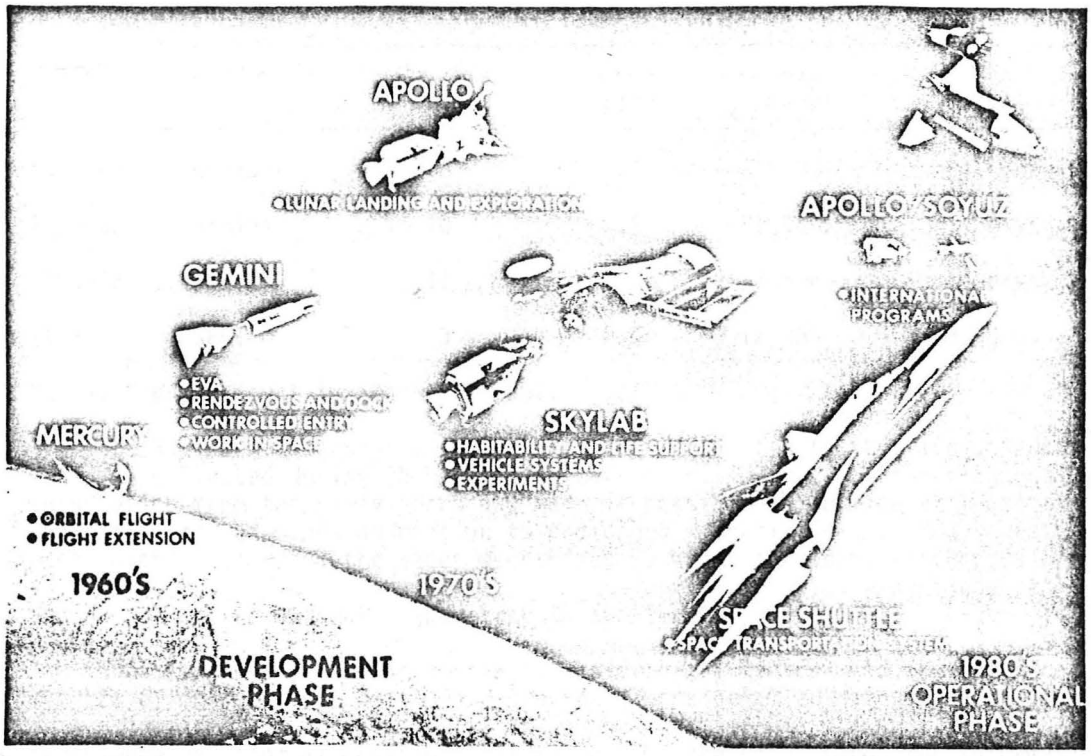
CARDIOVASCULAR

ADAPTATION TO ZERO GRAVITY



MEDICAL GRAND ROUNDS AT PARKLAND MEMORIAL HOSPITAL

JANUARY 15, 1976

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INTRODUCTION

The U. S. Manned Space Flight program was established in 1958. Shepard's initial 15 minute suborbital flight was accomplished in 1961. Various aspects of rocket engineering had high priority during the Mercury flights in the early 1960's. The Gemini program emphasized space mechanics and guidance engineering. The Apollo flights (1968-72) with lunar landings and exploration provided a wealth of material for the physical scientists.

Table I. Summary of U. S. Manned Space Flights

Year	Project	No. of Missions	Crew Size	Man Hours	Max. Duration
1961-63	Mercury	6	1	34	34 hours
1965-66	Gemini	10	2	1,940	14 days
1968-72	Apollo	11	3	7,506	14 days
1973-74	Skylab	3	3	12,351	84 days

Cumulative Man Hours in Space: 21,851.

The Skylab missions were in many respects dedicated to the life sciences. The data collected during these flights have clarified much of the fragmentary information from the early years and made it possible to outline at least the major features of man's adaptation to prolonged weightlessness. Many questions, particularly regarding the exact mechanisms by which the adaptive changes are accomplished, remain to be answered, but the combined Skylab experience still stands out as the ultimate experiment in applied human physiology.

This review will consider briefly the over-all medical and physiological aspects of manned space flight and provide a more detailed discussion of gravity as a determinant of cardiovascular function. The immediate impact of the space experience on clinical medicine is limited. On the other hand, the information gained during the Skylab flights have shed new light on basic mechanisms related to cardiovascular control and regulation of body fluids, and opened up exciting possibilities for the future with the vastly improved facilities for biomedical studies that will be part of the Space Shuttle program during the 1980's.

GENERAL MEDICAL AND PHYSIOLOGICAL CONSIDERATIONS

Salient medical and physiological data from the Mercury, Gemini, Apollo, and Skylab programs are now readily available. The present review is based on the following sources:

Murray, R.H. and McCally, M. (Eds.): Hypogravic and hypodynamic environments. Proceedings of a symposium held at French Lick, Indiana, June 16-18, 1969.

SP-269, NASA Scientific and Technical Information Office, Washington, D.C., 1971.

Johnson, R.S., Dietlein, L.F., and Berry, C.A. (Eds.): Biomedical Results of Apollo,
SP-368, NASA Scientific and Technical Information Office, Washington, D.C., 1975.

Johnson, R.S., and Dietlein, L.F. (Eds.):
The Proceedings of the Skylab Life Sciences Symposium, August 27-29, 1974.

JSC-09275, Vols. I and II, NASA TM X-58154, NASA Lyndon B. Johnson Space Center, Houston, Texas, 1975.

Weightlessness is the environmental stress of greatest concern during space flight. Several other stresses which are not unique to the space environment are superimposed, including exposure to ionizing radiation, temperature and humidity variations, unusual atmospheric composition with potential bacteriological and toxicological hazards, accelerations, noise and vibration, circadian rhythm disruption, and psychological stresses.

Crew health may be taken as a gross index both of man's ability to endure drastic environmental changes and the degree of success of the technology concerned with life support systems and environmental control. Overall, the manned space program has been highly successful but there have been catastrophies and near-catastrophies. There were three deaths prior to launch of the Apollo 204 mission 1967, at least partially attributable to an unfortunate combination of high-oxygen atmosphere and combustible materials. The final outcome of the exposure to noxious gases experienced during re-entry by the latest Skylab crew is still unknown. A serious explosion occurred during the Apollo 13 flight resulting in the loss of power and oxygen reserves but was handled without major clinical complications. The same was true for the failure of the temperature control systems during Skylab 2. The most alarming medical complications unrelated to hardware problems occurred during the Apollo 15 flight when one crew member had a brief period of frequent PVC's followed by a run of junctional bigeminy. A second crew member had 48 hours later a period of frequent supraventricular premature beats. Transient hypokalemia following a period of reduced potassium intake and heavy physical work with some heat stress were thought to be the immediate cuase, combined with latent coronary disease in one of these men who suffered a non-fatal myocardial infarction 2 years after the mission.

Medical problems that would be trivial under normal conditions represent potentially serious threats in space. A rigorous surveillance program of crew members and their primary personal contacts was instituted after the Apollo 12 mission and has greatly reduced the incidence of upper respiratory and gastro-intestinal infections during subsequent missions. The incidence of conditions requiring medical attention is apparent from Table II which lists the in-flight medical problems encountered in 33 astronauts during 7,506 manhours in space during the Apollo program.

TABLE II. Inflight Medical Problems in Apollo Crews

Symptom/Finding	Etiology	Number of Cases
Barotitis	Barotrauma	1
Cardiac Arrhythmias	Undetermined, possibly linked with potassium deficit	2
Eye irritation	Spacecraft atmosphere	4
	Fiberglass	1
Dehydration (Apollo 13)	Reduced water intake during emergency	2
Flatulence	Undetermined	3
Genitourinary infection with prostatic congestion	Pseudomonas aeruginosa	1
Headache	Spacecraft environment	1
Head cold	Undetermined	3
Nasal stuffiness	Zero gravity	2
Pharyngitis	Undetermined	1
Rhinitis	Oxygen, low relative humidity	2
Respiratory irritation	Fiberglass	1
Rash, facial, recurrent inguinal	Contact dermatitis	1
	Prolonged wearing of urine collection device (Apollo 13)	1
Skin irritation	Biosensor sites	11
	Fiberglass	2
	Undetermined	1
Seborrhea	Activated by spacecraft environment	2
Shoulder strain	Lunar core drilling	1
Subungual hemorrhages	Glove fit	5
Stomach awareness	Labyrinthine	6
Nausea, vomiting	Labyrinthine	1
	Undetermined (possibly virus-related)	1
Stomatitis	Aphthous ulcers	1
Excoriation, urethral meatus (Apollo 13)	Prolonged wearing of urine collection device	2
Urinary tract infection	Undetermined	1
Dysbarism (bends)*		1

*Also occurred during Gemini 10; later incidences were reported by the same crewmen five years after his Apollo 11 mission.

Psychological and psychodynamic in-flight problems were encountered, but none of major proportions despite the combination of considerable risks, extreme

mental and physical demands, and the confinement of 2 or 3 highly competitive individuals to cramped quarters for extended periods of time. The rigorous selection and training processes no doubt have produced a group of stable and highly motivated men.

Ionizing radiation and environmental effects on microbial flora and immunity were considered serious potential hazards early during the manned space flight program. However, the total radiation exposure even during the longest Skylab mission amounted to less than 2% of the established upper limits for lifetime exposure (dose equivalents of 400 rem for blood forming organs, 1200 rem skin, and 600 rem eye lens). Similarly, there were no changes in bacterial flora of clinical significance, nor were there any consistent humoral and cellular immunological effects.

EFFECTS OF PROLONGED WEIGHTLESSNESS

Exposure to prolonged weightlessness affects several organ systems. The most significant changes occur in the areas of body composition, including fluid and electrolyte balance, neurophysiology, musculo-skeletal and cardiovascular and pulmonary physiology. The Skylab flights were of much longer duration than the Mercury, Gemini, and Apollo missions. Furthermore, physiological changes recorded during and after the pre-Skylab flights must be viewed as representing the combined effects of weightlessness and a marked reduction in the level of physical activity. Skylab provided space and facilities for an extensive exercise program, and there is evidence that the deconditioning effects attributable to decreased physical activity were at least partially prevented.

Body Composition

It became evident early after both the American and Russian manned spaceflights that post-mission weight loss is a consistent feature also after flights of short duration. Skylab resources made it feasible to obtain in-flight measurements of body mass (which of course equals body weight at normal gravity). A device for measurement of inertia was employed.*

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*The mass to be measured is placed between two springs and constrained to linear motion in the plane of the springs. The mass is displaced from its resting position and released. The natural frequency of the oscillation that occurs after release is a function of mass (M) and the properties of the measuring device, i.e. $M=At^2$ where A is a constant and t the duration of a full cycle of oscillation. The accuracy of the body mass determinations obtained by this device was $\pm$ 1/4 pounds.

A typical series of body mass measurements (of the Skylab 3 pilot) appear in Figure 1. The average weight loss of the 9 Skylab crew members was 3.0 kg with a range of -5.2 to +0.2 kg from a mean weight at launch of 7 5 kg, i.e. a loss of 4.2 per cent which closely approximates the changes during the shorter Apollo flights (3.5 kg or 4.6 %).

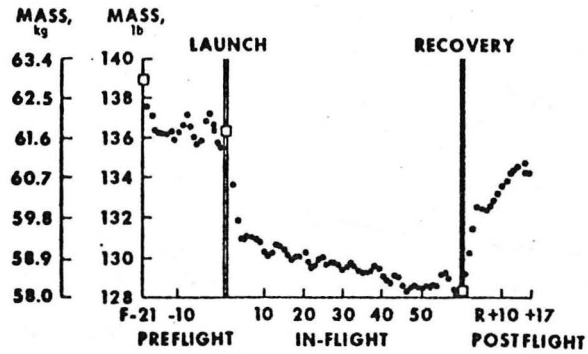


Figure 1. Body mass measurement of the Skylab 3 Scientist Pilot.

Anthropometric studies documented that the weight loss was associated with a redistribution of body mass. Figure 2 demonstrates a typical head-ward shift in the center of gravity during flight. Note that there was also a significant (3.5 cm or 2 per cent) increase in body height, presumably due to expansion of the intervertebral discs after unloading. Measurements of limb volumes (calculated from multiple circumferences utilizing Simpson's rule) demonstrated a combined leg volume loss of about 2 liters (Figure 3) with no change in arm volume.

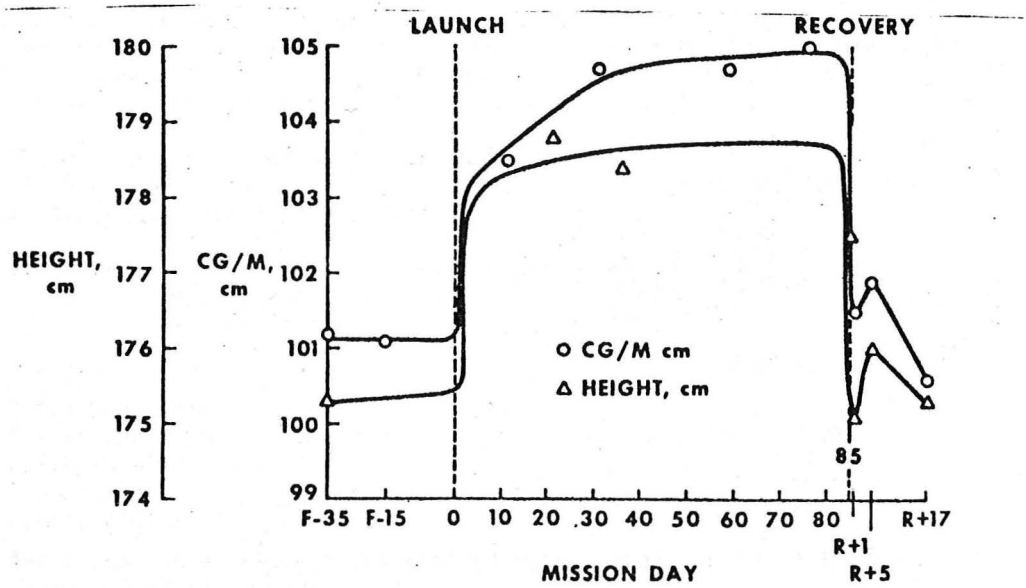


Fig. 2. Center of gravity/center of mass. Skylab 4 Pilot.

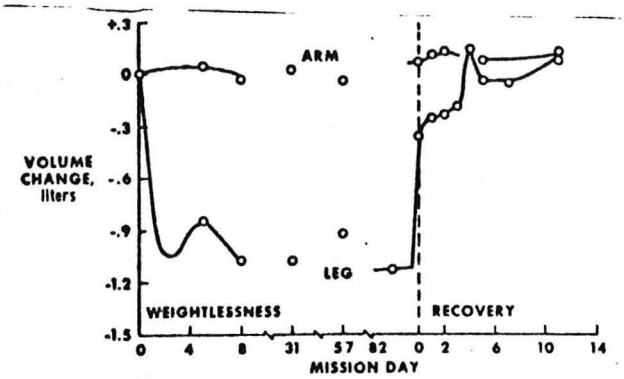


Fig. 3. Change in left limb volumes.
Skylab 4 Pilot.

The time course of these changes in-flight and after recovery clearly indicates that they mainly represent fluid shifts.

Biostereometric analysis, based on four-camera stereophotogrammetry, by which paired front and back body views are converted into area, shape, and perimeter plots of between 80 to 100 sections of different parts of the body, also confirmed a loss of leg volume in excess of the total body volume loss. Clinical observation also provided evidence for a head-ward fluid shift. Distended neck veins and puffiness of the face were consistent features.

Analysis of the time sequence of the changes in total body mass indicated that the weight loss had two components. There was a rapid loss of .5 to 2.5 kg during the first 3 days in space followed by a slow gradual decline in most crew members. This pattern was repeated in reverse order post-flight. The rapid loss almost certainly represented the loss of fluid while the slower component reflected a caloric deficit and some degree of muscle atrophy due to decreased demands, particularly in the legs. Fifty-two per cent of the total weight loss represented loss of lean body mass.

Changes in body fluid compartments and total exchangeable potassium as determined by radionuclide techniques in 9 crew members during the Skylab flights are summarized in Table III.

Table III. Effects on body fluid compartments and total exchangeable potassium. Post-flight change as per cent of pre-flight mean. N=9.

	Change, per cent
Total body water	- 1.7
Exchangeable potassium	- 6.4
Extracellular fluid	- 1.9
Plasma volume	-12.0
Red cell mass	-11.3 *

*No change in a ground level control group subjected to an identical sequence of blood withdrawal.

The changes in total body water and extracellular fluid were considerably less prominent that the changes in total body weight indicating a relative increase in body water content. The relative losses of exchangeable potassium, red cell mass, and plasma volume exceeded the decrease in total body weight.

A post-flight decrease in red cell mass has been a consistent feature. The average magnitude of change was -7% for the Gemini and Apollo missions. The largest change was seen during Apollo and Gemini missions utilizing a hypobaric (258 mmHg) atmosphere with 100% oxygen. However, the Skylab atmosphere contained 70% oxygen and 30% nitrogen at 5 psia which corresponds to a partial oxygen pressure of 175 mmHg compared to 159 mmHg in room air at sea level. Measurements of ^{51}Cr red cell half times and ^{14}C- glycine red cell mean life span during and after Skylab flights confirmed previous results from the Apollo program and provided new evidence for increased red cell destruction. Iron turnover rates were normal as were haptoglobin and bilirubin levels. The reticulocyte counts were low at recovery. Hematocrit did not change. A return to pre-flight levels of red cell mass was not achieved until approximately 30 days post-flight. Thus, the data suggest that the decrease in red cell mass was due to bone marrow inhibition.

Biochemical data relating to electrolyte and fluid balance are summarized in Tables IV, V, and VI. Changes in serum electrolytes were generally minor but calcium and phosphate levels showed small but consistent and significant elevations. Urinary excretion of calcium and phosphate, was also increased during the mission.

Plasma levels of aldosterone and angiotensin I (renin activity) were variable but tended to be lower than pre-flight toward the end of the mission and increased significantly after recovery. The opposite was true for cortisol.

Urine biochemistry demonstrated a decreased excretion of ADH and an increased excretion of aldosterone during flight based on pooled 1-month averages. Post-recovery measurements showed a significant increase during the first week in ADH and a decrease in aldosterone excretion relative to late in-flight levels.

Urinary excretion of sodium and potassium was elevated during the mission. Urinary volume decreased during the first 6 days in space in all nine crew members (average -400 ml), but there was an associated decrease in water intake of approximately 700 ml. Perspiration was not quantitated, but losses are likely to be high in the space craft environment.

The data on body composition, including fluids and electrolytes, may be summarized as follows:

1. Transition from 1 to 0g causes a rapid and significant head-ward shift of body fluids which is interpreted by the body as an increase in blood volume.

2. There is a rapid in-flight (within 3 days) loss of fluids and electrolytes resulting in a blood volume reduction.

TABLE IV.

SKYLAB SUMMARY, PLASMA BIOCHEMICAL RESULTS (9 Crewmen)

(Mean ± Standard Error)

NO.		CORTISOL µg/100 ml	ANGIOTENSIN I ng/ml per hour	ALDOSTERONE pg/100 ml	ACTH pg/ml	INSULIN µU/ml	HGH ng/ml	PTH ng/ml
39	Preflight	12.2±0.7	0.77±0.14	180±25	35.7± 3.3	17±0.6	1.3±0.2	17±1
	Mission Day							
9	3, 4	12.7±1.6	1.09±0.24	176±58	15.2± 4.9*	15±2	2.1±0.5*	17±2
8	5, 6	14.8±1.0*	1.75±0.42	163±75	26.5± 9.2	18±6	1.2±0.3	16±3
6	13, 14	13.4±1.7	.91±0.28	252±65	33.0± 8	18±3	1.5±0.2	14±1
6	20, 21	12.3±1.5	.52±0.12	163±90	11.9± 4*	8±1*	1.2±0.3	20±4
6	27, 30	13.6±2.1	.45±0.16	204±88	32.0± 7	20±3	3.2±2.0	14±2
6	38	13.7±1.0	.72±0.36	94±17	17.7±11.6	10±1*	1.1±0.3	15±2
6	45, 48	14.3±1.3	.37±0.10	118±7	12.1± 5.3*	9±2*	1.5±0.5	18±4
6	58, 59	13.5±0.7*	1.11±0.51*	148±31	32.3±18.7	9±2*	1.6±0.4	18±3
3	73	14.5±3.4	.27±0.08	117±39	6.5± 6.6*		0.6±0.1	24±2
3	82	16.1±0.6*	.32±0.04	142±17	8.7± 5.2		0.7±0.1	25±2
	Recovery (R)							
9	R+0	13.2±2.1	.71±0.23	215±74	23.8± 6.3	20±3	2.9±0.6*	17±2
9	R+1	10.8±1.0	2.15±0.55*	478±77*	24.0± 7.5*	20±2	2.8±0.8*	19±3
9	R+3, 4	13.7±3.0	.86±0.45	357±65*	23.3± 2.4*	18±2	2.6±0.8*	19±3
9	R+13, 14	10.6±0.7	.14±0.05*	153±35	38.2±13.9	17±3	1.2±0.2	18±4

* $p \leq 0.05$ Key: TV = Total volume
ACTH = Adrenocorticotrophic hormone
HGH = Human growth hormone
PTH = Parathormone

TABLE V. SKYLAB SUMMARY, PLASMA BIOCHEMICAL RESULTS, (9 Crewmen)

(Mean ± Standard Error)

No.		Sodium* meq/liter	Potassium meq/liter	Chloride meq/liter	Creatinine mg pct	Glucose mg pct	Osmolality mOsmoles	Calcium mg pct	Phosphate mg pct
36	Preflight	141±0.7	4.12±0.04	97.7±0.5	1.26±0.03	86.6±0.03	290±0.8	9.7±0.05	3.4±0.1
	Mission Day								
9	3, 4	139±2	4.26±0.08	96.8±0.7	1.31±0.03	90.3±2.4	289±1	10.4±0.1†	3.7±0.3
8	5, 6	137±2†	4.30±0.14	96.9±0.8	1.27±0.03	86.7±1.8	287±1†	10.2±0.1†	3.6±0.3†
6	13, 14	137±1	4.41±0.15	94.7±1.1†	1.28±0.03	86.7±1.8	286±2	10.2±0.1†	3.9±0.3†
6	20, 21	140±1	4.25±0.11	95.7±0.8	1.35±0.03	87.0±1.8	289±2	10.1±0.2†	3.4±0.1†
6	27, 30	138±0.8†	4.25±0.10	95.2±0.8†	1.27±0.03	84.3±2.3	287±2†	10.4±0.1†	3.9±0.3†
6	38	136±2†	4.05±0.15†	93.5±1.2	1.31±0.07	80.1±2.5†	280±4†	10.1±0.2	3.1±0.5†
6	45, 48	137±2†	4.30±0.13	94.5±0.7	1.34±0.03	84.4±1.4†	287±3	10.1±0.1†	3.8±0.1†
6	58, 59	137±2†	4.19±0.13	94.0±1.5	1.38±0.12	81.8±2.2†	286±4	10.1±0.2†	3.8±0.2†
3	73	139±2	3.75±0.20	94.6±1.2	1.51±0.05	80.9±2.2	284±2	10.1±0.3	3.9±0.2†
3	82	137±0.6	4.19±0.06	95.8±0.2	1.54±0.03	81.0±1.2†	285±2†	10.1±0.1	3.6±0.1
	Recovery (R)								
9	R+0	139±1	4.18±0.05	96.2±1.0†	1.28±0.05	100.5±2.6†	289±1	10.0±0.1†	3.9±0.2†
9	R+1	139±1	4.10±0.08	96.4±1.0†	1.31±0.06	92.3±2.8	289±1	10.1±0.1†	3.6±0.03†
9	R+3, 4	139±1	4.02±0.13	96.9±1.0	1.26±0.06	90.5±1.4†	294±2†	9.8±0.1	3.4±0.2
6	R+14	141±0.8	4.05±0.05	97.7±1.6	1.33±0.09	85.4±0.7	289±2	9.4±0.1†	2.8±0.2

* Corrected for Na-EDTA
† $P \leq 0.05$

TABLE VI.

SKYLAB SUMMARY, URINE BIOCHEMICAL RESULTS (9 Crewmen)

(Mean ± Standard Error)

UNITS		PREFLIGHT DAYS	IN-FLIGHT DAYS 1-28	29-59	60-85	POSTFLIGHT DAYS 1-6	7-13	14-18
meq/TV	Sodium	160.0± 3.0	174.0± 3.0	190.0± 7.0	199.0± 6.0	121.0±11.0	170.0± 6.0	173.0± 11.0
meq/TV	Potassium	74.0± 1.0	82.0± 2.0	80.0± 2.0	81.0± 3.0	65.0± 4.0	76.0± 4.0	82.0± 5.0
meq/TV	Chloride	148.0± 4.0	162.0± 5.0	177.0± 6.0	180.0± 5.0	116.0±11.0	160.0± 6.0	164.0± 11.0
mg/TV	Creatinine	1955.0±20.0	2079.0±40.0	2104.0±55.0	2081.0±31.0	2005.0±95.0	2037.0±78.0	1969.0±109.0
mOsmoles	Osmolality	650.0±17.0	789.0±27.0	791.0±19.0	717.0±24.0	593.0±60.0	549.0±49.0	584.0± 66.0
meq/TV	Calcium	8.0± 0.2	14.4± 0.8	14.5± 0.8	11.8± 0.4	11.2± 1.6	8.8± 1.0	8.3± 1.0
mg/TV	Phosphates	1045.0±15.0	1270.0±27.0	1196.0±35.0	1181.0±30.0	934.0±55.0	1029.0±55.0	1031.0± 50.0
mg/TV	Uric Acid	969.0±15.0	899.0±22.0	934.0±38.0	884.0±33.0	884.0±41.0	929.0±50.0	942.0± 53.0
meq/TV	Magnesium	8.9± 0.1	10.8± 0.2	9.4± 0.4	8.7± 0.5	7.7± 0.5	9.1± 0.4	9.1± 0.4
µg/TV	Cortisol	54.3± 4.1	94.4± 4.8	83.6± 4.0	90.2± 5.3	69.5± 5.8	63.3± 6.0	76.6± 8.0
µg/TV	Aldosterone	11.3± 1.1	32.8± 2.2	22.4± 1.7	30.0± 3.1	18.6± 4.3	11.8± 3.0	11.4± 3.3
µg/TV	Epinephrine	27.2± 4.6	24.3± 1.4	21.3± 1.7	38.1± 3.3	37.2± 3.1	33.7± 3.4	37.5± 7.2
µg/TV	Norepinephrine	69.4± 6.0	59.9± 2.0	66.7± 4.0	65.2± 6.4	99.4± 6.2	88.8± 6.4	89.6± 6.6
mµ/TV	Antidiruretic hormone	50.3±10.0	41.9± 4.3	24.1± 2.4	20.3± 2.5	46.5±10.0	25.6± 8.0	31.0± 8.2
mg/TV	Total 17 Hydroxycorticosteroids	6.1± 0.4	6.2± 0.4	6.5± 0.3	6.2± 1.0	5.2± 0.5	5.1± 0.4	5.2± 0.8
mg/TV	Total 17 Ketosteroids	7.0± 0.5	10.3± 0.4	10.8± 0.5	13.5± 1.3	7.0± 0.7	7.4± 0.5	7.6± 0.6

3. In-flight biochemical data, including plasma and urinary hormone levels, do not provide conclusive evidence regarding the mechanisms causing blood volume reduction. There were significant variations in fluid and electrolyte intake and probably high sweat losses, which are likely to compound the effects of the sudden exposure to zero g. Furthermore, transient changes in hormone and electrolyte levels may have gone undetected. Data from the initial 2 days in space, which may have been crucial, are incomplete.

Neurophysiology

The most significant neurophysiological changes during the Skylab missions were (a) overt motion sickness in several crew members during the first few days followed by a well-documented increased tolerance to motion as measured by rotation and head movements, and (b) post-flight hyperreflexia.

The mechanism precipitating the initial symptoms of motion sickness - which have also been reported from earlier U. S. and Russian flights - is unknown. It is possible that the central fluid shift caused transient increased pressure in the vestibular system. It is also evident that the otolith function is profoundly affected by the loss of gravity and that an adaptation occurs during flight. This adaptation was also reflected by a significant post-flight decrease in postural stability. The crew members also complained that walking represented a conscious effort during early recovery and that turning corners was particularly difficult. Mechanisms causing post-flight hyperreflexia are also unknown, but possibly related to increased strain and stretch of postural muscle after a period of disuse.

Musculo-skeletal physiology

Losses of calcium, phosphate, and nitrogen were observed during the Skylab flights and they were comparable to those recorded during bed rest studies of similar duration. Calcium was lost at a rate of 6 grams or (0.5 per cent of total body calcium) per month.

The mineral content of os calcis and right distal radius and ulna was measured pre-and post-flight using gamma ray absorptiometry. There were no changes in the upper extremity and only 3 of 9 crew members demonstrated losses of more than 1 per cent of the os calcis mineral content. These data indicate that missions of 8 to 9 months' duration should be safe even in the absence of any effective preventive measures. The nitrogen losses reflected a significant loss of muscle tissue which also resulted in a loss of muscle strength as illustrated in Figure 4.

Cardiovascular and pulmonary physiology

Extensive pulmonary function tests before and after missions failed to reveal any significant changes. The only in-flight measurement was of vital capacity which showed a decrease approximating 10 per cent, probably reflecting an upward shift of the diaphragm.

Cardiovascular dimensions and myocardial function. Decreased post-flight cardiothoracic diameter ratios were seen following the Mercury, Gemini, and Apollo missions, and the Skylab studies also demonstrated a significant decrease in systolic and diastolic radiographic heart size measured as frontal plane area

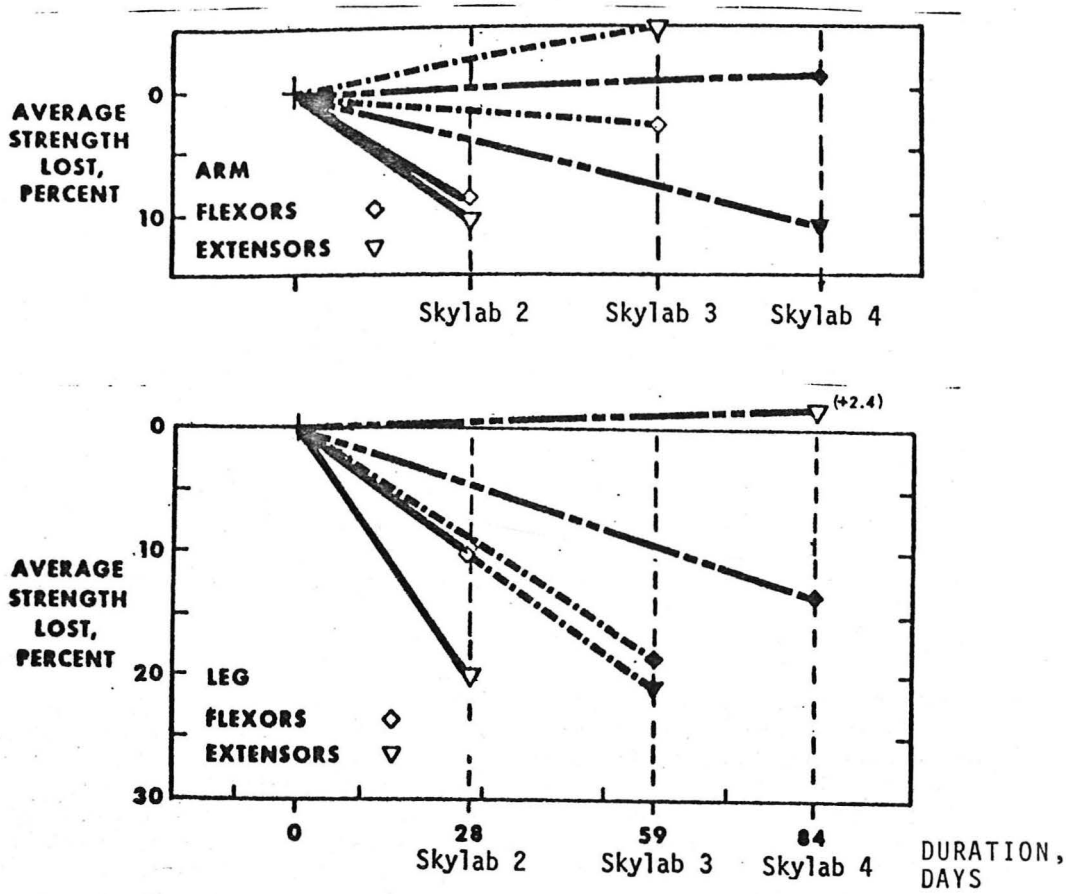


Fig. 4. Changes in muscle strength.

and diameters. The magnitude of change, translated into volume, was approximately 10 per cent.

Echocardiographic studies of the Skylab 4 crew confirmed the radiographic studies. Mean left ventricular end-diastolic volume decreased by 10 per cent. There was no change in septal or left ventricular posterior wall thickness implying that left ventricular mass also decreased. Cardiac dimensions returned to pre-flight levels within 30 days. Echocardiographic studies performed at rest and during lower body negative pressure pre- and post-flight were employed to derive ventricular function curves. A classical Starling curve relating stroke volume to end-diastolic volume is illustrated in Figure 5. The absence of any post-flight changes in slope or intercept is consistent with an unaltered contractile state.

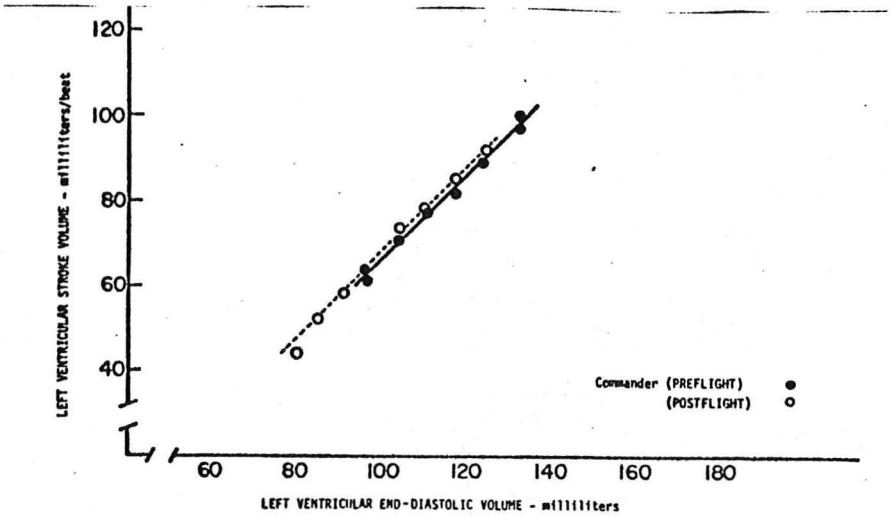


Fig. 5. Ventricular Function Curve, Commander of Skylab 4.

Cardiovascular response to stress. The impact of zero gravity on the integrated function of the cardiovascular system may be judged from the results of exercise tests and exposure to lower body negative pressure. Both procedures were performed in-flight during the Skylab missions. The exercise test provides data on the circulatory system's ability to satisfy an increased peripheral oxygen demand and an indirect estimate of maximal stroke volume and cardiac output. Application of lower body negative pressure causes venous pooling in the legs with a decrease in central blood volume and produces a circulatory response similar to the response to a transition from supine to standing position at normal gravity.

The results of exercise tests before, during, and after the Skylab missions are summarized in Figures 6, 7, and 8. Figure 6 demonstrates heart rate during bicycle exercise at a work load level corresponding to 75 per cent of pre-flight maximal oxygen uptake. Six of 9 crew members had significant post-flight heart rate increases, implying reduced stroke volume and reduced physical work capacity. By contrast, only 1 of 9 crew members had an elevated exercise heart rate during flight indicating that the exercise capacity was maintained in space. Post-flight measurements of cardiac output and stroke volume (Figures 7 and 8) demonstrated significant reductions.

Figures 9 and 10 demonstrate typical in-flight changes in the response to lower body negative pressure (LBNP). LBNP of -40 to -50 mmHg is the equivalent of a change from supine to standing position or a 90° head-up tilt. The control experiment shows a moderate increase in heart rate of about 15 beats per minute and only minor blood pressure changes. Leg volume increased by 3.5 per cent or by about 600 ml. suggesting a decrease in circulating blood volume of similar magnitude. The response to LBNP on mission day 6 includes a heart rate increase of more than 40 beats per minute, and a significant fall in systolic and diastolic blood pressures. The increase in leg volume was also much larger, 6 per cent, consistent with pooling of about 1,000 ml. The larger leg volume change suggests an increased vascular compliance. Pletysmographic measurements provided further evidence for an increase in vascular distensibility, but heart rates tended to be higher in-flight and blood pressures lower for any given level of venous pooling.

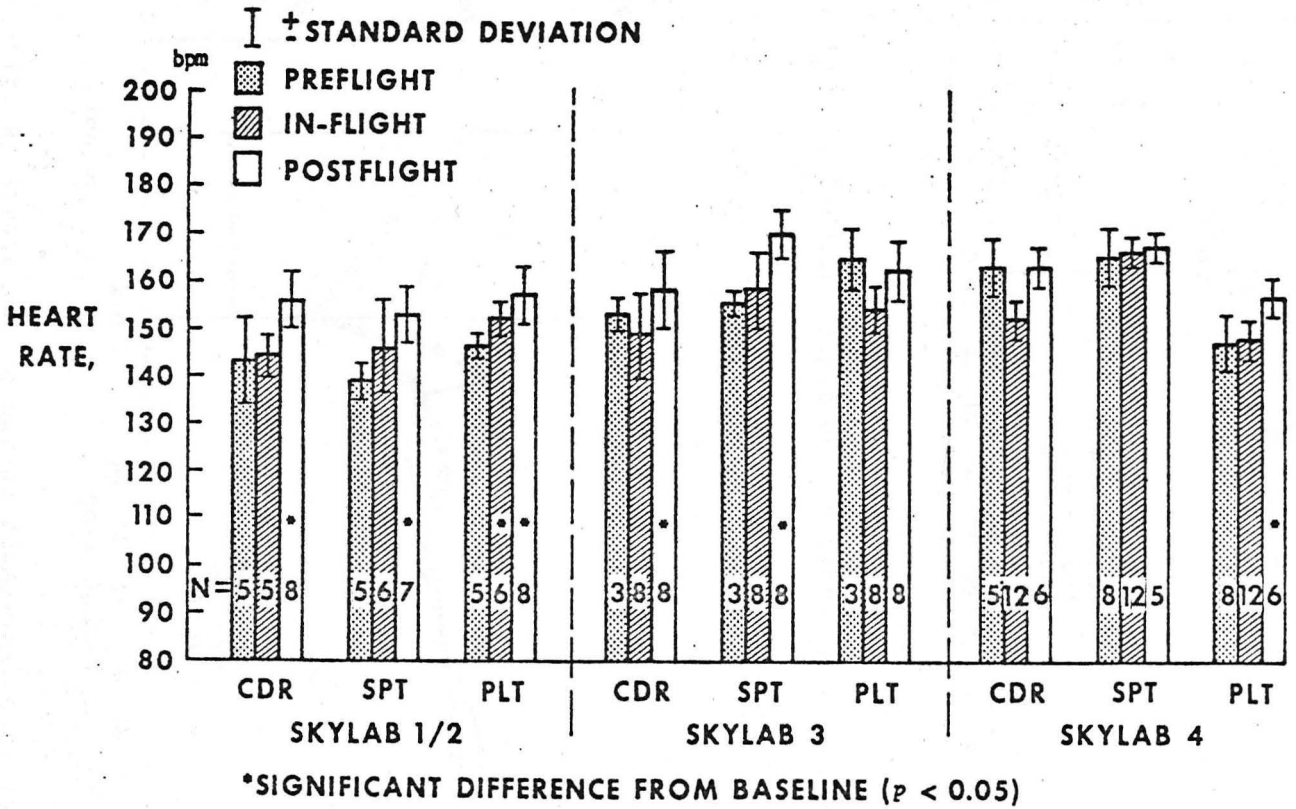


Fig. 6. Heart rate during exercise at a level corresponding to 75% of pre-flight maximal oxygen uptake.

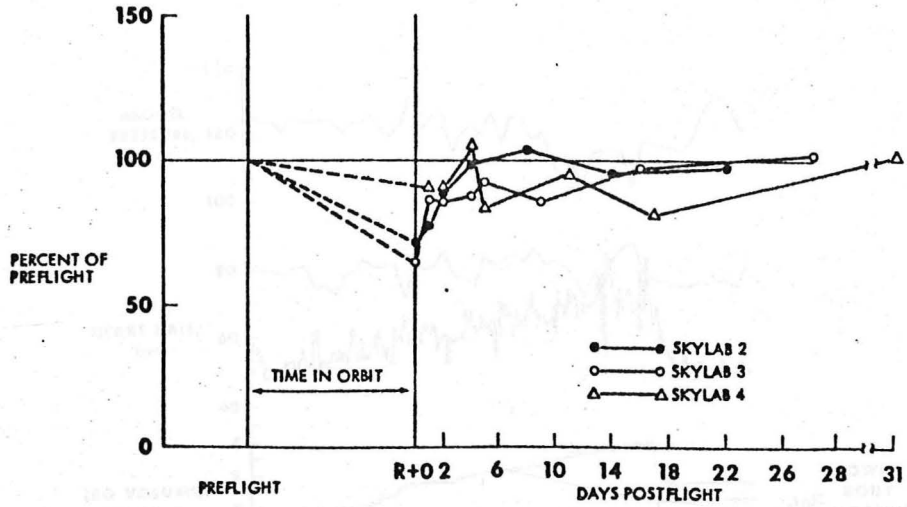


Fig. 7. Cardiac output during submaximal exercise.

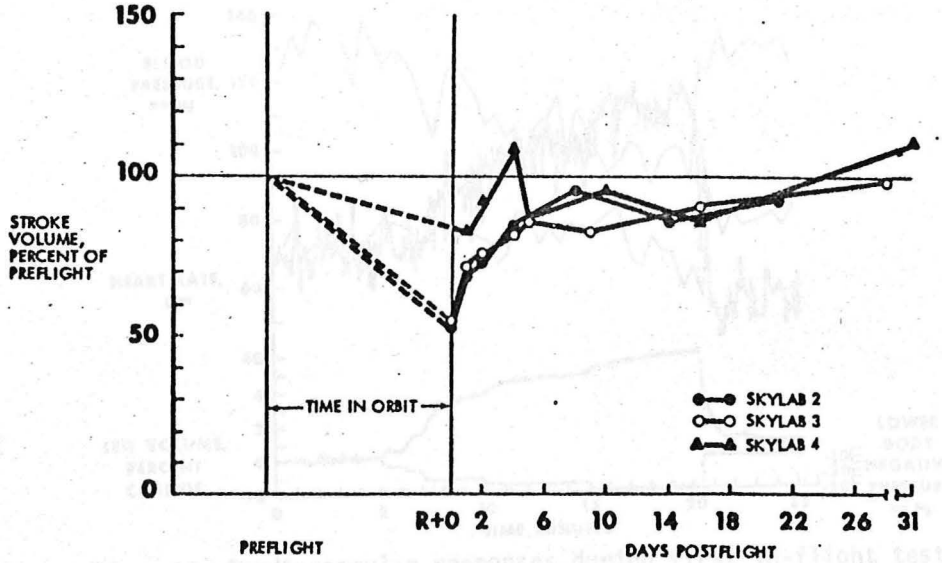


Fig. 8. Stroke volume during submaximal exercise.

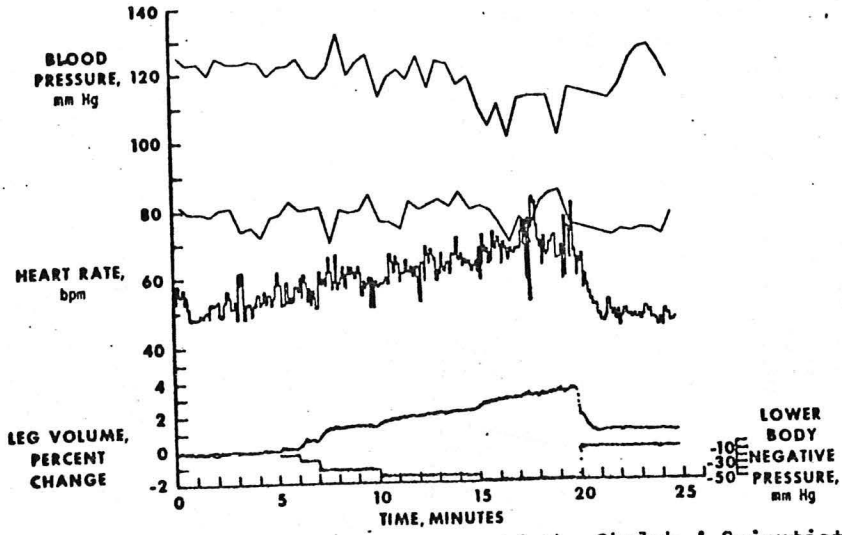


Fig. 9. Cardiovascular responses of the Skylab 4 Scientist Pilot during test 21-days prior to flight.

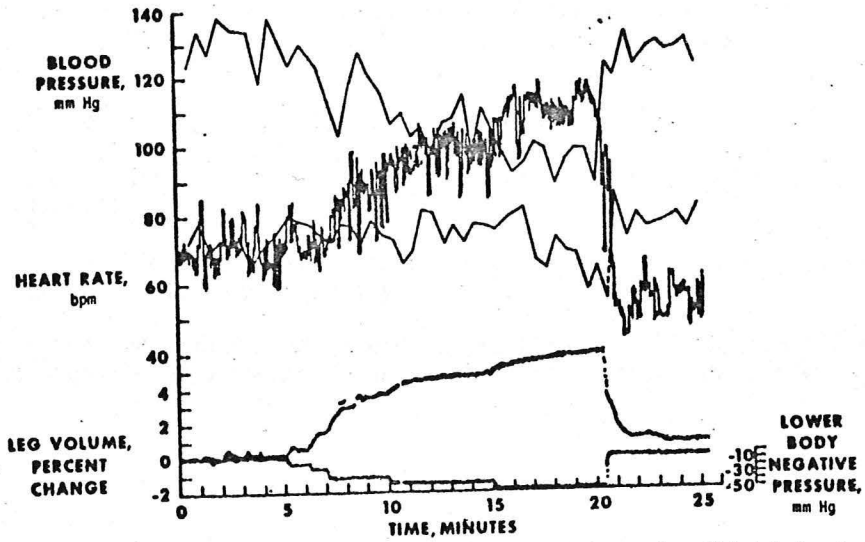


Fig. 10. Cardiovascular responses during first in-flight test of the Skylab 4 Scientist Pilot on mission day 6.

In-flight heart rates at rest and during LBNP during the Skylab 4 mission appear in Figure 11. A decreased orthostatic tolerance was manifest at the first in-flight test on mission day 5. There was no progressive deterioration. Rather, orthostatic tolerance tended to improve somewhat toward the end of the mission. Skylab 3 and 4 crews returned to pre-flight response patterns within 5 days and the Skylab 2 crew within 21 days.

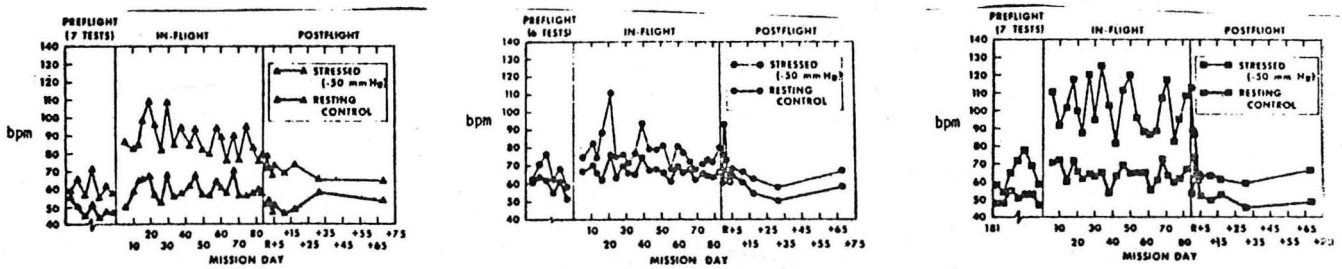


Fig. 11. Heart rate at rest and during lower body negative pressure at -50 mm Hg. in Skylab 4 crew members.

Decreased post-flight orthostatic tolerance has been a consistent finding in both Russian and American astronauts. The duration of the flight does not seem to be a major determinant of the degree of post-flight abnormality. Significant changes were observed also after the 9-hour Mercury 9 flight, and post-flight changes after the Gemini and Apollo missions were of the same order of magnitude as after the much longer Skylab flights.

Thus, the Skylab cardiovascular studies demonstrated:

1. Decreased post-flight heart size without any measureable effects on contractility.

2. Early in-flight decrease in orthostatic tolerance, rapidly reversible after return to normal gravity.

3. Exercise performance maintained at pre-flight levels during the mission but significantly impaired during the early post-flight period.

SUMMARY OF SKYLAB FINDINGS

The Skylab experience demonstrates that man can adapt to weightlessness and function effectively in space for prolonged periods of time. A large volume of data on body composition, fluid and electrolyte distribution, and cardiovascular function indicates that sudden exposure to zero gravity is associated with a rapid and significant central fluid shift. This shift is apparently sensed by the body as an increased intravascular volume. Compensatory mechanisms are activated and cause a decrease in blood volume. The absence of any in-flight changes in exercise capacity indicates that the contracted blood volume is an appropriate adaptation to zero gravity. However, this adaptation becomes inappropriate upon return to normal gravity. Post-flight circulatory measurements demonstrate decreased orthostatic tolerance and decreased exercise capacity and are consistent with a hypovolemic state. Changes in vascular compliance also occur in space, suggesting that there are further adaptive changes affecting cardiovascular reflexes and control mechanisms.

The data from the Skylab missions combined with the previous experience from manned space flights provide striking evidence for gravity as an important determinant of cardiovascular function. It seems pertinent to review in more detail the various mechanisms which counteract the effects of gravity on the cardiovascular system and maintain an adequate cardiac output and tissue perfusion during orthostasis.

EFFECTS OF GRAVITY ON THE CARDIOVASCULAR SYSTEM

Gauer and Thron (1965) have pointed out that clinicians and physiologists for generations have held that the recumbent position represents the physiological baseline while the erect position spells stress and danger, requiring immediate regulatory measures to prevent a circulatory crisis. On the contrary, they suggested, since normal man spends more than 2/3 of his day standing, walking, or sitting, it would be more reasonable to consider the upright position as the physiological resting posture. Blood volume and basic vascular tone are adjusted to provide adequate cardiac filling pressures and tissue perfusion in the upright position.

The fact that significant cardiovascular functional impairment is produced in normal subjects by prolonged space flight and prolonged bedrest, i.e. by conditions that eliminate or minimize the effects of gravity on the body, provides powerful support for this view.

The control mechanisms involved in the adaptation to changes in posture may conveniently be analyzed within the framework of intravascular pressure. Pressure at any point in the cardiovascular system has three components:

1. Hydrostatic pressure generated by the force of gravity.

2. Static filling pressure of the resting circulation which is the pressure measured immediately after sudden cardiac arrest. This pressure provides a measure of degree of filling of the cardiovascular system (mean circulatory filling pressure).

3. Dynamic pressure determined by flow and resistance to flow and dominating arterial hemodynamics.

Hydrostatic pressure

In the standing position with relaxed leg muscles venous pressures in the leg are equal to the height of the blood column extending from the point of measurement to a level near the right atrium. Right atrial pressure falls by a few centimeters of water upon transition from supine to standing position and the pressure in the neck veins drops to zero. The pressure becomes negative in the cranial veins which are held open by dural attachments. The jugular veins collapse, and there is evidence that the central veins collapse as far down as the innominate vein and the upper part of the superior vena cava.

Actual venous pressures in the leg also differ from the pressure head generated by the total length of the vascular column. Muscle movements cause a rapid fall in venous pressure with a relatively slow return to the level set by the hydrostatic column. Typical venous pressures at the ankle level are normally 20 to 30 mmHg rather than the hydrostatic pressure of about 90 mmHg.

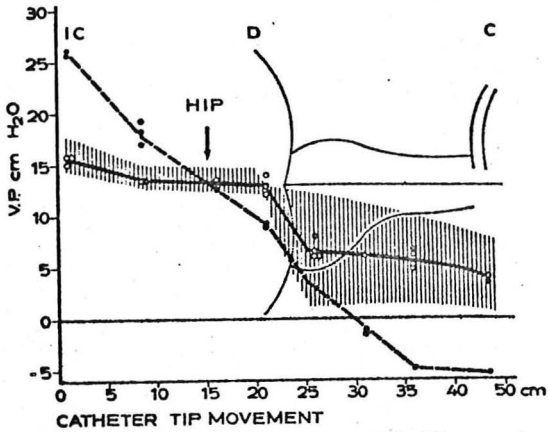
Since pressures increase in the lower part of the body and decrease in the upper part with a postural change from supine to standing, it follows that hydrostatic pressures stay constant in a transition zone. This level is referred to as the hydrostatic indifference point, HIP, and can easily be determined in the venous system as illustrated in Figure 12. The purely mechanical HIP as determined with the supine position as the starting point is normally located a few centimeters below the diaphragm. This implies that postural changes in hydrostatic pressure will be significant at the heart level and affect cardiac filling but will be minimal at the level of the liver and the kidney. The basal HIP in the arterial system is more difficult to measure due to the secondary changes in flow and resistance induced by changes in position, but studies after rapid tilt suggest a similar position as in the venous system.

The effective location of the HIP is variable and the purely mechanical hydrostatic effects are modified by dynamic changes in the pressure-volume relationship of the systemic and pulmonary veins and by reflex-mediated changes in cardiac output and peripheral resistance. These changes tend to move the point of no pressure change headward, decreasing the effects of posture on cardiac filling pressure.

Static filling pressures

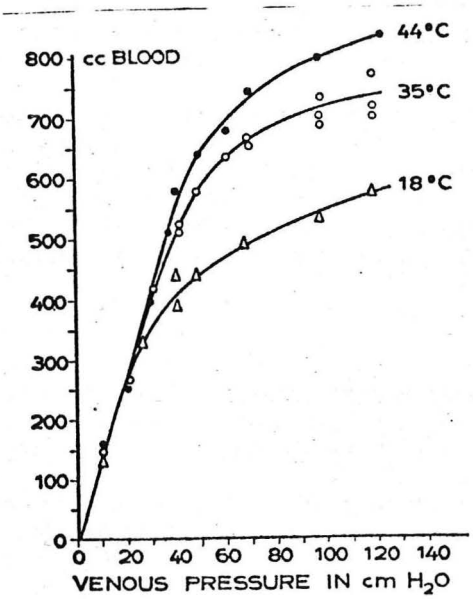
Static filling pressures are a function of intravascular volume and the capacity of the circulatory system. The systemic veins contain more than 50

Fig. 12.



Determination of the hydrostatic indifferent point (HIP) in the venous trunk of man. Evaluation of a record similar to figure 1. The *heavy solid line* represents the mean pressure gradient along the venous trunk obtained in the recumbent subject by the miniature manometer. The pressure gradients are very small, with the exception of a conspicuous pressure drop at the level of the diaphragm which might be interpreted as due to a partial vascular collapse in this region. The *shaded area* represents venous pressure pulsations due to cardiac activity and respiration. When the subject was tilted to a 60° head-up posture with the catheter tip in various locations, the *black points* were obtained and the *dotted line* indicates the pressure gradient in orthostasis.

Fig. 13.



. Pressure volume diagram of both legs up to the groin at various temperatures of the plethysmograph. In a vertical tilt, the mean venous pressure rises from approximately 15 cm H_2O to 80 cm H_2O. The concurrent volume increase at 35 C is about 500 ml.

per cent of the total blood volume in recumbent normal man. About 30 per cent of the volume is located in the heart and in the intrathoracic vessels (approximately 10 per cent in the heart), and only 15 to 20 per cent in the systemic arteries. Volume shifts are therefore almost entirely confined to the low-pressure system.

The largest pressure and volume changes occur in the legs. The amount of venous blood sequestered in the legs at various distending pressures is shown in Figure 13. The normal distending pressure in the standing position is about 80 cm of water corresponding to a pooled volume of about 500 cc.

Venous tone or compliance is mainly controlled by alpha-adrenergic outflow and by myogenic effects (Bayliss effect). Human cutaneous veins respond to a variety of stimuli, including temperature as illustrated in Figure 13, and emotional stress. Deep inspiration causes significant cutaneous venous constriction. However, there are essentially no acute changes in venous tone with a change in posture. Chronic changes in venous tone have been demonstrated in several clinical conditions, e.g. in hyperkinetic hemodynamic states including anemia and vasoregulatory asthenia. Venous tone is also elevated in patients with congestive heart failure, acute myocardial infarction, pheochromacytoma, and possibly in manifest essential hypertension. Pregnancy and oral contraceptives cause a decreased venous tone. Physical abnormalities of the veins, e.g. varicosities and congenital absence of the venous valves are associated with increased pooling due to increased compliance and also to loss of the muscle pump, predisposing to orthostatic sensitivity and poor physical work capacity in the upright position due to decreased ventricular filling and low stroke volumes.

The effects of venous pooling during prolonged quiet standing are amplified by depletion of the blood volume by extravasation of plasma filtrate. The loss of intravascular fluid is reflected by changes in hematocrit and plasma protein concentration during standing and after return to the supine position.

Seventy-five to eighty per cent of the displaced blood volume during standing is derived from the intrathoracic vascular compartment. This represents a loss of about 25 per cent of the central blood volume. Almost one-fourth, of 100 to 150 ml of the translocated volume is derived from the heart, predominantly from the atria. The change in central blood volume is associated with decreased right and left ventricular filling pressures and a Starling effect causing a fall in stroke volume.

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Dynamic pressure

Several mechanisms are activated to counter the orthostatic fall in stroke volume induced by the Starling effect in order to maintain arterial pressure and tissue perfusion.

Table VII. Circulatory Effects of Change in Posture Before and After Bed Rest. Mean Values in Five Normal Subjects (Saltin , et.al. 1968)

	Control		After Bed Rest	
	Supine	Sitting	Supine	Sitting
Stroke Volume (ml)	103	79	86	60
Heart Rate (bpm)	63	76	68	83
Cardiac Output (l/min)	6.4	5.7	5.8	4.9
Blood Pressure (mmHg)	125/67	131/75	126/63	134/74

Table VII illustrates the effects of these mechanisms in normal subjects. Stroke volume decreases by about 20 per cent upon transition from the supine to the sitting position. The decrease is even larger after bed rest, or 30 per cent, but arterial pressures are nevertheless maintained. Note that the heart rate increase in the upright position is not sufficient to bring cardiac output back to supine levels. Cardiac output during exercise is also approximately 1 liter per minute lower in the upright than in the supine position at any given level of oxygen uptake.

Bevegard, S: Studies in the regulation of the circulation in man. Acta Physiol Scand Vol 57, Suppl 200, 1962.

Saltin, B, Blomqvist, G, Mitchell, JH, Johnson, RL, Jr, Wildenthal, K, and Chapman, CB: Response to exercise after bed rest and after training. Circulation Vol 37-38, Suppl 7, 1968.

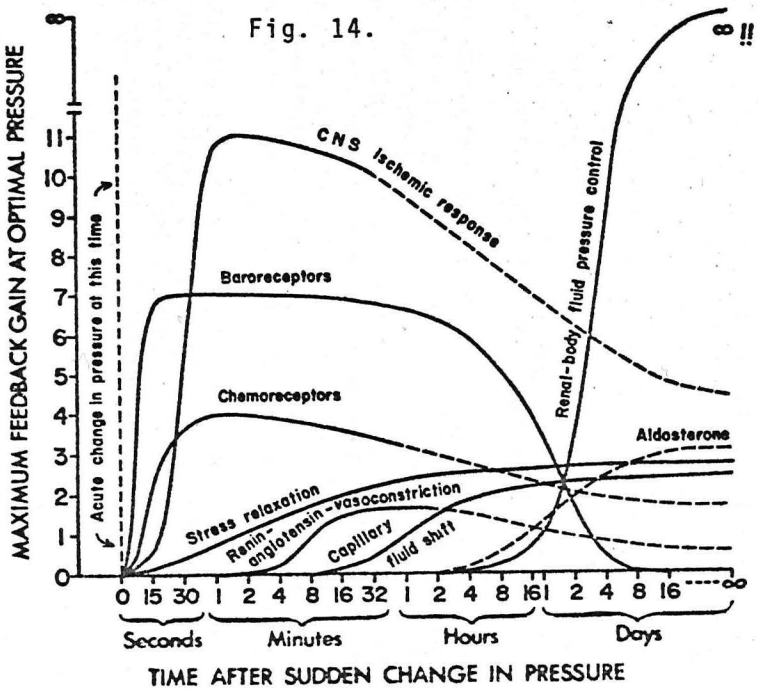
Guyton has recently reviewed the mechanisms involved in the control of arterial blood pressure. Figure 14 summarizes the response time and relative effectiveness of the various control mechanisms. Maximum feedback gain is a measure of the effectiveness of the mechanisms and is defined as the ratio between initial and residual pressure change, i.e. complete correction of a pressure fall of 20 mmHg would represent a gain of 20/0, or infinity, and a 50 per cent correction a gain of 20/10 or 2. Figure 15 defines the pressure range within which each control mechanism is effective.

It is evident that the chemoreceptors and the central nervous system ischemic response (sympathetic activation originating in the vasomotor center in the medulla oblongata) have little to do with postural circulatory changes in normal subjects since they are not activated until the arterial pressure has fallen to very low levels. Figure 14 also demonstrates that only the baroceptors have sufficiently short response time to be effective.

The term baroceptor covers a wide range of mechanoreceptors in the great vessels, atria, and ventricles. The carotid sinus receptors respond to deformation of the sinus wall and are sensitive both to the instantaneous pressure and to the rate of change of pressure. Increased pressure and increased firing rate cause (a) bradycardia, predominantly due to vagal stimulation with reduction of cardiac output, (b) arteriolar vasodilatation, predominantly in skeletal muscle, due to a decrease of sympathetic vasoconstrictor tone. The combined effect of (a) and (b) is a decrease in arterial pressure. A blood pressure fall produces changes in the opposite direction.

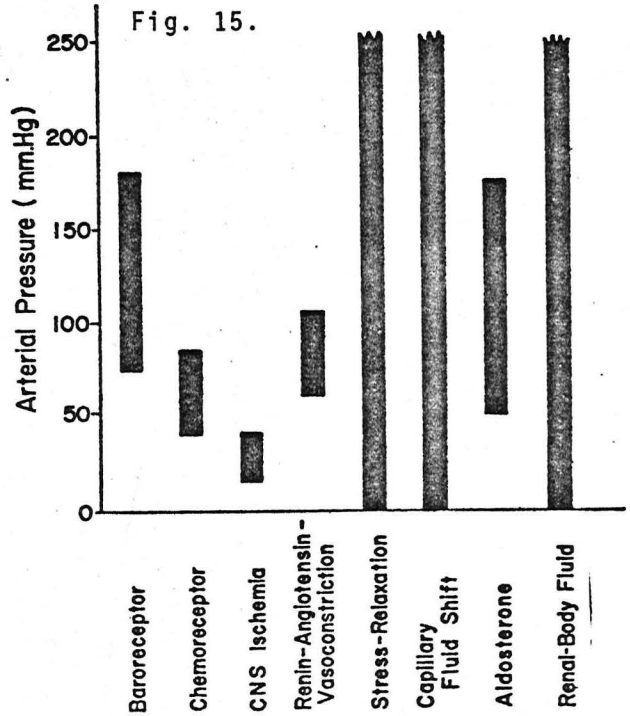
The aortic baroceptors have previously been considered equivalent to the carotid sinus receptors but probably have a different range of sensitivity. The aortic arch reflex is relatively ineffective in buffing a decrease in systemic arterial pressure below normal and acts predominantly as an antihypertensive mechanism.

Fig. 14.



Response times and maximum feedback gains in the optimum pressure ranges for the different well known arterial pressure control mechanisms. The dashed portions of the curves are not well determined.

Fig. 15.



Approximate pressure ranges for function of the different arterial pressure regulating mechanisms.

There are also ventricular high-pressure baroceptors. Activation always produces reflex bradycardia and hypotension (Bezold-Jarish reflex). Several different receptors have been identified but their physiological and clinical significance has not been firmly established. Activation of ventricular pressure or deformation sensors resulting in bradycardia and vasodilatation may be an important mechanism in acute myocardial infarction and in exercise-induced syncope in aortic stenosis. The role of this reflex in simple vaso-vagal syncope is controversial.

The physiological significance of the receptors in the atria and the atrio-venous junctions, i.e. the low-pressure baroceptors, illustrated in Figure 16, is better established. A receptor function was first attributed to the atria by Bainbridge, who 60 years ago observed that large infusions of saline or blood to anesthetized dogs caused tachycardia. It has been pointed out by Linden that there is no evidence in the original paper that the right atrium had anything whatsoever to do with this reflex or combination of reflexes. Recent studies have clearly demonstrated that distension of the right or left atrio-venous junction causes (a) an increased heart rate without any positive inotropic effect, probably by an increased activity in the sympathetic nerves to the sinus node, (b) a decrease in activity in the sympathetic nerves to the kidney, and (c) a diuresis induced by a decrease in plasma levels of antidiuretic hormone (ADH). Afferent pathways are vagal.

There is also experimental evidence that distension of the pulmonary vein-atrial junctions cause a sustained reflex systemic hypotension with little change in cardiac output. Moderate degrees of lower body negative pressure in human subjects, which causes a decrease in atrial ventricular filling pressures, is associated with a significant fall in cardiac output without any changes in systolic or diastolic arterial pressures, heart rate, or myocardial contractile state. These findings are consistent with reflex arteriolar vasoconstriction mediated by the low-pressure baroceptors.

There are several relatively well-documented clinical and physiological effects of the changes in renal sympathetic tone and ADH levels as mediated by activation of the low-pressure baroceptors.

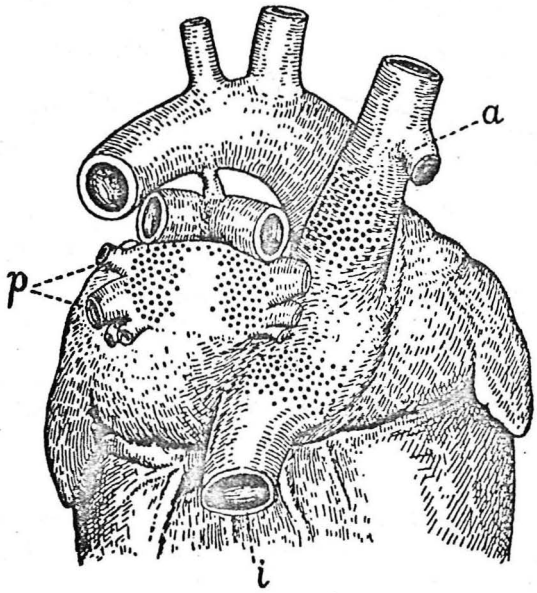
The ADH inhibition caused by atrial distension is well documented and thought to be a major factor in the blood volume changes occurring during space flight. The mechanism is referred to as the Henry-Gauer reflex. There is some evidence that atrial distension and ADH inhibition is at least partially responsible for the diuresis induced by paroxysmal tachycardia. Decreased sensitivity of the atrial baroceptors in chronic congestive heart failure has been documented and may contribute to the fluid retention. Changes in atrial receptor function may also be of significance in arterial hypertension.

Thus, the low-pressure baroceptors have an important role in the reflex regulation of arterial pressure during acute changes in posture and may be of considerable clinical importance. Activation of the low-pressure baroceptors also affects cardiovascular function by its effects on ADH and renal sympathetic tone.

Renin-angiotensin is the second major control mechanism to be activated after a sudden change in arterial pressure, followed by aldosterone. There is little doubt that the renal mechanisms are of overriding importance in the long-term control of blood pressure, but this area is beyond the scope of the present review.

However, it is pertinent to review briefly the relationship between blood volume and the circulatory response to stress.

Fig. 16.



Posterior view of the heart of a kitten showing the location of the receptor areas (dotted) at superior (a) and inferior (i) vena caval-right atrial junctions and pulmonary (p) vein-left atrial junctions.

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Circulatory effects of variations in blood volume

It is likely that long-term physiological changes in blood volume primarily reflect changes in the size of the vascular bed and that regulatory mechanisms under normal conditions control the degree of filling or the effective rather than the absolute blood volume. However, it is difficult to quantitate the absolute capacity of the vascular bed, and blood volume measurements have provided some interesting information.

Blood volume in normal man is proportional to body weight with normal values of approximately 70 milliliters per kilo body weight. The habitual level of physical activity is a major source of variation. Mean values 25 per cent above normal have been reported in runners and mean values 10 per cent below normal in sedentary groups. Physical training is regularly associated with an increased

blood volume, usually without any significant changes in hematocrit. Bed rest causes a significant decrease in blood volume with an initial rapid decline followed by a slower loss proportional to the duration of immobilization, and associated with proportional changes in red cell mass. Regulatory mechanisms have not been well defined.

Chronic expansion of the blood volume in the absence of primary changes in red cell mass has been demonstrated in a variety of clinical conditions. Increased blood volume may be associated with an expansion of the vascular bed, as in pregnancy or varicose veins, with impaired orthostatic reflex regulation as in idiopathic postural hypotension, or elevated ventricular filling pressures (required to maintain an adequate cardiac output) as in congestive heart failure. Findings in hypertension are controversial. The absolute blood volume is usually but not always expanded in primary hyperaldosteronism and reduced in pheochromocytoma and renal hypertension. The absolute volume is also often reduced in essential hypertension but subgroups with hypervolemia have been identified. Expansion of the extracellular volume and of the effective plasma volume, or volume related to vascular capacity, is a cardinal feature of low renin hypertension.

Patients with congestive heart failure and expanded blood volume typically have an increased orthostatic tolerance and may at times have a paradoxical increase in stroke volume. The orthostatic response in hypertension is variable. Increased orthostatic tolerance has been reported in patients with mild hypertension who tend to respond well to drug treatment, and in patients with renovascular hypertension, but these changes may reflect increased reflex activity rather than blood volume alterations.

Relatively large acute changes in blood volume may occur before any changes in cardiac output and arterial pressure can be demonstrated. An increase in blood volume of 10 per cent by infusion increases central venous pressure by about 2 to 3 centimeters of water but resting cardiac output is not effected by infusions up to 10 to 15 per cent of the blood volume. Arterial pressures usually do not decrease significantly until the volume loss approaches 25 to 30 per cent. However, blood withdrawal of as little as 200 to 250 cc has a negative effect on orthostatic tolerance as measured during lower body negative pressure. Even large variations in blood volume have little effect on the capacity to perform maximal exercise in the upright position. Dehydration with loss of up to 20 per cent of the plasma volume results in low stroke volume and increased heart rates at submaximal work loads but maximal oxygen uptake, stroke volume and cardiac output are not significantly altered. Acute expansion of the blood volume by autotransfusion of up to 25 per cent has no effect on maximal cardiac output despite a large increase (7 mmHg) in central venous pressure.

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MECHANISMS AND TIME-COURSE OF CARDIOVASCULAR ADAPTATION TO ZERO GRAVITY

The two preceding sections of this presentation have provided a review of the physiological findings during the Skylab missions and a review of homeostatic circulatory mechanisms related to the impact of gravity on the cardiovascular system. However, the Skylab data, voluminous as they are, are incomplete in several crucial areas, particularly with respect to the early stages of the missions. Furthermore, the mere demonstration of the presence of a reflex mechanism in an experimental animal, usually anesthetized and with open chest, provides little information on the physiological significance of the reflex in the intact human subject.

We recently attempted to obtain some of the missing information relating to early adaptation to zero gravity in a study of five young normal men who were subjected to a 24-hour period of simulated zero gravity. Several methods have been employed in the past to simulate 0g, e.g. bed rest and total body water immersion. Recent studies, including some Russian experiments, suggest that bed rest with slight (5^0) head-down tilt is a useful model and we elected to follow that procedure. Circulatory measurements were primarily based on non-invasive techniques, excluding a central venous catheter for pressure measurements and blood sampling.

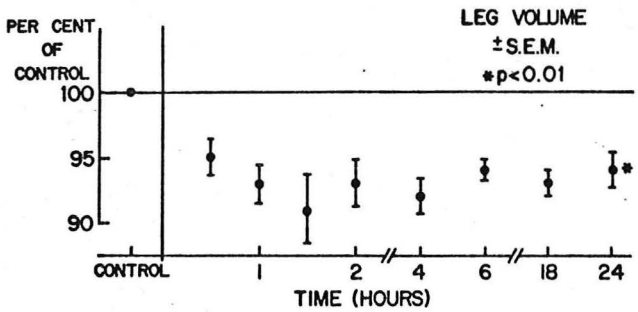

Figure 17. Change in left leg volume during 24-hour head-down tilt.

Head-down tilt induced a significant central fluid shift as demonstrated by measurements of leg volume (Figure 17). The decrease corresponds to a total of 800 cc. Total body weight decreased by 1.3 kilograms. Post-tilt measurements of physical work capacity (Table VIII) demonstrated a significant decrease of almost 20 per cent. An increased post-tilt heart rate during lower body negative pressure was also demonstrated (Table IX) and indicates a significant impairment of orthostatic tolerance. These changes were of the same order of magnitude as those reported after space-flight and suggest that the experimental model was appropriate.

Table VIII. Effect of 24-hour head-down tilt on maximal oxygen uptake.

MAXIMAL OXYGEN UPTAKE (ml kg^{-1} m^{-1})	SUBJECT 1	2	3	4	5	MEAN	±S.E.M.
PRE TILT	30	41	32	41	38	36	±2.4
POST TILT	22	29	26	34	31	29*	±2.0

*$p < 0.005$

Table IX. Effect of 24-hour head-down tilt on heart rate during lower body negative pressure (LBNP) at -40 mmHg.

HEART RATE DURING L.B.N.P. (beats/m)	SUBJECT 1	2	3	4	5	MEAN	±S.E.M.
PRE TILT	88	78	96	100	70	86	±5.6
POST TILT	110	110	110	105	120	111*	±2.5

*$p < 0.025$

Central venous pressures rose to a peak within one hour and then rapidly returned to basal supine levels (Figure 18A). As expected, left ventricular end-diastolic diameter - as measured by echocardiography - increased (Figure 18B) and this change was associated with an increase in stroke volume without any changes in contractile state (measured as echocardiographic mean velocity of circumferential fiber shortening), i.e. a pure Starling effect. There were no significant changes in heart rate, cardiac output (measured by the acetylene rebreathing technique) or arterial blood pressure. Blood volume decreased by almost 10 per cent at 6 hours (Figure 19).

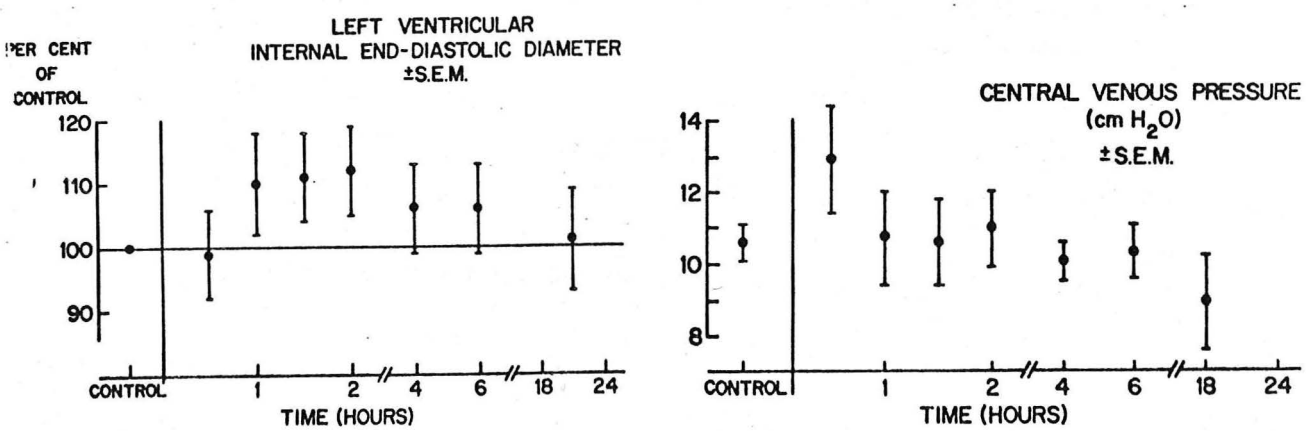

Figure 18. Changes in central venous pressure and left ventricular end-diastolic diameter during 24-hour head-down tilt.

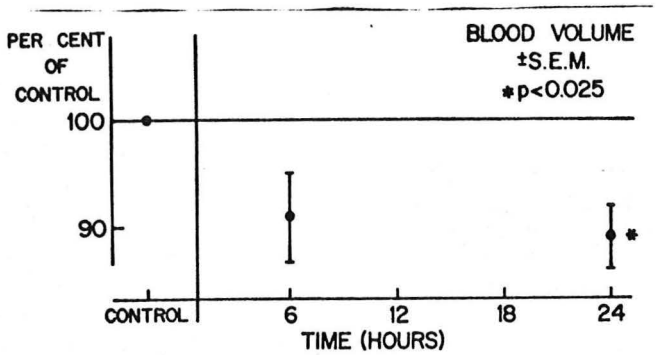

Figure 19. Effect of 24-hour head-down tilt on blood volume.

A significant diuresis occurred during the first 8 hours of tilt (Table X). Changes in plasma levels of aldosterone, renin, ADH, and urinary Na/K ratios are illustrated in Figure 20. All hormones showed a transient decrease and a return to control levels after 24 hours. The urinary Na/K ratios were reciprocal to the variations in aldosterone levels.

Table X. Rate of Urine Production (ml/min)

Time (Hours)	SUBJECT 1	2	3	4	5	Mean	±S.E.M.
0 - 8	2.22	1.96	2.21	2.60	0.89	1.98	±0.29
9 - 24	1.19	1.63	1.35	1.68	0.95	1.36*	±0.12
0 - 24	1.53	1.73	1.64	1.99	0.93	1.56	±0.18

* $p < 0.025$ for difference 0-8 and 9-24 hours

These data indicate that cardiovascular adaptation to reduced gravity is a rapid process. The expected increase in central venous pressure with a Starling effect was clearly demonstrated. Filling pressure and left ventricular diameter rapidly returned to control levels following the diuresis and contraction of the blood volume. There were no changes in serum electrolyte levels. The data do not allow definite conclusions regarding mechanisms, but are consistent with activation of the low-pressure baroceptors resulting in ADH inhibition (Henry-Gauer reflex) and decreased renal sympathetic tone associated with depressed

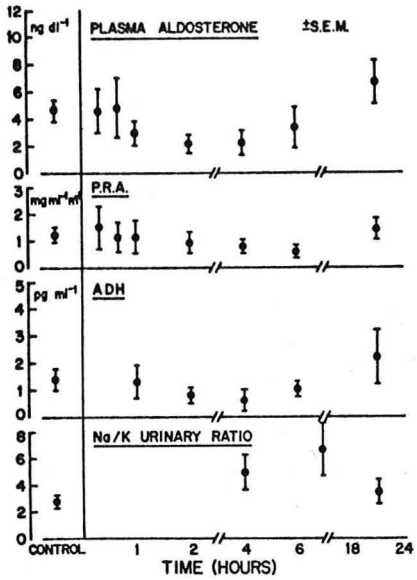

Figure 20. Effect of 24-hour head-down tilt on plasma, aldosterone, renin (PRA), antidiuretic hormone (ADH) and urinary Na/K ratio.

renin and aldosterone levels. The absence of any significant changes in heart rate or cardiac output makes it unlikely that the high-pressure baroceptors had a major role. For the same reasons, it is unlikely that there were any changes in renal hemodynamics directly attributable to central hemodynamics.

Thus, a 24-hour period of head-down tilt reproduced several major findings during and after space-flight. The sequence of a central fluid shift followed by an adaptation which becomes inappropriate when the circulatory system is re-exposed to gravitational forces, was confirmed. The magnitude of the post-tilt circulatory functional abnormalities were surprisingly large. The short duration of the tilt makes it unlikely that immobilization had any significant primary effects. The post-tilt reduction in maximal exercise performance was larger than expected from the magnitude of the reduction in blood volume. It is likely that tilt and space-flight also alter venous compliance and/or induce subtle changes in reflex regulation. Support for this view is provided by the Skylab leg volume data during lower body negative pressure and from bed rest studies during which expansion of the blood volume to pre-bed rest levels failed to prevent post-bed rest orthostatic impairment.

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