scheduling and procedural modifications during urine sample collection and processing in the preflight activities, the baseline control measurements of oxalate and citrate were not obtained. Inflight values were compared to the established values for the general population.

mission phases, each set separated no more than 2 days. When compared to their preflight values, inflight data on a single void basis did not exhibit the development of trends with respect to changes in any parameter. As expected, there was significant variation from

TABLE 3. PREFLIGHT URINARY BIOCHEMISTRY* VOID-BY-VOID SAMPLE ANALYSIS

	Day of Sample	Time	TV ml	Specific Gravity	Osmo** mosm	Na mEq/TV	K mEq/TV	Cl mEq/TV	Ca mEq/TV	Mg mEq/TV	IP04 mg/TV	Uric Acid mg/TV	Creat** mg/TV
Preflight	L-34 Days	8:15 a.m.	41	1.030	1086	4	8	7	0.1	0.3	40	28	132
		11:10 a.m.	70	1.030	1195	9	13	13	0.2	0.6	95	40	197
		1:30 p.m.	51	1.031	1194	4	10	7	0.1	0.4	107	18	166
		6:30 p.m.	138	1.032	1215	25	24	22	0.3	1.4	284	94	364
		10:05 p.m.	57	1.030	1108	12	6	8	0.3	0.5	75	28	108
	L-33 Days	3:45 a.m.	222	1.027	1007	29	10	17	0.8	2.3	384	106	390
		7:00 a.m.	142	1.025	1001	18	11	22	0.5	1.4	142	49	224
	L-31 Days	8:56 a.m.	102	1.023	964	20	5	21	0.8	0.9	54	29	96
		10:24 a.m.	306	1.011	463	17	15	22	0.4	0.7	28	43	101
		12:41 p.m.	235	1.015	578	18	17	20	0.4	1.2	57	46	146
		2:46 p.m.	117	1.026	944	26	10	16	0.5	1.1	110	62	136
		4:37 p.m.	164	1.023	876	37	10	24	0.6	0.8	106	79	139
		6:14 p.m.	175	1.018	728	27	8	20	0.4	0.8	98	55	116
		8:32 p.m.	163	1.019	782	23	7	19	0.4	1.0	108	63	143
		9:23 p.m.	66	1.025	1050	16	2	13	0.6	0.7	52	39	78
		10:08 p.m.	12	1.026	1090	3	1	3	0.1	0.1	6	8	16
	L-30 Days	5:45 a.m.	95	1.026	1041	18	2	16	0.9	1.0	71	55	144

*Urine contains 1% boric acid
**Affected by boric acid addition and storage
L = Launch Date

TABLE 4. URINARY BIOCHEMISTRY* VOID-BY-VOID SAMPLE ANALYSIS

	MET†	Time	TV ml	Specific Gravity	Osmott mosm	Na mEq/TV	K mEq/TV	Cl mEq/TV	Ca mEq/TV	Mg mEq/TV	IP04 mg/TV	Uric Acid mg/TV	Creattt mg/TV
Inflight	**000	20:30	78	1.032	1202	12	7	13	0.1	0.9	11	1	239
	001	0 hr 44 min	326	1.016	476	22	13	27	0.8	2.5	177	129	346
		2 hr 22 min	256	1.011	435	20	8	24	0.6	1.3	54	79	174
		4 hr 22 min	276	1.010	385	22	9	25	0.4	0.9	76	51	127
		7 hr 01 min	303	1.010	380	25	5	25	0.8	1.6	133	60	145
		11 hr 01 min	305	1.015	604	46	10	45	1.4	2.6	206	108	287
		19 hr 11 min	200	1.022	844	29	11	30	0.8	2.1	306	36	364
	002	18 hr 11 min	67	1.025	1005	12	3	11	0.4	0.7	107	11	123
		22 hr 40 min	398	1.020	736	60	16	58	2.3	3.4	337	163	553
	003	0 hr 30 min	250	1.013	500	25	9	24	0.8	1.1	77	76	188
		9 hr 54 min	294	1.021	737	39	10	26	4.5	2.7	409	47	450
		13 hr 29 min	164	1.014	503	25	9	19	0.7	0.9	224	110	227
		17 hr 30 min	343	1.011	400	17	6	13	0.7	1.4	247	94	268

*Each urine collection bag contained 1 gram boric acid
**This void collection after arising at 20:30

†Mission Elapsed Time
††Affected by boric acid addition and storage

RESULTS

The values for urine chemistries determined from single voids collected from one crewmember during preflight and inflight phases of one mission are presented in Tables 3, 4, and 5. As mentioned earlier, two 24-hour collections were made during each of the sample to sample in all parameters throughout the collection period. The latter is principally a consequence of the diurnal variation of individual parameters and the fluctuations in void volumes as a result of environmental influences.

The results of the urine analyses as standardized to a 24-hour specimen for both preflight and inflight data are summarized in

Table 6. Urine volume did not appear changed in this individual from the preflight control on

TABLE 5. INFLIGHT URINARY BIOCHEMISTRY*
VOID-BY-VOID SAMPLE ANALYSIS

	MET**	TIME	TV ml	CITRATE mg/TV	OXALATE mg/TV
Inflight	000	20:30	78	71.3	3.8
	001	0 hr 44 min	326	176.5	8.4
		2 hr 22 min	256	79.9	6.8
		4 hr 22 min	276	59.4	6.7
		7 hr 01 min	303	67.3	5.5
		11 hr 01 min	305	123.0	6.5
		19 hr 11 min	200	66.8	11.4
	002	18 hr 11 min	67	35.3	2.0
		22 hr 40 min	398	204.5	12.8
	003	0 hr 30 min	250	48.7	5.3
		9 hr 54 min	294	175.4	9.4
		13 hr 29 min	264	117.4	8.0
		17 hr 30 min	343	66.8	7.6

*Each urine collection bag contained 1 gram boric acid
**Mission Elapsed Time

either mission day. A trend to an increased excretion of calcium, phosphate, magnesium and uric acid was present. This is consistent with previous observations made in both space flight (1,2) and bedrest studies (Pak, personal communication). Urinary citrate and oxalate values early inflight were within the normal range of the general population. Observations made in bedrested subjects suggest that the development of hypocitraturia during space flight, if analogous to the ground-based model, would develop during the later adaptive phases of a mission when renal loss of potassium becomes significant. As seen in Table 6, potassium excretion did not appear elevated in the early flight days measured. This observation is tenuous at best in light of the limited data. Meaningful evaluation of all other urine parameters was equally limited due to the low number of data points available on a subject "n" of one in clinical parameters known to exhibit large variations from individual to individual.

Reliable assessment of the potential for urinary calculi during weightlessness will require the further analysis of urinary parameters and variables in a statistically valid population size over a wider range of mission days. The careful measurement of urinary parameters, including oxalate, citrate and saturation levels with respect to stone-forming salts, is warranted for inclusion in this evaluation (3). The importance of identifying pathogenic factors both of environmental and metabolic origin to future manned space flights of long duration are considered significant for proper safeguard implementation and timely institution of remedial measures when necessary.

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TABLE 6. URINARY BIOCHEMISTRY 24-HOUR COLLECTION

Mission Phase	TV ml/24 hr	Specific Gravity	Osmo mosm	Na mEq/24 hr	K mEq/24 hr	Cl mEq/24 hr	Ca mEq/24 hr	Mg mEq/24 hr	IP04 mg/24 hr	Uric Acid mg/24 hr	Creat mg/24 hr	Oxalate mg/24 hr	Citrate mg/24 hr
Preflight													
F-30	721	1.029	1090	101	82	96	2.3	6.9	1127	363	1581	-	-
F-33	1435	1.021	696	205	77	174	5.1	8.3	690	479	1115	-	-
Inflight													
MD2	1666	1.014	505	164	56	177	4.8	11.0	952	463	1443	45.3	572.9
MD4	1549	1.016	585	166	50	140	9.0	9.5	1294	490	1686	43.1	612.8

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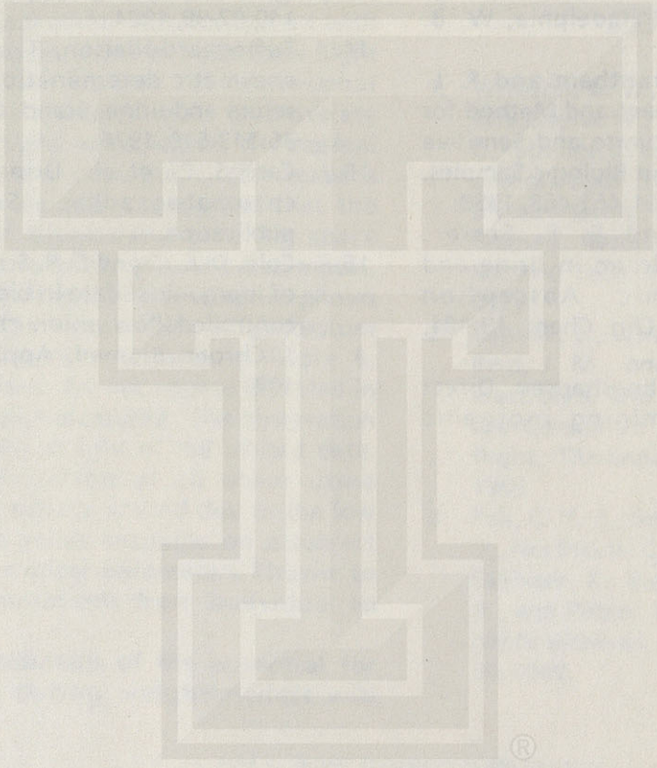

INFLIGHT PHARMACOKINETICS OF ACETAMINOPHEN IN SALIVA

Investigators: Nitza M. Cintron, Ph.D., Lakshmi Putcha, Ph.D., and James M. Vanderploeg, M.D., M.P.H.

INTRODUCTION

The observation that a wide range of physiological and biochemical changes occur during space flight suggests that these changes may alter the pharmacodynamics of drugs administered to crewmembers during flight. Conventional methods of therapeutic and pharmacokinetic evaluation of drugs using concentration profiles in the blood are invasive and require special technical expertise. These methods, therefore, are not suitable for space flight applications. In the recent past, salivary concentrations of certain drugs were reported to be useful for clinical drug monitoring and pharmacokinetic evaluations (1). Since saliva sampling is simple and noninvasive, this method may be successfully employed for pharmacokinetic assessment of drugs administered to crewmembers during space flight.

The usefulness of salivary concentrations for predicting blood levels depends upon the detectability of drug concentrations in saliva and the consistency of saliva/plasma ratios over a wide range of plasma concentrations (2). Earlier reports on salivary levels of acetaminophen, a commonly used pain relief medication, indicate that there is a positive correlation between plasma and saliva concentrations, and that the saliva concentrations are higher than those in plasma (3). Preliminary studies conducted in the investigators' laboratory to verify the feasibility of using salivary drug levels for predicting blood concentrations of acetaminophen following oral administration have indicated that therapeutic concentrations of the drug can be successfully detected in saliva. The saliva/plasma ratio of the drug was consistent and remained close to 1 over a wide range of plasma concentrations during the pre- and post-absorptive phases of drug dynamics. These data suggested that acetaminophen might be a suitable candidate for reliable pharmacokinetic evaluation and therapeutic drug monitoring using salivary drug concentration profiles. The widespread use of acetaminophen as a common pain medication and its relatively insignificant side effects encouraged the use of this drug for a preliminary investigation to assess the usefulness of salivary drug monitoring for space medical operations in the future.

The present investigation constitutes the beginning of a comprehensive pharmacokinetic characterization of drugs administered to crewmembers during space flight in general, and of acetaminophen as a representative drug in particular, by using salivary concentrations.

The limited inflight data obtained to date precludes the appropriate assessment of pharmacokinetic alterations associated with space flight. In this regard, the information presented here must be considered strictly as incomplete and preliminary.

Figure 1. A crewman poses with the vial (floating, foreground) and kit used for saliva collection.

PROCEDURES

The investigational design was comprised of two phases, a preflight control phase and an inflight experimental phase (Fig. 1). The overall protocol for both phases was identical and involved oral administration of the drug and collection of saliva samples at regular time intervals for 8 hours after dosing. The details of this experiment are as follows.

The participating crewmember was requested to collect preflight control samples any time between L-30 and L-15 days. Before initiating the study, the crewmember fasted from at least one hour before the sleep period until one hour post-dosing. No drinks were allowed for one hour before and after dosing.

The crewmember ingested two 325-mg tablets of acetaminophen with 100 ml of water followed by a thorough rinsing of the mouth with an additional 100 ml of water. Saliva samples were collected at 0.25, 0.5, 1, 2, 3, 4, 5, 6, and 8 hours post-dosing. Samples were collected using a cotton ball placed at the back of the mouth between the jaws for 5 minutes or until the cotton ball was saturated with saliva, whichever was earlier. Constant rolling of the cotton ball in the mouth facilitated saturation. Stimulation of saliva secretion was achieved by chewing on a teflon square for 30-60 seconds prior to sampling. Saliva samples were collected and stored in designated sample collection tubes until they were analyzed.

The concentration of acetaminophen in each saliva sample was determined later using an established HPLC analysis method (4).

RESULTS

The saliva concentration-time profiles of acetaminophen following oral administration during preflight and inflight conditions in five crewmembers from three separate missions are depicted in Figures 2 to 4. It appears from these profiles that concentration-time profiles of acetaminophen change significantly during space flight when compared to their control counterparts.

Table 1. Absorption Parameters of Acetaminophen

SUBJECT NO.	PEAK CONCENTRATION (mg/ml)		TIME TO REACH PEAK (h)	
	Control	Inflight	Control	Inflight
1*	9.6	6.4	0.5	1.1 (MD4)
2	8.9	6.1	0.5	1.0 (MD4)
3	9.8	14.1	0.5	1.0 (MD3)
4	12.6	14.8	0.5	≤0.25 (MD2)
5	13.0	15.6	0.5	≤0.25 (MD2)

*MD3 data (Fig. 2A) from this subject were inadequate to estimate these parameters.

Preliminary evaluation of the data collected from all five crewmembers suggests that significant changes in the absorption phase of drug disposition occurred, as shown in Table 1, while the elimination of the drug appeared to be unaffected. The peak concentration of the drug decreased in two subjects during space flight and increased in the other three subjects, when compared to the respective control values. The time to reach peak concentration increased in three subjects and decreased in the other two during space flight. While intersubject variability in peak concentration and time to reach the peak concentration was minimal during the ground-based control phase, large variations in these two parameters were noticed between the subjects during flight.

DISCUSSION

Preliminary evaluation of the inflight results indicated that the degree and magnitude of the pharmacokinetic changes observed in crewmembers during flight appear to be dependent on a number of inflight variables that could not be controlled or documented in this study. Some of these contributing parameters that are unique to space flight are discussed below.

SUSCEPTIBILITY TO SPACE MOTION SICKNESS (SMS)

The limited pharmacokinetic data collected in flight (during three missions) suggest that there may be a correlation between the pathophysiological condition of the crewmember and the disposition changes of acetaminophen during flight. In one crewmember who experienced severe SMS symptoms, the peak concentration of acetaminophen and the overall disposition of the drug appeared to be erratic, with an unexpectedly high peak concentration and faster than normal elimination. While experimental artifacts such as contamination of the first two saliva samples by a residual dose in the mouth due to inadequate rinsing after ingestion of the drug cannot be ruled out, symptoms of SMS, such as regurgitation and dehydration, may also have contributed to the abnormal disposition of the drug in this crewmember. Information regarding the incidence of SMS in other crewmembers was not available; therefore, a correlation between the physiological responses to space flight and the disposition kinetics of the drug could not be investigated.

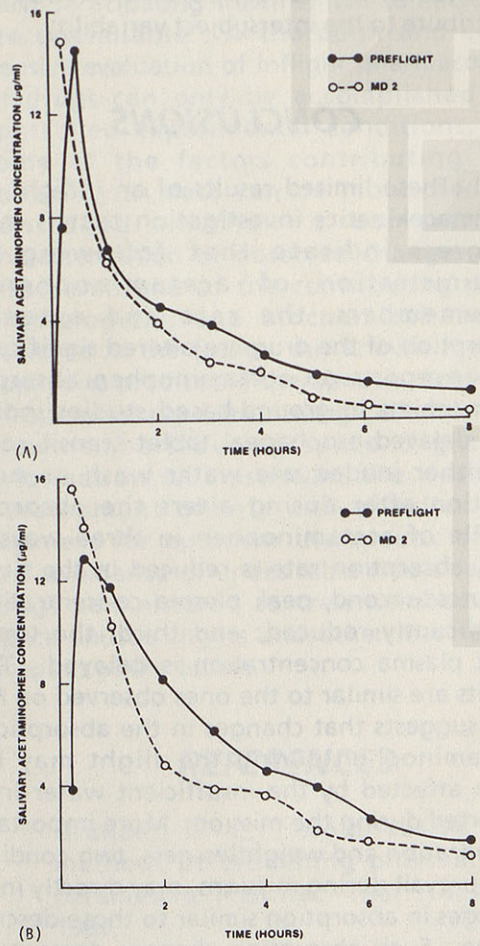

Figure 2. Salivary concentration-time profiles of acetaminophen following oral administration of 650 mg to crewmembers on mission day 2.

MISSION DAY

Among the studies completed so far during the three missions, two crewmembers implemented the study protocol on MD2, one

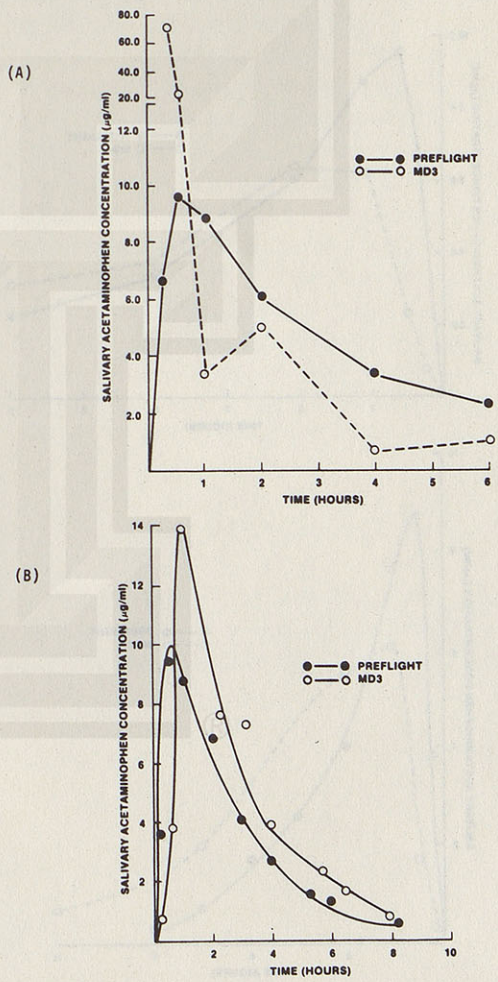

Figure 3. Salivary concentration-time profiles of acetaminophen following oral administration of 650 mg dose to crewmembers on mission day 3.

on MD3, one on MD4, and the other twice during one mission on MD3 and 4. On MD2, both crewmembers had a higher peak drug concentration and a faster time to reach peak concentration than during the preflight phase (Fig. 2). On MD3, the crewmember who had SMS manifestation showed an erratic disposition profile of acetaminophen while the other crewmember had a slower absorption but a higher peak concentration (Fig. 3).

On MD4, when the physiological adaptation to weightlessness may have reached an equilibrium, both crewmembers had a significant decrease in the absorption of acetaminophen as indicated by smaller peak concentrations reached later than during preflight (Fig. 4). These preliminary evaluations

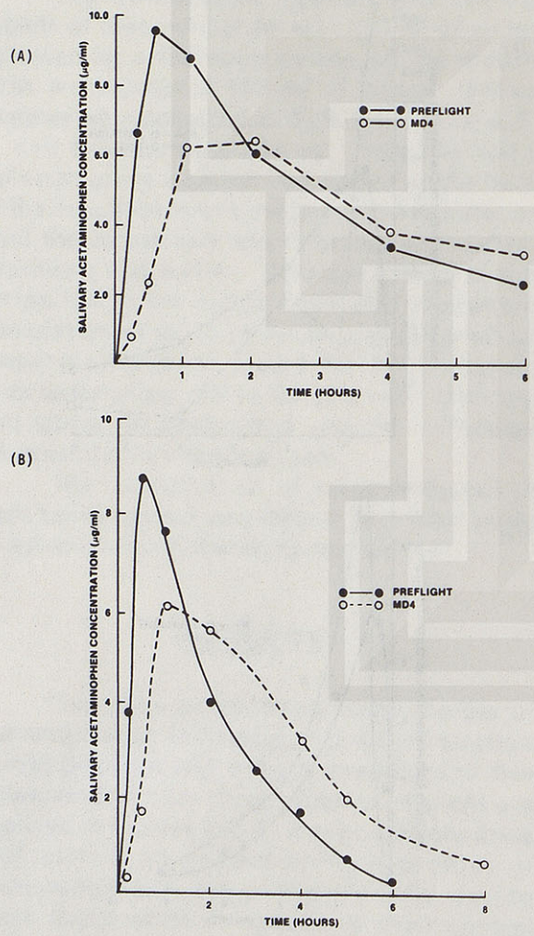

Figure 4. Salivary concentration-time profiles of acetaminophen following oral administration of 650 mg dose to crewmembers on mission day 4.

of the inflight data indicate that conducting the study on the same mission day may reduce the large differences in the experimental results.

INTERSUBJECT VARIABILITY

While no significant differences in pharmacokinetic parameters have been noticed between crewmembers during preflight control studies, large differences in the values of the same parameters between the same crewmembers have been observed during missions. These results suggest that the inter-individual differences in the physiological response to space flight may cause intersubject variability of drug disposition during space flight. In addition, any flight-specific activities such as exercise and ingestion of SMS medications like scopolamine may also contribute to the intersubject variability.

CONCLUSIONS

These limited results of an inflight drug pharmacokinetics investigation that is still in progress indicate that following oral administration of acetaminophen to crewmembers, the rate and extent of absorption of the drug are altered significantly. Earlier reports on acetaminophen absorption from tablets in ground-based studies indicate that delayed esophageal tablet transit caused by either inadequate water wash or supine position after dosing alters the absorption profile of acetaminophen in three ways (5). First, absorption rate is reduced in the first 60 minutes; second, peak plasma concentration is significantly reduced; and third, the time of peak plasma concentration is delayed. These results are similar to the ones observed on MD4. This suggests that changes in the absorption of acetaminophen during the flight may have been affected by the insufficient water intake reported during the mission. More importantly, dehydration and weightlessness, two conditions that prevail during missions, may directly induce changes in absorption similar to those described above. Such absorption changes decrease the effectiveness of acetaminophen as an analgesic (5). Similar changes in disposition have also been noticed with scopolamine, an anti-motion

sickness drug, in crewmembers during missions. These results are being reported separately. Changes in absorption of drugs could render them ineffective or lead to unfavorable therapeutic consequences when the drugs are administered by conventional dosing practices to crewmembers during space flight.

The limited inflight data accumulated thus far are inadequate for characterization of the degree and magnitude of the space flight-induced pharmacokinetic changes because of a number of interfering variables influencing the disposition profiles and kinetic parameter estimates of drugs. While information on some of these variables (such as mission day) is available, information about such factors as the incidence of space motion sickness, ingestion of other medications during the flight, and the overall physical and physiological responses of each participating crewmember to microgravity are unavailable. A thorough and comprehensive evaluation of inflight pharmacokinetics of drugs can only be accomplished under controlled experimental conditions, where some of the factors contributing to the variability in data can be monitored if not controlled. When a comprehensive characterization of observed changes in drug disposition and of the contributing physical, physiological, and biochemical factors is achieved in the future, this knowledge can be applied to predict the therapeutic consequences of operationally critical drugs administered to crewmembers during space flight. This information will assist in the design and development of safe and effective dosage regimens for optimum therapeutic efficiency and avoidance of undesirable side effects from drugs administered to crewmembers during Space Shuttle flights and other manned space missions of the future.

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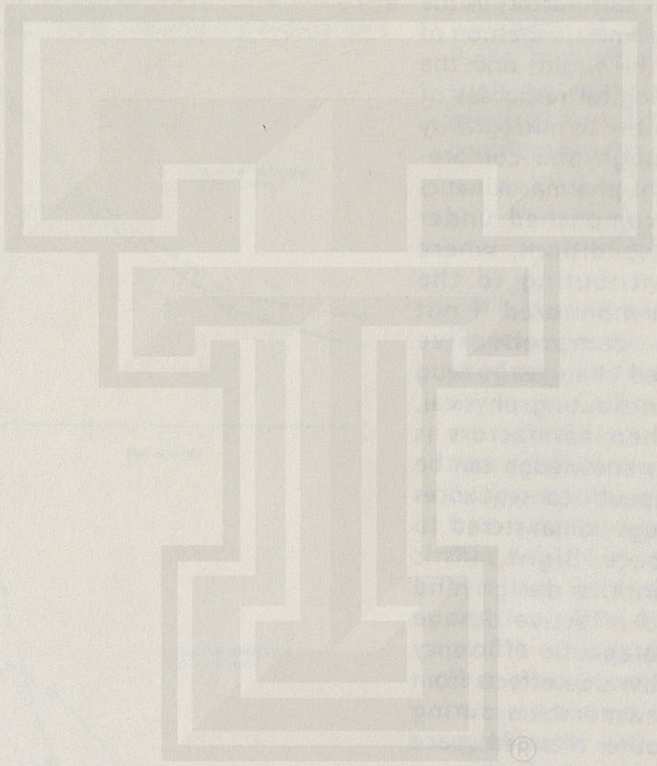

INFLIGHT SALIVARY PHARMACOKINETICS OF SCOPOLAMINE AND DEXTROAMPHETAMINE

Investigators: Nitza M. Cintron, Ph.D., Lakshmi Putcha, Ph.D., Yu-Ming Chen, Ph.D., and James M. Vanderploeg, M.D., M.P.H.

INTRODUCTION

The need for elucidating the pharmacokinetic changes occurring during space flight has been widely recognized, but the technical and operational constraints of collecting multiple blood samples for such studies limit their implementation during space flight. The usefulness of salivary concentration profiles as an alternate, noninvasive method for clinical monitoring of certain drugs has been established (1). The feasibility of such an application for salivary drug monitoring depends upon the distribution of detectable levels of the drug into saliva and establishment of a consistent saliva/plasma (S/P) ratio over the entire disposition profile of the drug (2). To determine the applicability of noninvasive salivary drug monitoring for pharmacokinetic evaluation of therapeutic agents during space flight, three drugs that are frequently used by crewmembers have been selected for inflight study - acetaminophen, a relatively innocuous, common pain relief medication whose disposition characteristics have been well established, and a scopolamine/dextroamphetamine combination, an operational medication used for the treatment of space motion sickness during missions.

Ground-based, in-house investigations to establish the S/P ratios of scopolamine have been conducted in normal subjects. Following IV and oral administration, scopolamine readily distributes into saliva with consistent S/P ratios over the entire disposition profile. In this preliminary investigation, the pharmacokinetics of scopolamine/dextroamphetamine following oral administration to crewmembers before and during space flight are being evaluated using salivary concentrations to estimate the disposition parameter changes of anti-motion sickness agents during missions.

The limited inflight data obtained to date preclude the appropriate assessment of pharmacokinetic alterations associated with space flight. In this regard, the information presented here must be considered strictly as incomplete and preliminary.

PROCEDURES

Participating crewmembers received an oral dose of 0.4 mg scopolamine and 5 mg dextroamphetamine in combination as a

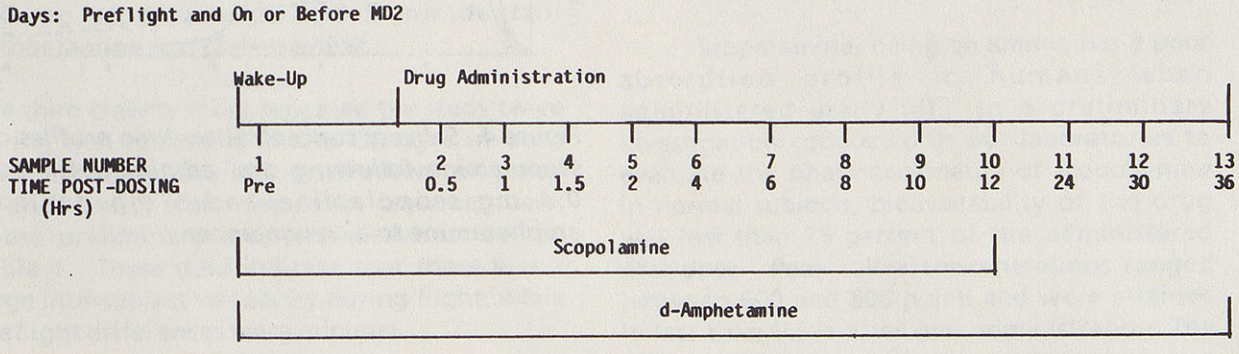

Figure 1. Saliva sample collection schedule.

capsule (SMS medication), twice on separate occasions during ground-based studies and once during space flight. Saliva samples were collected at designated time periods for 36

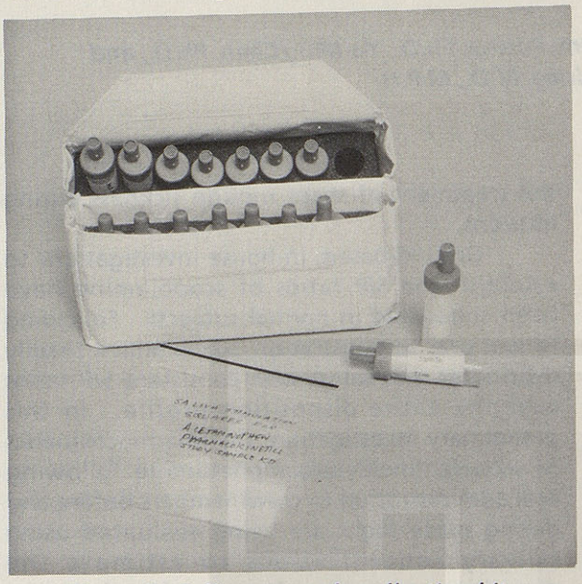

Figure 2. Salivary sample collection kit.

hours as shown in Figure 1, using the cottonball saliva collection kit designed and developed at the JSC (Figure 2). The saliva samples collected during the first 12 hours post-dosing were divided into two aliquots. Scopolamine concentrations were determined using the RPLC-receptor binding assay (3) in one set of the 12-hour sample aliquots. The remainder of the samples for the entire 36 hour duration of the study were frozen for later analysis to determine dextroamphetamine concentrations.

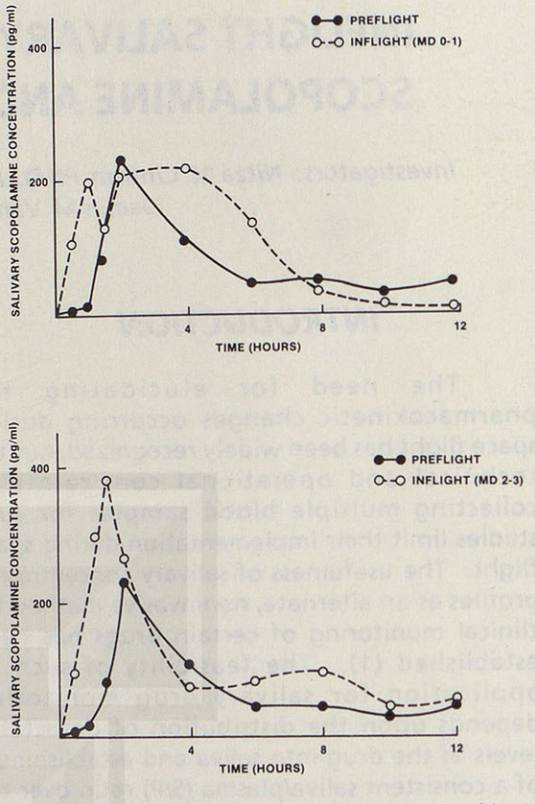

Figure 3. Salivary concentration-time profiles of scopolamine following oral administration of 0.4 mg scopolamine and 5 mg dextro-amphetamine to a crewmember.

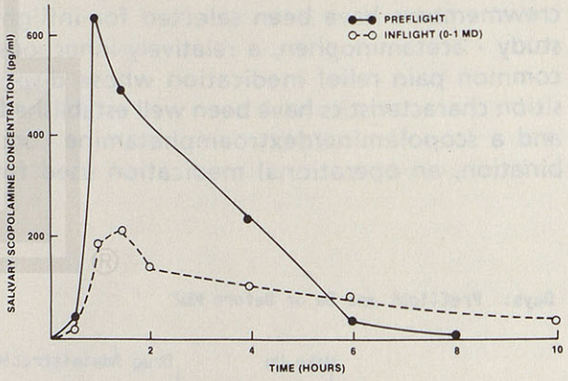

Figure 4. Salivary concentration-time profiles of scopolamine following oral administration of 0.4 mg scopolamine and 5 mg dextro-amphetamine to a crewmember.

RESULTS

Preliminary results from three crewmembers who participated in the study on two separate missions have been compiled and are presented in Figures 3-5. Preliminary evaluation of the salivary concentration-time profiles indicated that large deviations in the concentration-time profiles of scopolamine in crewmembers occur during space flight when compared to their ground-based control profiles. In one crewmember, a significant decrease in the peak concentration and an increase in the time to reach peak concentration were observed, while opposite results were obtained for another crewmember.

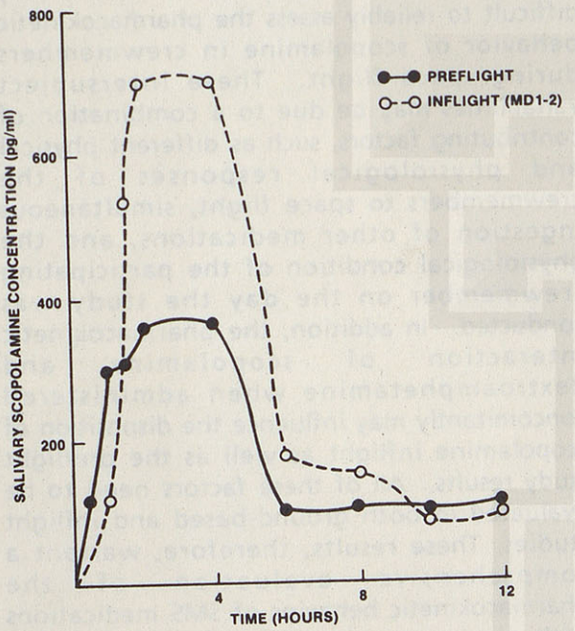

Figure 5. Salivary concentration-time profiles of scopolamine following oral administration of 0.4 mg scopolamine and 5 mg dextroamphetamine to a crewmember.

The third crewmember repeated the study twice during the mission, and the changes in both instances were relatively small when compared to the results from the other crewmembers. These preliminary results are summarized in Table 1. These data indicate that there was a large intersubject variability during flight, while preflight differences were minimal.

Table 1. Absorption Parameters of Scopolamine in Crewmembers

Subject No.	Peak Saliva Concentration (pg/ml)		Time to Reach Peak Concentration (h)	
	CONTROL	INFLIGHT	CONTROL	INFLIGHT
1	227	216 (MDO-1)	2.0	4.0 (MDO-1)
		383 (MD2-3)		1.5 (MD2-3)
2	633	212	1.0	1.5 (MDO-1)
3	356	690	3.0	3.0 (MD1-2)

DISCUSSION

The limited number of results collected so far indicate that the absorption of scopolamine, when administered to crewmembers as a combination SMS medication, may be influenced by the physical and physiological changes caused by weightlessness during space flight. However, the degree, nature, and magnitude of the pharmacokinetic changes could not be evaluated due to the limited number of results obtained thus far. Furthermore, large intersubject variability caused by a number of experimental differences such as mission day and concomitant ingestion of other drugs, in addition to inadequate sample size, make interpretation of the results difficult. Some of the flight-specific factors that may contribute to the variability are discussed below.

INTERSUBJECT VARIABILITY

Scopolamine, being an amine, has a poor absorption profile in humans when administered orally (4). In a preliminary investigation conducted in our laboratories to evaluate the pharmacokinetics of scopolamine in normal subjects, bioavailability of the drug was less than 25 percent of the administered oral dose. Peak saliva concentrations ranged between 600 and 800 pg/ml and were attained in less than 0.5 h after oral administration. The SMS medication used in the present study is a combination of scopolamine and dextro-

amphetamine, both of which are poorly absorbed from the gastrointestinal tract (4). The less than normal peak concentrations (227 and 356 pg/ml) noticed in two crewmembers during ground based control studies may be the result of an absorption interaction between the two drugs which should be evaluated in ground-based studies before definite conclusions can be drawn from inflight results. The crewmember whose salivary concentrations were in the normal range during the ground control study had a significant decrease in the peak saliva concentration during mission and an increase in the time to reach peak concentration. The results obtained from the other two crewmembers were highly variable.

MISSION DAY

As noticed in a similar study with acetaminophen, mission day may also influence the inflight results. This may be due to the fact that the physiological adaptation to space flight conditions is a dynamic process, and the degree and magnitude of these changes may influence the dynamics of drug disposition differently depending upon when the study was performed. The preliminary results obtained so far are from different mission days which makes interpretation of the data difficult.

SAMPLE SIZE

Since scopolamine causes dryness of the mouth in addition to the possible dehydration caused by SAS, adequate samples were not recovered for a large number of sampling times, especially during the absorption and distribution phases of the drug dynamics. This sample inadequacy might have resulted in less than efficient estimation of saliva concentrations in a large number of samples collected during the early phases of the study. Therefore, these results were insufficient for a comprehensive evaluation.

Preliminary evaluation of these limited results indicate that while significant changes in the disposition of scopolamine may occur during space flight, the degree and magnitude of these changes have to be evaluated in more crewmembers before reliable conclusions can be drawn.

CONCLUSIONS

The limited number of results obtained with three crewmembers from two separate missions suggests that scopolamine saliva concentration-time profiles were significantly different during space flight when compared to their preflight counterparts. Absorption of the drug during the flights appeared to be altered as indicated by peak concentration levels and time to reach the peak concentration. Large intersubject variability, inadequate sample volumes, and insufficient data make it very difficult to reliably assess the pharmacokinetic behavior of scopolamine in crewmembers during space flight. These intersubject variabilities may be due to a combination of contributing factors, such as different physical and physiological responses of the crewmembers to space flight, simultaneous ingestion of other medications, and the physiological condition of the participating crewmember on the day the study was conducted. In addition, the pharmacokinetic interaction of scopolamine and dextroamphetamine when administered concomitantly may influence the disposition of scopolamine inflight as well as the preflight study results. All of these factors need to be evaluated in both ground-based and inflight studies. These results, therefore, warrant a comprehensive evaluation of the pharmacokinetic behavior of SMS medications with a minimum number of variables that contribute to the disparity of inflight data. The results of such a comprehensive evaluation of SMS medications and other therapeutic agents for the treatment of pathophysiological disorders induced by space flight are important for determining the therapeutic efficiency and for predicting the incidence of undesirable side effects of drugs administered to crewmembers during missions. Furthermore, the results from the pharmacokinetic and bioavailability studies during space flight will provide information for the successful design and development of effective therapeutic regimens for both short and long duration missions.

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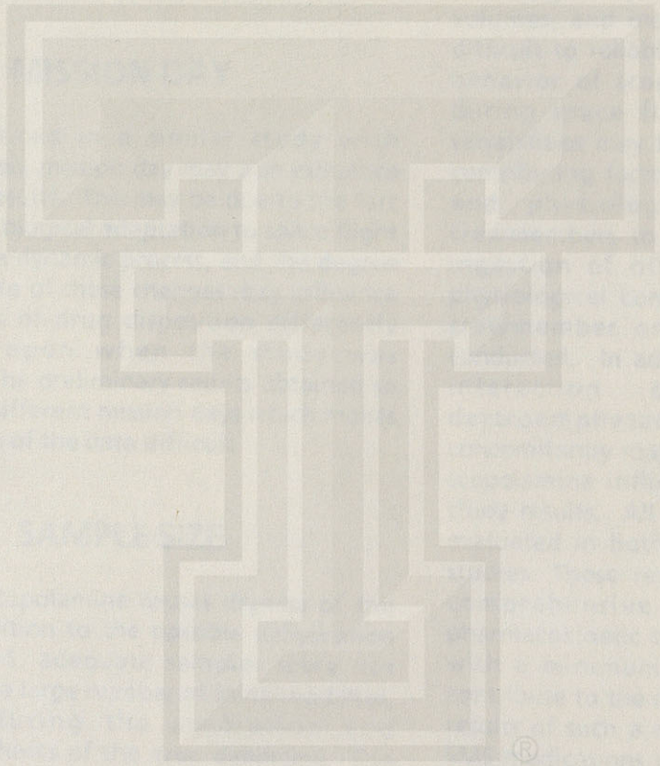

SALIVARY CORTISOL LEVELS DURING THE ACUTE PHASES OF SPACE FLIGHT

Investigator: Nitza M. Cintron, Ph.D.

INTRODUCTION

The complexity of the physiological response to weightlessness has stimulated research into identifying biochemical and endocrine parameters which might provide insight into the underlying mechanisms operative in the overall adaptation process. Available data from earlier inflight and ground-based studies substantiate the value of performing correlative studies to evaluate and assess the neuro-endocrinologic mechanisms associated with the various conditions of space flight-induced stress (1-3). As expected, these investigations clearly indicated the central involvement of autonomic neurotransmission in the etiology of stress-related imbalances (e.g. immunosuppression, motion sickness) and pointed to the potential of correlating early changes to hormonal alterations.

Cortisol, under the direct influence of adrenocorticotrophic hormone (ACTH), is one of the key hormones associated with the control and maintenance of normal neuroendocrine processes and with the response and onset of stress-related conditions. Plasma concentrations of cortisol have been found to increase during space flight (1). However, no data are currently available on its changes immediately after the achievement of weightlessness. It is during these first hours of a mission that the most dramatic changes are thought to occur as part of the adaptive response to weightlessness.

The lipophilic and neutral chemical nature of steroids have been shown to effect their rapid equilibration into saliva from plasma by passive diffusion (4). As a result, steroid concentrations in saliva represent those of the free fraction in the circulation and are independent of variations in salivary flow rate. For cortisol, salivary levels have been demonstrated to correlate with the free steroid fraction in both plasma (5) and serum (6). Recent improvements in steroid immunoassay and salivary extraction techniques have made feasible the routine assessment of adrenal activity by monitoring cortisol levels in saliva (7,8). For inflight application, collection of saliva represents a stress-free, non-invasive means of obtaining information about adrenal activity during the early inflight period; many samples can be collected with a minimum of disturbance of crewmembers' activities.

The primary objectives of this investigation were to determine the feasibility under operational Shuttle conditions of collecting saliva samples for cortisol analysis and, more importantly, to examine the key facets of endocrine function (i.e. adrenal activity) during the acute and adaptive phases of space flight as derived from the resultant cortisol measurements. Information about adrenal activity and about integrated neuroendocrine function have significance in formulating the total picture of the crewmen's health status and in predicting, in conjunction with all other available metabolic data, the possible duration of man's stay in weightlessness.

PROCEDURES

The general design of the overall investigation involved the serial collection of saliva samples throughout a specified 24-hour period during pre- and inflight phases of a mission (Figure 1). Saliva collection activities consisted of collecting 4 samples throughout each 24-hour period at approximately the same times (± 1 hour) during the sleep/activity cycle. To avoid an interruption of the sleep period, the first sample was collected soon after wake-up; the second sample at wakeup plus 5 hours (± 1 hour); the third sample at wake-up plus 10 hours (± 1 hour); and the fourth sample, shortly before the sleep period. These operations were performed once preflight at approximately one month prior to launch and twice inflight, once early and once late in the mission. All inflight

data were compared to preflight baseline data. A total of 6 subjects were required for appropriate assessment and evaluation of results.

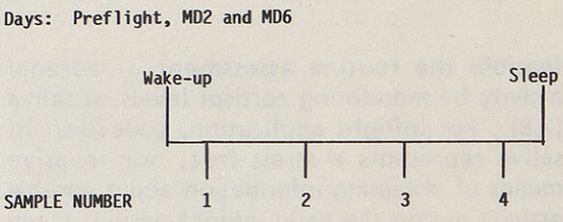

Figure 1. Inflight salivary cortisol sample collection schedule.

To date, two crewmembers have participated in this investigation. As scheduled, four samples were collected from each participating crewmember at approximately 6-hour intervals during a 24-hour period about a month before launch. During flight the crewmembers collected samples on mission days 1, 3 and 6.

Saliva samples were obtained using the Salivary Collection Assembly which consisted of a beta cloth pouch with foam inserts to retain Sarstedt syringe tubes, each containing a dental cotton roll (Figure 2). The syringe barrels had a screw cap on one end and a sliding plug on the other end into which the syringe plunger screwed, so that the barrels functioned as tubes for collection of samples as well as syringes for retrieval of the samples. Squares of Teflon film which could be chewed to stimulate salivation were also stowed in the pouch. Samples were collected by placing a roll of dental cotton between the lower teeth and cheek toward the back of the mouth. The cotton roll remained in place until it was saturated or for 20 min, whichever occurred first. The saliva samples were then stored in the designated tubes for subsequent analysis.

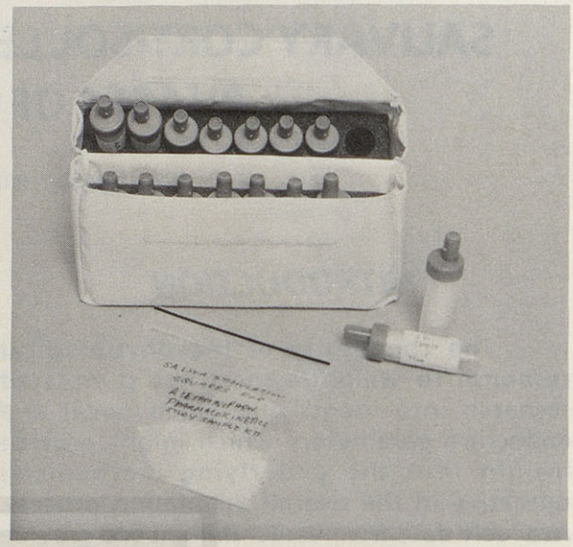

Figure 2. The saliva collection assembly with the Sarstedt syringe tubes containing dental cotton rolls and with the Teflon film squares used for stimulating salivation. The kit configuration shown is that used for saliva collection in conjunction with the Salivary Acetaminophen Pharmacokinetics investigation.

Samples were frozen at -70° C as soon as possible after landing. They were thawed and a plunger was inserted into each syringe. The contents of the cotton roll were squeezed into a 50-ml tube which was centrifuged with the syringe in a Beckman J-6B centrifuge. The roll was squeezed again so that as much sample as possible was transferred to the 50-ml tube. Samples were analyzed for cortisol by the radioimmunoassay described by Foster and Dunn (9).

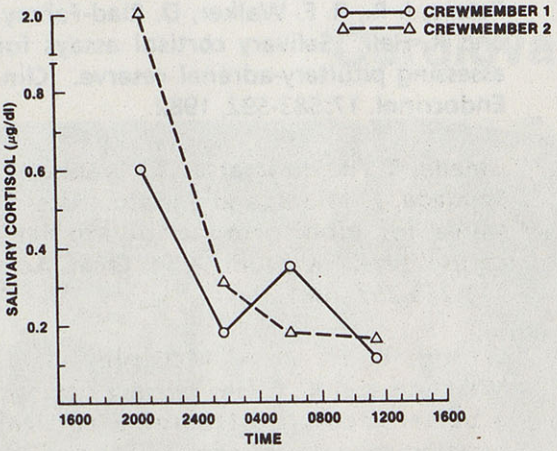

Figure 3. Preflight diurnal variation of salivary cortisol for Crewmembers 1 and 2. Samples were collected throughout a 24-hour period 30 days before flight and cortisol was determined by radioimmunoassay.

RESULTS

For both crewmembers the sample taken late at night (2030 hours) contained the highest concentration of cortisol (Figure 3). The concentration had dropped by at least two-thirds by the next sampling time (0140 hours).

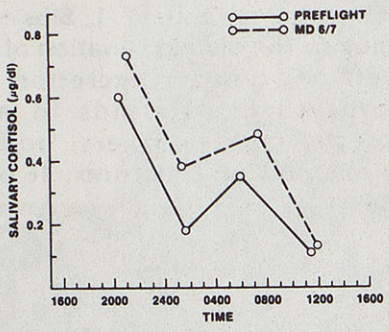

Figure 4. Comparison of preflight and inflight diurnal variation of salivary cortisol in Crewmember 1. The inflight samples were collected on mission day 6/7.

Only one complete set of inflight samples in which cortisol could be measured was obtained. It was collected on Mission Day 6/7. The graph of cortisol levels in these samples was almost parallel to the graph of cortisol in the same crewman's preflight samples (Figure 4); each of the samples taken on MD6/7 contained more cortisol than its preflight counterpart. For this crewmember (Crewmember 1) cortisol levels on day MD1 were higher than they were on MD3 (Table), but for the other crewmember the opposite was true (Table). Since the samples taken early in the flight were not taken at the same times of day as the preflight or MD6/7 samples (Table), cortisol levels in the samples from MD1 and MD3 could not be strictly compared to those from the other days.

Some of the samples collected by Crewmember 2 did not contain enough saliva for detection of cortisol.

CONCLUSION

Salivary cortisol is now considered by some investigators to give a more accurate picture of adrenal cortisol function than serum cortisol (7). Results show that saliva can be collected in zero gravity in quantities sufficient to measure cortisol. The noninvasive methods used in this experiment are highly advantageous for collecting samples frequently and with minimum disruption of the crewmembers' other work. The only problems encountered were insufficient saturation of the cotton rolls (possibly due to dryness of the mouth, a common side effect of antimotion sickness drugs), and inadequate labeling of some tubes. There may also be some difficulty with collection of samples at the same time on every day of the experiment, because of other demands on the crewmembers' time. It should

Table. Diurnal variation of salivary cortisol before and during space flight in two Shuttle crewmembers

Mission Day	Time	Cortisol µg/dl Crewmember 1	Crewmember 2
Preflight	2030	.60	2.04
	0140	.18	.31
	0600	.35	.18
	1130	.11	.16
MD1	2245	.55	.31
	0330	.28	.22
MD3	2215	.37	.53
	0345	.34	.42
	0850	.29	NS*
	2200	.16	NC+
MD6	2110	.73	NS
	0125	.38	NS
	0725	.48	NS
	1200	.13	NS

*NS = sample size not sufficiently large
+NC = not collected

be possible to solve these problems with further training and crew orientation.

The peak in plasma cortisol concentration generally occurs about 0700 hours (10), but for the two crewmembers in our study the peak occurred much earlier, not later than 2030 hours. This might be due to the strenuous preflight training schedule. There are not enough inflight data to draw any conclusions about the early effects of flight on cortisol levels in the body or on their diurnal variation, but in at least one crewmember the diurnal rhythm was the same after about a week of flight as it was preflight.

In conclusion, collection of saliva samples for measurement of cortisol during space flight appears to provide a feasible approach for studying change in adrenal function during adaptation of the body to weightlessness. Specific information regarding the status of adrenal activity in the initial phases of space flight will require additional data for the appropriate assessment of changes. In this regard, the current limited data must be considered strictly as preliminary.

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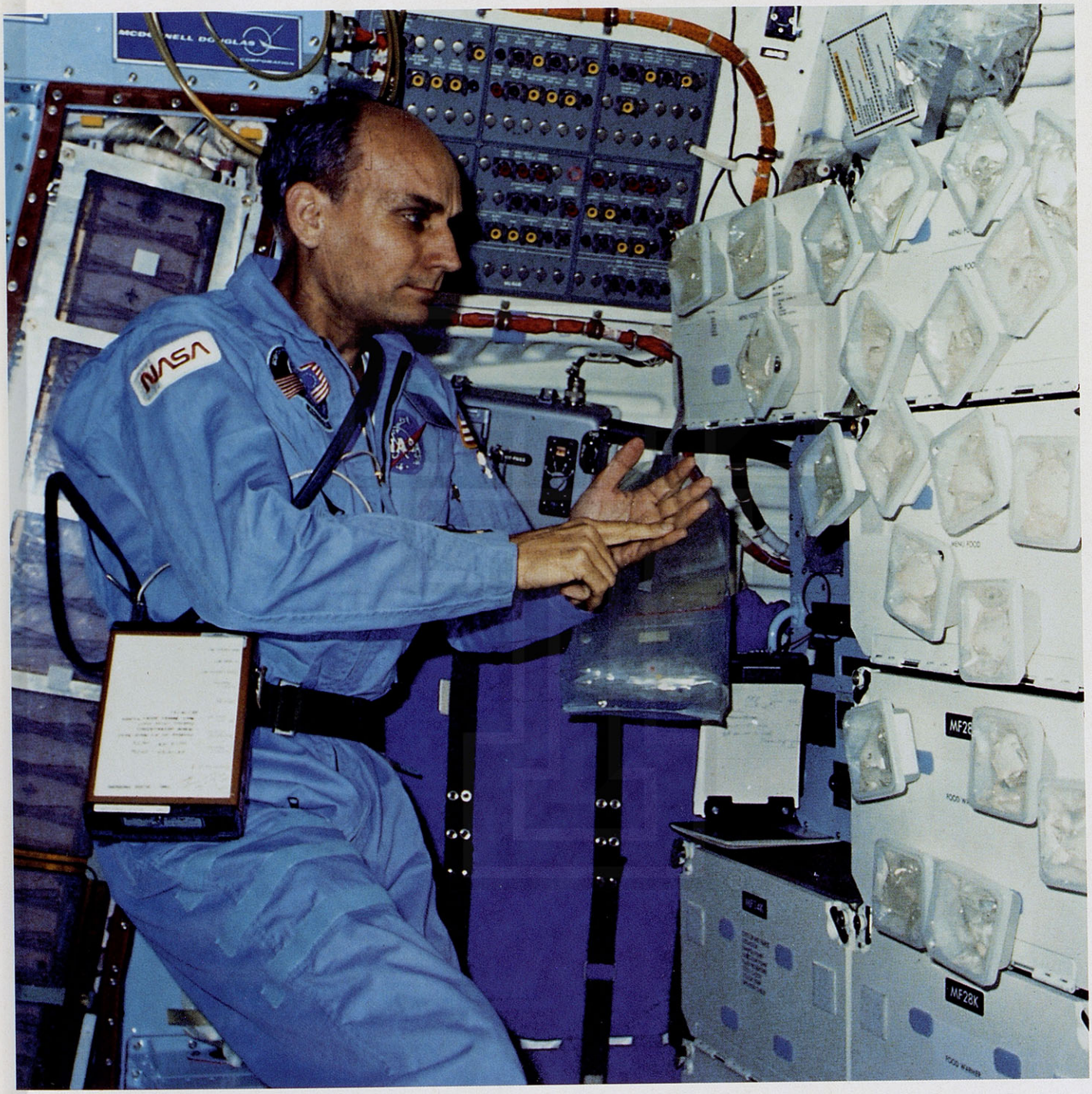
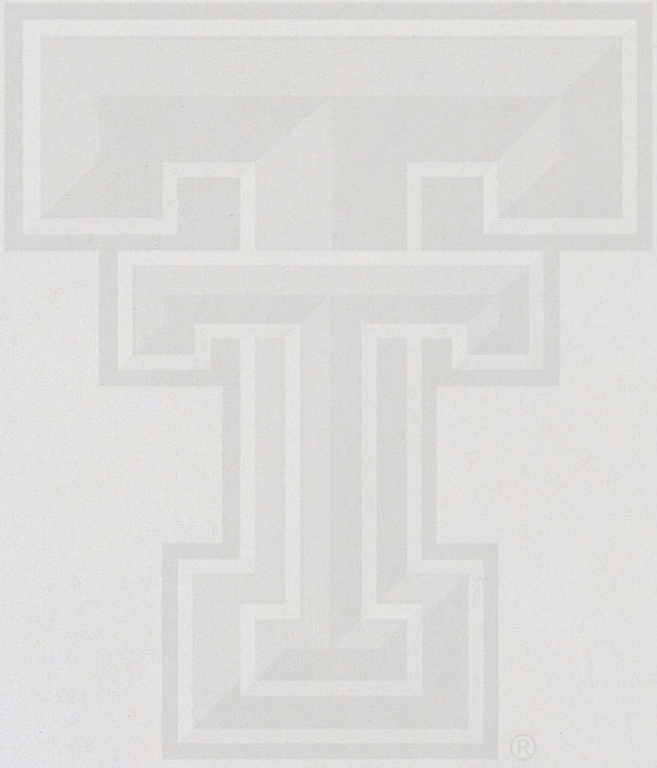
Section Two
Cardiovascular Effects and Fluid Shifts



A crewman prepares containers of drinking water and salt tablets to be consumed by his crewmates prior to reentry. DSO 402 demonstrated that fluid loading is an effective countermeasure to orthostatic intolerance upon return to gravity. Fluid loading is now a standard procedure on all Shuttle flights. The device on the crewmember's right hip is recording his blood pressure and heart rate as part of another DSO.



BLOOD PRESSURE AND HEART RATE DURING ORBIT AND ENTRY

Investigators: William E. Thornton, M.D., and Thomas P. Moore, M.D.

INTRODUCTION

Postflight orthostatic hypotension has been noted since the Mercury flights and can be expected after exposures to weightlessness. The problem is thought to arise from fluid shift and subsequent fluid loss, from decreased peak physical loads, and probably from neurological adaptation. There had been sufficient concern over hypotension during STS entry to provide the crew with anti-g suits (AGS). A commercial blood pressure-heart rate recorder was used in SMS studies on several missions, and by one crewmember during entry with anti-g suit activation and deactivation.

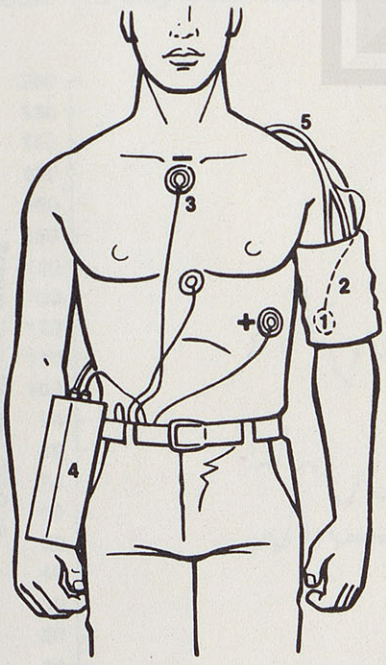


Figure BP-1. Installation of commercial BP-HR recorder showing conventional cuff (2), with microphone (1), over brachial artery and EKG electrodes (3), used to generate timing and rate signals. K-sound signals and cuff pressure are transmitted by cable and tubes (5), to recorder (4).

After several near-syncopal episodes on Shuttle missions following seat egress, presumed to be orthostatic hypotension, it was agreed to make a series of blood pressure and heart rate studies during entry and egress.

PATIENT: 0 DATE: 05-05-85

LINE#	TIME	SYS-TOLIC	DIA-STOLIC	HEART RATE	PULSE PRESSURE	MEAN PRESSURE	PR PRODUCT
1	1:21PM	113	85	95	28	94	10735
2	1:24	115	90	70	25	98	8050
3	1:31	109	83	70	26	91	7630
4	1:39	113	84	68	29	93	7684
5	1:46	116	85	70	31	95	8120
6	1:53	110	82	95	28	91	10450
7	2:01	*					
8	2:01	112	85	64	27	94	7168
9	2:09	118	86	74	32	96	8732
10	2:16	109	82	64	27	91	6976
11	2:24	106	84	63	22	91	6678
12	2:31	97	82	63	15	87	6111
13	2:39	105	80	62	25	88	6510
14	2:46	110	84	63	26	92	6930
15	2:54	112	92	64	20	98	7168
16	3:01	107	80	71	27	89	7597
17	3:09	98	80	64	18	86	6272
18	3:16	110	88	67	22	95	7370
19	3:23	119	85	64	34	96	7616
20	3:31	116	80	60	36	92	6960
21	3:38	115	80	61	35	91	7015
22	3:46	123	80	62	43	94	7626
23	3:53	117	84	71	33	95	8307
24	4:01	131	88	68	43	102	8908
25	4:08	117	83	71	34	94	8307
26	4:16	114	82	62	32	92	7068
27	4:23	112	80	63	32	90	7056
28	4:31	118	92	88	26	100	10384
29	4:38	121	85	74	36	97	8954
30	4:46	121	89	64	32	99	7744
31	4:53	114	84	69	30	94	7866
32	5:01	104	76	66	28	85	6864
33	5:08	115	83	65	32	93	7475
34	5:16	101	78	67	23	85	6767
35	5:23	119	86	70	33	97	8330
36	5:30	116	78	90	38	90	10440
37	5:38	113	79	72	34	90	8136
38	5:45	117	82	70	35	93	8190
39	5:53	114	79	70	35	90	7980
40	6:00	112	78	71	34	89	7952
41	6:08	98	85	80	13	89	7840
42	6:15	115	78	77	37	90	8855
43	6:23	114	85	77	29	94	8778
44	6:30	123	100	87	23	107	10701
45	6:38	101	81	90	20	87	9090

Figure BP-2. Record of digital data, generated by recorder and stored in memory (time, HR, SBP, and DBP). Other data shown are calculated from this by the replay unit. The missing line has been manually deleted for artifacts.

PROCEDURES

The BP-HR recorder was an extensively tested and used, commercially available, ambulatory unit modified only to the extent of decreasing minimum automatic sample time to 3 5 minute intervals. It used a conventional cuff

and K-sounds (Rivi-Rocci technique), was completely automatic, and was capable of recording and storing up to 200 lines of data (time, BP, and HR) internally. Equipment placement is shown in Figure BP-1. Postflight, these data were transferred to a standard digital format (Figure BP-2) and plotted by a companion data reduction unit. Accuracy of the unit has been examined and reported by a number of investigators who have used it in both clinical and aerospace applications. Each unit was repeatedly checked for accuracy by simultaneous comparison of its results with manual determinations made with a calibrated sphygmomanometer. Mean errors were typically less than 4 mmHg systolic and 3 mmHg diastolic.

RESULTS

Blood pressure and heart rate were obtained with this device pre- and postflight on Launch -59 days and Return +2 days and inflight on Mission Day 7 and through entry and egress on one subject. The records were edited and artifactual values removed. Results were then plotted and are shown in Figures BP-3, BP-4, BP-5 and BP-6.

CONCLUSIONS

The first record, Figure BP-3, was made during a one-g simulation. BP was approximately 120/80 and resting HR approximately 55 beats per minute (bpm). The inflight record, Figure BP-4, is equally unremarkable with lower systolic and diastolic BP and a low HR in spite of personal "acrobatics" performed during a portion of the record. Essentially the same values are seen during entry preparation with increase in BP and HR during seat ingress and then an increase in BP with onset of g-loads and an increase in and an upward trend of HR, Figure BP-5.

Thirty-two ounces of fluid with 8 gm of NaCl was ingested prior to entry and the AGS was worn and inflated to 1 psi. Blood pressure peaked during touchdown and egress and systolic pressure remained slightly elevated during the remainder of the record. It was during this period that the subject had symptoms which might have been characterized as orthostatic hypotension had the individual's BP and HR not been known. The most striking record was obtained on R + 2, Figure BP-6, when the HR is above 70 bpm and systolic BP is slightly elevated except during the period of 1415 to 1520 when systolic BP and pulse pressure (systolic BP minus diastolic BP) were decreasing and HR increasing. While there was no diary for this period, such a BP-HR signature is consistent with orthostatic stress, possibly caused by standing. All symptoms were denied during this period.

In summary, there was little change in HR and BP during an inflight record. During entry and seat egress, BP was normal for the situation with minimal HR changes in spite of being symptomatic on seat egress. Two days later there was a persistently elevated (for this individual) HR and one period consistent with orthostatic stress but without reported symptoms.

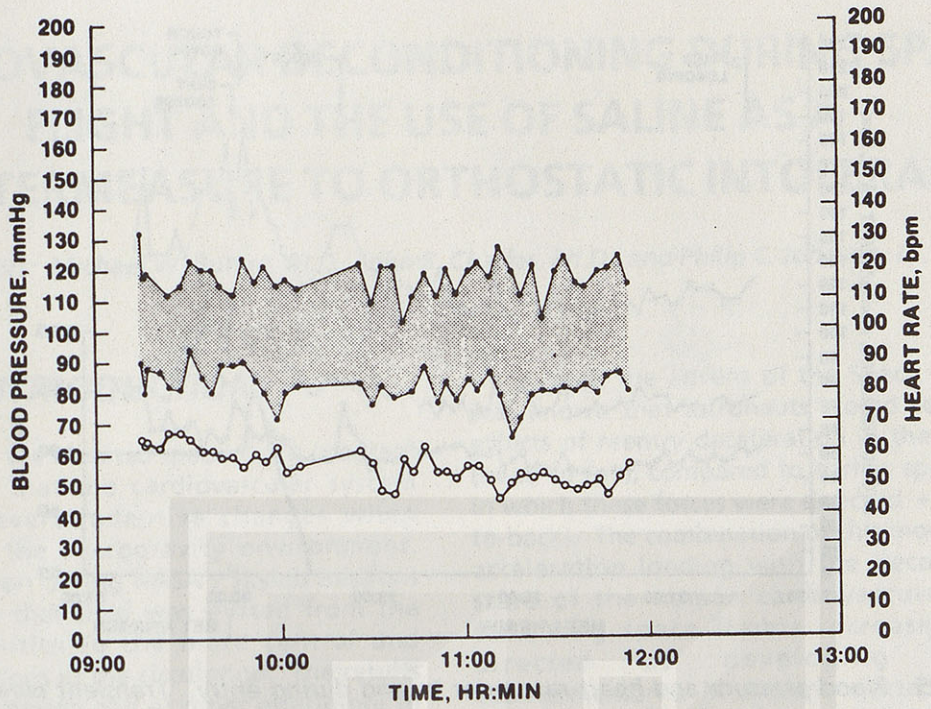


Figure BP-3. Blood pressure (shaded area) and heart rate (open circles) during simulation of entry preparation. The only remarkable feature is the low heart rate.

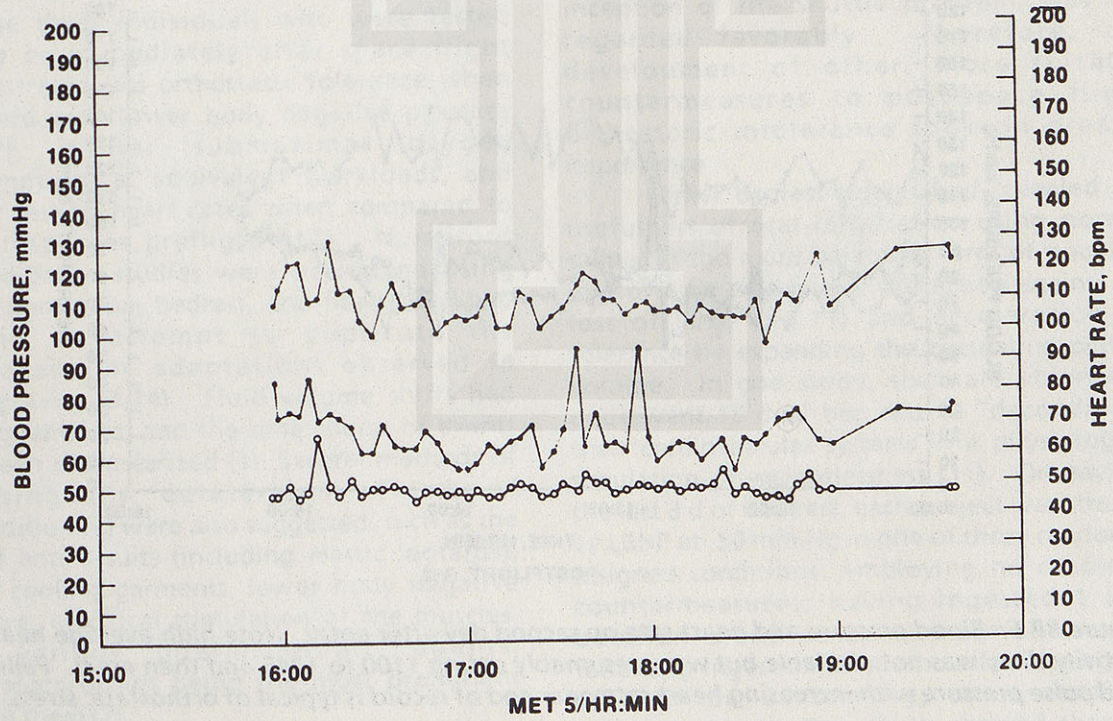


Figure BP-4. Blood pressure and heart rate during day prior to entry. Heart rate was equivalent to supine resting rate prior to entry.

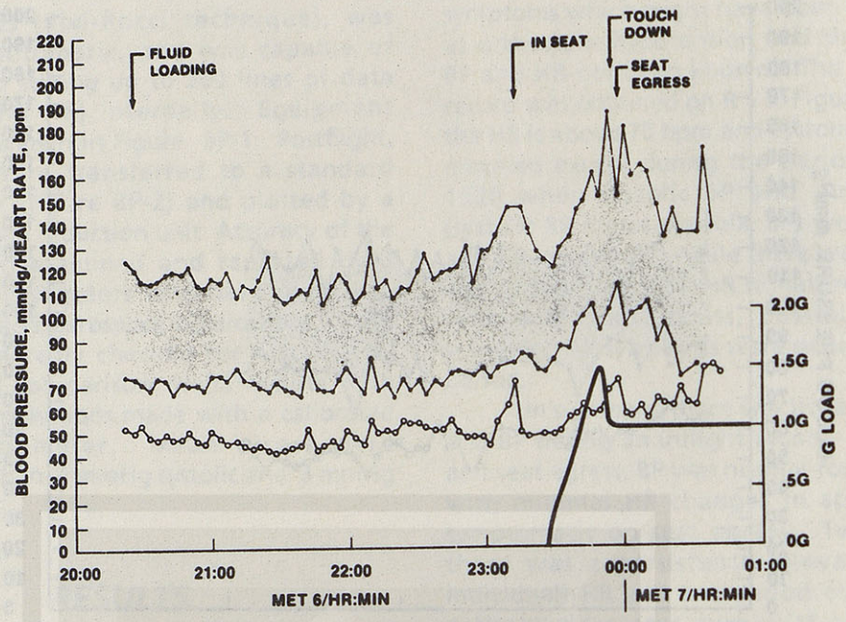


Figure BP-5. Blood pressure and heart rate prior to and during entry. Transient elevation at 2300 caused by activity associated with strapping into seat. Second increase is typical response to entry loads. Heart rate is relatively low for reexposure to one-g.

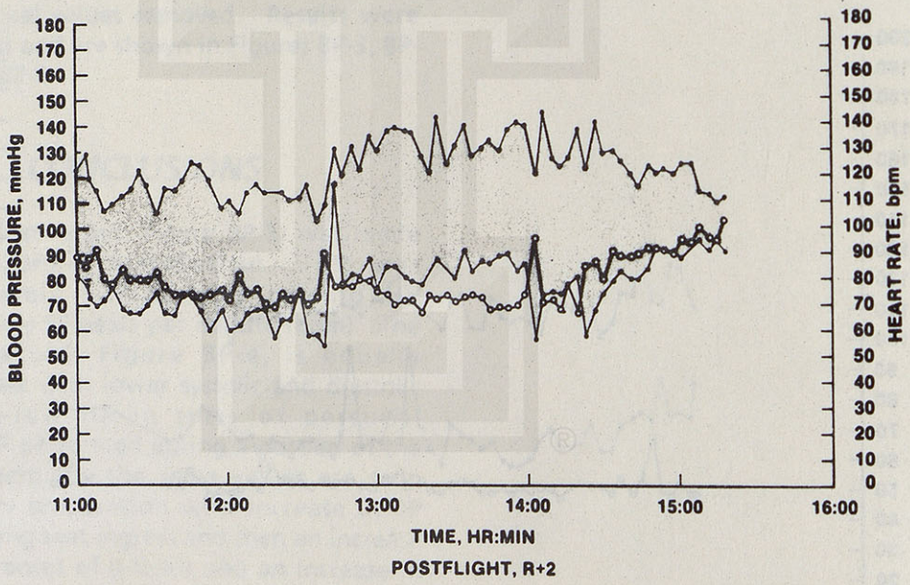


Figure BP-6. Blood pressure and heart rate on second day after entry. Note high average heart rate. Activity diary was not available but was presumably sitting 1100 to 1245 and then erect. Falling SBP and pulse pressure with increasing heart rate near end of record is typical of orthostatic stress.

CARDIOVASCULAR DECONDITIONING DURING SPACE FLIGHT AND THE USE OF SALINE AS A COUNTERMEASURE TO ORTHOSTATIC INTOLERANCE

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INTRODUCTION

Early in the manned space flight program it was noted that the cardiovascular system undergoes several adaptive changes when subjected to the microgravity environment. Experimentation during NASA's Skylab missions demonstrated that fluid was shifted from the lower extremities to the more central and cephalad portions of the circulation. The results of this redistribution and of other alterations in the controlling mechanisms of the circulation which were not well defined were termed "cardiovascular deconditioning." The term deconditioning was felt to be appropriate because those individuals who were tested during or immediately after space flight demonstrated less orthostatic tolerance when provoked with lower body negative pressure (LBNP), higher submaximal oxygen consumptions at equivalent workloads, and higher resting heart rates when compared to their responses preflight (12). Numerous ground-based studies were performed using water immersion, bedrest, and headdown bed rest in an attempt to duplicate the cardiovascular adaptations observed in microgravity (3,14). Fluid volume shifts had been quantified, and the time course of events had been characterized (1). Several methods of reversing the deleterious effects of deconditioning were also suggested, such as the use of anti-G suits (including elastic leotards), liquid cooling garments, lower body negative pressure, electrical stimulation of the muscles, and various pharmacologic agents, mineralocorticoids being the most prominent among them (2).

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With the advent of the Space Shuttle, it was known that astronauts would receive the effects of reentry deceleration in the +Gz axis (head-to-toe), compared to earlier space flights in which these forces were directed +Gx (chest-to-back). The combination of this more stressful acceleration loading with the deconditioned state of the human cardiovascular system following space flights increased efforts directed at developing suitable countermeasures. Most were rejected for actual use in the Space Shuttle due to either complex hardware requirements or objections by flight crews. Even the anti-G suit, considered by many as the only acceptable alternative at the inception of the Shuttle program, was not regarded favorably. Therefore, the development of other, more suitable countermeasures to post-space flight orthostatic intolerance took on greater importance.

Earlier bedrest studies had revealed the usefulness of oral rehydration using normal saline, in the more palatable form of bouillon, in providing a degree of protection against the loss of LBNP (10,11) and acceleration (4) tolerance by expanding the circulating plasma volume. In one study, six male volunteers underwent 15 d of bed rest to "decondition" their cardiovascular systems in a physiological simulation of weightlessness (11). On each of the last 3 d of bed rest, each subject was stressed by LBNP at -50 mm Hg in one of three randomly-assigned conditions: employing no candidate countermeasures; having ingested 1 L of bouillon alone as a countermeasure; or following ingestion of the bouillon during 3 h of LBNP at -30 mm Hg, as a combined countermeasure. The results showed that the combination of oral rehydration and prolonged LBNP provided a more sustained increase in plasma volume and reduction in stressed heart

rate response. However, oral rehydration alone provided a larger increase in plasma volume and essentially the same reduction in stressed heart rate response, but for a period of only a few hours. Considering the constraints of Space Shuttle operations, especially the inconvenience of providing for the appropriate LBNP treatment of the entire crew during the last 24 h of space flight, the relatively short-lived protection of oral rehydration alone was deemed the superior treatment. Accordingly, the simple technique of oral rehydration shortly before reentry into the earth's atmosphere was evaluated during several Space Shuttle flights.

PROCEDURES

On the day prior to Shuttle landing, all 26 crewmembers were to consume at least 3 quarts (2.7 L) of fluids as part of their usual meal and snack routine. This was intended to offset any dehydration due to low intake during the period of adaptation to weightlessness, or to high insensible loss; it was not expected that this consumption would alter the physiological adaptation to microgravity.

Preliminary testing revealed that Shuttle crewmembers found isotonic saline unpalatable even in bouillon form. Therefore, the crews were provided with salt (sodium chloride) tablets (1 g each) and advised to take one tablet with each four ounces (114 ml) of water consumed, to a total of 8 tablets and 912 ml of water. This concentration approximated isotonic saline. On the day of landing, starting 2 hours before entry into the earth's atmosphere, the participating crewmember was to begin oral intake of fluid and salt at a rate dictated by personal comfort. It was stressed that regardless of the total fluid volume consumed, the tablet-to-volume ratio be kept constant as prescribed. During the interval between 1 and 2 hours after landing, each crewmember's heart rate and blood pressure responses to a Passive Stand Test (9) were recorded, for comparison with their preflight values. During the Stand Test, the electrocardiogram was recorded continuously, and blood pressures were measured each minute for 5 minutes while the crewmember was in the supine position, and for 5 additional minutes immediately thereafter while the crewmember was standing. The individual stood with his/her feet six inches (15 cm) apart and nine inches (23 cm) from a wall, and leaned slightly backwards against the wall for support. Passive standing had previously been validated as a test of orthostatic intolerance (9).

Heart rate was determined from the electrocardiographic record as the number of QRS complexes occurring during each 1-minute interval. Mean blood pressure was calculated as one-third the sum of the systolic blood pressure plus two times the diastolic blood pressure. The average heart rate, systolic blood pressure, and diastolic blood pressure during the equilibrated portion of each 5-minute segment of this stand test were used in all calculations. In addition, the minute-by-minute group mean values for heart rate and mean blood pressure were plotted to illustrate the differences in the dynamic adjustments of cardiovascular function before and after space flight, and with and without the countermeasure. The results were similar to the averaged data.

A means of estimating the degree of cardiovascular deconditioning was formulated which standardizes each individual by his/her preflight testing response. This Cardiovascular Index of Deconditioning (CID) is defined as: CID = ΔHR - ΔSBP + ΔDBP, where ΔHR = heart rate (bpm) standing postflight minus heart rate standing preflight; ΔSBP = systolic blood pressure (mm Hg) standing postflight minus systolic blood pressure standing preflight; and ΔDBP = diastolic blood pressure (mm Hg) standing postflight minus diastolic blood pressure standing preflight.

The CID is a unitless index that reflects the numerical increase in heart rate and decreases in systolic and pulse pressures resulting from cardiovascular deconditioning, as documented in both space flight and bedrest experience (13). Therefore, as the numeric value of CID increases, the response of the cardiovascular system is greater, and the level of deconditioning (i.e., orthostatic susceptibility) more profound.

The experiment results were analyzed statistically using a two-factor mixed design analysis of variance (one factor between groups, and one within). The mean steady-state value of each variable during each 5-minute phase of the Stand Test, both preflight and postflight, was analyzed as a separate treatment.

RESULTS

All crewmembers from the first eight Space Shuttle flights were considered as the subjects of this investigation, for a total of 26 data sets from 24 individuals (two individuals flew twice). Of these subjects, 17 utilized the countermeasure and 9 did not. The space flights lasted from 54 hours to 192 hours, and flight length did not appear to correlate with the deconditioning parameters examined in this study.* Crewmembers participated in the study on a voluntary basis. Those that did not take the countermeasure did not use other countermeasures for the Stand Test and were considered the control population. The astronauts using the countermeasure consumed fluid and salt according to personal preference. Some drank water while others preferred various on-board beverages, especially fruit juices. Salt tablets were taken as prescribed or less than directed but not in excess. The operational environment in which the space-borne portion of this investigation took place made it impossible to control these individual variations. As a result, the amount of fluid consumed ranged from 0.5 L of hypotonic solution to 1 L of isotonic solution. Occasionally, crewmembers who had used the countermeasure prior to reentry consumed additional fluids postflight before the Stand Test was performed. Because of this pattern of compliance, any attempt at volume loading with salt and fluids prior to reentry was considered a use of the countermeasure.

* Subsequent to this analysis, additional data were collected which suggested an effect of flight duration on crewmembers using the countermeasure, but not on those who did not. This will be treated in more detail in a future publication.

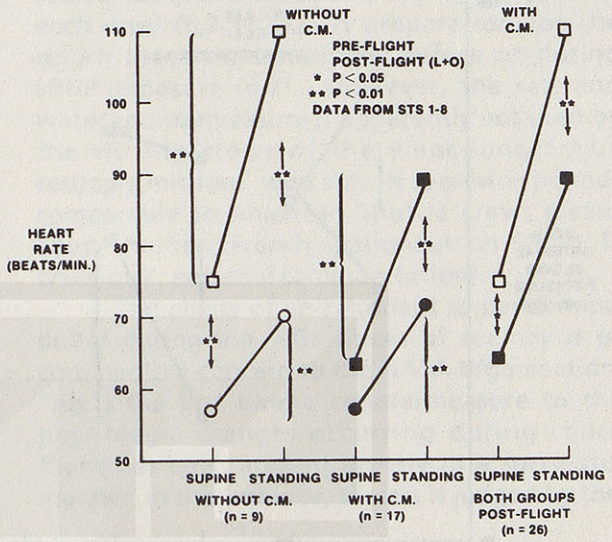

Figure 1. Responses of heart rate to orthostasis pre- and post-spaceflight, with or without countermeasure (C.M.).

The postflight Stand Test usually took place during the interval between 1 and 2 hours after landing. The heart rate responses to the orthostatic stress are summarized in Fig. 1. Both groups had mean supine heart rates of 57 bpm preflight, which upon standing increased to 70 bpm in the control group and 71 bpm in the countermeasure group. These changes in heart rate were statistically significant ($p < 0.01$), and the responses of the groups were essentially identical. Postflight, the control group's mean supine heart rate of 75 bpm was significantly elevated over the preflight supine value ($p < 0.01$). Their mean postflight standing heart rate rose to 110 bpm, a significant increase over both their postflight supine ($p < 0.01$) and preflight standing ($p < 0.01$) values.

In the group utilizing the countermeasure, the postflight mean supine heart rate of 64 bpm was only slightly elevated and increased ($p < 0.01$) to 89 bpm with standing. The postflight heart rates were significantly lower in the group using the countermeasure than in the control group, in

both the supine ($p<0.05$) and standing ($p<0.01$) positions.

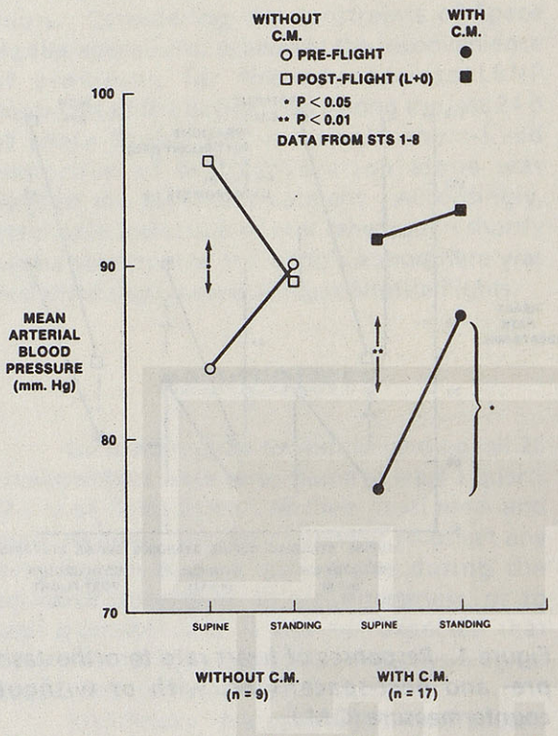

Figure 2. Responses of mean blood pressure to orthostasis pre- and post-spaceflight, with or without countermeasure.

Mean blood pressure responses to the orthostatic stand test are summarized in Fig. 2. The preflight response to assuming the upright posture was a 6 to 10 mm Hg rise in mean blood pressure. Postflight, the control group's mean blood pressure dropped 7 mm Hg when the astronaut assumed the standing position. In the group which utilized the countermeasure, the mean blood pressure rose 2 mm Hg when changing from supine to upright posture. In both the control and experimental groups, the supine mean blood pressure was significantly higher ($p<0.05$) postflight than preflight.

The individual responses to orthostasis before and after space flight are presented in Table I. The Cardiovascular Index of Deconditioning (CID) was calculated for each crewmember and listed in Table II. For those who did not use the countermeasure, the average CID was 49.4 ± 9.6 S.D. For those crewmembers utilizing the countermeasure, the average CID was 21.4 ± 15.9 S.D., a significantly ($p<0.003$) lower value than for the abstainers. Of the two crewmembers who had more than one Shuttle flight, one individual did not use the countermeasure either time; his CID values were 45 and 63. The other crewmember did not use the countermeasure on his first flight (CID = 46), but did use a partial countermeasure on his second flight (CID = 24).

Of the 26 crewmembers on the first eight Shuttle flights, 1 suffered an episode of outright postflight orthostatic syncope, and 2 had episodes of presyncope. None of these three individuals had utilized either the fluid loading or any other countermeasures for the Stand Test.

DISCUSSION

The use of orally consumed salt tablets and water has been shown in these studies to have a beneficial effect on orthostatic tolerance as measured by heart rate and blood pressure responses to a post-space flight stand test. The cardiovascular adaptation to microgravity, termed "deconditioning," therefore apparently has fluid redistribution and subsequent elimination as a significant component. Nevertheless, employing the countermeasure did not completely reverse the effects of space flight. This might be due to inadequate utilization of the volume loading protocol. However, given the complexity of the cardiovascular system's control mechanisms, and their potential susceptibility to alteration by space flight factors, it is probably also a result of other such alterations which are not so readily reversed. Future basic research will aid in discriminating these factors.

Although not providing the fine increments of orthostatic stress that a tilt table or lower body negative pressure device might generate, the stand test produced reproducible provocation that was clinically simple to use and easy to evaluate.

Since the countermeasure was utilized to various degrees of adherence to the protocol, the larger spread of CID values in the experimental group is not surprising, yet the statistical difference from the control group is maintained.

The instance of the crewman who used the countermeasure only after his second and

longer space flight demonstrates its effectiveness. The lower value of the CID after his second flight clearly implies that his orthostatic tolerance with the countermeasure was improved over that without the countermeasure.

The Cardiovascular Index of Deconditioning is a simplistic reflection of a complex, as yet unsolved, clinical research problem. However, this index can be helpful to those responsible for making operational judgements with minimal facilities for data acquisition. Certainly it can serve as an indication of the obvious clinical effects of deconditioning.

Oral rehydration using salt and fluids has also been evaluated for use during Soviet space flights (8), and is employed in the Salyut space station program (5-7, 15-17). During the final 1-3 weeks of their long-duration space flights, the Salyut crewmen have spent time in their "Chibis" LBNP garments (5-7, 15-17) to reaccustom the vasculature of the lower limbs to blood pooling. Some crewmembers also drank "15 sips" of water about 20 min prior to the later LBNP sessions (16), although they apparently did not take salt, as was done in the Americal bed rest study (11). On the last day of flight, the cosmonauts consumed 30 g of salt (in tablet form) and drank 300-400 ml of water at each meal (6,7,16,17), in preparation for the return to earth, sometimes before or during LBNP exposure (6,7). However, the salt and water countermeasure is apparently not used by the visiting crews of the week-long Soyuz resupply missions, who stay in space for periods comparable to American Shuttle crews (Jean-Loup Chretien, French spationaut on Soyuz T-6/Salyut-7: personal communication).

The ability of an astronaut to perform his duties during the +Gz forces of reentry is of considerable concern to the NASA organization. This is the first time a countermeasure to the physiologic changes occurring during space flight has been applied acutely in a successful manner. In this instance, success is judged by the

Table 1

INDIVIDUAL STAND TEST RESULTS

Subject number	Time in flight (hours)	Counter-measure yes/no	Preflight						Postflight						
			Supine			Standing			Supine			Standing			
			HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	CID
1	54	N	61	127	88	73	145	92	61	120	80	99	110	80	49
2	54	N	59	129	76	65	137	86	66	140	110	85	135	110	46
3	54	N	78	118	76	102	118	76	103	117	75	126	90	62	38
4	54	N	54	110	70	71	105	68	80	118	82	111	118	86	45
5	192	N	52	118	80	70	105	80	77	140	84	120	120	98	53
6	192	N	53	100	70	65	100	72	77	118	82	137	104	70	66
7	169	Y	57	110	68	65	98	66	69	108	78	93	100	68	28
8	169	Y	53	130	80	60	118	78	69	128	84	97	126	82	33
9	122	Y	58	103	65	68	112	77	67	120	88	89	110	90	36
10	122	Y	68	100	60	86	107	73	65	119	75	92	110	80	10
11	122	Y	49	100	67	67	117	79	51	106	60	71	116	79	5
12	122	Y	57	102	68	66	110	74	60	114	56	82	122	72	2
13	120	Y	69	109	68	90	120	80	69	119	80	79	109	86	6
14	120	Y	65	108	63	82	120	80	59	137	88	90	129	96	15
15	120	Y	48	110	69	62	118	78	77	106	62	120	114	69	53
16	120	Y	49	95	50	60	110	68	50	112	57	74	113	77	20
17	146	Y	59	96	60	71	120	82	72	149	101	87	136	106	24
18	146	Y	53	100	60	72	119	76	72	132	96	94	125	103	43
19	146	Y	51	96	60	66	110	70	57	122	79	77	116	80	15
20	146	Y	55	80	60	78	90	65	64	124	92	91	96	63	5
21	146	Y	71	100	60	83	120	72	61	126	80	83	114	79	13
22	145	N	52	100	60	64	112	72	79	110	70	120	105	72	63
23	145	Y	52	90	60	66	113	72	47	110	72	82	112	83	28
24	145	Y	53	100	58	73	110	75	75	100	73	107	116	89	42
25	145	N	54	98	60	59	110	72	68	109	78	105	112	72	44
26	145	N	52	100	60	64	118	78	61	122	83	89	84	60	41

Legend: SBP = systolic blood pressure
DBP = diastolic blood pressure
HR = heart rate
CID = Cardiovascular Index of Deconditioning (see text)

Table 2

SPACE SHUTTLE

CARDIOVASCULAR INDEX OF DECONDITIONING - INFLUENCE OF SALINE COUNTERMEASURE

With Countermeasure	Without Countermeasure
28	49
33	46
33	38
10	45
5	53
2	66
6	63
15	44
53	41
20	49.4 ±SD9.6
24	
43	
15	
5	
1	
28	
42	
21.4 ±SD15.9	

Legend: Difference between two CID values is significant to the $p<0.003$ level

CID = ΔHR - ΔSP + ΔDBP (see text)

acceptance and regular utilization of a technique by the crewmembers, and the objective demonstration of statistically significant beneficial physiological effects. Indeed, this success has resulted in the official adoption of oral fluid and salt loading as an operational countermeasure for all Space Shuttle crewmembers.

In addition, a clinically useful index, the CID, has been developed to assist the flight surgeon in his assessment of the degree of deconditioning.

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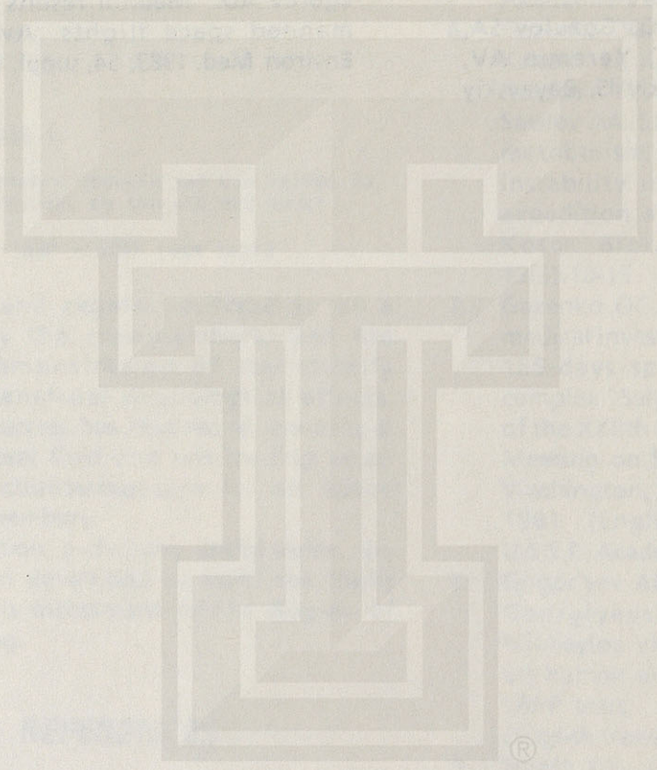

CHANGES IN TOTAL BODY WATER DURING SPACE FLIGHT

Investigators: Carolyn S. Leach, Ph.D., L. Daniel Inners, Ph.D., and John B. Charles, Ph.D.

INTRODUCTION

The objective of this experiment was to measure the changes in total body water (TBW) occurring in humans as a consequence of exposure to microgravity.

It was hypothesized that total body water decreases by about 1.0-2.0 liters within the first three days of weightlessness and is maintained at that level for the duration of a 7-10 day flight.

Fluid shifts occurring during the first few hours of weightlessness have been identified as the probable cause of early adaptive responses of the human cardiovascular and renal/endocrine systems (3). Fluid shifts have also been implicated as possible contributory factors in altered vestibular function. Despite this role in triggering the response of major pathways of adaptation, the timing and extent of the exchanges of water and electrolytes between compartments is unknown.

TBW measurements are particularly important to the goal of tracking fluid shifts. Not only are the overall changes in total water content of interest, but also changes in intracellular fluid volume cannot be calculated without reliable estimates of TBW.

Although exposure to weightlessness has long been known to affect the distribution of body fluids, previous measurements of total body water have been confined to preflight and postflight periods. Leach and Rambaut (4) measured TBW pre- and postflight on Skylab Missions 2, 3, and 4 on a total of nine subjects, using tritiated water as the tracer. Comparison of pre- and postflight measurements indicated a mean decrease of 1.7 % in postflight TBW relative to preflight. On the other hand, the ratio of TBW to body mass was observed to increase slightly in this comparison.

With the development of noninvasive techniques employing stable isotopes (5), it was possible to make direct, precise measurements of TBW at almost any conceivable time during a mission while making very minor demands on crew and spacecraft resources. Moreover, these newer methods are capable of a resolution of events separated by only three to six hours.

PROCEDURE

SUBJECTS

The subjects for this experiment were three male crewmembers. Height, age, percent body fat, and preflight body mass are summarized in Table 1.

Table 1. Height, body mass, percent body fat, and age for the three subjects who participated in this experiment. All data except body mass were recorded as part of the previous annual physical exam for the crewman. Body mass was taken from F-33 preflight data.

Subject	Height (cm)	Body Mass (kg)	% Body Fat	Age
A	178.5	80.6	14.7	39
B	170.0	68.5	14.2	35
C	177.7	71.9	14.4	43

Table 2. Body mass of subjects.

Subject	F-33	F-30	F-24	F-7	L+0	L+3
A	80.6		81.2	83.9	80.6	79.7
B	68.5		69.6	70.3	67.1	68.9
C	71.9	72.2		73.5	70.8	71.0

The proposed schedule of the experiment is summarized in Figure 1. The design included no special control group or control experiment. Instead, all inflight and postflight data were compared to preflight baseline data. Because of a delay in the launch of the mission and the unavailability of some crewmembers during the immediate pre- and postflight periods, the first preflight measurements were at F-34 to F-30, while some measurements were missed entirely. The actual schedule of measurements was as indicated in Table 3.

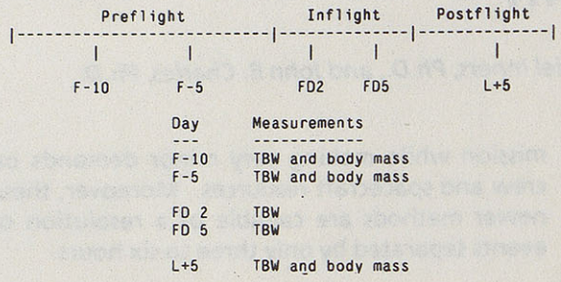

Figure 1. Nominal schedule of experimental sessions for measurement of total body water.

Table 3. TBW Measurements. Total body water in kg for three crewmembers, A, B, and C, on the mission days indicated. This is the unbalanced data matrix used for the general mixed model analysis of variance.

Hour		F-34	F-31 F-30	F-3	FD 2	FD 4 FD 5	L+6
	A	47.33	47.87	49.65	44.87	46.82	50.05
3 hr	B	40.02	40.19	41.41	43.46	39.20	41.32
	C	44.41	47.53		43.74	46.58	
	A	47.14		49.94	44.38		
5 hr	B	40.83	42.01	42.79	41.80		43.42
	C	47.18	47.43		44.17	45.71	

TBW was measured by the isotope dilution technique utilizing oxygen-18-labeled water ($H_2{}^{18}O$) as the tracer. Briefly, this method requires the ingestion of a known mass of ^{18}O water followed by sampling of representative body fluids such as urine or saliva over a period of several hours following the administration of the tracer. The protocol for a typical measurement is shown in Figure 2. The measurements were initiated immediately after a sleep cycle with the crewman in a fasted state. After the collection of background samples the dose was consumed followed by at least 50 ml of fruit juice or galley water. The subject was allowed to consume a light breakfast 30 min after dose administration and was requested to abstain from caffeine-containing beverages for the duration of the experiment. All food consumed during the experiment was recorded on a log sheet.

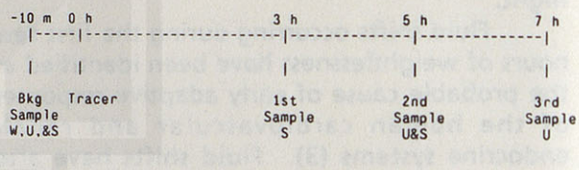

Figure 2. Schematic representation of a typical inflight experimental session (U = urine sample, S = saliva sample, W = galley water sample).

A sample of galley water was collected on FD 2. The experimental design called for galley water sampling on all days on which TBW was measured, since it had been observed on several previous occasions, including STS 51-D, that water sampled from the galley was enriched in ^{18}O content. Urine samples collected during inflight testing of the Urine Monitoring System on Spacelab 3 also exhibited ^{18}O enrichment.

Dental cotton rolls were used for saliva collection. All cotton used in the experiment was from one batch, and rolls were packaged individually in vapor-tight, 10-ml glass lyophilization vials (Wheaton) in a single operation lasting about 30 min. Once closed, the sample vials were opened only for sample collection and sample removal. The sample collection vials were packaged in a Nomex kit (Figure 3) for inflight use.

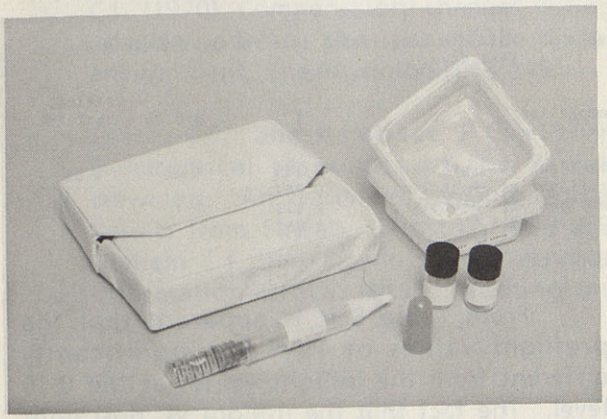

Figure 3. The Nomex dose syringe kit, an assembled dose syringe, the syringe cap, two saliva sample vials, and two beverage containers used to collect Shuttle galley water samples. A similar, separate kit was used for stowing the sample vials.

^{18}O water (95-98 %) was purchased from Mound Laboratories, Miamisburg, OH. The dose was approximately 6 g. The labeled water was filtered directly into a sealed, sterile syringe vial through a nonsterile 13-mm Millipore Type HA filter (0.45 micrometer pore) using a disposable filter holder. The syringe used was a two-piece disposable type manufactured by IMS (El Monte, CA), consisting of a glass vial containing the dose and a separate plastic injector with a lavage tip (Figure 3). This syringe was weighed three times: empty, filled with the labeled water, and after use to determine the dose delivered and the amount remaining in the syringe (usually about 0.3 ml). Syringes were stowed in a separate kit similar to that used for the sample vials. To ingest the dose, a crewman removed the protective caps, assembled the syringe, and delivered the contents directly into his mouth. Used dose syringes were left assembled with the tips capped and stowed in an empty food locker.

A test subject collected saliva by placing a dental cotton roll under his tongue for several minutes and then replacing the saturated cotton in the vial. It was determined in supporting studies that samples could be stored for over a week at ambient temperature without affecting isotope content, provided they were protected from evaporation. Sample vials were replaced in the original kit and stowed in a different locker from the used dose syringes. This precaution was taken to minimize the possibility of accidental contamination of the sample vial contents. The samples were frozen at -70° C after being returned to the laboratory.

The usefulness of the TBW measurement is greatly enhanced if body mass can be measured as well, since this enables the calculation of the TBW to total body mass ratio. Body mass measurements were obtained on days F-33, F-30, F-24, F-7, L + 0, and L + 3 (Table 2). Since these measurements were obtained at three different locations and presumably under three different protocols, their interpretation is difficult.

OXYGEN-18 ANALYSIS

Analyses of the samples were carried out in ground-based facilities of the Stable Isotope Laboratory at Baylor College of Medicine. Frozen samples were thawed and approximately 0.3-0.5 g aliquots were transferred to preweighed 20-ml Vacutainer serum tubes using disposable plastic tuberculin syringes. The tubes were reweighed to determine the mass of the sample. The tubes were then filled with 5% carbon dioxide, 95% nitrogen and equilibrated for 48-72 hours at 25° C. The cryogenically purified carbon dioxide was analyzed using a Model 3-60 Gas Isotope Ratio Mass Spectrometer (Nuclide Corp., University Park, PA). Details of the analytic procedure and calculation are found in Schoeller et al. (5,6).

RESULTS

The results of the experiment are summarized in Table 3. The eight gaps in this table represent five missing samples, one sample collected late, and two values which were spuriously high, perhaps owing to inadvertent dilution of the sample during collection. The values in the table are not corrected for fluid intake during the period of the experiment.

The data were analyzed according to the general mixed model analysis of variance, utilizing BMDP module BMDP3V (BMDP

Statistical Software, Los Angeles, CA). Subject was treated as a random variable, while mission day and sample time were regarded as fixed variables. Various null hypotheses were tested to identify the source of the variance. These are listed in Table 4. In addition, the multiple comparisons test (1,2) was applied to test for significantly different means of TBW for the different phases of the mission. This test is summarized in Table 5.

No attempt has been made at this time to make a similar analysis using the ratio of TBW to body mass.

In agreement with previous observations, the galley water was found to be enriched in ^{18}O, i.e., the enrichment was approximately 40 parts per thousand. The actual ratio of ^{18}O to ^{16}O in galley water was 0.00216, which may be compared with the ratio observed in normal surface water, 0.00208. The source of this enrichment has not been identified, although it is possibly due to boil-off during ground storage of the liquid oxygen used in the fuel cells.

Table 4. Results of analysis of variance using the general mixed model.

Source of variation	Type of factor	Chi-squared	df	p-value
Subject	random	10.729	1	0.001
Hour	fixed	2.538	1	0.111
Day	fixed	10.931	5	0.053
Hour * Day	fixed	7.060	5	0.216
Hour * Subject	random	0.0	1	0.998
Day * Subject	random	9.514	1	0.002
Hour * Day * Subject	random	0.0	1	0.998

The analysis summarized in Table 4 was based on the assumption that the day of measurement, i.e., the phase of the mission, was a fixed treatment effect. Under the hypothesis that this treatment had no effect, the resulting ratio of variances would be observed with a probability of 0.053, indicating that day of observation was a significant factor in explaining the observed variance. According to the usual convention of rejecting a null hypothesis for p-values smaller than 0.05, the decision to reject was borderline at this level of probability.

Table 5. Multiple comparisons test for arithmetic means of test days.

Comparison	F	Critical F p=0.05	Critical F p=0.10
Preflight vs. Inflight	5.145	6.61	4.06
Preflight vs. Postflight	0.254		
Inflight vs. Postflight	2.073		
FD 2 vs. FD 4,5	1.852		

From Table 5 it is apparent that the preflight values of TBW are significantly different from the inflight values at the 0.10 level. The fact that the inflight vs. postflight means are not significantly different can possibly be traced to the limited number of measurements conducted postflight.

It is clear from the foregoing discussion that additional measurements under similar conditions are highly desirable. Future measurements would ideally be made on the same schedule as was actually obtained on this flight, even though this schedule departed from the planned protocol.

CONCLUSIONS

It was concluded that TBW probably decreases by about 3% during exposure to microgravity. On the other hand, the differences between FD 2 and FD 4,5 were not significant, suggesting that the decrease had occurred by the second day inflight. These tentative conclusions were based on a limited number of observations on a small number of subjects, and must therefore be accepted with a degree of reservation until further measurements can be made under closely similar conditions.

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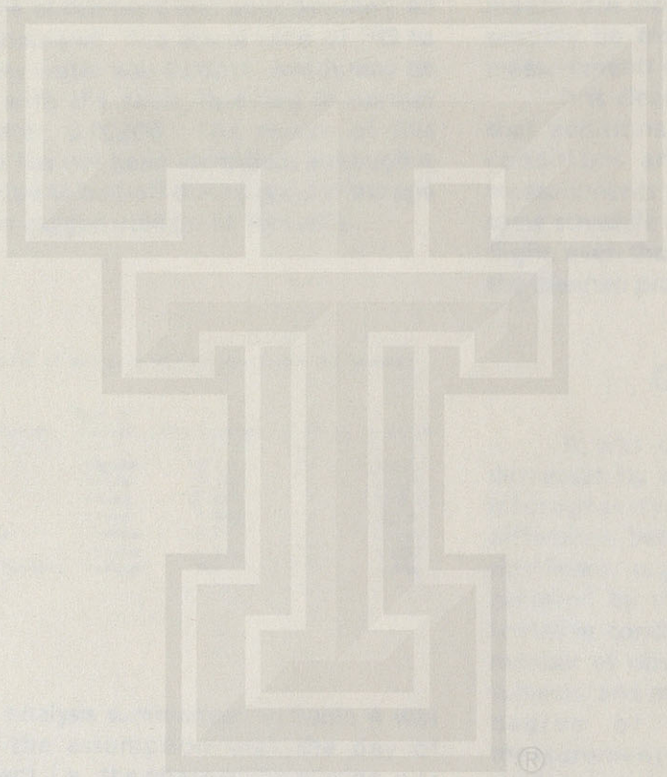


HEIGHT CHANGES IN MICROGRAVITY

Investigators: William E. Thornton, M.D., and Thomas P. Moore, M.D.

INTRODUCTION

Variations in height with position, from supine to upright and vice versa, and slow decreases in height from time of arising through the course of the day have been noted for some time. Difficulties were experienced by some crewmen in donning their unyielding space suits inflight and on the moon.

Changes in height during weightlessness were first documented on Skylab Mission 4, and again demonstrated on the Apollo Soyuz Test Project. Supine and upright height variations on Earth and the time course of these changes with and without varying loads have been investigated by Thornton and others. A series of inflight studies was also performed on the Shuttle missions. These studies and experiences resulted in adding an inch to the spacesuit torso length.

Results from the studies are consistent; the intervertebral discs expand or compress with changing load in a biphasic fashion. There is an immediate change in height with load followed by a slower change with a time constant of hours.

While the magnitude of such changes is fairly well established for weightlessness, their time course was unknown; this was studied as follows.

PROCEDURES

The barefooted subject was positioned standing fully erect, back against a wall and exerting downward pressure with his hands to ensure maintaining solid contact with the floor, Figure 1. A square jig was placed against the wall with its top just touching the subject's vertex, and an index mark was made on the wall. Pre- and postflight measurements were made in a similar fashion and the changes were measured to 1/16 of an inch.

RESULTS / CONCLUSIONS

The height data for one subject are tabulated in Table 1 and plotted in Figure 2. The model proposed by the investigator, and independently by Kazarian, predicts an exponential increase in height under flight conditions. When plotted in semilogarithmic fashion, all but one of the points follow such a curve with a time constant (1/e point) of 10 hours.

Table 1. Height of Subject Crewmember

Height, in.								
Preflight	Inflight*							Postflight
	02:40	04:20	08:00	23:30	29:30	50:32	73:30	R+1.5 h
71.5	72.00	72.50	72.50	72.75	73.00	73.00	73.00	71.5
	.5	1.0	1.25	1.5	1.6	1.5	1.5	0
%	(.70)	(1.40)	(1.75)	(2.10)	(2.10)	(2.10)	(2.10)	

*MET - Mission Elapsed Time

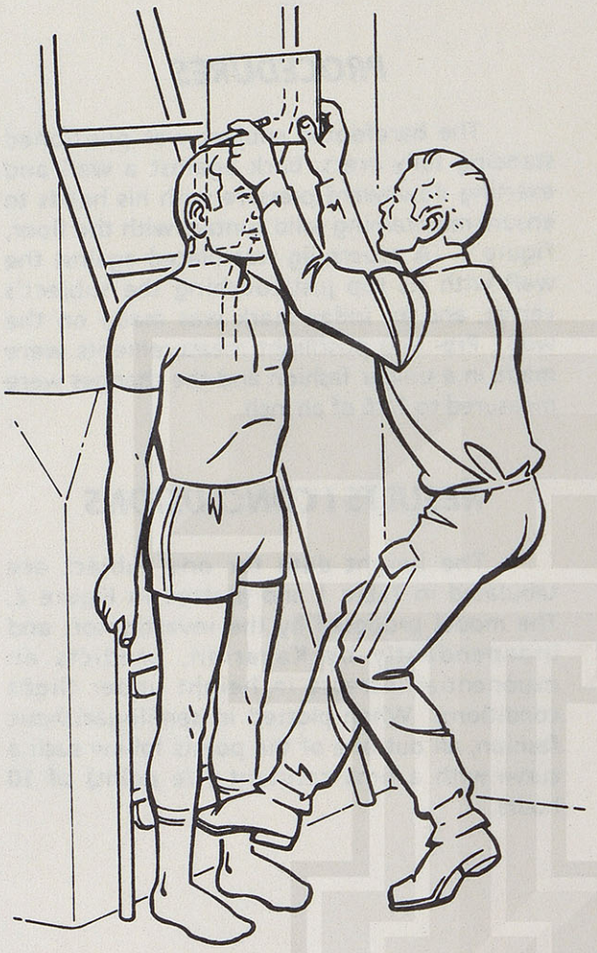


Figure 1. Sketch of inflight height determination. Level of mark above floor was measured and recorded.

COMMENTS

This was the first opportunity to follow the time course of these changes in weightlessness and the results were consistent with the theory of the phenomenon. The absolute value of observed change was 1.5 inches.

It would seem reasonable to extend this measurement to a population large enough to be statistically significant. Should it ever become necessary to accurately allow for such changes, as in equipment design, prediction procedure might be developed by studying the correlation of inflight to one-g changes in the same subject from a suitable population; if a consistent relationship were found, the flight value could be predicted from one-g changes.

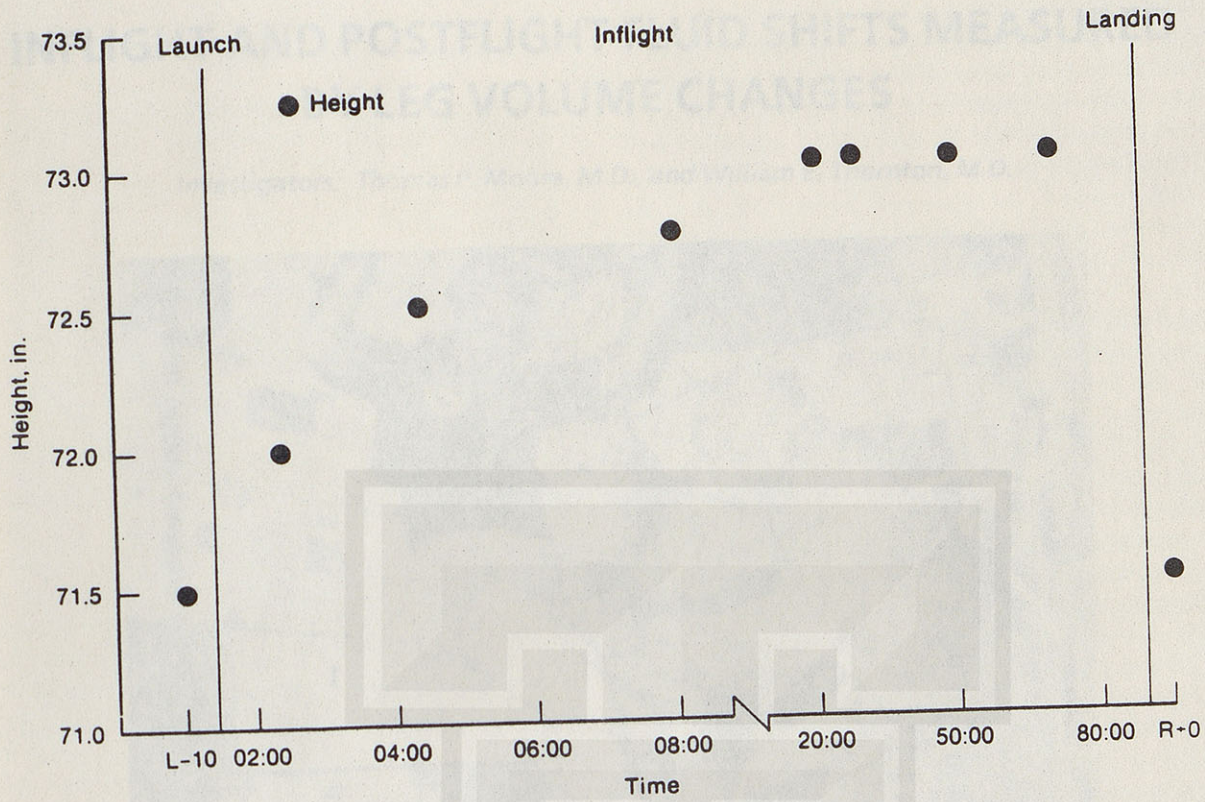
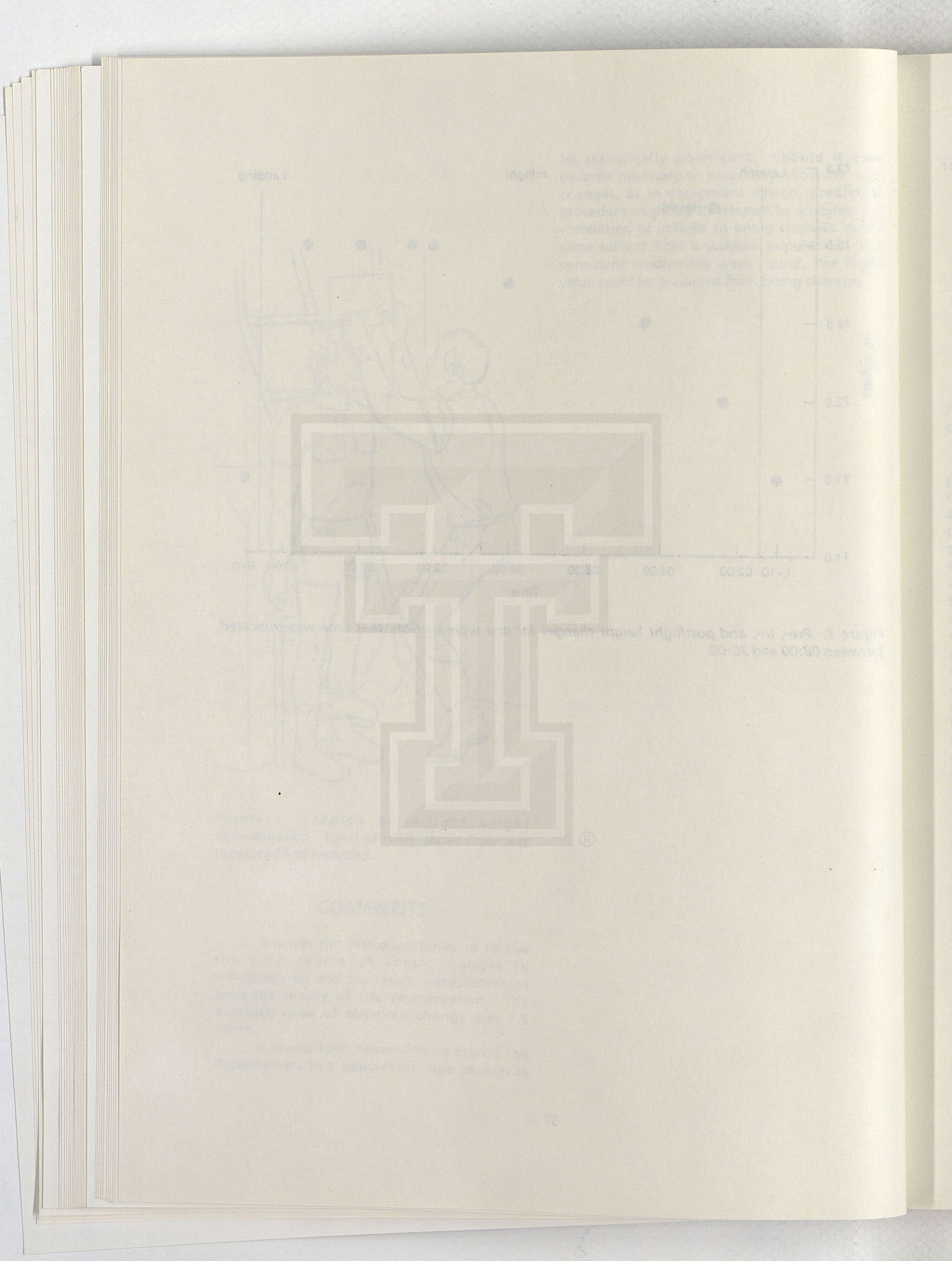


Figure 2. Pre-, in-, and postflight height changes for one subject. Note that time was truncated between 08:00 and 20:00.



INFLIGHT AND POSTFLIGHT FLUID SHIFTS MEASURED BY LEG VOLUME CHANGES

Investigators: Thomas P. Moore, M.D., and William E. Thornton, M.D.

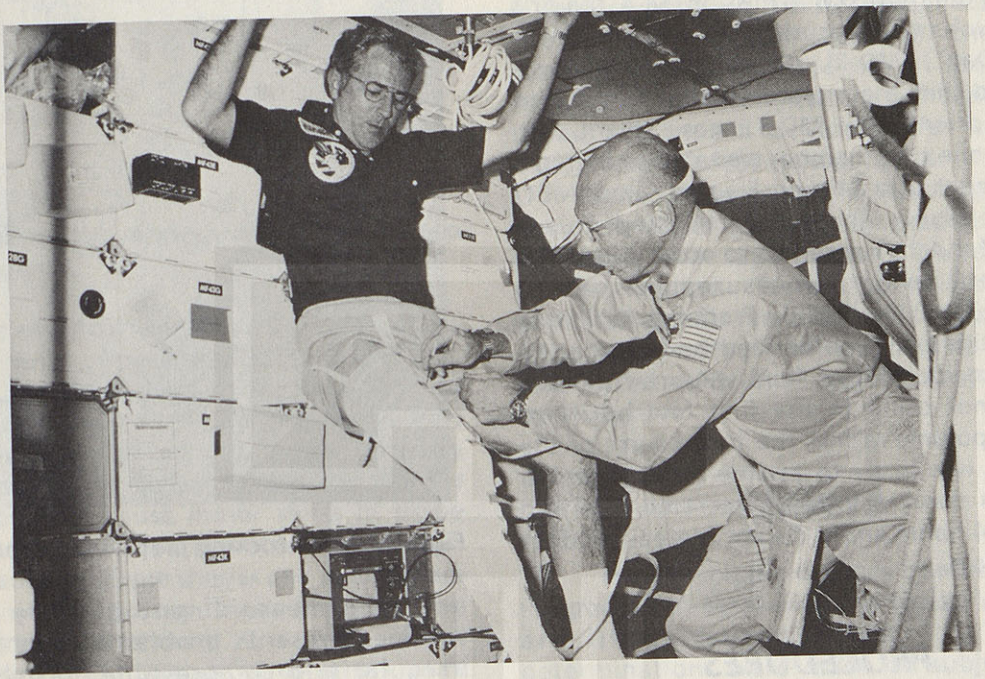


Figure 1. Shuttle crewmembers taking plethysmograph measurements.

INTRODUCTION

Signs and symptoms secondary to fluid shifts in weightlessness were among the first physiologic effects noted in the manned spaceflight program. These effects included puffy faces, nasal congestion, inflight and postflight weight loss, orthostatic hypotension, cardiovascular changes and the "bird legs of space"(1). The headward shift of body fluids, both intravascular and extravascular, results from the absence of the 1-G hydrostatic gradient.

Measurement of changes in leg volume were made pre- and postflight on Apollo 16 and 17 and subsequently on Skylab 2, 3, and 4 by Hoffler et. al (3). The volume measurement was accomplished by using a modification of a measurement system for fitting support stockings. Single-point calf girth measurements were also done inflight on Skylab 2, 3, and 4. The postflight leg volume measurements made on these missions were late in the recovery period after the return of fluid was largely over. The inflight calf measurement was subsequently shown not to be characteristic of the entire leg volume, and hence neither the time course nor magnitude of the changes were appreciated.

On Skylab 4, inflight changes in leg volume were documented using a tape measure system. The results showed volume losses of several liters from the legs (5). This data provided the initial groundwork for formulation of a basis of understanding of postflight weight loss, orthostatic hypotension and other observed space flight phenomena.

A repeat of the leg volume study was performed on the Apollo-Soyuz Test Project (ASTP) which confirmed the volume changes but raised questions on the time course of the fluid shifts (2). While these studies answered a

fundamental question regarding the approximate magnitude of fluid shifts, many significant details remained unknown, including the time course during launch and recovery, the volume distribution as a function of time, and the volume and distribution during orthostatic stress.

On the third Skylab mission, SL-4, the first inflight volume measurement was made on Mission Day 3 (MD-3). From this data it was concluded that the major volume change had occurred prior to the MD-3 measurement. On the ASTP one crewmember was able to obtain a measurement at a Mission Elapsed Time (MET) of 06:00 hours. This value reflected only a portion of the shift observed to occur during the subsequent inflight measurements which started at 32:00 hours MET. From the ASTP data the investigators hypothesized and concluded that the major shift of fluid volume from the legs did not occur in the first few hours of orbital exposure; rather, the time course of the fluid shift was likely to assume an exponential form with maximal rate of decrement within the first 24 hours and a distant plateau evident by 3 to 5 days.

PROCEDURES

The methodology used for these studies was tedious and time consuming. There was no opportunity for repeat studies until the Space Shuttle became operational. Other methods of volume determination, such as water displacement, are impractical in the weightless environment of space or are logistically difficult and time and equipment intensive. A simpler, much more rapid scheme for obtaining volumes was therefore devised and resulted in the stocking plethysmograph used during the Shuttle program (Fig. 2). This scheme was routinely used on several Shuttle flights (Fig. 1). Inflight data from early Shuttle missions was obtained at 11:00 and 13:00 hours MET (4). The conclusion from these data was that by the time of these measurements the fluid shift from the legs was essentially complete since later inflight measurements showed no further significant leg volume loss. Therefore, this experiment was designed to obtain data during the critical early on-orbit time frame as well as throughout the mission, in order to define and delineate the time course and hopefully to further understand the dynamics of the fluid shifts.

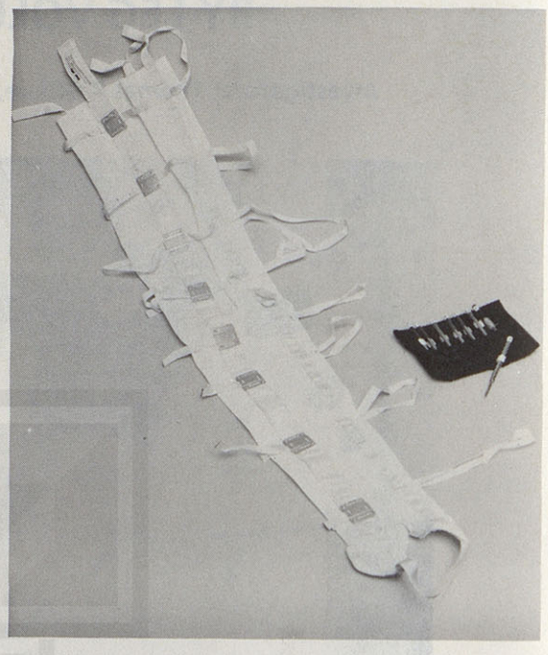


Figure 2. The stocking plethysmograph.

The measurement of body segment volumes presents problems since they are irregular and compressible. The stocking plethysmograph employed the use of direct girth-length measurements. From a series of circumferential measurements, volume was calculated under the assumption that a truncated cone represents a reasonable approximation of a leg volume segment. Using the formula for the frustum of a cone, $V = \pi L/3(R_1^2 + R_1 R_2 + R_2^2)$, the volumes of individual leg segments were calculated. Leg girths were measured to the nearest 5mm and the volume derived for each volume segment with total volume determined by the summation of these volume segments (Fig. 3). This assumption represents the first source of error in this method since the human leg is not shaped as a perfect cone. However, with the number and location of the volume segments used, this error was minimized. Another potential source of error existed in reproducing vertical location of the measuring tapes over successive measurements. Nonelastic longitudinal tapes were used to ensure consistent vertical location of the circumferential measuring tapes.

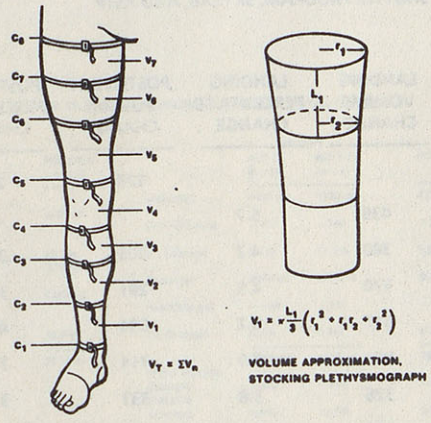


Figure 3. Volume approximation, stocking plethysmograph.

Physiological and anatomical factors produce a series of potential errors. Changes in relaxation or contraction of muscles and the anatomical position of leg segments will produce volume changes. Changes in body position as one moves from the supine to the standing position cause minor shifts in tissue volume and subsequent volume changes. Similar changes in tissue shapes and volumes are induced when going from 1-G to the weightlessness environment.

These potential sources of errors were realized and, insofar as possible, were examined or controlled. It was decided to anatomically divide the leg into 7 volume segments, 3 above the knee, 3 below the knee and 1 including the knee. Therefore, the stocking plethysmograph utilized 8 circumferential measuring tapes. Specific anatomical landmarks and locations were used for the determination of position of the 8 circumferential tapes. Eight different colored pens were used to mark the circumferential tapes and record the mission elapsed time (MET) directly onto the stocking. Each circumferential tape was then measured upon return from flight.

A large effort was put into the design, selection of materials, and design testing of the stocking plethysmograph. Due to limited development time for the first flight of the stocking, a plastic marking window was used. It was found that it did not produce uniform friction on the measuring tapes, introducing significant errors in measurements. A uniform and consistent metal marking window was then designed and used on subsequent missions.

A series of repeatability and validity tests was run, comparing the stockings to a tape measure. For repeatability, multiple tests of 5 on and off repetitive measurements were made. The standard deviation of the circumference measurement of the stocking was .25 cm versus .36 cm for the tape measure. The average difference between the stocking measurement and the tape measure was + .27 cm for the stocking method. In looking at the vertical variation of the location of the 8 circumferential tapes, a standard deviation for repeated measurements of .50 cm was found.

When comparing the stocking method versus the water displacement method, a mean difference of + 380 mls was found for the stocking method. This was believed to be well within acceptable limits taking into account the compressive effects of hydrostatic pressure associated with the water displacement method.

RESULTS

The leg volume changes from the Shuttle Program with comparison to Skylab and ASTP are illustrated in Table 1. Volume determinations were made on subjects on 5 different Space Shuttle flights. Two of the subjects made measurements on 2 separate Shuttle missions as indicated. Over 140 inflight measurements were made. The inflight volumes, illustrated in the table, reflect the mean of all measurements made during the missions except for early-on-orbit measurements (Mission Day 1) made on 3 subjects on two separate missions. These measurements were not included because they reflect volume determinations made during the time periods of active shifting of fluids from the legs (launch position). The data for these three subjects are presented in Tables 2 to 4 and Figures 4 to 6.

Table 1. SUMMARY OF LEG VOLUME CHANGES FOR THE SPACE SHUTTLE PROGRAM, SKYLAB, AND ASTP

	PREFLIGHT TOTAL VOLUME (ml)	INFLIGHT VOLUME CHANGE (ml)	INFLIGHT PERCENTAGE CHANGE	LANDING VOLUME CHANGE	LANDING PERCENTAGE CHANGE	POSTFLIGHT VOLUME CHANGE	POSTFLIGHT PERCENTAGE CHANGE
SHUTTLE CREWMAN A (1)	8,549	952	11.1	-	-	229	2.7
SHUTTLE CREWMAN B	7,735	962	12.4	439	5.7	-	-
SHUTTLE CREWMAN C	9,003	1,069	11.9	380	4.2	305	3.4
SHUTTLE CREWMAN D	8,227	860	10.5	370	4.5	291	3.5
SHUTTLE CREWMAN E	9,028	1,116	12.4	517	5.7	394	4.4
SHUTTLE CREWMAN F (2)	10,612	1,790	16.9	951	8.0	714	7.0
SHUTTLE CREWMAN G	8,656	1,096	12.7	326	3.8	337	3.9
SHUTTLE CREWMAN H (1)	8,422	685	8.3	200	2.4	88	1.0
SHUTTLE CREWMAN J (2)	10,540	1,164	11.4	+ 89	+ .8	43	.4
SHUTTLE CREWMAN K	8,011	855	10.7	597	7.5	402	5.0
SHUTTLE CREWMAN L	7,560	740	9.8	119	1.6	30	.4
MEAN	8,758	1,026	11.6	381	4.3	283	3.2
SKYLAB	7,679	931	12.2	574	6.6	312	3.2
ASTP	7,957	803	10.0	477	6.0	387	4.9

(1) (2) - INDICATES THE SAME CREWMEMBER ON DIFFERENT MISSIONS

The volume change and percentage change are all compared with the preflight volume determinations. The landing measurements were made within 1.5 hours of touchdown. The postflight measurements were made during the first week postlanding through recovery plus 6 days (R + 6). It should be noted that the 1-G leg volume measurements for Skylab and ASTP were made with the crewmembers in the supine position, whereas the measurements in the Shuttle program were made with the crewmembers standing. When going from standing to supine, there is a shift of approximately 300ml of blood out of the legs.

Table 2. SEGMENTAL LEG VOLUME CHANGES FOR SHUTTLE CREWMAN G

	PREFLIGHT (n = 23)		INFLIGHT MD 1 (n = 1)	INFLIGHT MD 2-7 (n = 8)	POSTFLIGHT (n = 3)
ABOVE KNEE	5656 ml	(Volume)	5025 ml	4867 ml	5440 ml
		(Vol. Change)	- 631	- 789	- 216
	65.3% OF TOTAL	(% Change)	11.1%	14.0%	3.8%
BELOW KNEE	3000 ml	(Volume)	2825 ml	2693 ml	2879 ml
		(Vol Change)	- 175	- 317	- 121
	34.7%	(% Change)	5.8%	10.6%	4.0%
TOTALS	8656 ml		7850 ml	7560 ml	8319 ml
		(Total Volume Change)	- 806	- 1096	- 337
		(Total % Change)	9.3%	12.7%	3.9%

This should be recognized and taken into account when comparing the data from these different space flights. There was an average inflight shifting of 1026ml, or 11.6% per leg. This compares with the Skylab findings of 931ml and 12.2% and ASTP of 803ml and 10%. Landing volume determinations showed a mean decrease of 381ml or 4.3%. Postflight measurements taken at various times from recovery plus 1 day through 1 week post recovery show a residual volume decrement as compared to preflight of 283ml or 3.2%.

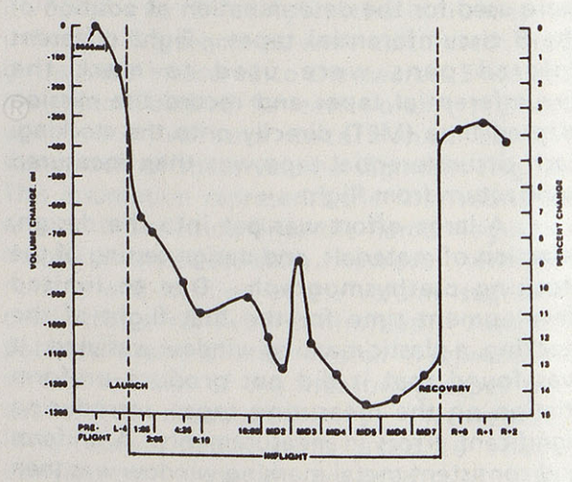


Figure 4. Leg volume changes for Shuttle crewman G.

Table 3. SEGMENTAL LEG VOLUME CHANGES FOR SHUTTLE CREWMAN K

	PREFLIGHT (n = 9)		INFLIGHT MD 1 (n = 5)	INFLIGHT MD 2-7 (n = 4)	POSTFLIGHT (n = 6)
	5656 ml	(Volume)	4402 ml	4300 ml	4575 ml
ABOVE KNEE		(Vol. Change)	- 442	- 544	- 269
	60.5% OF TOTAL	(% Change)	9.1%	11.2%	5.6%
	3000 ml	(Volume)	2957 ml	2856 ml	3034 ml
BELOW KNEE		(Vol Change)	- 210	- 311	- 133
	39.5%	(% Change)	6.6%	9.8%	4.2%
	8011 ml		7359 ml	7156 ml	7609 ml
TOTALS		(Total Volume Change)	- 652	- 855	- 402
		(Total % Change)	8.9%	10.7%	5.0%

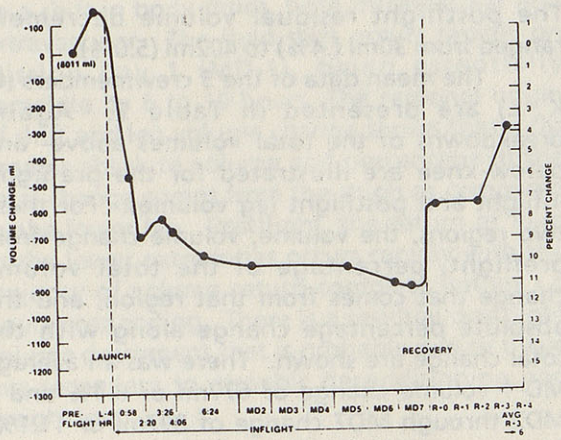


Figure 5. Leg volume changes for Shuttle crewman K.

Tables 2 to 4 and Figures 4 to 6 show the leg volume changes in the 3 crewmembers who wore the stocking plethysmograph during launch and were able to make a series of measurements during Mission Day 1 (MD1). Figures 4 to 6 illustrate the time course of the volume changes throughout the missions as compared with the mean of preflight measurements. The measurements represented are: one taken 4 hours prior to launch, five inflight volumes during MD1 (represented by mission elapsed times [MET] on the graph), those taken on MD2 through MD7, one taken at recovery, and those made postflight through the sixth day after landing.

The leg volumes in Tables 2, 3 and 4 are broken down into above- and below-knee values and percentages along with the relative changes inflight and postflight in these two regions of the leg. The mean MD1 volume change ranged from a decrease of 573ml (7.6%) in Subject L to 806ml (9.3%) in Subject G. MD2-7 volume decreases were also greatest in Subject G of 1096ml or 12.7%, with the lowest being 740ml or 9.8%. All of the crewmembers exhibited significantly greater absolute volume changes as well as relative percentage changes occurring above the knee as opposed to below the knee.

Table 4. SEGMENTAL LEG VOLUME CHANGES FOR SHUTTLE CREWMAN L

	PREFLIGHT (n = 8)		INFLIGHT MD 1 (n = 5)	INFLIGHT MD 2-7 (n = 3)	POSTFLIGHT (n = 7)
	4819 ml	(Volume)	4397 ml	4296 ml	4822 ml
ABOVE KNEE		(Vol. Change)	- 442	- 532	+ 3
	63.7% OF TOTAL	(% Change)	8.8%	10.9%	0%
	2741 ml	(Volume)	2590 ml	2524 ml	2708 ml
BELOW KNEE		(Vol Change)	- 151	- 217	- 33
	36.3%	(% Change)	5.5%	7.9%	1.2%
	7560 ml		6987 ml	6820 ml	7530 ml
TOTALS		(Total Volume Change)	- 573	- 740	- 30
		(Total % Change)	7.6%	9.8%	.4%

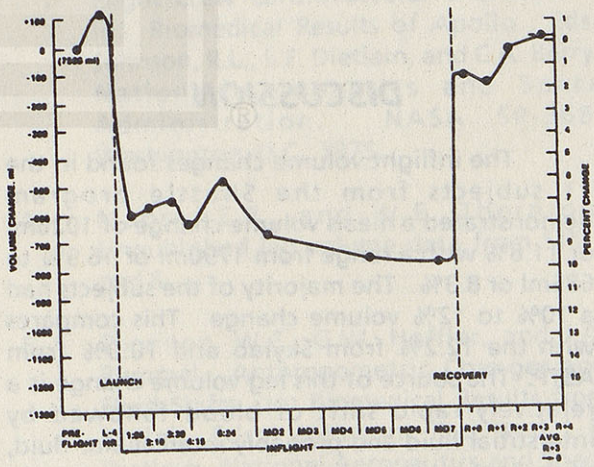


Figure 6. Leg volume changes for Shuttle crewman L.

The postflight residual volume decrement ranged from 30ml (.4%) to 402ml (5.0%).

The mean data of the 3 crewmembers (G, K, L) are presented in Table 5. Again, breakdowns of the total volumes above- and below-knee are illustrated for the preflight, inflight and postflight leg volumes. For these two regions, the volume, volume change from preflight, percentage of the total volume change that comes from that region, and the absolute percentage change along with the total change are shown. There was an average MD-1 volume change of 677ml or 8.4% and a MD2 through MD7 change of 897ml or 11.1%. An average 619ml or 69% of this volume change came from above the knee or the thigh with only 287ml or 31% arising from below the knee. There was a postflight volume decrease of 257ml or 3.2% as recorded during the first week postflight.

Table 5. MEAN SEGMENTAL LEG VOLUME CHANGES ON TWO SHUTTLE FLIGHTS (CREWMEN G, K, AND L)

	PREFLIGHT		INFLIGHT MD 1	INFLIGHT MD 2-7	POSTFLIGHT
ABOVE KNEE	5107 ml	(Volume)	4608 ml	4488 ml	4946 ml
		(Vol. Change)	- 499 ml	- 619 ml	- 161 ml
		(% of Total Change)	74%	69%	63%
	63.2% OF TOTAL	(% Change)	9.8%	12.1%	3.2%
BELOW KNEE	2969 ml	(Volume)	2791 ml	2691 ml	2873 ml
		(Vol Change)	- 178 ml	- 278 ml	- 96 ml
		(% of Total Change)	26%	31%	37%
	36.8%	(% Change)	6.0%	9.4%	3.2%
TOTALS	8076 ml		7399 ml	7179 ml	7819 ml
		(Total Volume Change)	- 677 ml	- 897 ml	- 257 ml
		(Total % Change)	8.4%	11.1%	3.2%

DISCUSSION

The inflight volume changes found in the 11 subjects from the Shuttle program demonstrated a mean volume change of 1026ml or 11.6% with a range from 1790ml or 16.9% to 685ml or 8.3%. The majority of the subjects had a 10% to 12% volume change. This compares with the 12.2% from Skylab and 10.0% from ASTP. The source of this leg volume change is a relatively rapid shift of blood followed by interstitial fluid and probably intercellular fluid, with some tissue loss secondary to muscle atrophy. It should be noted that one crewmember (Subject F, J) had a significantly larger volume change on his first flight (1790ml, 16.9%) than the mean, and also the volume change of his second flight was considerably smaller than the first (1164ml, 11.4%). There is no good explanation for these findings. No procedural or experimental error was identified, and the same stocking plethysmograph was used on both flights. The crewmember did experience Space Motion Sickness symptoms on both missions. He related that he believed his level of hydration was the same for both flights; however, there was noted a greater weight loss on his first flight (11 lbs. versus 7 lbs. for the second flight). The three crewmembers from whom data were obtained shortly after launch and throughout MD1 provided valuable information concerning the dynamics of the fluid shift. The actual fluid shift is complicated by the prelaunch position of lying on one's back in the spacecraft with the legs elevated for up to 2 hours prior to liftoff. The crewmembers universally commented that they believed this position is a stimulus to shifting of fluid prior to launch because of noted bladder distension and the common need to urinate while still on the launch pad. Another environmental stimulus to the fluid shift is the increase in G forces encountered during the launch profile. As stated, the crewmember is positioned on his back at T-zero; then, as the Space Shuttle rotates to an inverted position shortly after clearing the launch tower, the crewmember is also rotated to an inverted position. While in this position throughout the launch and entry profile, +G forces are exerted and reach a maximum of 3.4 G's during the approximate 8 minutes prior to main engine cut-off, orbit insertion and weightlessness. Taking into account these factors, the total volume curves show a logarithmic decrement for approximately the first 6 to 10 hours on orbit, after which there appears to be a plateauing with slight downward slope, with some variability in the daily measurements. The variability may be related to circadian rhythm variations. This is not consistent with the ASTP data, where a subject showed only a 260 ml change from his launch minus 1 day volume at an MET of 0600 hours, reflecting only a 30% shift of his mean total inflight volume reduction of 900 ml. The repeated measurents of these three crewmembers at the various time intervals on the two missions gives one more assurance of accuracy. Of great interest is the source of shift.

The reduction in leg volume is not evenly distributed, with the mid-thigh losing more than 12% of its volume versus 9.4% from the lower leg. When the much larger volume of the thigh is considered, the importance of the upper leg can be appreciated; e.g., more than twice the volume was removed from the thigh versus lower leg (619 versus 278ml- see Table 5). Possibly of more interest than this removal is the replacement of fluid upon return to earth and the gravity environment. Landing and postflight data from Table 1 shows the inflight reduction in leg volume was not totally restored following landing and postflight. However, it does appear that the majority of volume return was complete within 1.5 hours after landing. On the Shuttle crewmembers there was a reduction of 381ml or 4.3% 1.5 hours after landing and 283ml or 3.2% postflight. Skylab and ASTP had higher landing volume reductions and similar postflight reductions. This phenomena was previously observed and the assumptions are that (A) fluid redistribution under 1-G is more rapid than loss in weightlessness (such an assumption is consistent with the difference in driving forces), and (B) the remaining volume deficit is lost tissue due to atrophic changes from deconditioning. As noted, there is considerable variation between subjects which could reflect variations in weight loss. No consistent and reliable prelaunch and landing crewmember weights are recorded. However, in personal conversations, the crewmembers usually note a 3 to 7 pound weight loss during the missions.

Because of medical confidentiality, it is not indicated on Table 1 which crewmembers experienced symptoms of Space Motion Sickness (SMS). However, it may be reported that 7 of the 11 subjects did experience SMS. There was no difference in the leg volume change in those with SMS (11.6% change) when compared to those without SMS (11.7% change).

CONCLUSIONS

This was a study of the inflight and postflight leg volume changes associated with spaceflight. The results of this study show that there typically is an inflight volume change of 2 liters in the lower extremities, 1 liter from each leg. The vast majority of this change appears to be a shift in body fluids, both intravascular and extravascular. The fluid shift occurs rapidly on Mission Day 1 (MD-1), being essentially complete by 6 to 10 hours. The regional origin of shift and leg volume change shows that a far greater absolute volume and percentage of the total change comes from the thigh as compared to the lower leg. Postflight, the return of fluid to the lower extremities occurs rapidly with the majority of volume return complete within 1.5 hours postlanding. There is a residual postflight volume decrement that is probably due to tissue loss secondary to atrophic deconditioning and weight loss.

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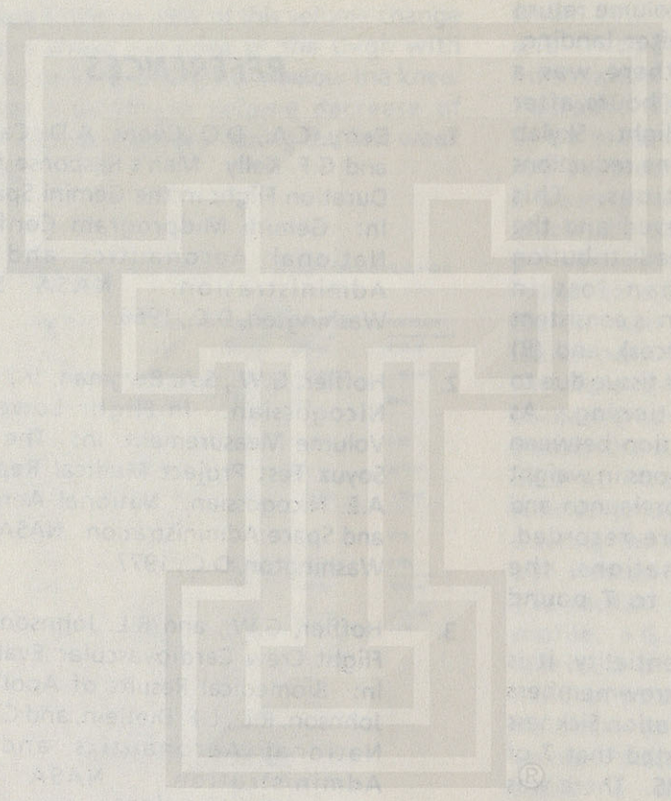

INFLIGHT HOLTER MONITORING

Investigators: Michael W. Bungo, M.D., and John B. Charles, Ph.D.

INTRODUCTION

The incidence of cardiac rhythm abnormalities during Space Shuttle Extravehicular Activities (EVAs) is about 40% in individuals who do not exhibit such abnormalities during equivalent preflight stresses. It was hypothesized that some aspect of the space flight EVA environment was the instigating factor. Potential candidates included: a physiological response to microgravity (including fluid volume loss due to diuresis and/or vomiting; uncorrected electrolyte imbalance due to diuresis and/or vomiting) which is detected only during EVA due to the lack of ECG information during other flight phases; a response to the EVA workload; a response to the EVA environment of pure oxygen at 4.3 p.s.i.; a response to other environmental factors, such as low humidity. Strenuous activities during previous U.S. manned space flights did not produce equivalent frequencies of arrhythmias, for reasons that are unknown. Therefore, efforts to document the current phenomenon are considered of operational importance.

PROCEDURES

Baseline responses to treadmill stress testing were recorded during the physical exams. In addition, the subject wore a Holter recorder for 24 hours at some time during the preflight period.

Training included maintenance and use of a Holter recorder, familiarization with the STS onboard treadmill and its accessories, and familiarization with the Operational Bioinstrumentation System ECG harness assembly.

As planned preflight, the proposed test procedures were to be as follows: During the last 24 hours inflight, the subject was to instrument himself with ECG electrodes, attach and activate the Holter recorder, and go about his normal activities. During this period, he was to don the Operational Bioinstrumentation System (OBS) harness, mount the treadmill, don the bungee restraint cords, and "stand" quietly on the treadmill for 5 minutes. He was then to exercise at 70-85% of his maximum heart rate for a period of about 30 minutes. Following the exercise period, he was to remove the OBS harness, stow the treadmill, replace any ECG electrodes loosened by sweat, and resume his normal daily activities.

The subject was to continue wearing the Holter recorder through deorbit preparations, landing, seat egress, and arrival at the medical facility for post-flight testing.

FLIGHT EVENTS

The subject attempted to perform the experimental protocol exactly according to the Medical Check List; however, because of real-time changes in the flight timeline and minor equipment malfunctions, the events are summarized as follows.

The Holter Monitor was placed as appropriate on the morning of the treadmill run. The treadmill test was begun according to established procedure. At the end of a twenty minute treadmill run, it was noted that the Treadmill Data Recorder was not functioning, and the recorder was recycled and began functioning correctly. Thirteen additional minutes of exercise were performed. Treadmill speed was approximately 2.5 m.p.h. during the duration of the run. After 9-10 minutes of exercise (a heart rate of 130-135 b.p.m.) it was noted that the pulse meter was not tracking well and the subject voluntarily increased his work load to 150-155 b.p.m. for the remainder of the thirteen minute exercise period. At the end of that flight day it was noted that the Holter Monitor had jammed and most of the data had been lost. A backup Monitor was donned and worn for the remainder of the

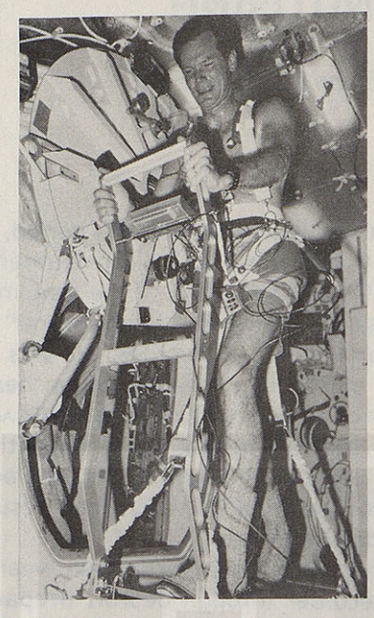

Figure 1. Subject performs an inflight treadmill stress test.

flight (shut off for a period of time because of a delay in landing) which included the entry profile. In all, 22 hrs. of recording were obtained on the inflight Holter Monitor and an additional exercise period as above recorded on the Treadmill Data Recorder. Two 24 hr. preflight Holter records were made as baseline data. All hardware discrepancies were investigated and corrected.

RESULTS

Preflight monitoring revealed a rare Ventricular Premature Beat (VPB) and rare Atrial Premature Beat. The inflight recording revealed four isolated VPBs during the recording period, and none during exercise nor entry.

CONCLUSIONS

There was no increase in ectopic activity in this crewmember during space flight and/or exercise in contrast to increased dysrhythmias seen during previous Shuttle EVA activities. This may be due to the natural variability between subjects or may relate more specifically to the particular environmental conditions unique to EVA. Further investigations are suggested.

NONINVASIVE ESTIMATION OF CENTRAL VENOUS PRESSURE USING A COMPACT DOPPLER ULTRASOUND SYSTEM

Investigators: John B. Charles, Ph.D., and Michael W. Bungo, M.D.

INTRODUCTION

The headward fluid shift encountered during space flight involves the redistribution of body fluids from the legs and abdomen into the thorax and head. This fluid shift is believed to initiate the cardiovascular read aptation syndrome (CRAS) of responses to space flight by stimulating arterial and cardiopulmonary sensors. The physiological responses to this stimulation may include reduction in plasma volume and resetting of cardiovascular reflexes controlling vascular volume and tone. These adaptive changes are appropriate for space flight, but inappropriate for life on earth after the space flight. The ability to counter those changes which are deleterious requires a complete understanding of the changes involved in CRAS, starting with a thorough documentation of the fluid shift and its effects. One means of tracking the fluid shift is by observing its effects on the central venous pressure (CVP), which is the filling pressure of the heart. A technique for the rapid, convenient and noninvasive estimation of CVP in space flight crewmembers would provide important insights into the reflex control of the cardiovascular system both in space flight and on earth.

METHODS

The method of Durr et al. (1) was used. Briefly, a small uni-directional vascular doppler flow detector was used to monitor the jugular venous blood flow while end-expiratory intrathoracic pressure was increased by partially occluded expiration. The intrathoracic pressure (mouth pressure, as indicated by a digital display on an electronic manometer) which transiently interrupted jugular blood flow was taken as an estimate of central venous pressure.

One crewmember was the subject for this experiment (Fig. 1). Preflight control measurements were made in the supine position at 34, 33, 31, and 10 days before launch. Inflight measurements were made at regular intervals during the first, second, third, fourth, and sixth days.

Figure 1. Subject performing an inflight CVP estimation.

RESULTS

The averaged values from each flight day are shown in Figure 2 [with the Spacelab 1 values from Kirsch et al. (2) for comparison]. The averaged values for each inflight data collection session are shown in Figure 3 (NB: the pressure axis is not corrected to cm. H_2O). Preflight supine values averaged about 4.2 cm. H_20. Inflight values were always lower than the

preflight average, and decreased over the first three flight days to their minimum, where they remained for the duration of the flight. Measurements during the first two flight days indicate an increase in CVP over the awake period; measurements from flight days 3-5 suggest a small increase followed by a pronounced decrease in CVP over the awake period.

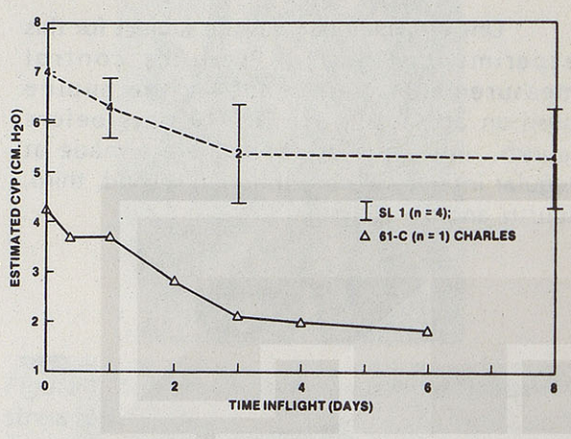

Figure 2. Estimated CVP during space flight.

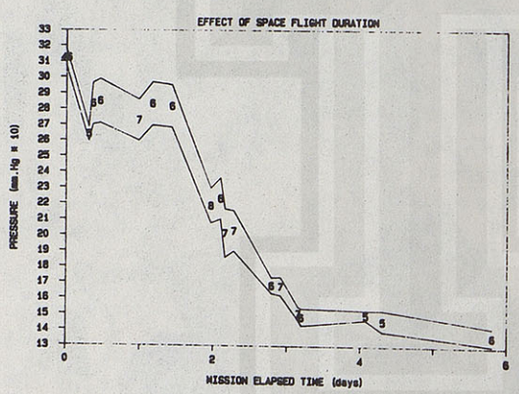

Figure 3. Jugular venous stop flow pressure.

DISCUSSION

The noninvasive estimates of CVP reported here for one subject parallel the average of the invasive measurements from 4 subjects during the Spacelab 1 flight, suggesting that the method has application for monitoring the time course of changes in CVP during space flight. The noninvasive data are of a smaller absolute magnitude than the invasive data, suggesting that the noninvasive technique is actually measuring a parameter directly related to CVP rather than CVP itself. However, the data of one of the Spacelab subjects are similar in magnitude, indicating that individual variability may explain the difference. Such an "offset" has not been detected in measurements on earth (1), but may exist during space flight. This hypothesis may be tested in a future space flight by comparing estimated CVP using the noninvasive method with CVP measured simultaneously using a right atrial catheter.

The applicability of this technique to repeated measurements will allow the testing of hypotheses regarding the acute and chronic redistribution of body fluids during space flight. For example, this flight data set suggests diurnal variations in CVP. A hypothesis (3) based on Skylab data is that inflight tolerance of lower body negative pressure (LBNP, which causes blood volume redistributions similar to standing upright) is higher in the morning than in the afternoon because the frequent use of the legs during the day for station keeping and propulsion causes a headward distribution of blood, prompting an acute decrease in leg interstitial fluid. LBNP stress during the afternoon sequesters some of the circulating volume in the "dehydrated" interstitium, decreasing the blood volume available for cerebral perfusion and reducing orthostatic tolerance. This hypothesis may be tested quickly and easily by the noninvasive estimation of CVP periodically throughout the waking hours. Similarly, the acute redistribution of fluid by exercise can be tracked by CVP measurements before and after treadmill exercise.

Another application is the determination of the influence of space motion sickness (SMS) on fluid volume adjustment. From the limited evidence to date, SMS may be associated with high levels of circulating antidiuretic hormone. Thus, afflicted individuals will retain fluid until they have adapted to space flight, while the unafflicted should begin diuresis soon after reaching orbit. These differences may be discernible in the time course of changes in CVP. Confirmation of this hypothesis could lead to new treatments for some of the effects of SMS.

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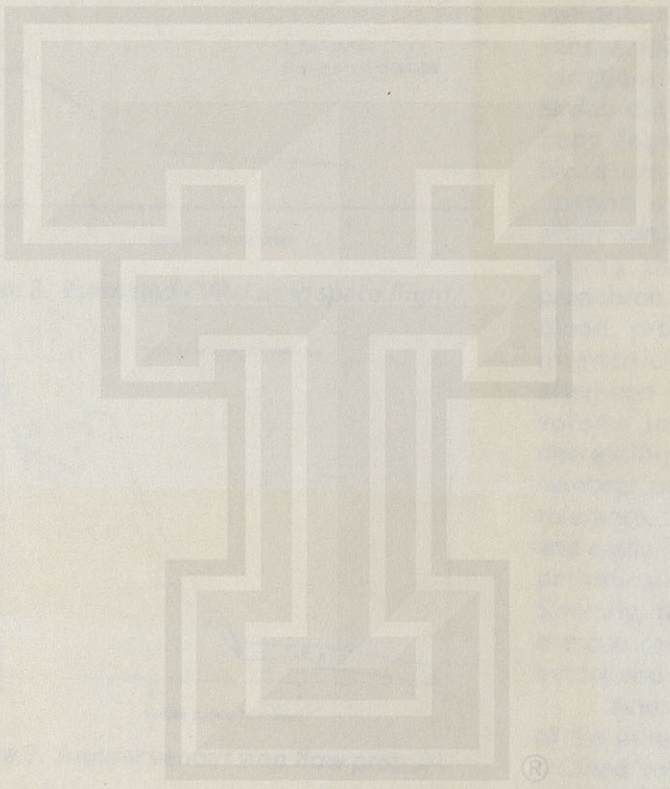
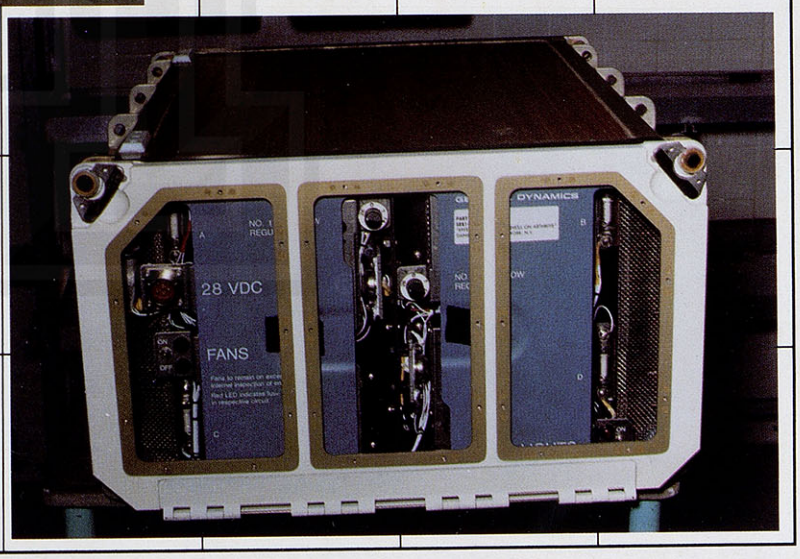
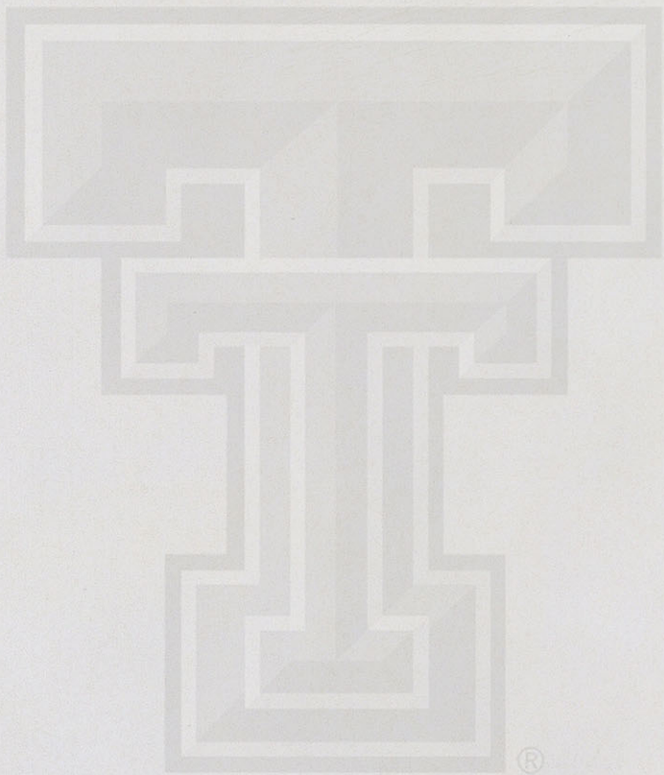


Section Three

Equipment Testing and Experiment Verification



One important function of the DSO program is evaluation of hardware prior to its use for a complex experiment. These photographs show the Animal Enclosure Module, a self-contained habitat for small laboratory animals that was tested as a DSO. The AEM fits into a standard Shuttle middeck locker (right).



ANIMAL ENCLOSURE MODULE INFLIGHT TEST

Investigators: Malcom C. Smith, Jr., D.V.M., Philip C. Johnson, M.D., and Adrian LeBlanc, Ph.D.

INTRODUCTION

"Verification of the Mid-deck Animal Enclosure Module (AEM)" was flown as a DSO to test the efficacy of the AEM in supporting healthy animals without compromising crew safety and comfort. This study represents the first attempt to fly animals in the crew compartment of a United States space vehicle, and ground testing was accordingly rigorous.

Ground testing and logistical support procedures for the DSO are described in two reports: JSC #18858, dated March 21, 1983, "Test and Implementation Plan for Verification of the Mid-deck Animal Enclosure Module for STS DSO-0421" and JSC #19204, dated July 15, 1983, "Logistical and Operational Support Requirements for DSO-0421".

DESCRIPTION

FLIGHT HARDWARE

The AEM was originally built to support a Shuttle Student Involvement Project (SSIP) experiment entitled, "Effects of Weightlessness on Arthritis." Modifications to the AEM for flight qualification and to improve its operation included:

1. Microbial filter material on the exhaust side of the cage was glued to the metal housing to overcome leaks which occurred as a result of stitching.
2. Improved the seal of the filter housing to the cage to prevent channeling and leakage around the housing.
3. Installed a microbial filter on the inlet side of the cage to prevent back flow of unfiltered air into the cabin.
4. Provided an air-tight seal of the Lexan covers of the filter areas and the animal habitation area.

The AEM was installed in a mid-deck locker in the Shuttle Orbiter. Operation of the AEM required a 28 v DC power supply to operate air intake/exhaust fans and interior lights. Otherwise, it was a self-contained system designed to maintain 6 adult rats (250-300 g each) for seven days.

Exhaust air filtration in the AEM was accomplished by a 4-layer filter system. Layers consisted of Fiberglass (H_3PO_4 treated), Activated Carbon (H_3PO_4 treated), Fiberglass (H_3PO_4 treated), and a microbial filter (0.3-.5 μ) held between two 6 mm wire grids. Make-up air was pulled into the AEM from the Orbiter mid-deck environment by four axial flow fans. Food for the full 7-day mission was provided by a solid bar of nutrients (Teklad autoclaveable rat diet). Water was provided from raw potatoes. The AEM was tested at JSC with 6 live rats, a combination of 2 live and 4 dead rats, and 6 dead rats. In each instance there were no objectionable odors detected by a panel of "smellers" in the exhaust gases after periods of 6 to 10 days of operation.

Testing to assure that the crewmembers would not be exposed to obnoxious or noxious odors and pathogenic microorganisms was accomplished. Inflight crew involvement in the experiment was limited to activating lights to maintain nominal circadian rhythms, a 10-minute video tape on days 2 and 5, and daily observation of animal behavior. At no time did the crew handle the animals outside of the AEM.

TEST ANIMALS

Six Specific Pathogen Free (SPF) male albino rats (Lewis Wistar strain), age 56 days and weighing approximately 275 g at launch were to be used for flight. A group of 6 controls and 6 flight back-ups were required. However, the animal supplier could not guarantee that the rats would be free of one of the microorganisms on the restricted list, *Klebsiella pneumoniae*. Therefore, it was determined that germfree

(cesarian derived and isolator reared) rats would be required in order to meet all of the microbiological requirements. These germ-free rats were stabilized with a "cocktail" of *Lactobacillus* spp 4 days prior to shipment from the vendor's facility to the Life Science Support Facility (LSSF) at Kennedy Space Center (KSC). Only 15 of the germ-free rats were available, and these were subsequently divided into one group of 6 flight animals, one group of 6 back-up flight animals, and one group of 3 controls.

FACILITIES AND PROCEDURES

Housing facilities preflight were provided by the KSC LSSF in Hanger L. Procedures for handling and maintaining germ-free animals at this facility are as specified by the Association for Laboratory Animal Science. Procedures and equipment at the KSC LSSF were consistently within specification and animal comfort and exposure to microbial contamination was not compromised.

Animals were received in the LSSF on 18 August 1983 (F-12 days). Physical exams and microbiological analyses were accomplished upon receipt, at F-5 days, and at F-18 hours.

RESULTS

Average pre- and postflight body weight changes in the flight animals and in the various controls, Table I, are not remarkable if taken as a whole. Flight animals lost an average of 11 g (3.7%) in side A of the cage or gained an average of 3 g (1.3%) in side B. Controls gained an average of 5, 29, and 2 g (1.7%, 11%, 0.6%). The flight rats failed to gain weight at their expected rates and some even lost weight while the ground based controls either gained weight as expected or gained slightly less than expected.

Flight rats were at a disadvantage in that their food supply was glued to the sides of the cage and was slightly more difficult to access than the food in the cages of the controls. Flight animals consumed an average of 175 g of food whereas controls consumed 223 g. Control group KSC-1 did not gain at the expected rate, probably due to the fact that this group was anesthetized for a blood sample on 8-30-83. Control group ARC-5 did not gain at their expected rate due to the fact that this group was disturbed by transfer from KSC to ARC, and they had no food supply for about 24 hours.

Gnotobiotic rats were used in this test for reasons previously mentioned. These animals were isolator reared and had not been handled since birth. Birth dates varied from 6-10-83 to 7-5-83 which resulted in a group of animals varying in age of from 46 to 81 days at the time of launch. Selection of the flight animals resulted in a "small" group of 3 weighing an average of 228 g each and a "large" group of 3 weighing an average of 293 g each.

Postflight examination of the flight animals revealed that they were in good physical condition. They were alert and were actively grooming themselves and each other. Their supply of water in the raw potatoes was exhausted on Side A and nearly exhausted on Side B. Their hair coat was slightly discolored and stained which was probably due to their inadvertent rubbing against the food bars in microgravity. Postflight examination of the cage and inflight video tapes indicated that the air flow through the cage was not great enough to quickly pull urine, feces, and debris out of the cage area and onto the exhaust filter grid. Therefore, coprophagy was not prevented.

Microbiological analyses of the flight animals, food supply, water supply (raw potatoes), and AEM were accomplished by microbiology laboratories at KSC and JSC. Complete results of these tests are contained in separate reports but there was good general agreement between the laboratories.

Preflight microbial testing of the animals yielded *Lactobacillus* spp as expected, but no organism on the exclusion list was found. Testing of the raw potatoes revealed a variety of organisms in spite of using ionizing radiation and a chlorine scrub to provide a sterile potato. The potato-borne organisms were not on the exclusion list.

Postflight microbial testing of the animals yielded two organisms in the animals which had not been recovered preflight. These were *Streptococcus vividans* and *Staphylococcus aureus*, and it is presumed that these organisms were introduced by the raw potatoes and/or by the lack of complete sterility of the AEM. These organisms were not recovered from the exhaust ports of the AEM, and this supports the contention that the AEM is an effective

microbial isolator and does not result in contamination of the external environment.

CONCLUSIONS

The AEM successfully maintained 6 healthy rats for the duration of the mission (6 days). Improvements in the water supply (to provide a margin of safety of at least 20%) and an increase in the rate of air flow through the AEM are highly desirable. The AEM can be used for a variety of flight experiments using small laboratory animals without impairing crew time, crew safety, and crew comfort.

Table I - Animal Enclosure Module (AEM)

Average Body Weight Change

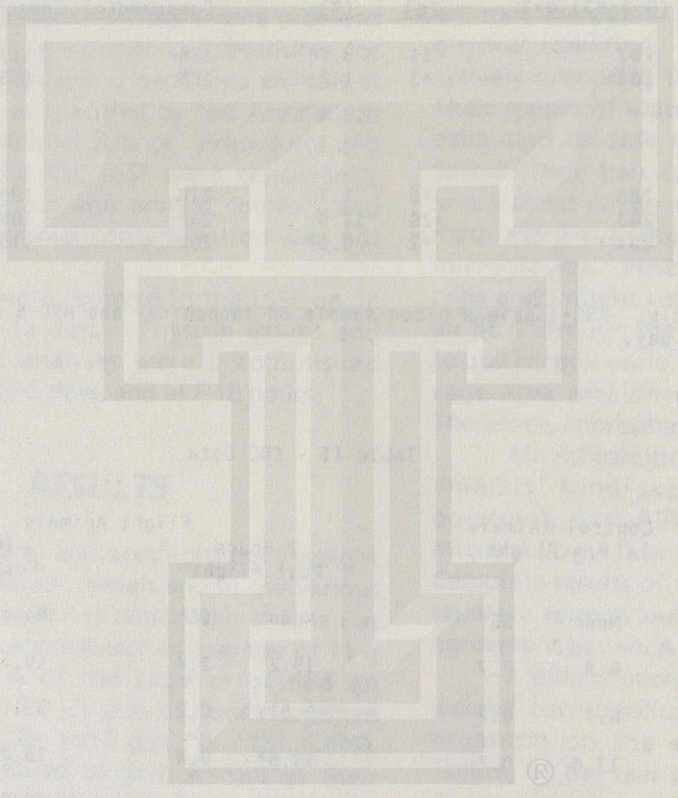
Flight	Preflight(g) (8-29-83) n=3	Postflight(g) (9-5-83) n=3	(g)	(%)	Food Consumed(g)	Potatoes Consumed(g)
Side A	293	282	-11	3.7	186	1170
Side B	228	231	+3	1.3	165	1162
Controls						
KSC-1	278	283	+5	1.7	216	1054
*KSC-4	264	293	+29	11.0	252	1059
ARC-5	292	294	+2	0.6	202	1155

* KSC-4 were true controls. KSC-1 gave a blood sample on launch day and ARC-5 were transported to NASA-ARC on launch day.

Table II - CBC Data

	Control Animals Pre Flight		Flight Animals 2 Hours Post Flight		Flight Animals 10 Days Post Flight	
	Mean	SE	Mean	SE	Mean	SE
WBC	9.8	0.7	15.2	2.4	10.5	0.4
RBC	8.7	0.2	9.8*	0.2	9.1	0.1
Hgb	17.6	0.2	19.6*	0.4	16.7	0.2
Hct	45.6	1.0	54.6*	1.5	48.3	0.4
MCV	52.2	0.3	55.9*	0.5	52.8	0.5
MCH	20.1	0.1	20.0	0.2	18.3*	0.2
MCHC	38.5*	0.4	35.8	0.3	34.6	0.4
Plt	539	59	752	42	600	
Retics	1.2	0.4	1.3	0.2		

* Significantly different from the two other means at the .01 level as determined by Analysis of Variance and Multiple Range Test



PROTOCOL/HARDWARE VERIFICATION OF THE SPACELAB-3 AUTOGENIC FEEDBACK TEST EXPERIMENT #3AFT23

Investigator: Patricia S. Cowings, Ph.D.

INTRODUCTION

A "pilot study" of the Spacelab-3 experiment, "A Preventive Treatment for Zero-Gravity Sickness" (#3AFT23), was flown as a DSO to examine the efficacy of inflight procedures planned for the subsequent formal experiment. There were three opportunities to speak to the one subject post-flight: a private, 2-hour debrief between the crewman and two of the investigators; a 2-hour public debrief, which was held by Johnson Space Center SBRI personnel; and a telephone conversation. A number of unforeseen problems arose inflight and were corrected for the subsequent flight after discussion of possible solutions with the crewman. The information obtained from this mission that was relevant to proposed changes in inflight procedures for the SL-3 mission is outlined below.

PROCEDURES / RESULTS

PREFLIGHT DONNING OF AFT HARDWARE AND EQUIPMENT CHECKOUT

The preflight donning procedures book developed for SL-3 was used. No modifications were recommended. Preflight donning of the Autogenic Feedback Test (AFT) hardware and STS garments took approximately 30 minutes for the one crewman. Participants in this study should perform this task while the flight crew receives their weather briefing. A maximum of 45 minutes to one hour may be needed for 4 crewmen as only two Ground Support Equipment units are available for "check-out."

URINE COLLECTION DEVICE (UCD) MODIFICATION TO THE AFT GARMENT

It was recommended that all crewmembers participating in this study allow a UCD modification for the AFT garments used during launch. The material of the flap may "bunch-up" in the crewman's back causing discomfort while seated in the launch chair. Further, the snaps on this flap prevent the garment from "riding-up" while the crewman sits in launch configuration. Lastly, this modification would save time post-insertion in that the crewman will not have to snap the flap into place while in zero-g (again, to prevent the garment from riding up).

AUTOGENIC FEEDBACK SYSTEM (AFS) ACTIVATION PRELAUNCH

The feedback display was carried to the Orbiter by close-out crew and handed to the crewman after seat ingress. The close-out crew turned the powerswitch of the AFS on before exiting the orbiter. It is recommended that at this time, the crewman follow the AFS activation cue card (mounted before each seat). However, after the unit is in "check-out mode" (refer to flight data file book, NOM-2, AFS activation) only one additional button push is required to start the tape recorder. It was strongly recommended that this final button push not occur until the L-10 minute hold. Because each tape operates for 7 hours, if all crewmen activated the recorder at the same time (i.e., L-10 minutes), it would then be possible to accurately time-line the cassette change on the first mission day (refer to Flight

Data File Book [FDFB], NOM-5). After this final button press, the crewmen should remove the display from their wrists and place them in FDFB pouches mounted on the sides of each launch chair: this location was chosen for its convenience and because the high vibration environment of launch might make the display fall off the wrist mount.

POST-INSERTION PROCEDURES

FEEDBACK DISPLAY

It was recommended that upon orbital insertion all crewmembers participating in this study remove the feedback display from the FDFB pouch on their launch chairs. Treatment subjects should re-attach the display to their cable harnesses at this time. Controls may place the display in a pocket. It became apparent that crewmembers should keep this display with them at all times while on shift. The display must be available for Treatment Subjects (i.e., feedback) and is used by all crewmen to input "events" to the recorder, (i.e., indicating the onset of symptom episodes if and when they occur). This display may also be kept in the AFS pouch pocket used for holding the belt.

MIDDECK PROCEDURES

Most of the following post-insertion procedures were practiced during a class held in the 1-g trainer. Input from the crew was welcomed, especially from those crewmen who had flown before. After consultation among the investigators, it was determined to be imperative to obtain continuous in-flight physiological monitoring. The first mission day was particularly important in this regard. Therefore, the requirement for reconnecting the AFS to the crewmember's cable harness within one hour post-insertion was maintained. The crewman indicated that tugging the underseat pouches (containing the AFS) may produce unnecessary head movements. He recommended that these may be avoided by unbolting the launch chairs from the deck, leaving them in the air (or velcroing them to the wall), and then removing the pouches. This procedure could also save time in reconfiguration activities performed post insertion. Further, if this procedure were done one chair at a time with crewmembers assisting one another, it could reduce the time required.

AFT FLIGHT DECK PROCEDURES

This procedure must be considerably modified to accommodate MS-1, located on the flight deck. Because this crewman is responsible for payload activation and must perform many of his tasks in the confined area of the flight deck, it may not be possible for him to attach his AFS unit for up to 5 hours post insertion. This would result in a significant loss of critical data to this experiment. Nominally, MS-1 remains in his launch seat until the completion of OMS-2 (approximately 42 minutes). Instead, it was recommended that he brace himself in the hatch to the right of his seat such that his head is level with the underseat pouches, remove the AFS from the pouch, and connect it to his cable harness during this time. Because of his location, this activity should not disturb other critical flight tasks underway. Further, the recommended changes to the AFS pouch/belt assembly (see below, E.1.) should facilitate his attachment of the AFS and enable his unimpeded performance of mission-related activities in the flight deck.

INFLIGHT OPERATION OF TIME-LINED AND SYMPTOM-CONTINGENT PROCEDURES

MODIFICATION TO AFS POUCHIBELT ASSEMBLY

There was no Spacelab flown on this mission and the subject crewmember was required to make numerous translations from the middeck to the flight deck. Because the hatch connecting the two decks was significantly narrower than the "tunnel" leading to Spacelab, the AFS unit tended to "hang-up" on obstructions. This necessitated his making twisting and turning motions - again unnecessary head movements. After discussion of this

matter with the crewman post-flight, it was agreed that this problem could be avoided by making the AFS pouch detachable from the belt while remaining connected to the cable harness. In this way, the AFS could be held above the crewman's head (or between his legs) during translation. If working in confined spaces, the unit could be attached to the bulkhead with velcro, while the crewman remained tethered. The crewman recommended that the shoulder strap be used in-flight because it stabilized the AFS unit. The size of the AFS unit did not impede his movement or performance of mission related activities while he was in a relatively open volume of space (middeck and flight deck), as he was able to slide the unit (on the belt) to his back, side, or front, if needed. It was also recommended that a square of velcro be placed on the AFS unit itself to facilitate battery change-out procedures (refer to FDFB, NOM-6).

EVALUATION OF THE "RING" TRANSDUCER

The crewman did not have any difficulty using his fingers and hands to perform mission-related activities. The ring transducer did not get in his way. It was recommended that SL-3 crewmen keep a roll of elastoplast tape in the Spacelab should it be necessary to re-attach the ring transducer for any reason. This type of tape did hold the transducer firmly in place.

USE OF WRITTEN PROCEDURES - FLIGHT DATA FILE BOOK AND CUE CARDS

Explicit detail is required in the FDFB and on cue cards. No matter how well trained, an individual may "forget" a critical step in one or more of the flight procedures. Examples of this are discussed below under Section G., Paragraph 1. "Use of Foot Restraints;" and Section H., "De-Orbit Prep."

USE OF DIAGNOSTIC LOG BOOK OR VOICE CASSETTE RECORDER

It was essential to the science of this investigation that crewmembers provide a subjective report of their malaise levels during time-lined and symptom-contingent episodes inflight. The crewman used a voice microcassette recorder to perform these tasks. He did use the diagnostic book as a "cue card" so that his reports used the standardized terminology of the diagnostic scale. It is recommended that the use of a written log or taped report be made a crew option. It was observed that one crewman (during an early SL-3 simulation), attached his voice recorder with velcro to his flight suit (left side of chest) so that it would be convenient for verbal reports.

PRE-SLEEP DOFFING PROCEDURES

Removal and stowage of the AFS hardware and garment proceeded within timeline allowances (less than 10 minutes). This crewman further reduced the necessary time by leaving his cable harness attached while removing the garment.

POST-SLEEP DONNING PROCEDURES

USE OF FOOT RESTRAINTS

Post-sleep donning required 45 minutes. This was largely due to: a. difficulty with the Basal Skin Resistance (BSR) cable snap lead (see below, paragraph 2, "Modification of BSR electrode snap leads"); and b. failure to use foot restraints during donning. Although this crewman (and two from SL-3) participated in a class on the KC-135 zero-g flights which documented the fact that use of foot restraints shortened donning time from 45 to 15 minutes, this procedure was not performed inflight. It was strongly recommended that foot restraints be placed permanently in the vicinity of the stowage lockers for SL-3, and that instructions to use these restraints be written into the flight

data file book. Further, use of restraints reduces unnecessary head movements which might be made while "floating as you dress".

MODIFICATION OF BSR ELECTRODE SNAP LEADS

The snaps on the disposable BSR electrodes worn on the crewman's wrist tended to tear off the electrodes and remain mated to the cable harness. This tended to slow down donning procedures as the crewman had to find an implement (i.e., screw driver) to remove the snaps. For SL-3, these BSR snap leads were replaced on the harness so that this would not occur.

PRE-STRINGING THE CABLE HARNESS

The crewman discovered that donning time could be reduced by attaching the cable harness to the AFT garment before putting it on. Appropriate changes to the FDFB were made.

PROPOSED MODIFICATION TO AFS GARMENT

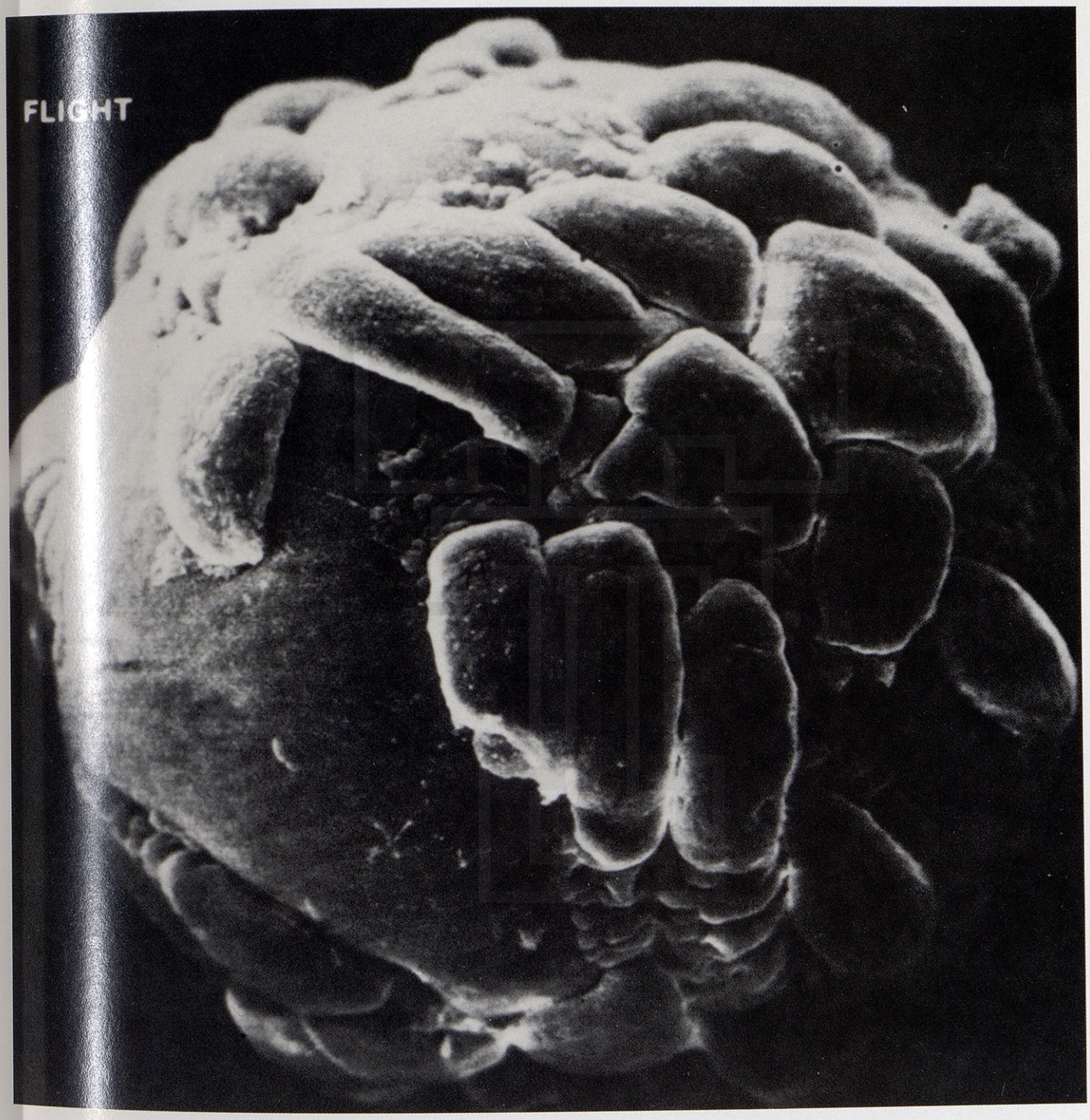
On the second mission day, the crewman noted that the garment felt uncomfortably tight, particularly in the abdominal region. He emphasized in his debriefing that he did not know if this was unique to himself or if others were likely to also feel discomfort caused by the garment. A possible solution to prevent the recurrence of the problem on SL-3 was to modify the AFT garment by inserting a second zipper on the right side (alternatively, the existing zipper could be modified to open from the bottom, rather than the top). This would loosen the fabric around the abdominal region and result in the loss of the abdominal respiration signal and relative respiratory tidal volume. However, the chest respiration gauge will remain intact and respiration rate will still be available as feedback to the treatment group crewmember. The experimenters would still be able to assess the effects of respiration rate on cardiovascular measures.

DE-ORBIT PREP PROCEDURES

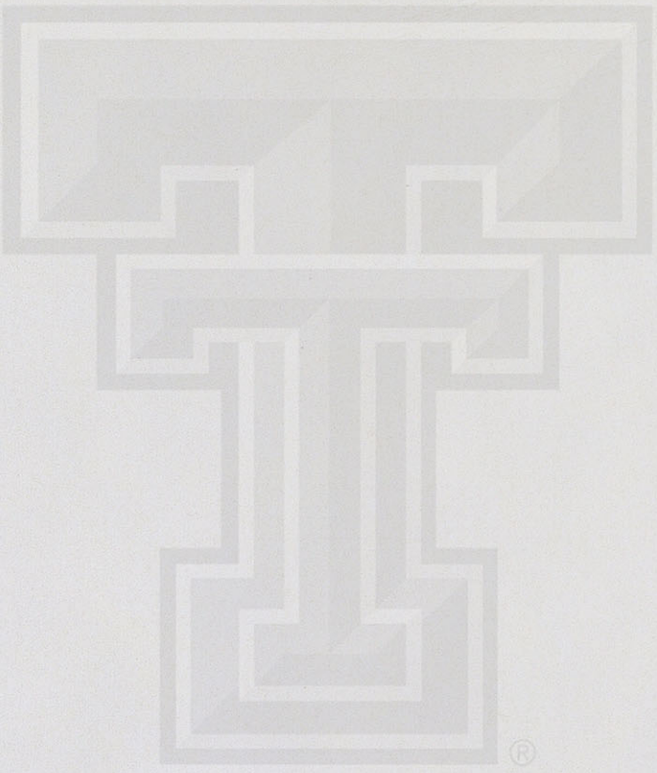
It was strongly recommended that a de-orbit prep check-list be written and followed carefully. The crewman took great care in his preparations for re-entry. This essentially amounted to performing post-insertion procedures in reverse (i.e., mounting the AFS under the middeck seat, and performing AFS activation). However, it was discovered that although the AFS worked as is should, no re-entry tape was made. It is believed that the crewman inadvertently failed to make the final button press (which starts the tape running) before he removed his wrist display.

In summary, the results of this mission were extremely valuable to the SL-3 experiment.

Section Four
Microbiology



Two DSOs were successful in demonstrating the attachment of cells to microcarrier beads in zero gravity, as is evident in this scanning electron photomicrograph. These findings have exciting implications for bioprocessing in space.



CELL ATTACHMENT IN MICROGRAVITY

Investigators: Dennis R. Morrison, Ph.D., and Marian L. Lewis, Ph.D.

INTRODUCTION

Before cells can be cultured in space for electrophoretic separation or as mini-factories for producing selected natural cell products such as urokinase, studies must be done to assess growth characteristics of cells in the microgravity environment. Human kidney cells survive and proliferate in culture only when attached to growth surfaces such as flasks or microcarrier beads. On STS-7, a very simple study was conducted with the objective to determine if cells could attach to microcarrier beads in microgravity. The experiment was conducted at ambient cabin temperature rather than at optimal conditions in a 37° C incubator since an incubator was not available for STS-7. The study was designed to simply demonstrate feasibility of seeding cultures in microgravity. A subsequent experiment in an incubator was performed as a DSO on STS-8 to investigate attachment and proliferation at 37° C.

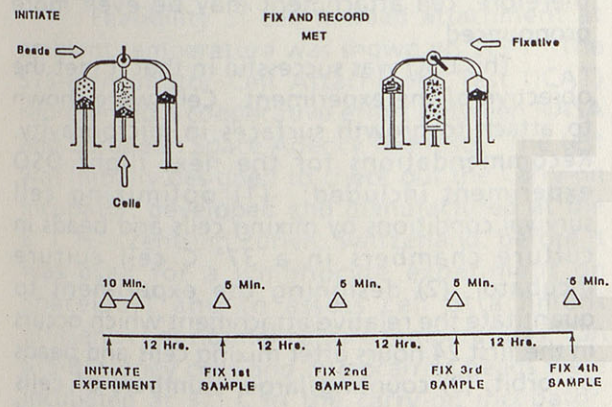


Figure 1. Cell attachment procedure.

PROCEDURES

Human kidney cells were maintained in four different syringe packs during launch. Early in the first day of orbit, beads were transferred into the syringes containing the cells. At 12 hour intervals, thereafter, fixative was added to a syringe according to the schematic procedure shown in Figure 1.

Figure 2a shows one of four cell bead packs. The pack consisted of an aluminum tray with a three-way valve attached to the tray and to three 5 ml syringes. One syringe contained the bead suspension, one contained cells, and

TABLE 1. MATERIALS

CELLS:	HUMAN EMBRYONIC KIDNEY (HEK)-(M.A. BIOPRODUCTS, USA)
GROWTH MEDIUM:	1:1:1 - MEM ALPHA, DULBECCO'S MEM, AND M-199 (GIBCO, USA) PLUS 10% FETAL CALF SERUM (BIOLABS, USA) AND OTHER CELL GROWTH SUPPLEMENTS
MICROCARRIER BEADS:	CYTODEX 3 - COLLAGEN COATED - (PHARMACIA, SWEDEN)
TRYPSIN-EDTA:	(GIBCO) 0.05% EACH IN Ca^{++} Mg^{++} FREE PBS
GLUTARALDEHYDE:	(TOUSIMAS, USA) DILUTED TO 2.5% IN DULBECCO'S PBS

GENERAL METHODS

PRE-LAUNCH	IN-FLIGHT (MICROGRAVITY)	POST-FLIGHT
1. TRYPSINIZE PRIMARY CULTURES 2. SUSPEND CELLS IN MEDIUM 3. SUSPEND BEADS IN MEDIUM 4. LOAD FIXATIVE SYRINGES	1. INJECT BEADS INTO CELL SUSPENSION 2. MIX BY SHAKING GENTLY 3. FIX AT SELECTED TIMES BY INJECTING GLUTARALDEHYDE	1 EVALUATE ATTACHMENT CELL/BEAD COUNTS (MICROSCOPE)

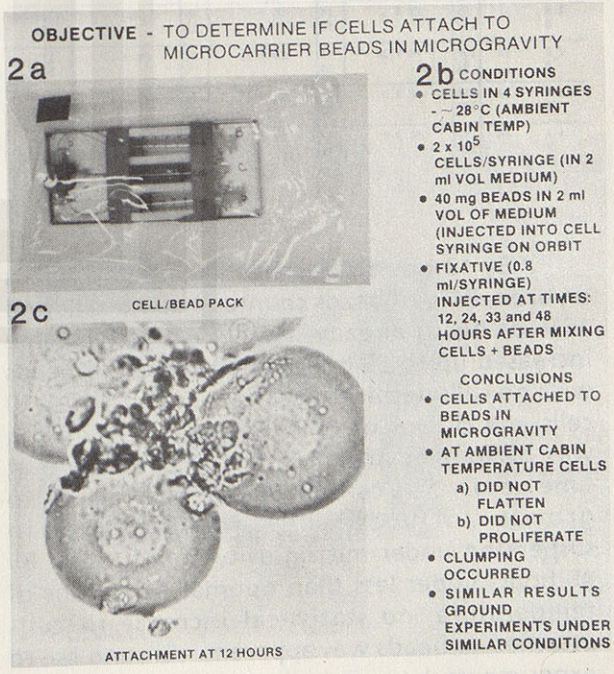


Figure 2. STS-7 cell/bead packs.