine systolic and diastolic pressures and heart rate. Significant difference between groups: *$P < 0.05$; **$P < 0.01$.

The third study (DSO 613) showed that on landing day supine plasma norepinephrine and epinephrine levels were increased 34% and 65%, respectively, from the preflight norm, and standing norepinephrine and epinephrine levels were increased 65% and 91% (Figure 1-14). Supine and standing norepinephrine levels remained elevated 3 days after landing while epinephrine levels returned to preflight levels. On landing day, supine heart rate and systolic blood pressure were elevated 18% and 8.9%, respectively, when compared to the preflight norm. Standing heart rate and diastolic blood pressure were elevated 38% and 19%, respectively (data not shown).

In the fourth study (DSO 626), 40 crew members were tested. However, 11 were excluded for violations of test constraints or contamination of blood samples. Of the remaining 29 astronauts, 8 could not complete their stand tests on landing day because they became presyncopal. These subjects displayed arterial pressure and heart rate responses to standing that were similar to those seen in adrenergic failure (Figure 1-15). On landing day, their standing norepinephrine levels were significantly lower than the norepinephrine levels of the astronauts who did not become presyncopal (Table 1-6a). The failure of the sympathetic nerves to increase norepinephrine release with standing translated into lower peripheral vascular resistance and ultimately presyncope. Plasma volumes were not different between groups either before or after flight.

There were also significant preflight differences between the presyncopal and non-presyncopal groups

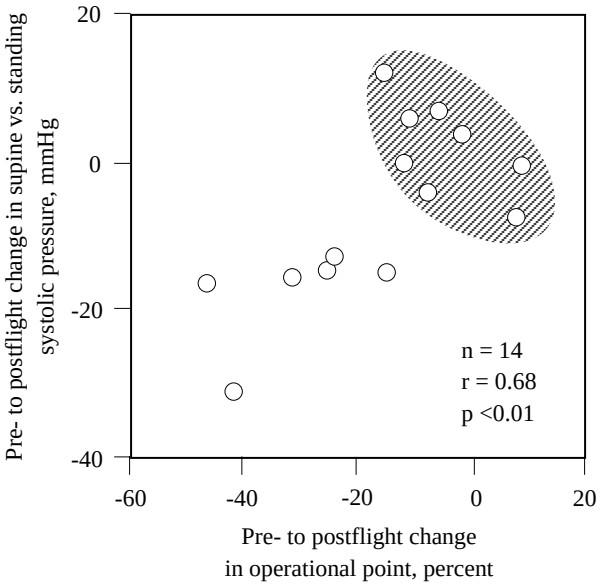


Figure 1-8. Preflight-to-postflight (landing day) changes of operational points and systolic pressure responses to standing. Linear regression correlation coefficients are for all data. Cluster analysis of these data identified 2 distinct groups, which have been termed less and more resistant to postural change. Hatched area, more resistant group.

(Table 1-6b). While still well within normal ranges, the group that became presyncopal on landing day had lower preflight supine and standing diastolic pressures and peripheral vascular resistance than the non-presyncopal group. The supine heart rates of the presyncopal group were also higher and their standing systolic pressures were lower. Three days after landing, norepinephrine levels and diastolic pressure were again similar in the two groups (Table 1-6c). However, peripheral vascular resistance and systolic pressure were lower in the presyncopal group during standing.

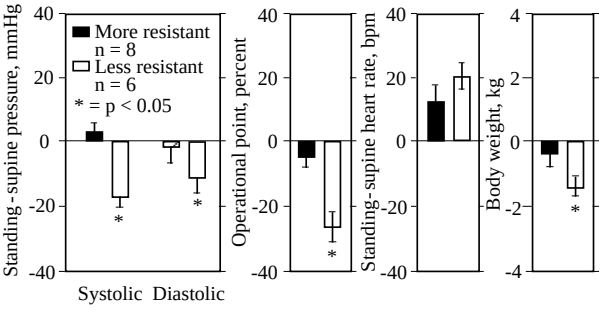


*Figure 1-9. Comparisons of preflight to landing day changes between 2 groups identified by cluster analysis. *P* < 0.01.

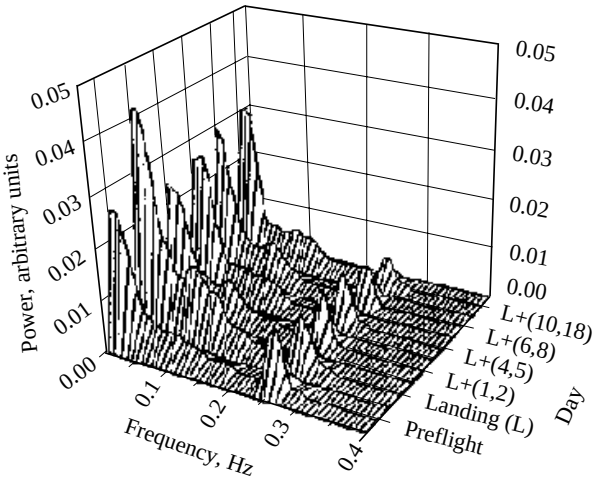


Figure 1-10. Three-dimensional plot of power spectra of R-R intervals during controlled frequency breathing for 12 subjects, all days.

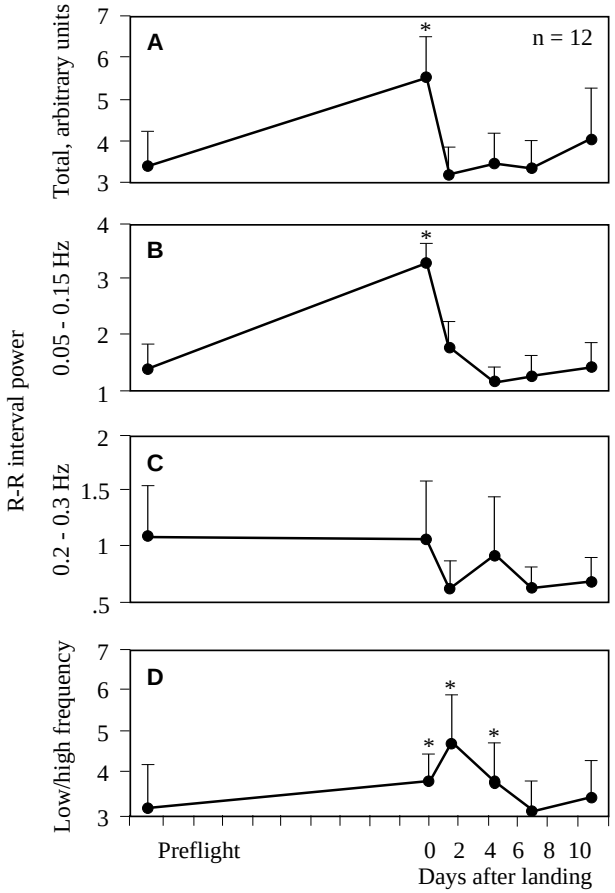


*Figure 1-11. Average total power (A), power in 0.05- to 0.15-Hz band (B), 0.2- to 0.3-Hz band (C), and ratio of low- to high-frequency power (D) throughout study. n, no. of subjects. *P* < 0.025 *compared with preflight.*

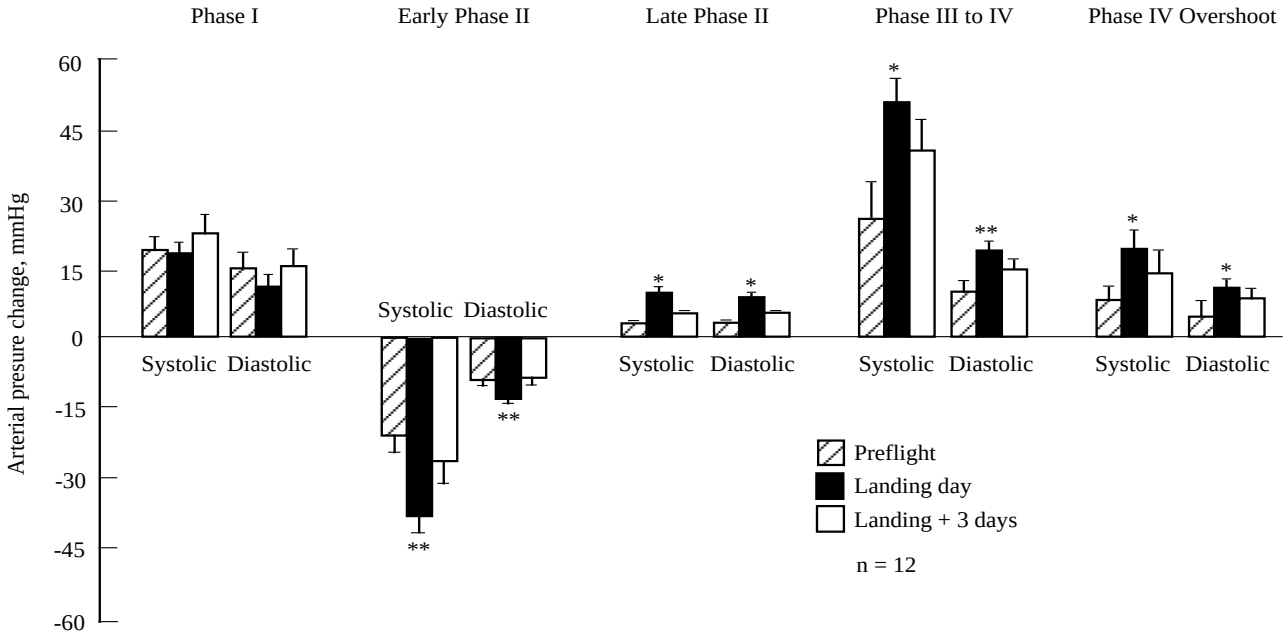


*Figure 1-12. Arterial pressure responses during Valsalva maneuvers preflight, on landing day, and 3 days after landing. *P < 0.025 compared with preflight. **P < 0.01 compared with preflight.*

Conclusions

The results from the first two studies show that short duration spaceflight leads to significant reductions in vagal control of heart rate that may contribute to orthostatic intolerance. The results from long duration flights (10 days or longer) provide further evidence of functionally relevant postflight disruption of autonomic regulation of arterial pressure and heart rate.

The results from the third study showed an apparent uncoupling between sympathetic nerve activity and peripheral resistance. Responses of presyncopal and nonpresyncopal astronauts were not compared in this study.

The results of the fourth study have both spaceflight and Earth-bound importance. They suggest that spaceflight caused changes in central modulation of baroreflex function which were manifested as a hypoadrenergic response to standing. Furthermore, drastically differing susceptibilities to postflight orthostatic intolerance were observed in the astronaut population. This study also suggests that there was a subset of the astronaut population that had orthostatic responses well within normal ranges before flight, but was nevertheless predisposed to experience presyncope during upright posture after spaceflight. Data obtained from the preflight stand test show promise in predicting which crew members might be susceptible to postflight orthostatic intolerance. The flight surgeons may use this information to identify individuals who may be most likely to benefit from the application of an in-flight countermeasure.

GOAL 3 – COUNTERMEASURE STUDIES

Introduction

Orthostatic intolerance is a well-documented consequence of spaceflight. Causes could be postflight hypovolemia and/or autonomic dysfunction. Although preventive measures of fluid-load and use of a g-suit are required of every crew member, they have not been successful in totally preventing this problem [18]. Before EDOMP, the standard operational countermeasure in the U.S. Space Program was 8 gm salt, mixed in approximately 1 liter of water to provide isotonic saline [1]. New countermeasures to postflight orthostatic intolerance were evaluated during EDOMP. These included ingestion of hypotonic and hypertonic saline solutions before landing, in-flight use of fludrocortisone to expand plasma volume, and in-flight use of lower body negative pressure while ingesting isotonic saline to unload cardiopulmonary receptors and expand plasma volume.

Methods and Materials

In the first countermeasure study (DSO 478), the orthostatic tolerance and presyncopal symptoms of each crew member were documented at least 2 months before flight, using lower body negative pressure (LBNP) tolerance tests [19]. In this protocol, LBNP was applied in stepped decrements of 10 mmHg until the crew member

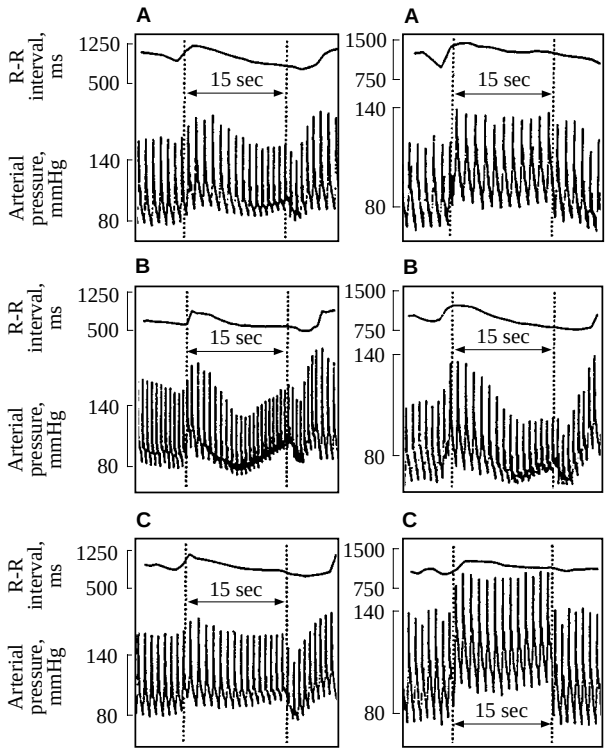


Figure 1-13. Left: blood pressure and R-R internal responses of 1 subject during Valsalva maneuvers preflight (A), on landing day (B), and 3 days after landing (C). Right: blood pressure and heart rate responses of different subject during Valsalva maneuvers preflight (A), on landing day (B), and 3 days after landing (C). This individual was a square-wave responder preflight.

exhibited evidence of presyncope, such as a sudden decrease in heart rate (a change of more than 15 bpm within 1 minute), or a systolic pressure less than 70 mmHg.

Baseline heart rate and arterial pressure data were also collected on each crew member using a preflight LBNP "ramp" test. The LBNP ramp test protocol began with 30 minutes of supine baseline data collection, followed by consecutive 5-minute stages at 0 (atmospheric pressure), -10, -20, -30, -40, -50, and -60 mmHg decompressions, and a 5-minute recovery stage at atmospheric pressure. Heart rate and arterial pressure were measured at least once each minute. Changes in leg circumference were measured continuously with a mercury-in-silastic strain gauge positioned over the largest area of the calf. Ultrasound echocardiographic measurements of heart dimensions and aortic blood flow velocity were also acquired on four missions, for correlation with similar in-flight measurements.

A collapsible LBNP device, developed for use aboard the Shuttle, was used for all in-flight LBNP exposures. A modified clinical automatic blood pressure monitor measured heart rate and arterial pressure once per minute and provided analog signals for telemetry to the ground station. A modified clinical ultrasound echocardiograph was used on four missions to document changes in heart volume and blood flow during LBNP.

The LBNP treatment protocol (called a soak) began with a stepwise decompression to -50 mmHg, followed by about 3.5 hours of decompression at -30 mmHg below ambient pressure. One liter of water or artificially sweetened fruit drink, and 8 gm of sodium chloride, were ingested during the first hour of -30 mmHg decompression. The treatment was evaluated by comparing heart rate and arterial pressure responses to the in-flight ramp

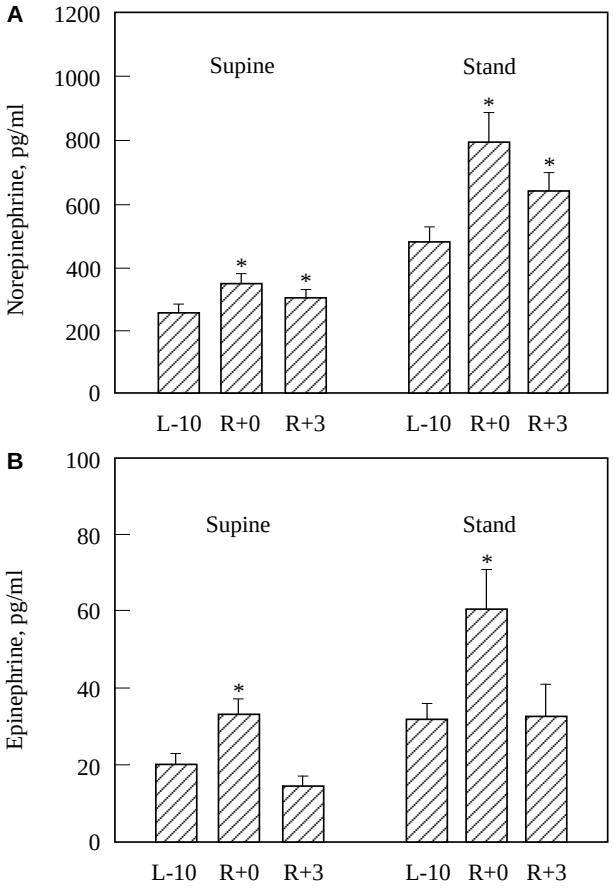


*Figure 1-14. Supine and standing plasma norepinephrine and epinephrine concentrations before and after spaceflight. Norepinephrine and epinephrine were quantified from samples obtained 10 days before flight (L-10), on landing day (R+0), and 3 days after flight (R+3). A: supine (n = 24) and standing (n = 16) norepinephrine levels. B: supine (n = 23) and standing (n = 15) epinephrine levels. *Significantly different from corresponding L-10 value, $P < 0.05$ (analysis of variance; Dunnett's test).*

Table 1-5. Supine measurements from all subjects on all test days

			Days Postflight				
	Preflight	*Landing Day*	*1-2*	*3*	*4*	*6-8*	*10-18*
Baseline measurements							
Systolic pressure, mmHg	110±2	115±2*	112±2	112±2	114±1	112±2	112±2
Diastolic pressure, mmHg	73±1	75±2	74±2	74±2	73±2	73±1	74±2
R-R interval, ms	1,159±49	1,003±51†	1,024±45†	1,132±54	1,088±48	1,069±53	1,020±43
Body wt, kg	78.5±3.7	76.0±3.8*	76.5±3.5	76.9±3.8	77.2±3.7	77.1±3.6	77.4±3.5
Norepinephrine, pg/ml	290±35	332±39*		303±23			
Epinephrine, pg/ml	27±5	36±6*		22±3			
Baroreflex measurements							
Maximum slope, ms/mmHg	4.7±0.4	4.0±0.4*	3.8±0.4*	4.7±0.6	4.4±0.5	5.6±0.6	3.4±0.6
R-R range, ms	244±23	186±17*	181±16†	233±24	214±21	245±22	233±24
Operational point, %	36.3±3.8	29.8±4.7	34.2±3.9	36.9±4.9	35.0±3.6	32.0±3.9	31.0±4.2
Minimum R-R, ms	1,080±42	968±48*	980±86*	1,090±50	1,008±42	1,022±51	979±40
Maximum R-R, ms	1,323±54	1,154±51*	1,162±51*	1,323±61	1,222±53	1,267±61	1,212±51
Carotid distending pressure at minimum R-R, mmHg	75±2	80±4	75±3	75±3	76±2	75±3	78±3
Carotid distending pressure at maximum R-R, mmHg	162±4	165±5	161±4	159±5	165±4	160±4	168±3

Values are means ± SE; n=16 subjects, n = 12 subjects used for all comparisons between landing day and preflight measurements and those between landing day and days 10-18 measurements. *$P < 0.025$: †$P < 0.01$.

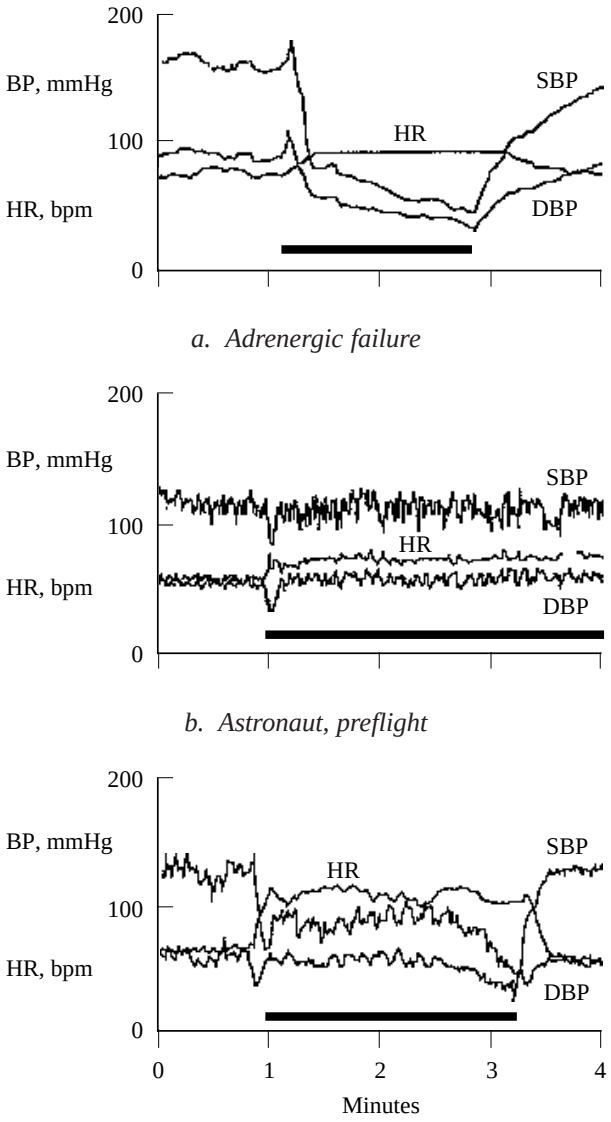
tests, at 3-day intervals before, and 1 or 2 days after, the soak treatment. The stepwise decompression at the beginning of the treatment also provided information on cardiovascular function immediately before treatment.

The second countermeasure study (DSO 623) sought to determine if the soak treatment described above, performed 24 hours before landing, would preserve orthostatic tolerance after landing [19]. In this study, the orthostatic tolerance and presyncopal symptoms of each participating crew member were documented during two LBNP tolerance tests occurring between 120 and 90 days before launch. Baseline heart rate and arterial pressure were measured on each crew member, using a ramp test on two preflight sessions between 90 and 30 days before launch. During each test, heart rate and arterial pressure were measured once per minute, along with continuous recordings of electrocardiogram and noninvasive, beat-to-beat, finger blood pressure using the Finapres™ device. Ultrasound echocardiographic measurements of heart dimensions and aortic blood flow were also acquired on two crew members for correlation with similar in-flight measurements. Crew member subjects also performed a preflight stand test to measure baseline orthostatic responses.

In flight, "active" crew member subjects participated in a single 4-hour soak treatment on the nominal day before landing. The average heart rate (HR), systolic (SBP) and diastolic pressures, mean arterial pressure (MAP), pulse pressure, tolerance index (MAP/MAP baseline)/ (HR/HR baseline), and shock index (SBP/HR) were determined at each stage of decompression. Results from subjects who performed the soaks (active subjects) were compared with those who did not perform the soaks (inactive subjects).

In the third countermeasure study (DSO 479), 23 astronauts from five Shuttle flights each consumed one of three fluid loading solutions 1 to 2 hours before landing. The solution choices were: (1) hyperosmotic (1.07%) salt tablets/water solution, (2) isotonic saline solution, and (3) salt tablets and water to equal isotonic saline solution. These solutions had previously been evaluated in ground-based studies for their efficacy in increasing plasma volume [20]. Each crew member performed a stand test two times before flight, on landing day to assess the effectiveness of the candidate fluid loading countermeasure, and three days after landing to verify return to preflight baseline status.

In the fourth countermeasure study (DSO 621), fludrocortisone was tested as a means to expand plasma volume and improve postflight orthostatic tolerance. The following regimens for fludrocortisone were used: (1) 0.2 mg twice daily (B.I.D.) for the last 5 days of flight, (2) 0.1 mg B.I.D. for the last 5 days of flight, or (3) a single dose of 0.3 mg taken 7 hours before landing. Supine blood volume, supine and standing heart rate and arterial pressure, and plasma catecholamines were measured before and after flight.



a. Adrenergic failure

b. Astronaut, preflight

c. Astronaut, landing day

Figure 1-15. Beat-to-beat blood pressure and heart rate during stand tests.

Results

In the first countermeasure study (DSO 478), data applicable to the evaluation of the LBNP countermeasure were obtained for 4 of the 13 crew member subjects. The protective effect of the LBNP and concurrent saline ingestion were evaluated by comparison of heart rate and systolic and diastolic pressures at maximum decompression. Two of the four subjects did not reach the maximum planned level of decompression (–50 mmHg) at least once during flight. However, they did achieve the –40 mmHg level at each session. Therefore, for those two subjects, the reported heart rate and arterial pressure responses are from –40 mmHg decompression preflight and in flight.

The heart rate and systolic and diastolic pressures during maximum LBNP before and during flight, both before and after the soak treatment, are shown in Figure 1-16. Heart rate increased significantly between preflight and early in-flight tests (flight days 3 to 5), but thereafter plateaued between the mid-flight and late in-flight tests before treatment. One day after the soak treatment, the heart rate response to maximum LBNP was significantly less than before the soak, indicating that the soak had a beneficial effect. Two days after treatment, the heart rate response to LBNP was returning toward the pre-soak value, indicating that the beneficial effect was lost (Figure 1-16a). Neither systolic nor diastolic pressures during LBNP differed across all preflight and in-flight values (Figures 1-16b, 1-16c).

In the second study (DSO 623), which was an actual trial of the countermeasure, data were obtained from five crew members who underwent the soak on the day before landing, and seven crew members (including one who participated in LBNP ramp tests but not the soak) from the same missions who did not participate in other countermeasure studies. Data from two crew members whose landing was delayed by one day were pooled with data from three crew members who landed as planned on the day after LBNP treatment. There was no practical possibility of repeating the treatment on a wave-off day because of crew time constraints.

Data collected shortly after landing, during the Orbiter stand test with g-suit inflated, show a difference between the crew members using, or not using, LBNP during the flight. Diastolic pressure was lower in LBNP subjects, both seated and standing, than in non-LBNP subjects (Figure 1-17a). The non-LBNP subjects showed a greater tendency for systolic pressure to decrease after standing than the LBNP subjects (data not shown). Finally, the LBNP subjects showed a lower heart rate both seated and standing than the non-LBNP subjects (Figure 1-17b). There were no differences between LBNP and non-LBNP subjects in red blood cell volume, plasma volume, or heart rate and arterial pressures during stand tests 1 to 3 hours after landing (data not shown).

In the fourth countermeasure study (DSO 621), the results indicate that fludrocortisone, as administered by the first two protocols, was not tolerated by the crew members. None of the protocols restored blood volume. The percent change in plasma and red blood cell volume from preflight to postflight was not significantly different in the fludrocortisone vs. non-fludrocortisone group (Figure 1-18). Fludrocortisone subjects did not have greater orthostatic tolerance than control subjects on landing day. Participation in protocols was incomplete and limited by subjective evaluation of the medication; therefore, only limited conclusions could be made.

Table 1-6. Comparison of landing day values for presyncopal vs. non-presyncopal astronaut subjects

a. Landing day measurements

	Presyncopal on Landing Day (n = 8)			*Nonpresyncopal on Landing Day (n = 21)*		
	Supine	*Standing*	*Standing-supine*	*Supine*	*Standing*	*Standing-supine*
Plasma norepinephrine, pg/ml	330 ± 67	420 ± 46*	105 ± 41*	278 ± 18	618 ± 88*	340 ± 62*
Peripheral vascular resistance, mmHg • l^{-1} • min	16.0 ± 1.3	22.9 ± 2.5*	6.4 ± 2.9	21.1 ± 1.6	33.8 ± 2.7*	12.6 ± 2.6
Diastolic pressure, mmHg	74 ± 4	61 ± 4†	-14 ± 7†	76 ± 2	81 ± 2†	3 ± 2†
Systolic pressure, mmHg	110 ± 4*	80 ± 3†	-28 ± 4†	120 ± 2*	109 ± 3†	-11 ± 3†
Heart rate, beats/min	72 ± 5*	114 ± 8†	41 ± 6*	62 ± 2*	91 ± 4†	29 ± 3*
Stroke volume, ml	78 ± 4	28 ± 2	-51 ± 5	77 ± 5	32 ± 9	-44 ± 5
Cardiac output, l/min	5.5 ± 0.3	3.3 ± 0.3	-2.4 ± 0.3	4.7 ± 0.3	2.9 ± 0.2	-1.8 ± 0.3
Mean flow velocity (middle cerebral artery), cm/s	52.4 ± 4.7	40.0 ± 2.9	-12.4 ± 2.2	47.6 ± 2.3	39.7 ± 1.6	-7.5 ± 1.2
Cerebral vascular resistance, mmHg • cm^{-1} • s	1.7 ± 0.3	1.1 ± 0.1†	-0.7 ± 02	2.0 ± 0.1	1.6 ± 0.1†	-0.4 ± 0.1
Plasma epinephrine, pg/ml	42 ± 5	66 ± 12	20 ± 13	23 ± 2	48 ± 6	25 ± 7
Plasma renin activity, ng • ml^{-1} • h^{-1}	2.7 ± 1.2	3.4 ± 1.5	1.3 ± 0.6	2.2 ± 0.3	3.7 ± 0.6	1.5 ± 0.3
Plasma volume, liters	2.7 ± 0.2			3.2 ± 0.2		

Values are means ± SE; *n*, no. of subjects. Supine, standing, and standing-supine difference measurements for all variables (plasma volume was only measured supine) are separated into presyncopal and nonpresyncopal groups on landing day. *$P < 0.05$ between groups. †$P < 0.01$ between groups

b. Preflight measurements

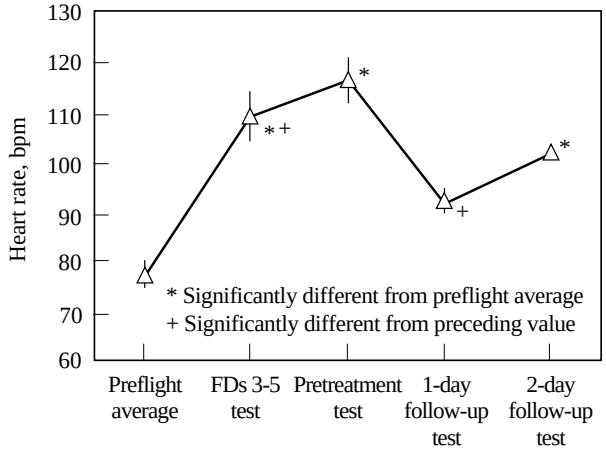
	Presyncopal on Landing Day (n = 8)			*Nonpresyncopal on Landing Day (n = 21)*		
	Supine	*Standing*	*Standing-supine*	*Supine*	*Standing*	*Standing-supine*
Plasma norepinephrine, pg/ml	213 ± 28	467 ± 42	254 ± 37	209 ± 15	466 ± 44	257 ± 38
Peripheral vascular resistance, mmHg • l^{-1} • min	15.5 ± 0.9*	22.9 ± 1.8*	7.4 ± 1.5	21.2 ± 1.9*	31.8 ± 2.3*	10.6 ± 1.9
Diastolic pressure, mmHg	66 ± 2†	69 ± 4†	3 ± 3	73 ± 2†	77 ± 2†	4 ± 1
Systolic pressure, mmHg	109 ± 3*	99 ± 4†	-10 ± 2*	114 ± 2*	108 ± 3†	-5 ± 2*
Heart rate, beats/min	62 ± 2†	81 ± 5†	19 ± 5	54 ± 1†	71 ± 2†	17 ± 2
Stroke volume, ml	86 ± 5	45 ± 5	-41 ± 3	83 ± 4	41 ± 2	-43 ± 3
Cardiac output, 1/min	5.3 ± 0.5*	3.6 ± 0.4*	-1.7 ± 02	4.4 ± 0.2*	2.9 ± 0.2*	-1.6 ± 0.2
Mean flow velocity (middle cerebral artery), cm/s	58.9 ± 5.7	51.2 ± 2.5*	-7.5 ± 1.6	53.4 ± 5.5	43.1 ± 2.1*	-11.4 ± 2.3
Cerebral vascular resistance, mmHg • cm^{-1} • s	1.5 ± 0.2	1.1 ± 0.2*	-0.4 ± 0.1	1.9 ± 0.1	1.5 ± 0.1*	-0.4 ± 0.1
Plasma epinephrine, pg/ml	19 ± 3	30 ± 3	12 ± 2	24 ± 3	38 ± 4	14 ± 4
Plasma renin activity ng • ml^{-1} • h^{-1}	1.7 ± 0.4	2 ± 0.5	0.3 ± 02	1.3 ± 0.2	1.6 ± 02	0.2 ± 0.1
Plasma volume, liters	3.2 ± 0.2			3.4 ± 0.1		

Values are means ± SE, *n*, no. of subjects. Supine, standing, and standing-supine difference measurements for all variables (plasma volume was only measured supine) are separated into presyncopal and nonpresyncopal groups before flight (average of 2 preflight data sessions). *$P \leq 0.05$ between groups. †$P \leq 0.01$ between groups

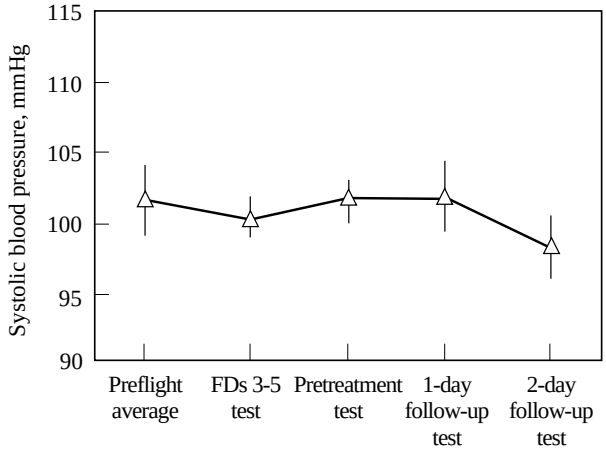
c. Measurements 3 days after landing

	Presyncopal on Landing Day (n = 8)			*Nonpresyncopal on Landing Day (n = 21)*		
	Supine	*Standing*	*Standing-supine*	*Supine*	*Standing*	*Standing-supine*
Plasma norepinephrine, pg/ml	234 ± 36	552 ± 86*	318 ± 57	252 ± 23	509 ± 53*	256 ± 39
Peripheral vascular resistance, mmHg • l^{-1} • min	16.3 ± 0.9	23.9 ± 0.9†	7.6 ± 2.5*	21.5 ± 1.9	36.4 ± 2.5†	14.9 ± 2.0*
Diastolic pressure, mmHg	68 ± 2†	71 ± 4†	3 ± 3	77 ± 1†	81 ± 2†	5 ± 2
Systolic pressure, mmHg	110 ± 7*	96 ± 5†	-14 ± 4*	118 ± 2*	114 ± 3†	-5 ± 2*
Heart rate, beats/min	60 ± 2*	83 ± 6	23 ± 5	57 ± 2*	75 ± 2	20 ± 2
Stroke volume, ml	87 ± 8	54 ± 7	-42 ± 7	83 ± 5	37 ± 3	-46 ± 4
Cardiac output, 1/min	5.1 ± 0.3	3.6 ± 0.4	-1.5 ± 0.3	4.7 ± 0.3	2.8 ± 0.2	-1.9 ± 0.2
Mean flow velocity (middle cerebral artery), cm/s	63.3 ± 7.2	57.0 ± 6.8	-6.3 ± 1.2	50.6 ± 3.0	46.1 ± 3.0	-3.9 ± 1.3
Cerebral vascular resistance, mmHg • cm^{-1} • s	1.4 ± 0.2	1.1 ± 0.2	-0.4 ± 0.1	1.9 ± 0.1	1.5 ± 0.1	-0.4 ± 0.1
Plasma epinephrine, pg/ml	18 ± 4	25 ± 4*	7 ± 5	25 ± 4	38 ± 4*	14 ± 4
Plasma renin activity ng • ml^{-1} • h^{-1}	1.9 ± 0.7	1.7 ± 0.8	0.4 ± 0.2	1.2 ± 0.2	1.4 ± 0.3	0.3 ± 0.08
Plasma volume, liters	3.5 ± 0.2			3.6 ± 0.1		

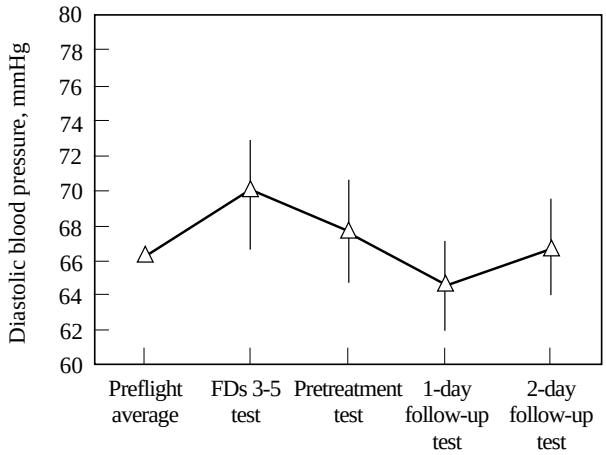
Values are means ± SE, *n*, no. of subjects. Supine, standing, and standing-supine difference measurements for all variables (plasma volume was only measured supine) are separated into presyncopal and nonpresyncopal groups three days after landing. *$P \leq 0.05$ between groups. †$P \leq 0.01$ between groups.



a.

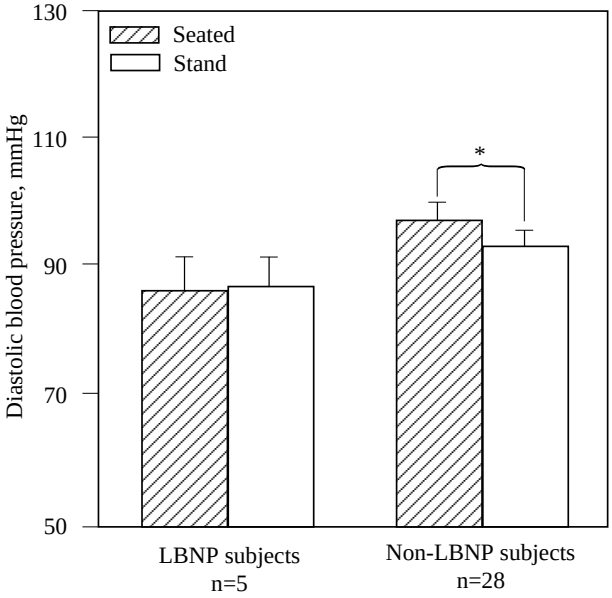


b.

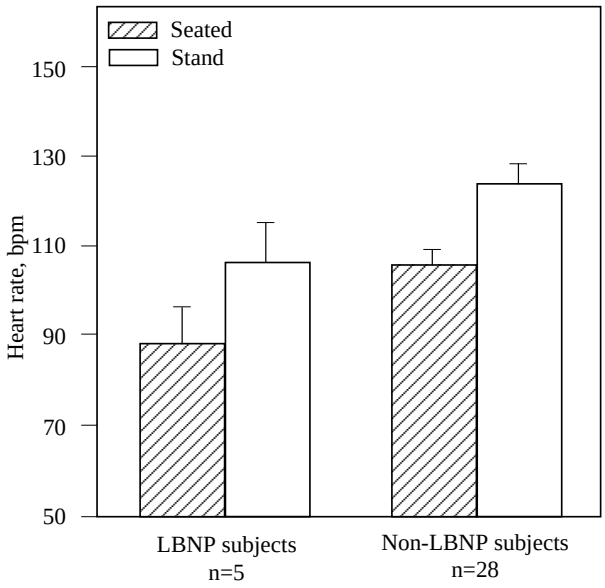


c.

Figure 1-16. Heart rate, systolic blood pressure, and diastolic blood pressure during LBNP test preflight and in flight at maximum level of LBNP for four astronauts.



a. Diastolic blood pressure



b. Heart rate

Figure 1-17. Postflight stand test with g-suit inflated.

Conclusions

In-flight heart rate, during -40 to -50 mmHg lower body ramp decompressions, increased until the day of the LBNP soak. One day after LBNP soak, the heart rate response to -40 to -50 mmHg lower body decompression indicated that the soak had a protective effect. Two days after the combined countermeasure, the effect was gone. These data were obtained in flight as part of DSO 478.

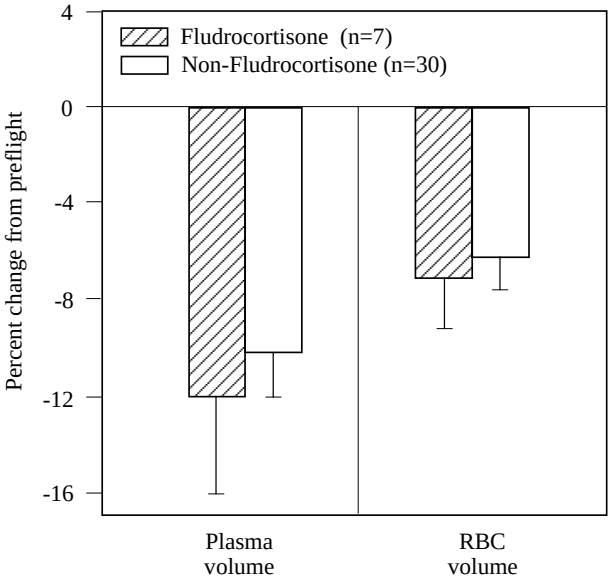


Figure 1-18. Effect of fludrocortisone on plasma volume losses.

The combination of LBNP with ingestion of fluid and salt is a potentially efficacious countermeasure against postflight orthostatic intolerance. Early in-flight loss of orthostatic capacity was documented in this study. This suggests that the significant cardiovascular deficit observed after long duration missions is already well developed after much shorter flights of 10 days or less. We would infer that the same type of protective or ameliorative measures envisaged for long duration crew members should also be made available to their short duration counterparts. However, in terms of a cost/benefit analysis, the soak has not been accepted for general operational applications, since approximately 5 hours are required to treat one subject.

In the third countermeasure study (DSO 479), evaluation of the relative efficacy of the different candidate fluid loading solutions was difficult due to the existence of several factors that compromised data quality. These factors were: (1) a flight rule requiring crew members to repeat half of the fluid load protocol in the event of a one revolution wave-off of landing, (2) variations in the amount of solution ingested, (3) subsequent uncontrolled fluid ingestion after completion of the fluid loading protocol, which, in effect, diluted the prescribed solutions, and (4) use of fluids other than water, as prescribed, which altered not only the conditions of the investigation but also the efficacy of the countermeasure.

Evaluation of the candidate fluid loading countermeasure solutions and their ability to maintain orthostatic function after spaceflight was terminated without providing a conclusive answer to the question of the efficacy of a hypertonic solution as an end-of-mission rehydration countermeasure. Results from in-flight use of fludrocortisone led us to conclude that fludrocortisone, as administered, had no effect on orthostatic intolerance.

DISCUSSION

Cardiovascular deconditioning was observed in astronauts early in the manned spaceflight program [21]. A component of deconditioning included a cephalid fluid shift and resultant loss of fluid [22]. Bed rest studies revealed the usefulness of oral rehydration in providing a degree of protection against orthostatic intolerance [23]. One of the early DSO studies showed some improvement in cardiovascular deconditioning by using fluid loading as a countermeasure [1]. Subsequently, oral fluid and salt loading was adopted as an operational countermeasure for all Shuttle crew members. Nevertheless, virtually every astronaut returning from space continued to suffer from some degree of orthostatic intolerance. Returning astronauts typically developed orthostatic intolerance attributable to autonomic dysfunction when subjected to upright posture [7, 8, 18, 24]. Signs and symptoms include tachycardia, nausea, vomiting, lightheadedness (presyncope), and fainting (syncope). Common treatments for orthostatic intolerance, such as blood volume expansion (oral fluid loading) or shock trousers (antigravity suits), when modified to protect astronauts, have not been completely effective [18, 25]. Orthostatic intolerance in returning astronauts normally resolves without treatment in 1 to 2 days.

Various cardiac dysrhythmias have been reported throughout the U.S. spaceflight experience. These have occurred during activities both inside and outside the space vehicle [21]. In flight, Holter monitoring of astronauts showed the incidence of dysrhythmias to be no greater during flight than before flight, leading to the conclusion that spaceflight alone does not cause an increase in the incidence of dysrhythmias [10].

Documented responses to landing day activities show that the cardiovascular system is under significant stress during entry, landing, and seat egress [15]. No differences were found that were related to flight duration between 4 to 14 days. Nominal entry, landing and seat egress are associated with blood pressure decreases and heart rate increases. The cardiovascular systems of about 30% of the subjects were compromised during the landing period.

Immediately after Shuttle landing, the cardiovascular system was challenged to support arterial pressure, resulting in standing heart rates as high as 160 bpm and systolic pressure drops by as much as 25 mmHg [15]. Landing day studies conducted one to two hours after landing have shown that heart rates, arterial pressures, and supine and standing plasma catecholamine levels all were elevated, but increases in peripheral vascular resistance per unit increase in circulating norepinephrine were reduced.

Changes in autonomic regulation affect postflight cardiovascular function. Attenuation of the vagally mediated carotid baroreceptor cardiac reflex response may begin early in flight and persist for about a week postflight. On landing day, reductions in this reflex correlate directly with lower standing systolic pressures. Decreases in heart rate and arterial pressure during flight were reversed on landing day, and the frequency of cardiac dysrhythmias decreased in flight, compared to preflight values. These reports suggest that sympathetic activity may be low during spaceflight, but they do not support the conclusion that loss of plasma volume was the primary cause of postflight orthostatic hypotension.

There was a wide range of individual susceptibility to orthostatic intolerance after spaceflight. Some individuals had severe symptoms, while others were less affected [7, 8]. These data, taken as a whole, provide convincing evidence that the precipitating factor for orthostatic intolerance after spaceflight was a hypoadrenergic response to orthostatic stress. The parallel insufficient levels of plasma norepinephrine, diastolic pressure, and peripheral vascular resistance strongly support this.

These data suggest that human cardiovascular adaptations to the microgravity encountered during spaceflight included changes in central modulation of baroreceptor inputs that contributed to a hypoadrenergic response to orthostasis and presyncope in 25% of returning astronauts. The idea of changes in central modulation is supported by other symptoms, including retention/incontinence; diarrhea; constipation; changes in vision, taste, smell, thirst, and appetite; and hypesthesias as well as parasthesias in the feet.

These data not only suggest a mechanism for postflight orthostatic intolerance, but also show clear differences between susceptible and non-susceptible individuals. The data, for the first time, also raise the possibility of predicting susceptible individuals before launch. The intergroup differences before flight suggest that there was a subset of the normal population with orthostatic responses within the normal range before flight that was somehow predisposed to postflight orthostatic intolerance. In this subgroup, the norepinephrine responses to standing were normal both before and 3 days after flight. However, during every test session the subgroup tended to have somewhat lower vascular resistance and arterial pressures, and higher heart rates than the other group. This suggests possible preflight intergroup differences in venous compliance or vascular responsiveness. Spaceflight somehow caused this subgroup to have greatly subnormal adrenergic responses after they landed, while their norepinephrine responses to standing were very similar to those in patients with autonomic dysfunction known to be centrally modulated.

A number of countermeasures to prevent orthostatic intolerance have been studied. Fluid loading has shown some benefits as mentioned earlier. A second trial procedure has been the LBNP soak, which typically decompresses the legs and abdomen by up to -30 mmHg and allows fluid to pool in the legs and abdomen [26, 27]. Brief decompression of up to -50 mmHg (ramp) was used as a gravity-independent test of orthostatic capacity. Longer decompression (soak), either alone or in combination with salt and water ingestion, has been used as a countermeasure trial in an attempt to restore orthostatic tolerance. One day after LBNP soak, decreased heart rate response to -40 to -50 mmHg lower body decompression indicated in flight (DSO 478) that the soak provided a protective effect. Diastolic blood pressure was lower in LBNP subjects, both seated and standing, than in non-LBNP subjects, suggesting that the LBNP subjects required a smaller increase in total peripheral resistance to maintain adequate blood pressure. The non-LBNP subjects showed a greater tendency for systolic blood pressure to decrease after standing than did the LBNP subjects. The LBNP subjects showed a lower heart rate both seated and standing than the LBNP subjects. This suggests that the LBNP subjects treated by the soak procedure had a greater reserve capacity to increase heart rate if required by the metabolic demand. However, these differences were not statistically significant.

A third countermeasure under study was fludrocortisone, which causes renal retention of sodium with consequent plasma volume expansion. Fludrocortisone has shown some ability to restore plasma volume and orthostatic tolerance at the end of bed rest [23]. The use of fludrocortisone did not restore blood volume when used in flight by astronauts, using the single-dose regimen noted. Further, fludrocortisone subjects did not seem to have greater orthostatic tolerance than control subjects on landing day.

SUMMARY

Findings from the Cardiovascular EDOMP studies include:

1. Changes in central modulation of baroreceptor inputs result in a hypoadrenergic response to orthostasis and presyncope in 25% of returning astronauts, as documented by a 10-minute clinical stand test.

2. Spaceflight alone does not increase the incidence of dysrhythmias, nor does it constitute a significant cardiovascular stress.

3. Landing poses a significant cardiovascular stress.

4. There are clear differences between susceptible and non-susceptible individuals.

5. Susceptibility of individuals to postflight orthostatic intolerance may be predicted before launch.

RECOMMENDATION

With the conclusion of the EDOMP, the Cardiovascular Laboratory at JSC has reported some significant findings that might be quickly translated into countermeasure trials for postflight orthostatic intolerance. A comparison of presyncopal and non-presyncopal astronaut responses to standing has shown significant differences between the two groups on landing day. The most fundamental intergroup difference was the low standing norepinephrine levels in the presyncopal group, which ultimately resulted in inadequate cerebral perfusion and presyncope. The failure to increase norepinephrine translated into lower peripheral vascular resistance, lower arterial pressures, and lower heart rate responses to decreasing systolic pressure in the presyncopal group. Crew members who became presyncopal on landing day also showed some differences before launch, such as lower peripheral vascular resistance, and lower systolic and diastolic pressures with standing.

This loss of the pressor response suggests that a pharmacological countermeasure could be utilized to combat orthostatic intolerance. A systematic study using pressor agents could prove the efficacy of the pharmacological approach. Coupling a successful pressor agent with the at-risk crew members, diagnosed as described above, would allow flight surgeons to more effectively manage postflight orthostatic intolerance in astronauts.

REFERENCES

1. Bungo MW, Charles JB, Johnson PC Jr. Cardiovascular deconditioning during space flight and the use of saline as a countermeasure to orthostatic intolerance. Aviat Space Environ Med 1985; 56(10):985-990.
2. Charles JB, Bungo MW, Fortner GW. Cardiopulmonary function. In: Nicogossian AE, Huntoon CL, Pool SL, editors. Space physiology and medicine. 3rd ed. Philadelphia: Lea & Febiger; 1994; 286-304.
3. Charles JB, Lathers CM. Cardiovascular adaptation to spaceflight. J Clin Pharm 1991; 31:1010-1023.
4. Johnson RL, Hoffler GW, Nicogossian AE, Bergman SA Jr, Jackson MM. Lower body negative pressure: third manned Skylab mission. In: Johnston RS, Dietlein LF, editors. Biomedical results from Skylab (NASA SP-377). Washington: U.S. Government Printing Office; 1977; 284-312.
5. Michel EL, Rummel JA, Sawin CF, Buderer MC, Lem JD. Results of Skylab medical experiment M171-metabolic activity. In: Johnston RS, Dietlein LF, editors. Biomedical results from Skylab (NASA SP-377). Washington: U.S. Government Printing Office; 1977; 372-387.
6. Blomqvist CG, Nixon JV, Johnson RL Jr, Mitchell HH. Early cardiovascular adaptation to zero gravity simulated by head-down tilt. Acta Astronaut 1980; 7:543-553.
7. Fritsch JM, Charles JB, Bennett BS, Jones MM, Eckberg DL. Short-duration spaceflight impairs human carotid baroreceptor-cardiac reflex responses. J Appl Physiol 1992; 73:664-671.
8. Fritsch-Yelle JM, Charles JB, Jones MM, Beightol LA, Eckberg DL. Spaceflight alters autonomic regulation of arterial pressure in humans. J Appl Physiol 1994; 77(4):1776-1783.
9. Robertson D, Biaggioni I, Mosqueda-Garcia R, Robertson RM. Orthostatic hypotension of prolonged weightlessness: clinical models. Acta Astronaut 1992; 27:97-101.
10. Fritsch-Yelle JM, Charles JB, Crockett MJ, Wood ML. Microgravity decreases heart rate and arterial pressure in humans. J Appl Physiol 1996; 80(3): 910-914.
11. Mulvagh SL, Charles JB, Riddle JM, Rehbein TL, Bungo MW. Echocardiographic evaluation of the cardiovascular effects of short-duration spaceflight. J Clin Pharm 1991; 31:1024-1026.
12. Sahn DJ, DeMaria A, Kisslo J, Weyman A. The committee on m-mode standardization of the American Society of Echocardiography: Results of a survey of echocardiographic measurements. Circulation 1978; 58:1072-1083.
13. Teichholz LE, Kreulen T, Hermand MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence or absence of asynergy. Am J Cardiol 1976; 37:7-11.
14. Cooper RH, O'Rourke RA, Karliner JS, Peterson KL, Leopold GR. Comparison of ultrasound and cineangiographic measurement of the mean velocity of circumferential fibre shortening in man. Circulation 1972; 46:914-922.
15. Jones MM, Charles JB. Human blood pressure and heart rate changes during space shuttle landing and crew egress. (Abstract) FASEB 1993; 7:A665.
16. Eckberg DL, Fritsch JM. Human autonomic responses to actual and simulated weightlessness. J Clin Pharm 1991; 31:951-954.
17. Whitson PS, Charles JB, Williams WJ, Cintron NM. Changes in sympathoadrenal response to standing in humans after space flight. J Appl Physiol 1995; 79:428-433.
18. Fritsch-Yelle JM, Whitson PA, Bondar RL, Brown TE. Subnormal norepinephrine release relates to presyncope in astronauts after space flight. J Appl Physiol 1996; 81(5):2134-2141.

19. Charles JB, Lathers CM. Summary of lower body negative pressure experiments during space flight. J Clin Pharm 1994; 36:571-583.

20. Frey MAB, Riddle J, Charles JB, Bungo MW. Blood and urine responses to ingesting fluids of various salt and glucose concentrations. J Clin Pharm 1991; 31:880-887.

21. Bungo MW, Johnson PC Jr. Cardiovascular examinations and observations of deconditioning during the space shuttle orbital flight test program. Aviat Space Environ Med 1983; 54:1001-1004.

22. Thornton WE, Hoffler GW, Rummel JA. Anthropometric changes and fluid shifts. In: Johnston RS, Dietlein LF, editors. Biomedical results from Skylab (NASA SP-377). Washington: U.S. Government Printing Office; 1977; 324-338.

23. Vernikos J, Dallman MF, van Loon G, Keil LC. Drug effects on orthostatic intolerance induced by bedrest. J Clin Pharm 1991; 31:974-984.

24. Mulvagh SL, Charles JB, Fortney SM, Bungo MW. Changes in peripheral vascular resistance may account for orthostatic intolerance after space flight. (Abstract) Circulation 1990; 82:Supp III, 515.

25. Bungo MW. The cardiopulmonary system. In: Nicogossian AE, Huntoon CL, Pool SL, editors. Space physiology and medicine. 2nd ed. Philadelphia: Lea & Febiger; 1989; 179-201.

26. Wolthius RA, Bergman SA, Nicogossian AE. Physiological effects of locally applied reduced pressure in man. Physiol Rev 1974; 54(3):566-595.

27. Johnson PC, Driscoll TB, Leblanc AD. Blood volume changes. In: Johnston RS, Dietlein LF, editors. Biomedical results from Skylab (NASA SP-377). Washington: U.S. Government Printing Office; 1977; 235-241.