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MONITORING CARDIOVASCULAR FUNCTION IN THE PRIMATE UNDER PROLONGED WEIGHTLESSNESS

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UNIVERSITY OF SOUTHERN CALIFORNIA
HUMAN CENTRIFUGE AND
ENVIRONMENTAL PHYSIOLOGY LABORATORIES

FINAL REPORT

TITLE: MONITORING CARDIOVASCULAR FUNCTION IN THE PRIMATE UNDER PROLONGED WEIGHTLESSNESS

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ACKNOWLEDGEMENTS

Only by the dedicated involvement of a broad spectrum of individuals can a project of this magnitude be completed. While a personal commendation is in order for each person who contributed to this program, preparing such a roster would be formidable. However, the following individuals deserve special mention for their extra measure of dedication: From NASA, we acknowledge the assistance of Dr. Orr Reynolds, Mr. Charles Wilson, and their staffs. From industry we compliment Mr. Mike Shapiro of Philco-Ford and Mr. Robert Morgan of Marshall Laboratories (Time-Zero) for their tireless efforts in manufacturing and delivering hardware on a tight production schedule. At General Electric, in commending Mr. John Glancy with whom we spent the last frantic days preparing for launch, we also commend the many others who worked with us on the project. From UCLA, whose personnel, though deeply involved in their own tasks, still found time to counsel others, we mention Dr. Ross Adey and Mr. Pierre Hahn. Finally, we believe Mr. Leo Casados exemplifies the devotion of the entire staff at USC in his work on this project.

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I. INTRODUCTION

The broad objectives of the primate orbital mission were to determine the physiological effects of earth orbit on subhuman primates, to provide insights into possible hazards associated with long-term space flights, and to acquire information on basic physiological adjustments to extended weightlessness. To obtain these objectives, the investigational efforts were divided into four subgroups: Neurophysiological Studies (Dr. W. R. Adey, University of California, Los Angeles); Cardiovascular Studies (Dr. J.P. Meehan, University of Southern California); Metabolic Studies (Dr. N. Pace, University of California, Berkeley); and Bone Density Studies (Dr. P. B. Mack, Texas Woman's University). Dr. W. R. Adey was the principal investigator for the project. Project coordination was accomplished by UCLA.

The specific studies conducted by the University of Southern California related to the effects of long-term weightlessness on the cardiovascular system. The basic premise was that in weightlessness, as a consequence of reduction of the gravitational effect on the long columns of blood in the body, pooling of blood in the large vessels in the chest area occurs; and because of the apparent high blood volume, as indicated by stretch receptors in the large venous vessels, a compensatory mechanism would act to decrease the blood volume. The reflex mechanism described above, called the Henry-Gauer reflex after its discoverers, has been shown to be operational in bed rest and immersion experiments; and it was predicted that it would also be operational in reduced gravity fields.

The most relevant parameter indicating the operation of this reflex is the pressures in the large vessels near the heart. These pressures can be reliably obtained only by surgical implantation of catheters. The catheters so located in the flight monkey did reveal an initial increase of pressure in these areas as predicted. The pressure declined after several days, eventually falling to levels below preflight values.

It is evident that any factor causing pooling of blood in the chest region can potentially be confused with the predicted responses of weightlessness. Thus, prior to the flight experiment, considerable testing of immobilized subjects was conducted in order to acquire data which could be used in order to resolve the effects of weightlessness from the effect of other stresses. As predicted, central venous pressure generally decreased during the course of a restraint test. However, the change of the pressure in the large central venous vessels of the flight animal was greater than the average of test animals, and may constitute a confirmation of an important, theoretically anticipated response to weightlessness. Final assessment of the flight results will require a complex correlation and careful analysis of a variety of biological and environmental capsule data obtained on the flight and ground tests. Analysis of the cardiovascular data, separate from the other data, is presented in this report as support for the more complete analysis.

II. CARDIOVASCULAR EXPERIMENT, PLANNING AND DEVELOPMENT

In 1964, the University of Southern California (USC), Department of Physiology, accepted the responsibility of performing cardiovascular instrumentation on the male macaque monkey (Macaca nemistrina) for the Biosatellite III Primate Mission.

The assignment included development of practical experimental objectives within constraints such as payload, available power and space, and acceptable interference to other planned experiments. Specific tasks included developing and testing signal conditioners and ground support equipment, testing couched subjects along with the associated hardware, obtaining cardiovascular baseline information on the male macaque, preparing subjects for flight, and analyzing the resultant cardiovascular data.

The project required close coordination with National Aeronautics and Space Administration (NASA) Ames Research Center, General Electric Company, and other principal investigators and subcontractors. All hardware was designed, tested and packaged at USC; specifications were written by staff members before quotes were requested for fabrication of flight hardware. The subcontractors were often allowed to modify basic designs to improve overall function or reliability. Portions of the equipment were built at USC by qualified staff members.

Because of an exacting time schedule and the lack of reliable alternate methods in measuring blood pressure, a decision was made to adapt the techniques that were successfully used in the Ham and Enos flights (1). In these flights vascular pressures were obtained by catheterization techniques and recorded without amplification on an orbital galvanometric oscillograph. A motor-driven constant flow infusion system was used to prevent catheter stoppage.

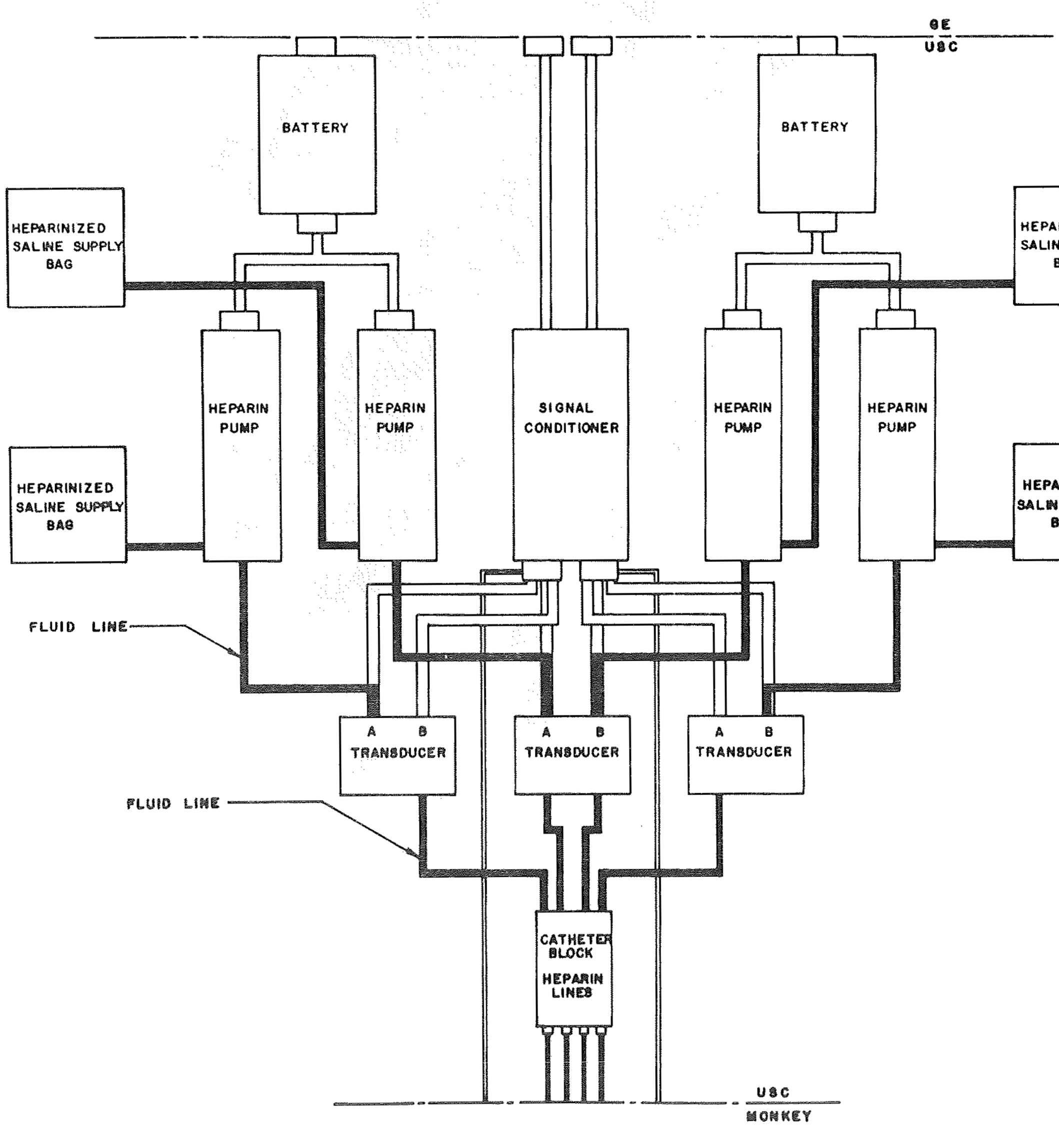


FIGURE 1: CARDIOVASCULAR INSTRUMENTATION PICTORIAL DIAGRAM

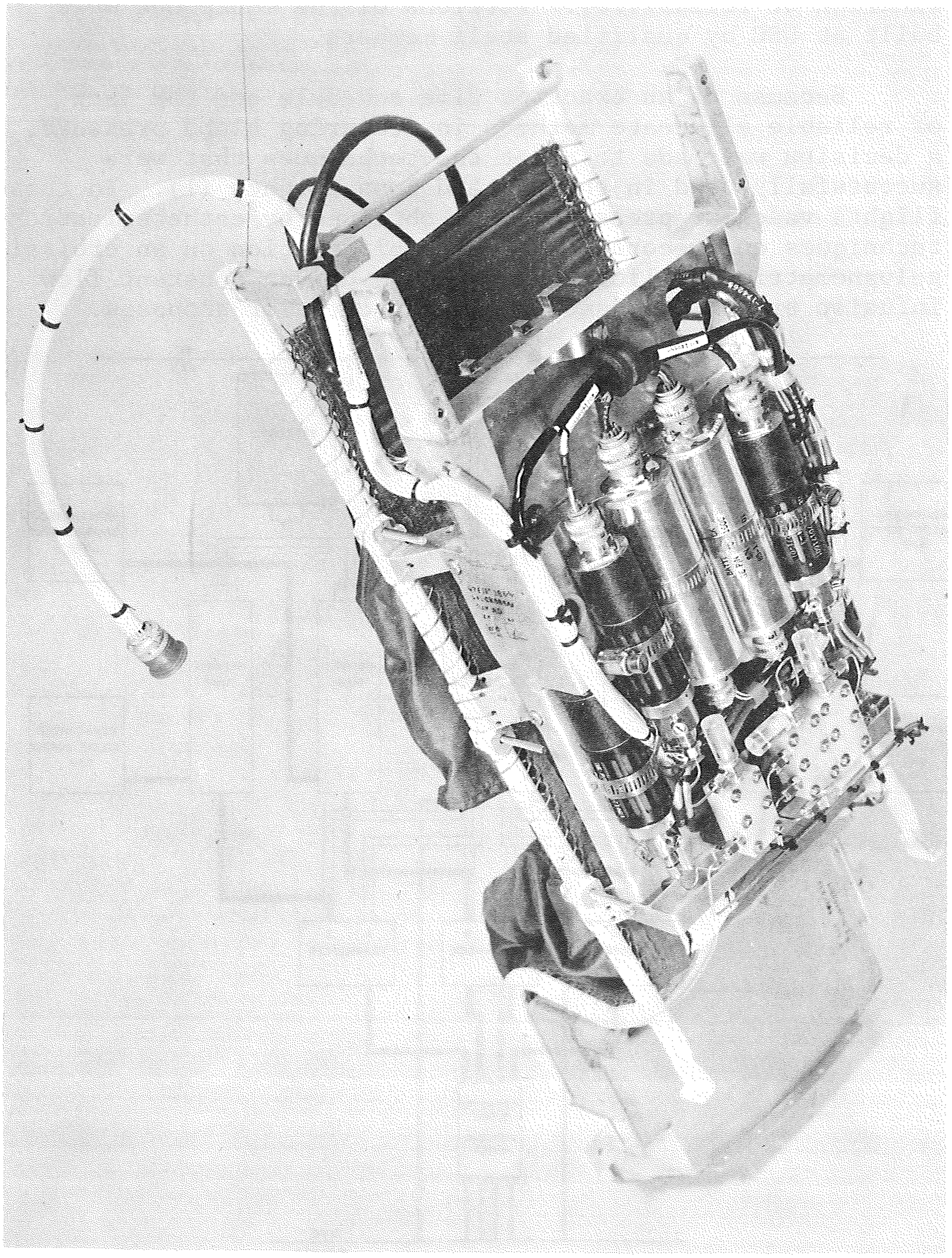


FIGURE 2: RESTRAINT COUCH ILLUSTRATING THE CARDIOVASCULAR HARDWARE

Since the power requirement of a replicated system for the Biosatellite was in excess of the amount allocated for USC use, and the output voltage was considerably below that needed for transmission, an extensive modification was undertaken to solve these problems. A low power infusion system and a proper signal conditioner system were designed. Amplification was required to obtain signal levels compatible with the on-board telemetry system. In addition to pressure data, one pair of electrodes provided (lead I) electrocardiographic and respiratory information. Four indwelling catheters, two venous and two arterial, produced redundant pressure measurements: additional redundance was obtained by connecting two transducers to each arterial catheter.

The resultant cardiovascular hardware (Figs. 1-7) consisted of four stainless steel lines connecting indwelling teflon catheters to the pressure transducers; four

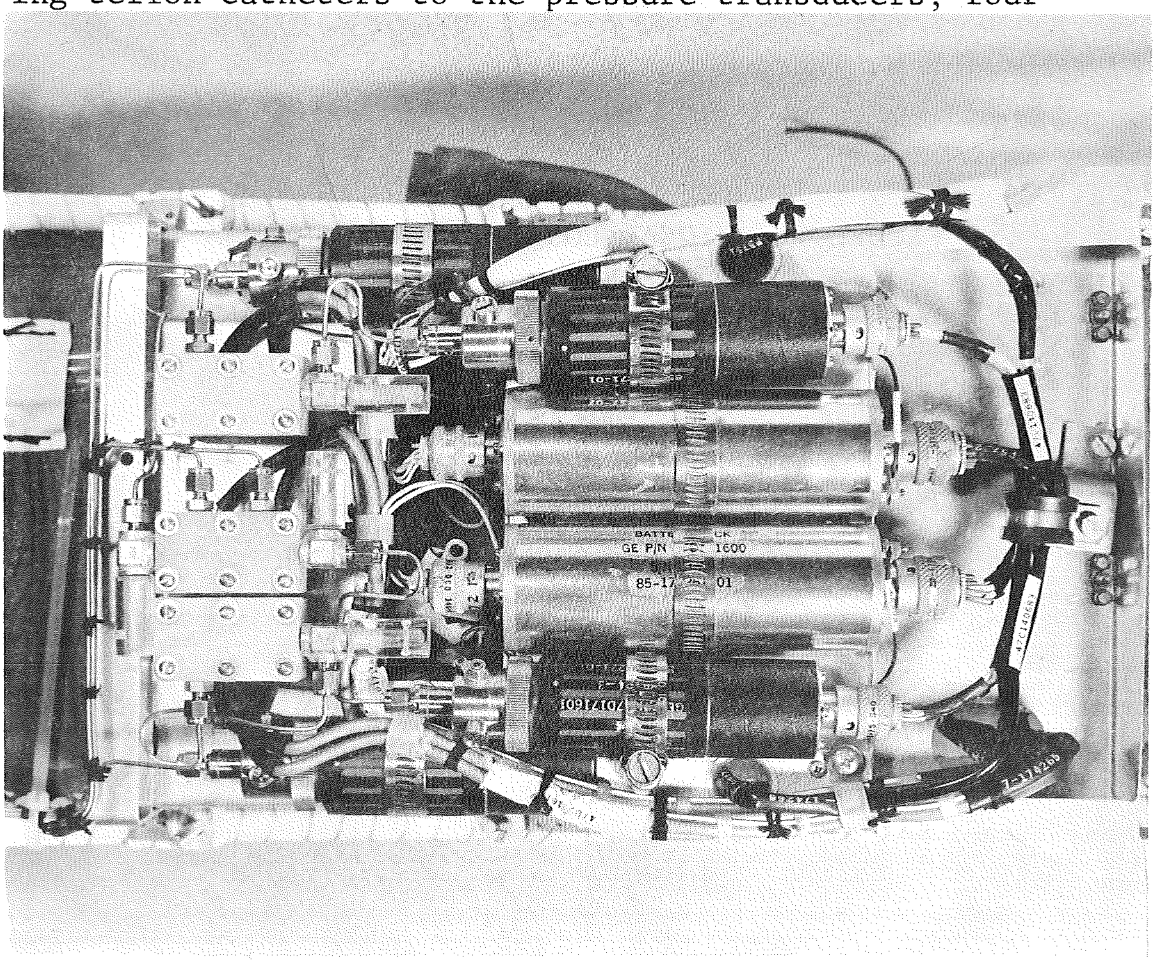


FIGURE 3: CLOSE-UP OF CARDIOVASCULAR HARDWARE

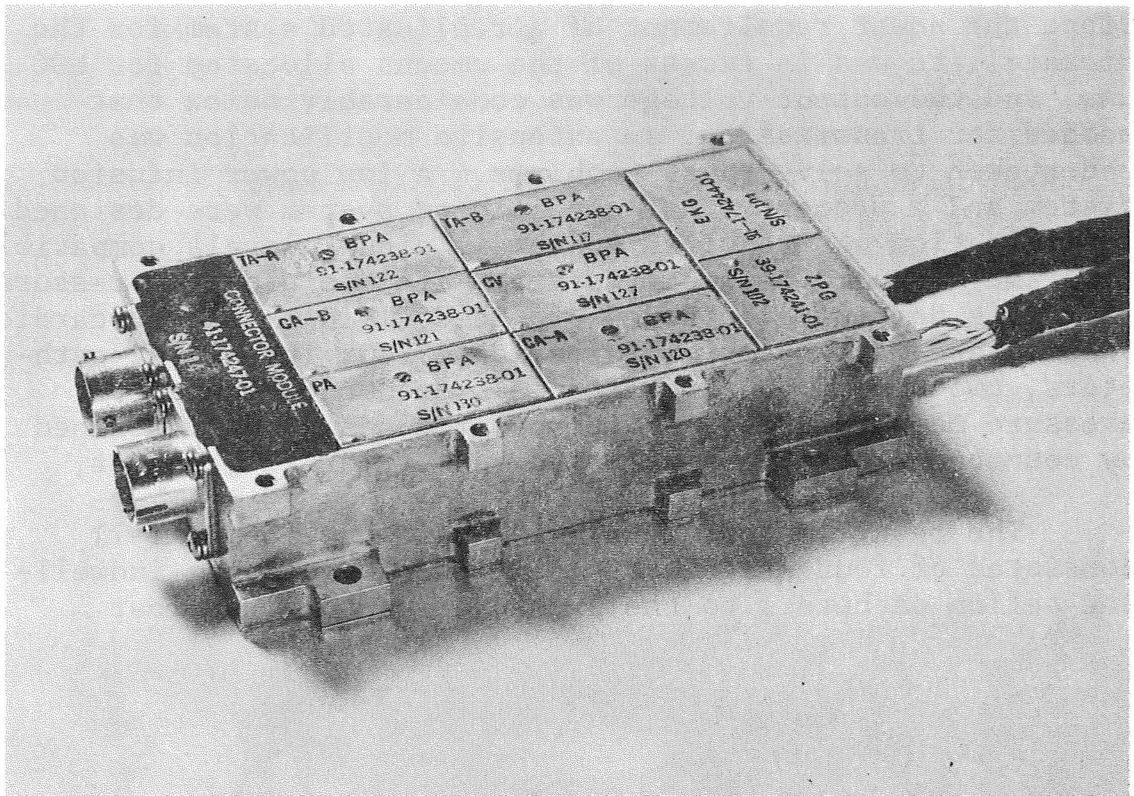


FIGURE 4: SIGNAL CONDITIONER ASSEMBLY

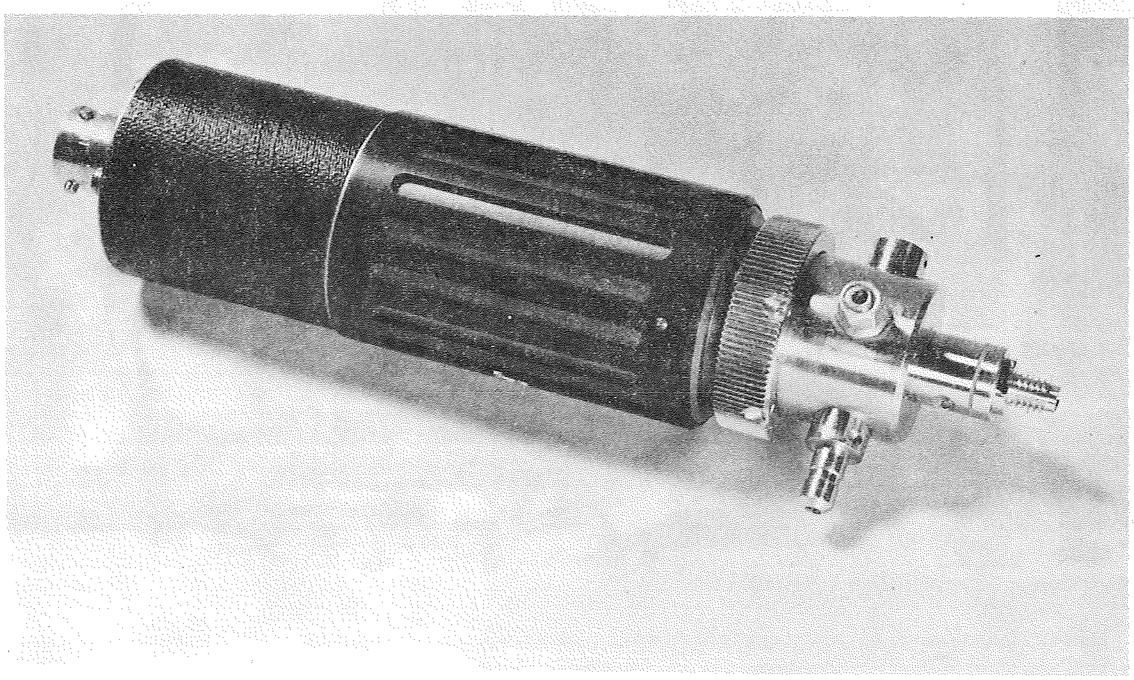


FIGURE 5: HEPARIN PUMP

heparin pumps operating once each minute to impel 0.008 cc of heparinized solution through the catheters; two nickel-cadmium batteries supplying power to the heparin pumps; one signal conditioner assembly with six blood pressure amplifiers; one biopotential amplifier (electrocardiogram); and one impedance detector (respiration monitor). The pressure transducers (four-arm resistive bridges - Statham PM 131 T.C.) were supplied with power from a regulated voltage source contained within each signal conditioning module. A current-limiting resistor fixed the current at approximately 3 ma per bridge. A full-scale pressure of 50 mm Hg for venous and 250 mm Hg for arterial transducers produced a full-scale output of 5 volts from the blood pressure signal conditioners. A full-scale input was equivalent to approximately 1.5 mv. The heparin pumps were specially modified lambda pumps (Harvard Apparatus) with an electronic assembly attached to switch power to drive each unit; they were triggered once each minute by an on-board clock pulse with one battery supplying the power for two pumps.

The nickel-cadmium batteries (8 cells at 1.25 volts per cell) with a longevity of 500 ma hours were encased in a metal cylinder with connectors at each end. When the pumps were triggered, the current was approximately 6 amperes per battery for approximately 25 msec. A constant 8 ma trickle charge was sufficient to replace this energy and maintain the batteries at an adequate charge for continuous operation. Figures 8 to 11 illustrate the circuits for the electrocardiogram amplifier, the impedance pneumograph signal conditioner, the blood pressure amplifier and the heparin pump driver.

Typical characteristics of each type of signal conditioner are listed below:

<u>Pump Controller</u>

(1)	Input Signal Amplitude	+3 v
(2)	Input Signal Pulse Width	300 msec
(3)	Output Pulse Width	25 msec
(4)	Current Pulse Amplitude	2.6 amp
(5)	Threshold Trigger Level	+1.4 v
(6)	Transient Susceptibility	100 μ sec
(7)	Steady State Current	1 μ amp

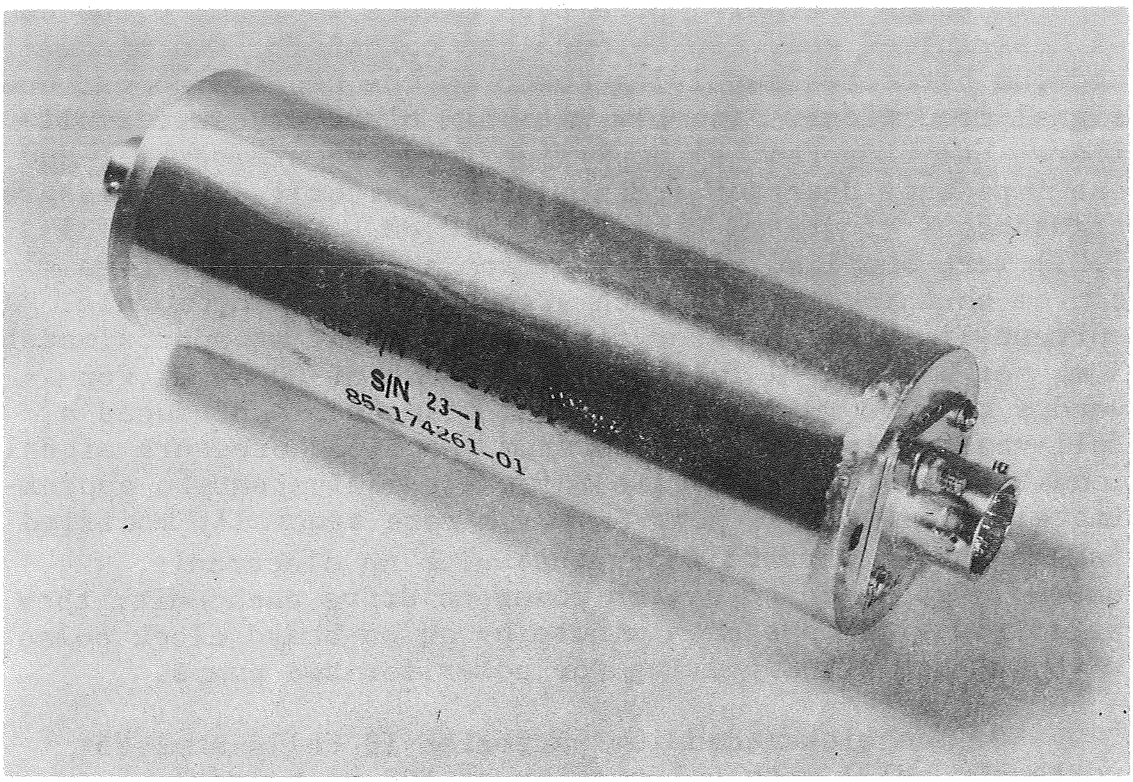


FIGURE 6: HEPARIN PUMP POWER SUPPLY

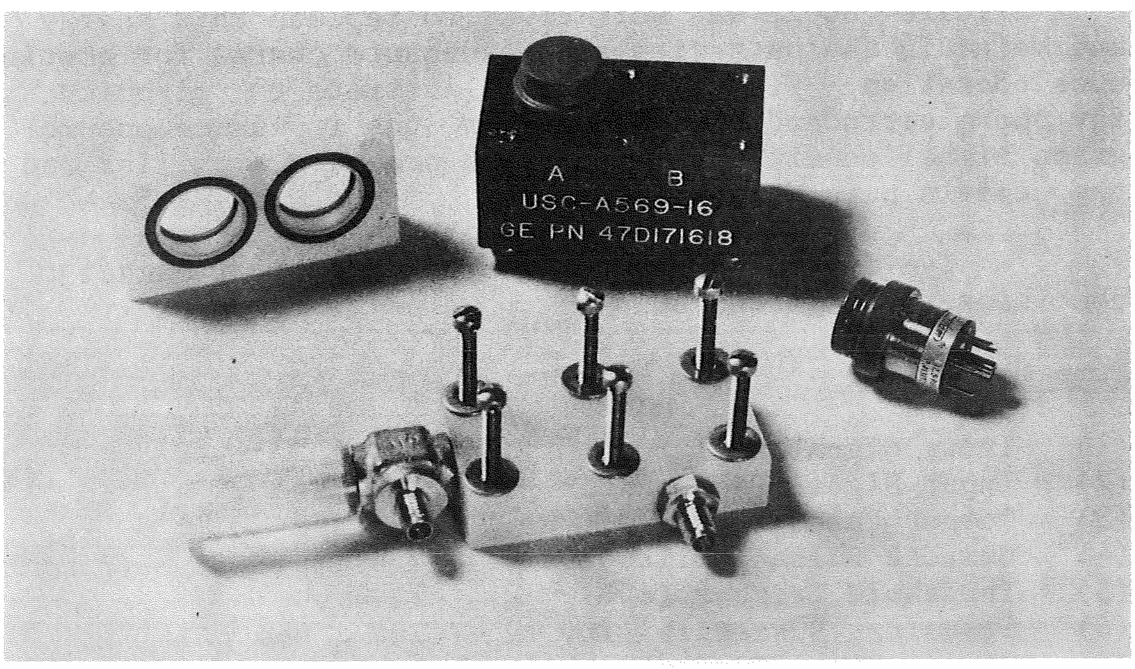


FIGURE 7: TRANSDUCER MOUNT ASSEMBLY

(8)	Input Impedance	1 MΩ
(9)	Typical Value of R5	13 k
(10)	Weight	31 g

Blood Pressure Amplifier

(1)	Steady State Current	7.2 ma
(2)	Series Regulator Voltage	18.0 v
(3)	Oscillator Frequency	2.5 KHz
(4)	Gain:	
	Arterial	3.2 v/200 mm Hg
	Venous	3.2 v/40 mm Hg
(5)	Noise Level	30 mv p-p

Blood Pressure Amplifier (continued)

(6)	High Frequency Rolloff Point (-3db)	41 Hz
(7)	D-C Offset	Adjustable
(8)	D-C Offset Stability Temp. 40°-125°F Voltage 21-31	$\pm$ 30 mv
(9)	Output Impedance	16 K Ω
(10)	Typical Value of R5	16 K Ω
(11)	Typical Value of R8	33 K Ω
(12)	Typical Value of R24	820 Ω
(13)	Weight	25 g

Impedance Pneumograph Signal Conditioner

(1)	Steady State Current	3.8 ma
(2)	Series Regulator Voltage	10 v
(3)	Oscillator Frequency	69.5 KHz
(4)	Gain	64 mv/Ω
(5)	Output Noise Level	8 mv p-p
(6)	Frequency Response	0.07 - 14 Hz
(7)	D-C Offset (Fixed)	2.6 v
(8)	D-C Offset Stability Temp. 40°-125°F Voltage 21-31	$\pm$0.17 v
(9)	Output Impedance	15 K
(10)	Typical Value of R8 and R9	68 K Ω
(11)	Weight	18.3 g

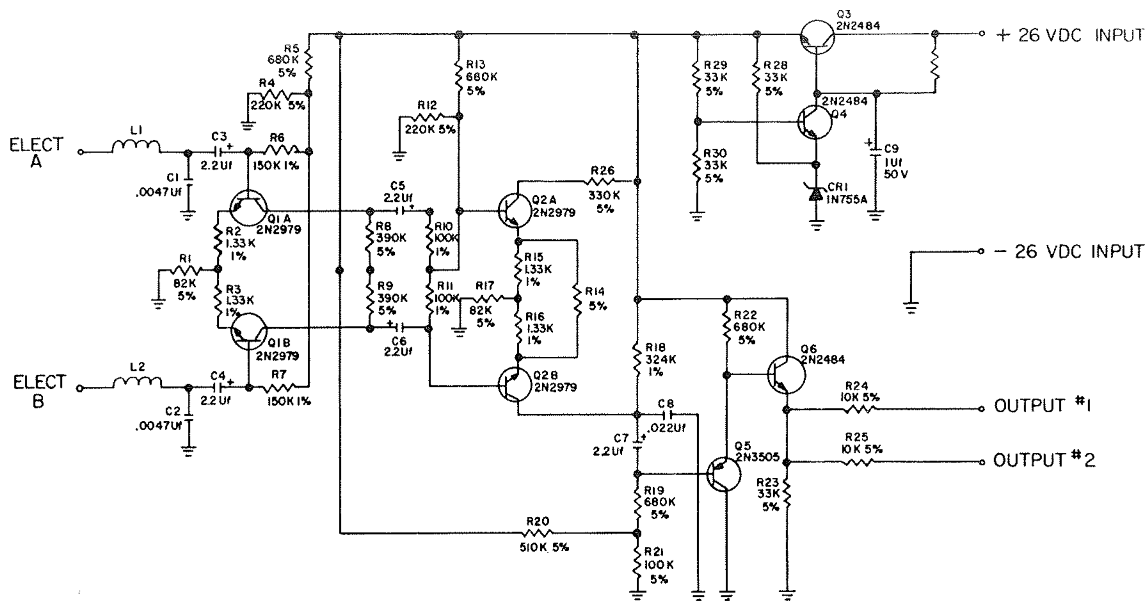


FIGURE 8: ELECTROCARDIOGRAM AMPLIFIER

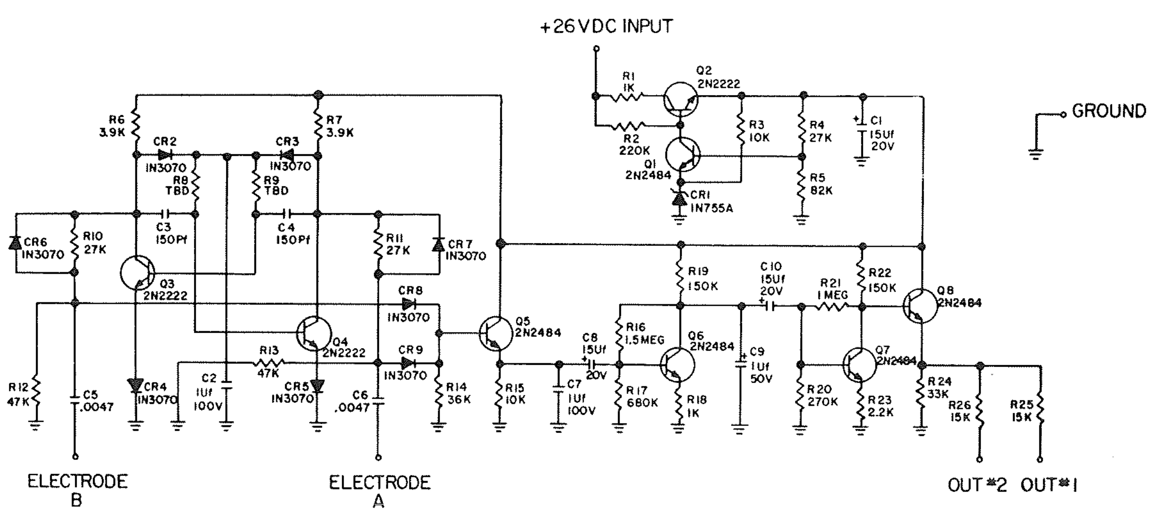


FIGURE 9: IMPEDANCE PNEUMOGRAPH SIGNAL CONDITIONER

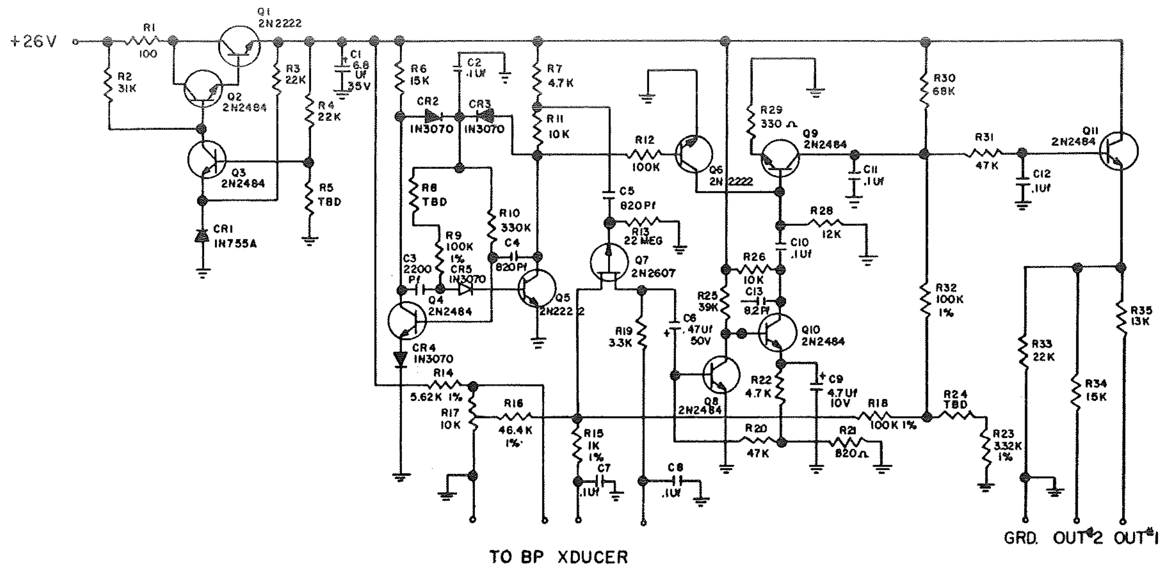


FIGURE 10: BLOOD PRESSURE AMPLIFIER

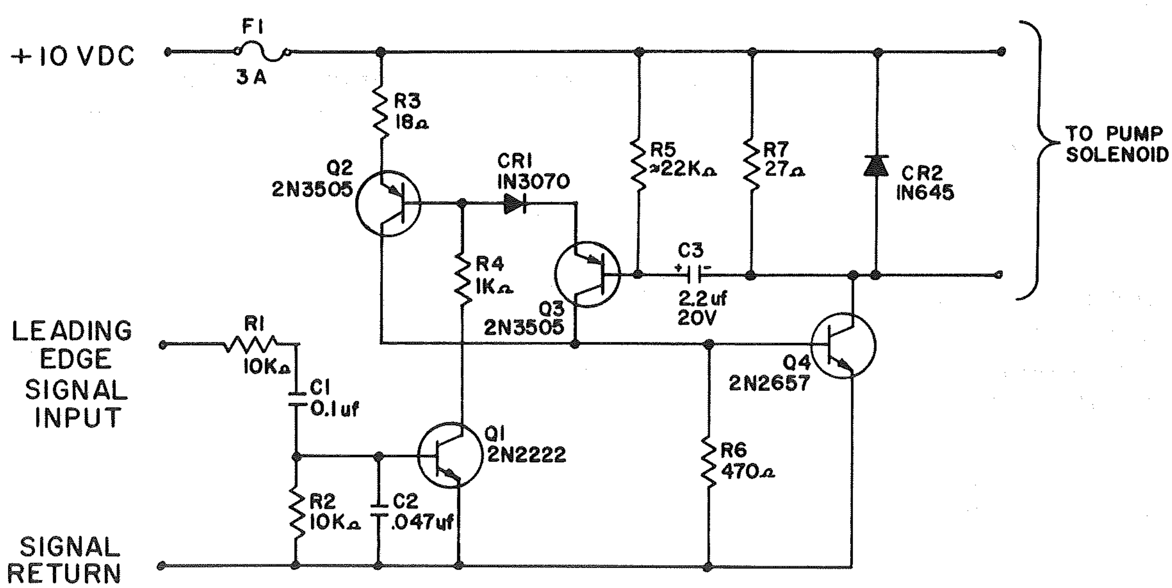


FIGURE 11: PUMP CONTROLLER

Electrocardiogram Amplifier

(1)	Steady State Current	0.8 ma
(2)	Series Regulator Voltage	15 v
(3)	Gain	1500
(4)	Output Noise Level	8 mv p-p
(5)	Frequency Response	0.65 - 35 Hz
(6)	D-C Offset (Fixed)	2.65 v
(7)	D-C Offset Stability Temp. 40^{o}-125^{o}F Voltage 21-31	$\pm$35 mv
(8)	Input Impedance	260 K Ω
(9)	Output Impedance	10 K Ω
(10)	Common Mode Rejection	500
(11)	Weight	23 g

The fluid supply for the catheter infusion system was contained in PVC bags secured in a light metal container placed behind the animal's legs. A normal saline solution with 30 units of heparin/cc of fluid was used; approximately 1500 cc was required for the 30-day mission.

III. GROUND TESTS

Several integrated tests were conducted before and after the orbital experiment to gain experience in flight preparation, to test hardware and to obtain physiological baseline information on the Macaca nemestrina monkey.

UCLA Primate 601 and 602 Tests: All Biosatellite personnel participated in the UCLA 601 and 602 Tests with each group having the opportunity to test its own hardware and countdown procedures in these two simulated flight tests held at the University of California at Los Angeles (UCLA).

GE Primate Interface, Endurance and Thermal Vacuum Tests: The next major test held at the General Electric (GE) plant in Philadelphia to evaluate the interface between the monkey and the capsule yielded no valuable physiological information, but served to further evaluate all hardware and countdown procedures. The formal endurance and thermal vacuum tests which followed produced acceptable baseline information.

KSC Baseline Tests: Ten flight candidates underwent short duration tests at the Kennedy Space Center (KSC) in Florida. These tests were set up to acquire additional baseline information in selecting the flight subject. The baseline test was also performed on four of the flight candidates during and after the flight.

USC Post Flight Tests: Two post flight tests were conducted at the University of Southern California to evaluate the effect of isolation and restraint on the animal.

A. Primate 601 and 602 Tests

The 601 Test for animal #208 was primarily a hardware test; consequently all the cardiovascular data were not properly recorded and analyzed. The 602 Test for animal #223 in a simulated capsule was performed at UCLA during

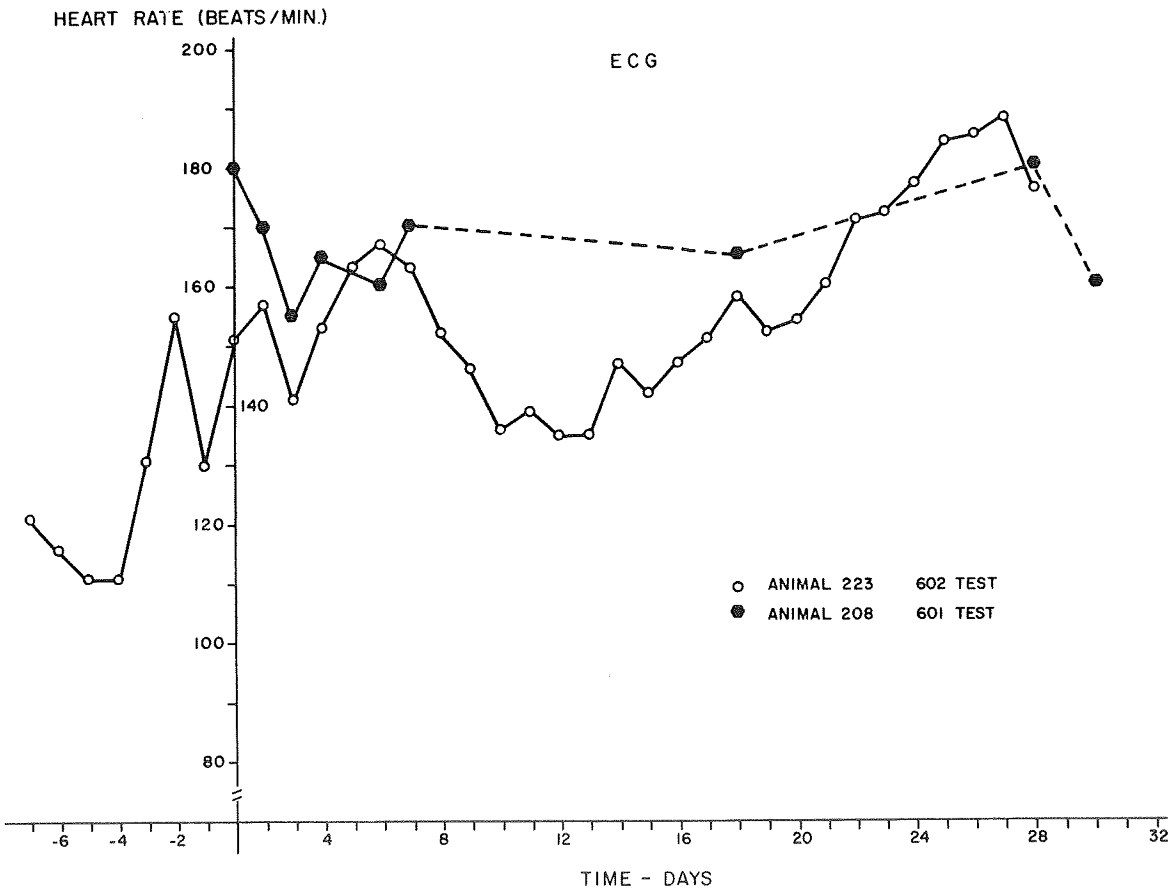


FIGURE 12: AVERAGE DAILY HEART RATE FOR TEST ANIMAL IN THE 601 and 602 TESTS

July and August of 1968. The monkeys used in these tests were not completely isolated from humans. The rear of the capsule was open to ambient environment and the animals were therefore likely to detect the presence of workers in the general area.

Electrocardiogram rates for both monkeys are shown in Fig. 12, and arterial blood pressure for #223 in Fig. 13. Both systolic and diastolic pressures increased gradually for #223 from approximately 80 mm Hg to 100 mm Hg diastolic and 120 mm Hg to 140 mm Hg systolic. Animal #223 also experienced a heart rate increase from start to finish, commencing six days after the initial instrumentation at 115 beats/min and rising to 175 beats/min toward the end of the test (Fig. 12) -- an approximate 40% increase over a 29-day period. Animal #208 maintained an essentially constant heart rate.

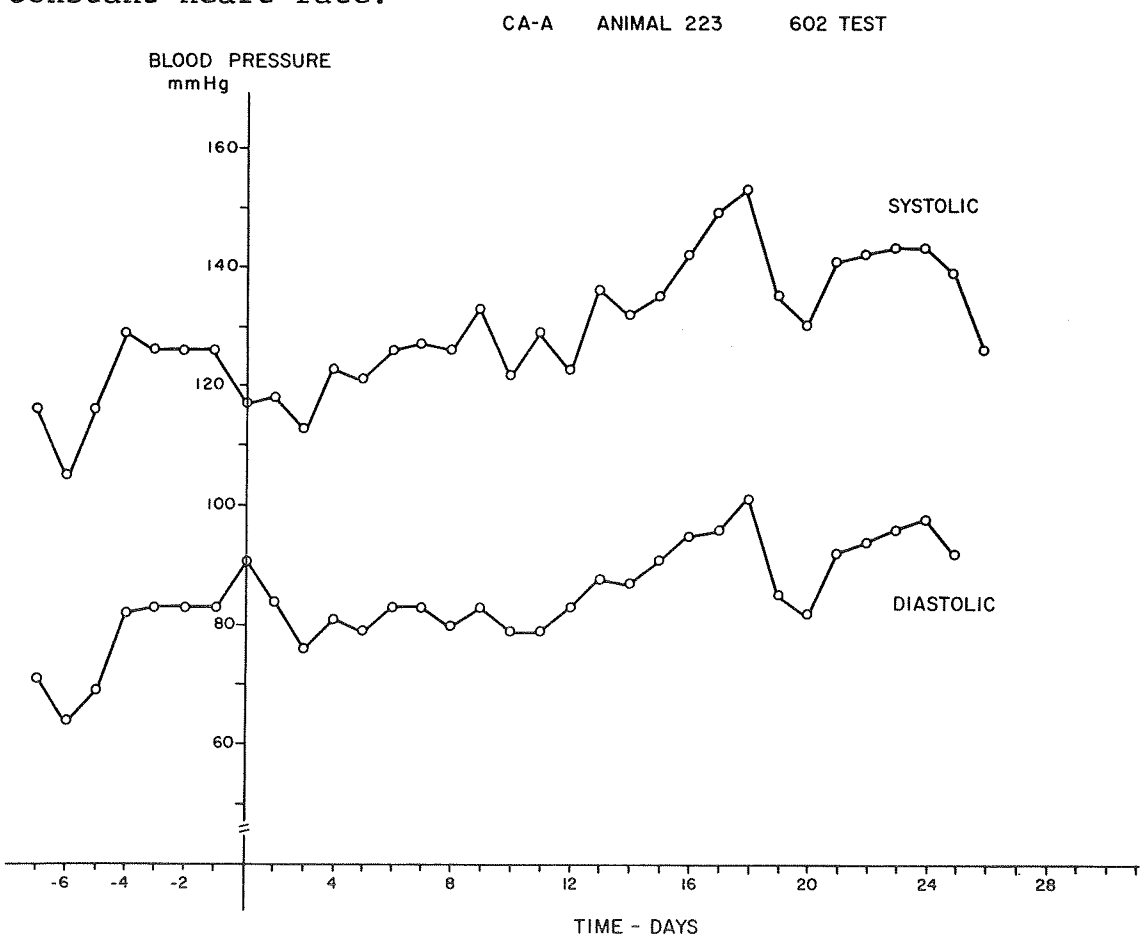


FIGURE 13: AVERAGE DAILY ARTERIAL BLOOD PRESSURE FOR TEST ANIMAL IN THE 602 TEST

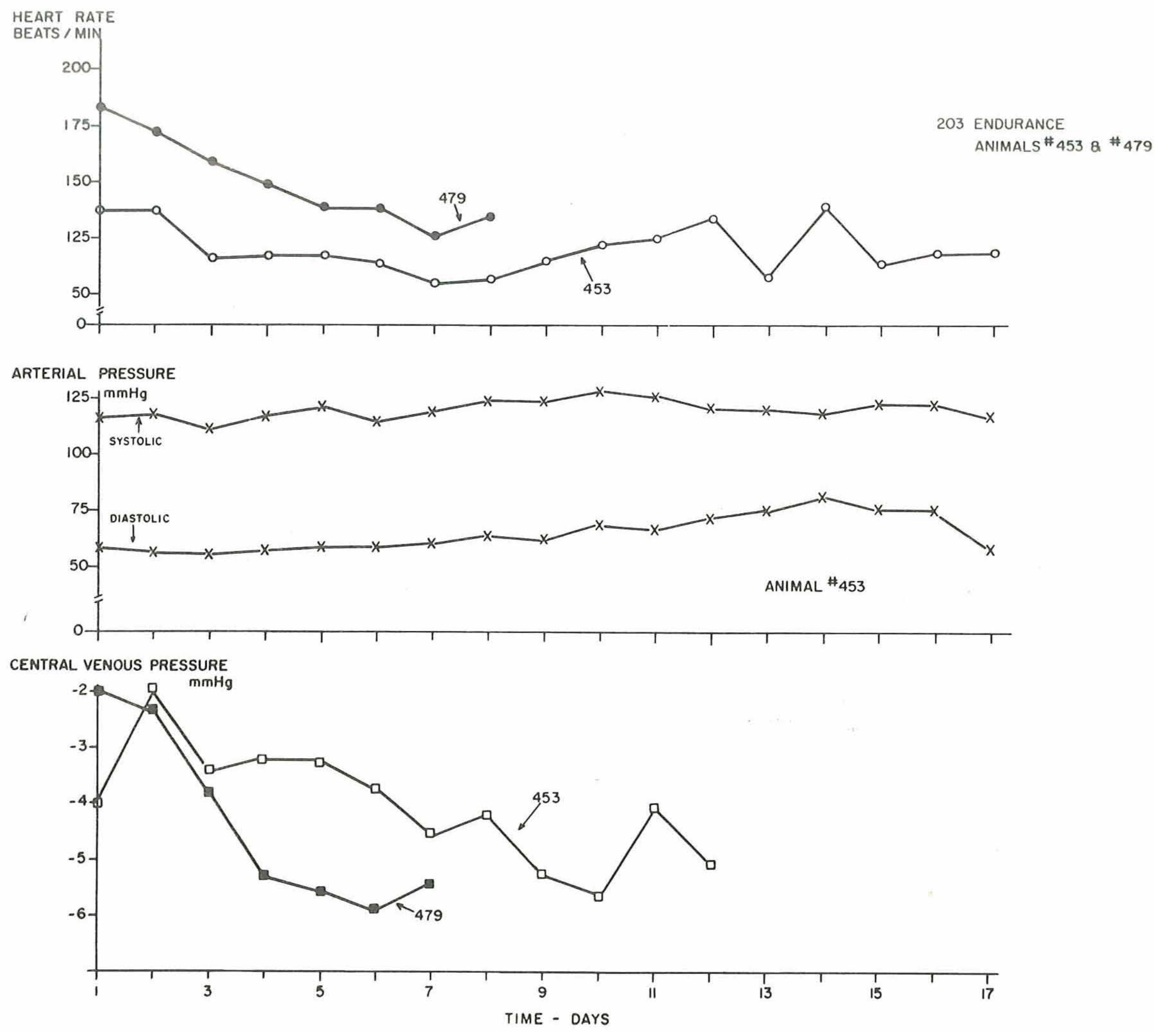


FIGURE 14: COMPARISON OF CARDIOVASCULAR DATA OBTAINED DURING THE ENDURANCE TESTING

B. Endurance Tests

Four monkeys were prepared as subjects but only two were used in the capsule test. Animal #479 was put into the capsule February 8, 1969, remaining there until February 17. The next day (February 18), monkey #453 was inserted in the capsule as a replacement: #453 was in good health when removed on March 8, 1969. Data from both monkeys is shown in Table 1 which also includes back-up data from #453 before entering the capsule.

(1) #479 Endurance

Heart rate and central venous pressure (Fig. 14) were the most labile parameters of cardiovascular data for #479. After insertion into the capsule, the monkey's heart rate dropped rapidly from a daily average of 185 beats/min to 130 beats/min in eight days: central venous pressure decreased rapidly from the initial insertion into the capsule, until his recovery. Arterial blood pressure could not be analyzed adequately, however, because of inoperative arterial blood pressure transducers. The animal was removed from the capsule after indications of failing health and was found in poor condition.

Extensive analysis was made of the animal's deteriorating condition in an attempt to identify the cause. Toxicity appeared to be a probable cause.

(2) #453 Endurance

Animal #453 was inserted in the capsule February 18, 1969, to replace #479. The heart rate of this test animal (Fig. 14) showed a similar trend for the first few days, falling from approximately 140 beats/min to 100 beats/min in six days. This trend was reversed after six days; and the mean rate increased and eventually settled at about 125 beats/min. The arterial blood pressure was rather constant, showing only a slight increase. Venous pressure decreased during the test.

C. Thermal Vacuum Test

Two monkeys, #478 and #422, were prepared for this test. Animal #478 was selected as a test subject and #422 remained as a back-up. Data for both animals were recorded from February 23 through March 6 and 7, 1969. There was a notable tendency for the heart rate of the capsule-test animal to decrease more rapidly than that of the back-up animal. The central venous pressure of the test animal also dropped rapidly. The test was successfully completed on March 7. Data from the back-up animal are also presented in Table 1.

	ANIMAL NUMBER	TEST	HEART RATE - BPM INSERTION	HEART RATE - BPM RECOVERY	HR CHANGE BPM/DAY AVERAGE	CENTRAL VENOUS mmHg	CENTRAL VENOUS mmHg/DAY	ARTERIAL BLOOD PRESSURE mmHg ABSOLUTE	ARTERIAL BLOOD PRESSURE mmHg CHANGE	ARTERIAL BLOOD PRESSURE mmHg CHG/DAY	BRAIN/BODY TEMPERATURE DIRECTION	DATE	DURATION
1	208	601	180	180	0							11/67	29
2	223	602	150	175	+1.00			117/90 - 143/100	+26/+10	+1.00/+0.40		8/68	26
3	472	THERMAL VACUUM BACK-UP	199	195	-0.66	0	0	117/77 - 126/81	+9/+4	+1.50/+0.66		2/69	6
4	453	ENDURANCE BACK-UP PERIOD	174	140	-3.70			112/67 - 115/59	+3/-8	+0.37/-1.00		2/69	8
5	467	KSC GROUND TEST	170	110	-6.60	+1.00	+0.11	102/66 - 113/71	+11/+5	+1.20/+0.55	↘	7/69	9
6	446	KSC GROUND TEST	215	160	-6.10	-1.00	-0.11	124/84 - 128/80	+4/-4	+0.44/-0.44	↘	7/69	9
7	264	KSC GROUND TEST	165	185	+2.20	+1.00	+0.11	122/80 - 150/87	+28/+7	+3.10/+0.77	↗	7/69	9
8	589	KSC GROUND TEST	180	130	-7.10	0	0	107/77 - 100/65	-7/-12	-0.77/-1.30	↘	7/69	7
9	581	POST FLT. FIRST 8 DAYS	160	137	-3.00	-2.25	-0.28	109/68 - 104/62	-5/-6	-0.60/-0.80	↘	10/69	8
10	581	TOTAL POST FLIGHT	160	90	-4.30	-3.00	-0.18	109/68 - 99/67	-10/-1	-0.60/0	↘	10/69	16
11	479	ENDURANCE	185	135	-6.20	-3.40	-0.42	108/58			↘	2/69	8
12	453	ENDURANCE FIRST 7 DAYS	140	105	-5.00	-1.00	-0.14	115/59 - 120/61	+5/+2	+0.70/+0.30	↘	2/69	7
13	453	ENDURANCE ENTIRE TEST	140	125	-0.75	0	0	115/59 - 127/68	+12/+10	+0.60/+0.50	↘	2/69	20
14	478	THERMAL VACUUM	237	175	-15.00	-1.30	-0.32	96/67 - 94/62	-2/-5	-0.50/-1.20		2/69	4
15	470	FLIGHT	170	50	-13.00	-3.50	-0.39	132/82 - 64/25	-68/-57	-7.50/-6.30	↘	7/69	9

TABLE I

D. <u>Endurance and Thermal Vacuum Test Summary</u>

The outcome of the endurance test was somewhat unsatisfactory due to the change of animals after eight days in order to complete the 30-day test; however, the test did validate the mechanical function of all cardiovascular hardware. There was some doubt that the environmental control system was adequate for coping with toxic substance; also, since the failing health of #479 could not be singularly attributed to the toxicity problem, there was doubt

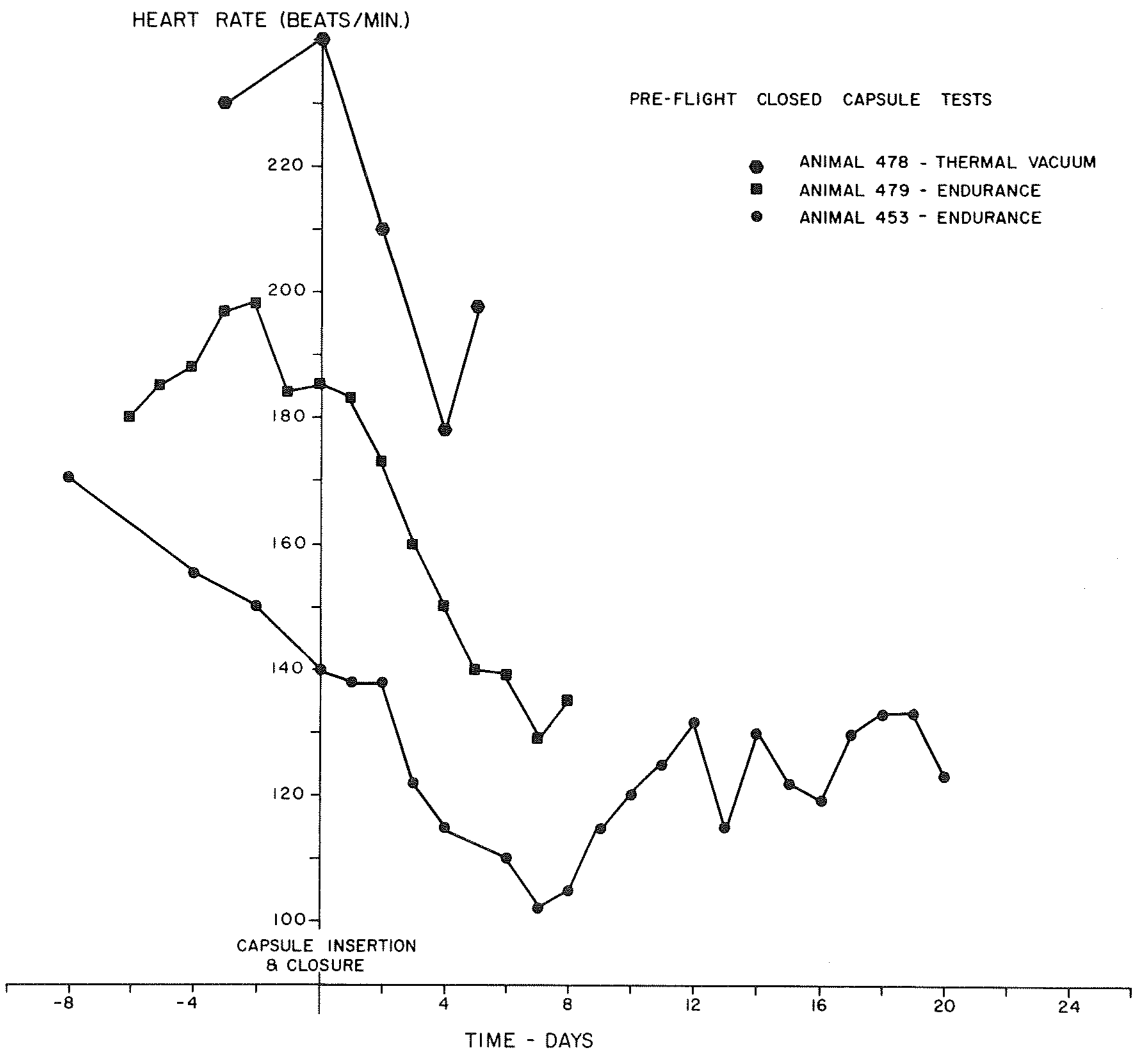


FIGURE 15: COMPARISON OF AVERAGE DAILY HEART RATE OF TEST ANIMAL USED IN THE ENDURANCE AND THERMAL VACUUM TEST

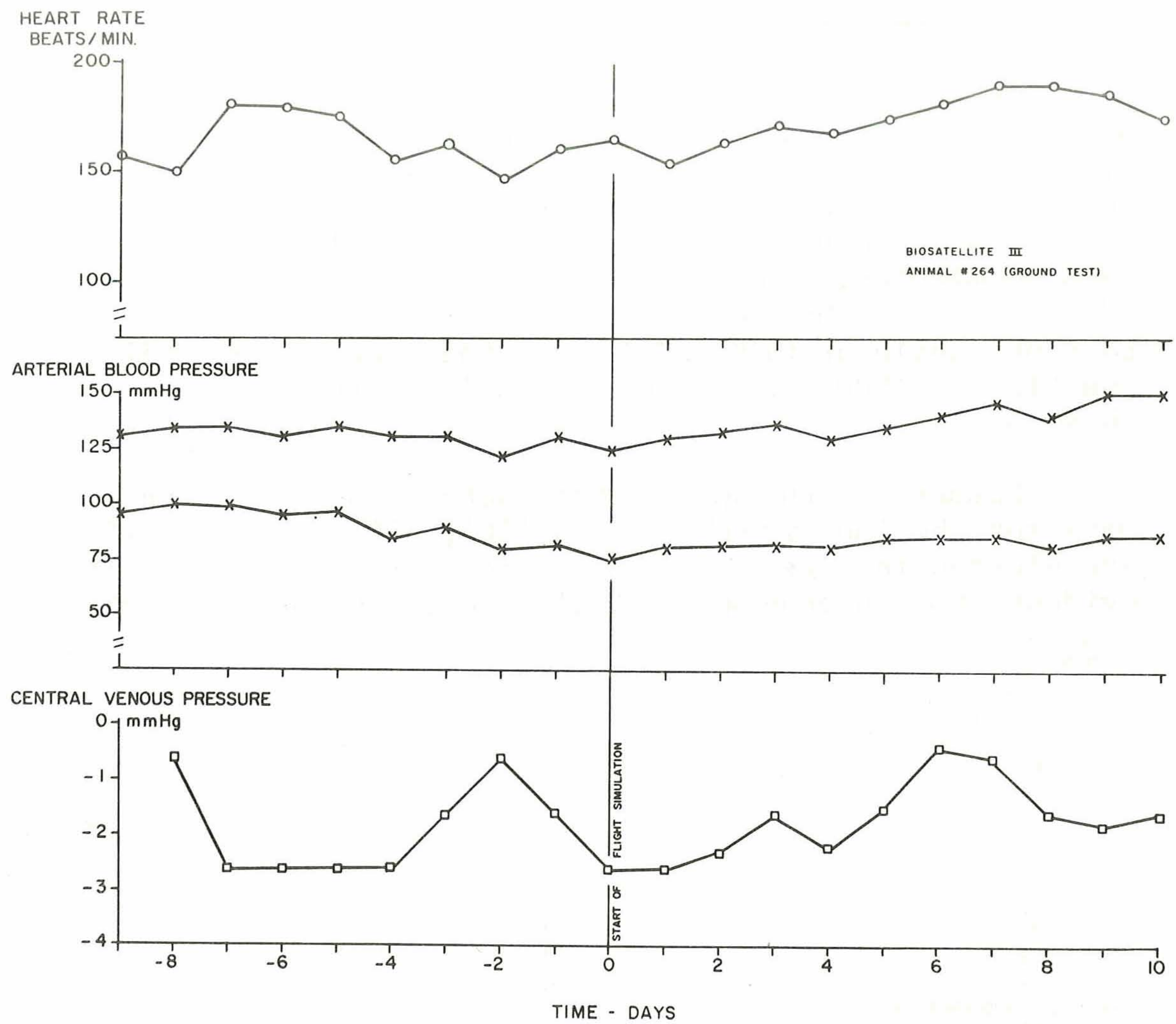


FIGURE 16: GROUND TEST DATA ON SUBJECT #264

whether an animal would be able to survive a 30-day period in a closed capsule environment. A pronounced decrease in heart rate occurred when the monkeys were put into the test capsule (Fig. 15). It appeared that the animals were adjusting to a new environment where the presence of man was less obvious. Consequently, a compromise in the definition of a successful flight resulted in shortening the acceptable flight time to 14 days.

The thermal vacuum test results were quite acceptable. Both animals and hardware performed satisfactorily throughout the test. The rapid decrease in heart rate was attributed to the adjustment to the new environment.

E. Kennedy Space Center Simulated Flight Tests

Ground test animals followed a routine similar to that of the flight animal with a 48 hour time lag to incorporate flight conditions regarding food and water and temperature and humidity. Each animal was placed in a capsule simulator housed in a sound-proof room. Cardiovascular data was taken each 90 minutes, and food and water were offered at prescribed intervals. The animal was moved from a reclining position to a 60^{o} angle at 0700 E.S.T. and then back to a reclining position at 1900 E.S.T.; urine bottles were also changed at these hours.

Summary of the ground test data is shown in Table 1. Data for the individual animals #264, #446, #467 and #589 are plotted in Figs. 16, 17, 18 and 19 respectively. It is evident that in general, animals #589, #446 and #467 show

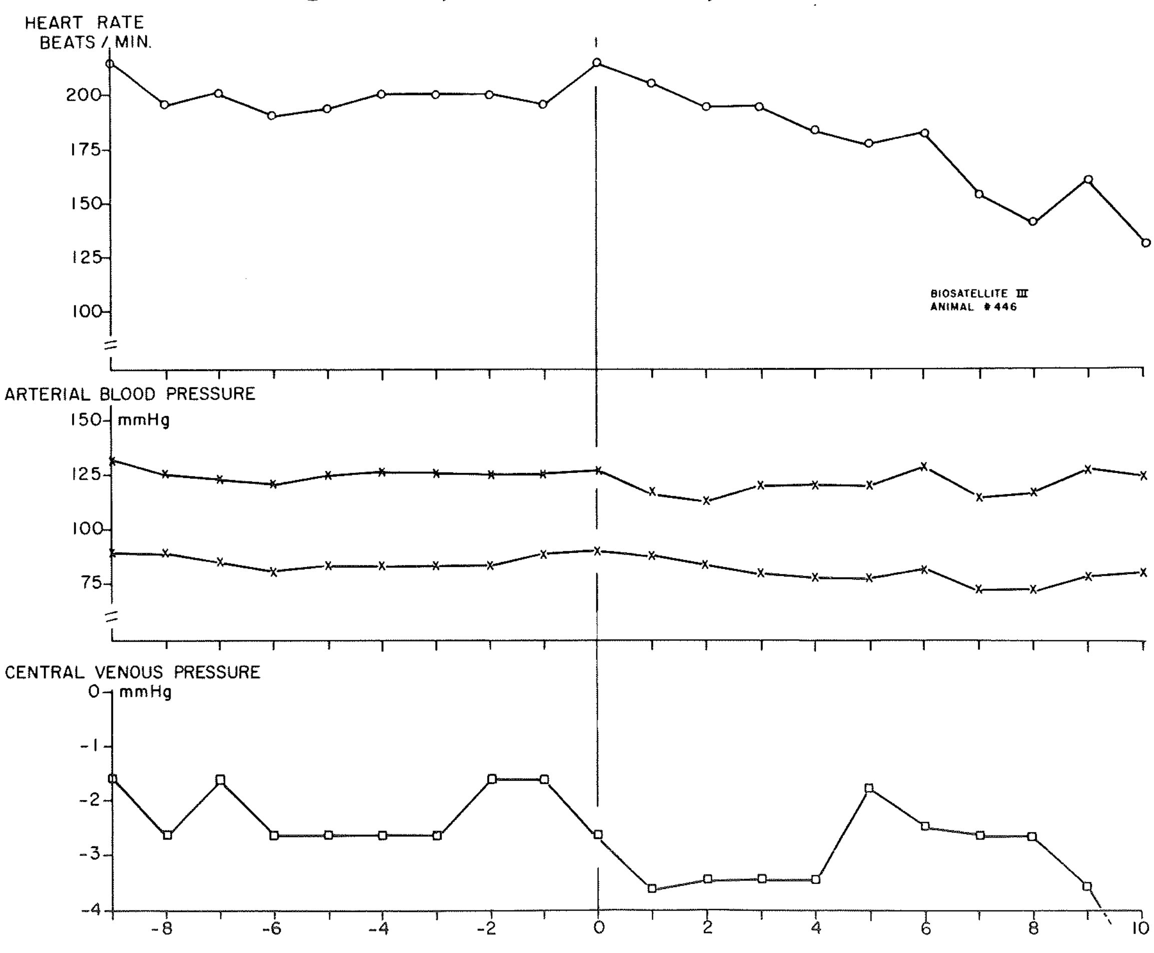


FIGURE 17: GROUND TEST DATA ON SUBJECT #446

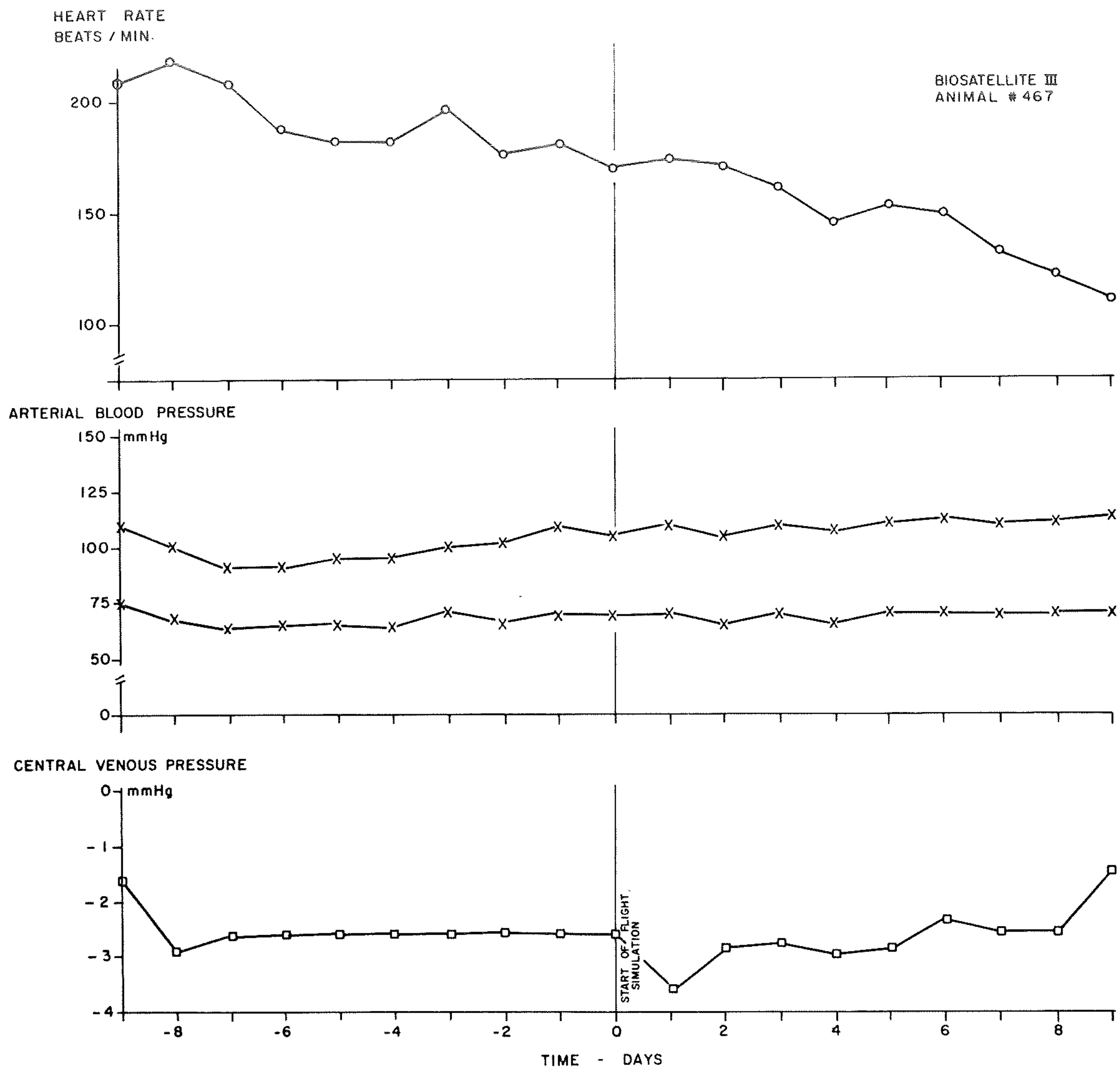


FIGURE 18: GROUND TEST DATA ON SUBJECT #467

similar responses except for central venous pressure. Heart rates declined for all except #264. Arterial pressure remained fairly constant for all animals. Note that #264 showed responses different from the other ground test animals (Table 1). This response is atypical, for no other test animal shows an increasing heart rate and an increasing temperature.

F. Post Flight Tests

As part of an effort to evaluate the physiological responses of space monkey #470 in relation to his total environment, additional experiments were conducted to determine the effects of long-term restraint, isolation and cold stress on adult male macaques. The first animal was kept in a restraint suit from October 1, to October 28, 1969. During this time he was put into isolation for 5 and 7 days respectively, which were separated by 4 days of nonisolation. He was subjected to cold (63^{O}F average) for the final 11 days which included the 4-day nonisolation and the 7-day isolation periods. He was monitored for heart and respiration rates, arterial and venous pressures, skin temperature of the thighs,

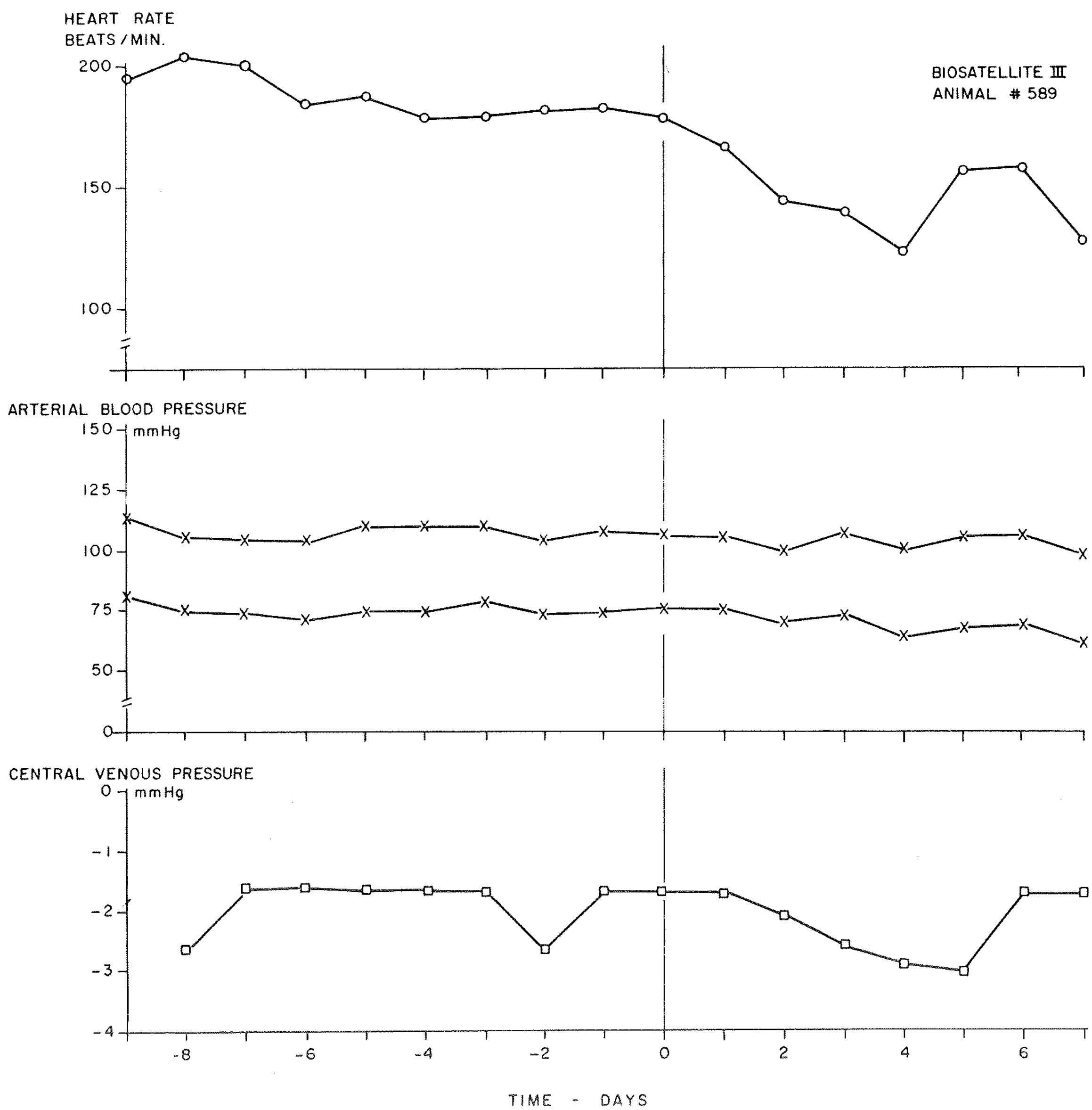


FIGURE 19: GROUND TEST DATA ON SUBJECT #589

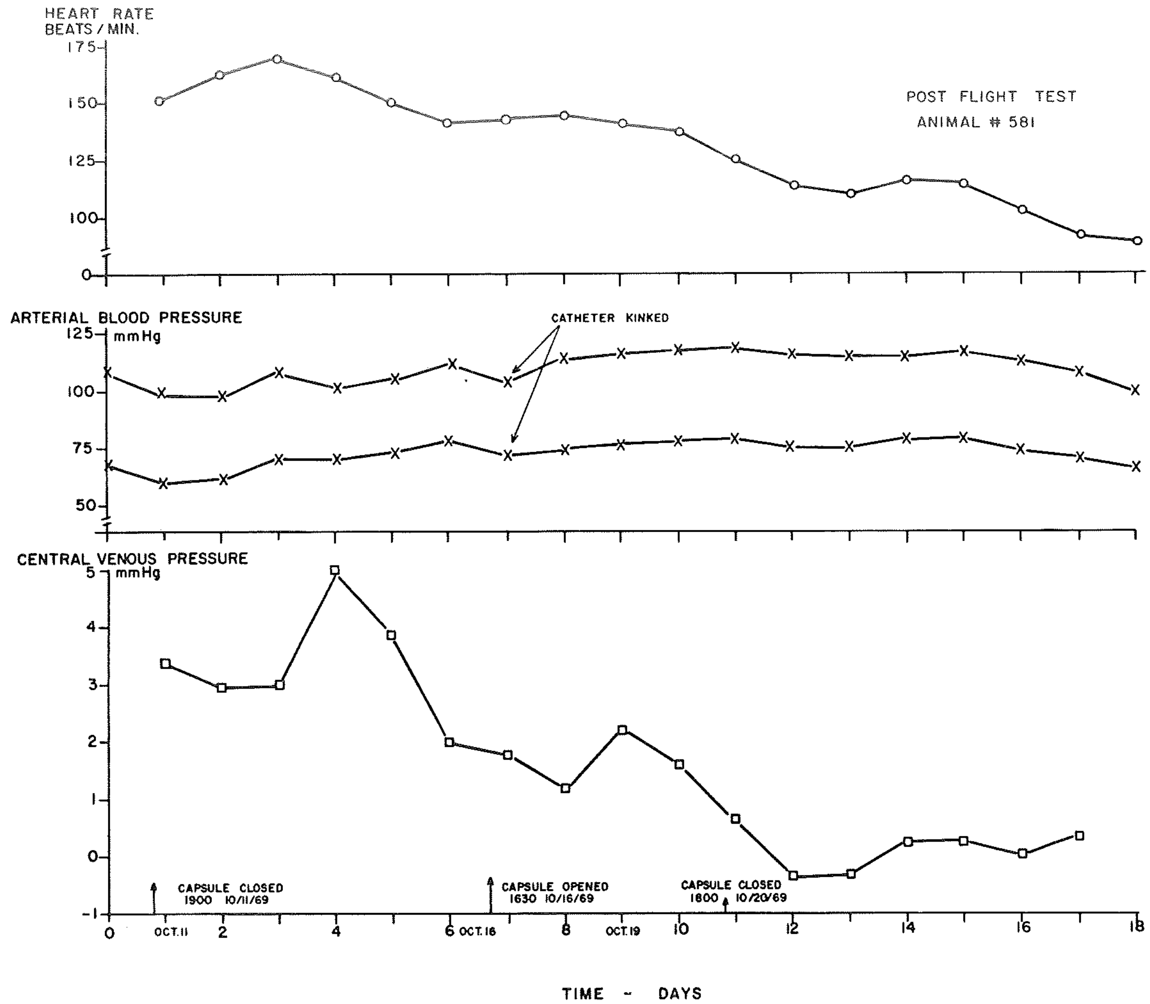


FIGURE 20: POST FLIGHT TEST DATA ON TEST SUBJECT #581

feet and neck, water intake and urine output. Ambient temperature was measured. His general activity was observed on closed-circuit television.

Results of the experiment are shown in Fig. 20. Average values of three different parameters were plotted daily from October 11 to October 27. Skin temperature of the thigh showed a general decline throughout the test, indicating that it was relatively little affected by the presence or absence of isolation. Cold stress below an ambient temperature of 65°F seems to have been sufficient to cause a steady drop in thigh temperature as indicated by all recordings between October 11 and October 27. Respiratory rate also showed a general decrease. Water balance as determined by the relationship between water intake and urine output appeared to be adequately maintained. The monkey did not show signs of dehydration when removed from isolation on October 28. He was, however, somewhat lethargic and had a rectal temperature of 89°F. He gained one-half pound within three days after his removal from isolation (October 28-31).

A second animal was subjected to a similar test except that no attempt was made to achieve isolation. Only stress related to environmental temperature and angle of body position was intermittently imposed. A thermister implanted in the thoracic cavity measured core temperature and venous pressure was measured by a miniature pressure implant in the vena cava. The data correlated against test

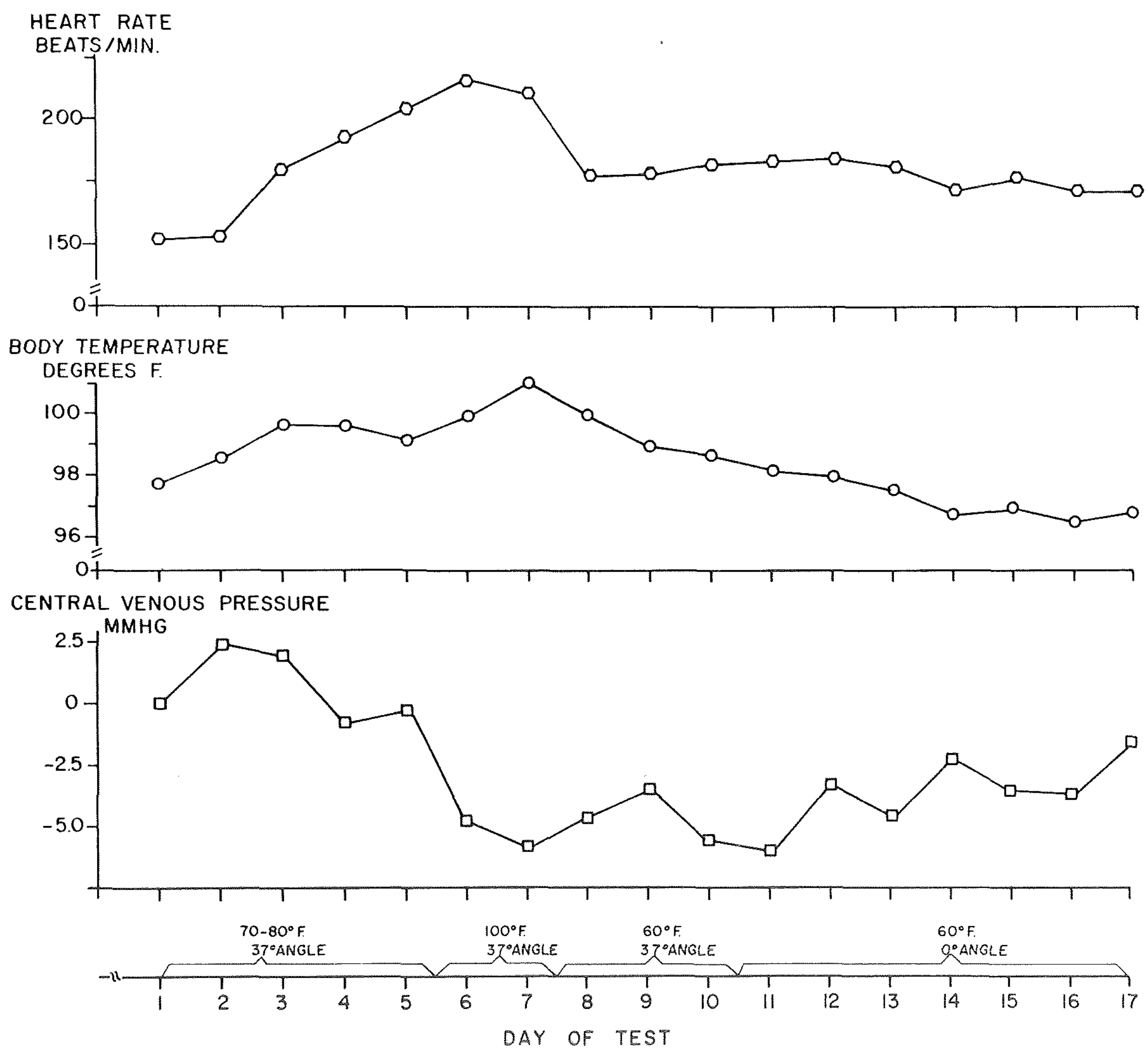


FIGURE 21: POST FLIGHT TEST DATA ON TEST SUBJECT #664

conditions is shown in Fig. 21. The heart rate, body temperature and venous pressure decreased and ratio of urine/water was near unity except during the high temperature interval where water intake exceeded the urine output by a factor of more than 3.

IV. FLIGHT EXPERIMENT

A large number of flight candidates were implanted with brain probes by UCLA personnel several months before the scheduled launch date; however, these animals first received extensive training and were screened to select the most desirable among them.

UCLA trained these monkeys to perform two tasks: The DM task of delayed matching of symbols tested recent memory and perception, and the VM task, a hand-eye coordination test, required the ability to detect coincidence of two rapidly rotating objects.

Transparent switches were used for the DM task. A special light tube capable of displaying four symbols -- square, X, circle and triangle -- was placed beneath each switch. One of four symbols was flashed at random and the monkey was required to touch the center switch when a symbol appeared beneath it, thus extinguishing the symbol. Eighteen seconds later the same symbol reappeared beneath one of the four outer switches and the three remaining symbols also appeared beneath their respective switches. To make a correct response, the animal was required to press the outer switch which contained the same symbol presented earlier on the center switch. Two such correct responses resulted in a food pellet as a reward. If he selected another symbol, i.e., the wrong selection, the task was terminated.

A transparent surface disk was used in the VM task so the monkey could see the button on the inner disk at all times. This button, which the animal was required to press, was exposed when the coincidence hole of the surface disk was in alignment with it. Both disks rotated continually during the task. The surface disk revolved at approximately 65 rpm, and the inner disk revolved in the same direction but at a slightly higher rate. At these velocities the opportunity button was exposed for pressing approximately 2 seconds every 45 seconds. Every second successful completion of this task was also rewarded with food. At each session 20 trials of DM tasks were followed by 20 trials of VM tasks. Each trial lasted approximately 45 seconds.

The monkey could collect his food pellet reward from a dispenser by operating a lever and had access to periods of ad lib feeding also. Water was available at a maximum rate of 480 ml/24 hours, but the supply could be adjusted by ground command if necessary or desirable.

The first phase of the cardiovascular surgical preparation of the five flight candidates consisted of attaching two suture electrodes across each animal's thorax. The right electrode was placed at about the sixth intercostal space, and the left one somewhat lower in order to obtain a higher amplitude electrocardiogram. These electrodes also measured respiration depth and rate.

The second phase of the surgery consisted of inserting small teflon catheters into the vascular system. Two were placed in the venous system and two in the arterial system. One venous catheter was placed in the right atrium by entering the straight saphenous vein in the left leg below the knee, then advancing the catheter tip progressively through the femoral and iliac veins, through the vena cava, and, subsequently, terminating the catheter tip in or close to the right atrium. The second venous catheter was placed at approximately the level of the inferior vena cava or at the entrance to the right atrium by a similar route via the right leg. These two catheters supplied a redundant measure of central venous and/or right heart pressures. Arterial circulatory pressures were obtained from two catheters which were placed in the abdominal or thoracic artery with the access to this area gained through the anterior tibial arteries of both legs, then through the femoral and iliac arteries.

When the four catheters were properly positioned, the animal was put into a snug-fitting suit and placed on a specially designed restraint couch. The catheters were connected to the data conditioning system with approximately 30-inch 0.042 I.D. stainless steel tubing. The electrodes were also connected to the signal conditioning equipment. Electrical analog of the pressures, the electrocardiogram and the respiration rate were then recorded as appropriate.

Of the five candidates, monkey #470 was selected as the optimum flight subject and launched on June 28, 1969 at 2310 E.D.T. The active portion of the experiment was terminated after the death of the animal on July 8, 1969 at approximately 2400 Hawiian Standard Time.

Cardiovascular data was obtained from seven days preceding the launch until the monkey's death. The animal exhibited a marked reduction in heart rate, arterial and venous pressures and body temperature (UCLA data) during flight. He was dehydrated when recovered and failed to respond to remedial treatment.

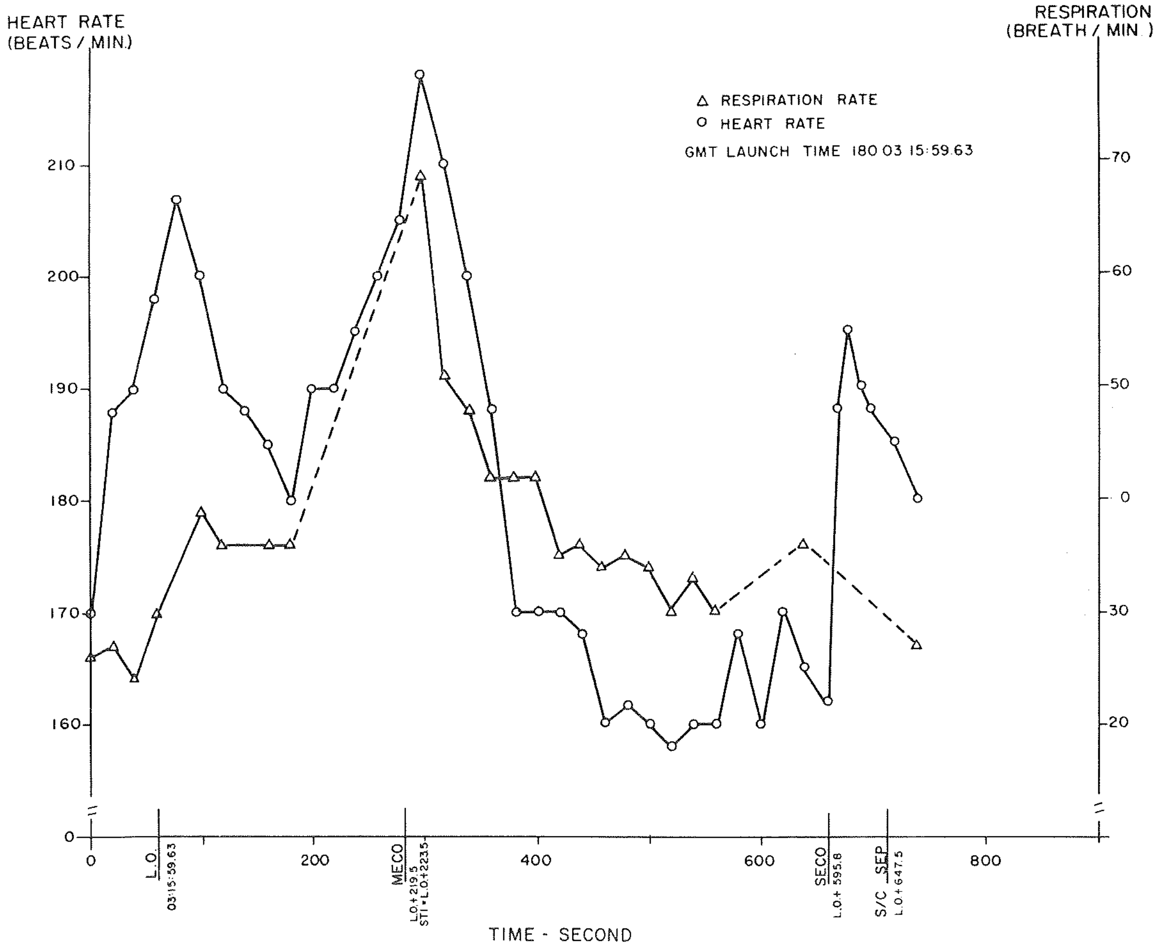


FIGURE 22: HEART AND RESPIRATION RATE CHANGES DURING LIFT-OFF SEQUENCE

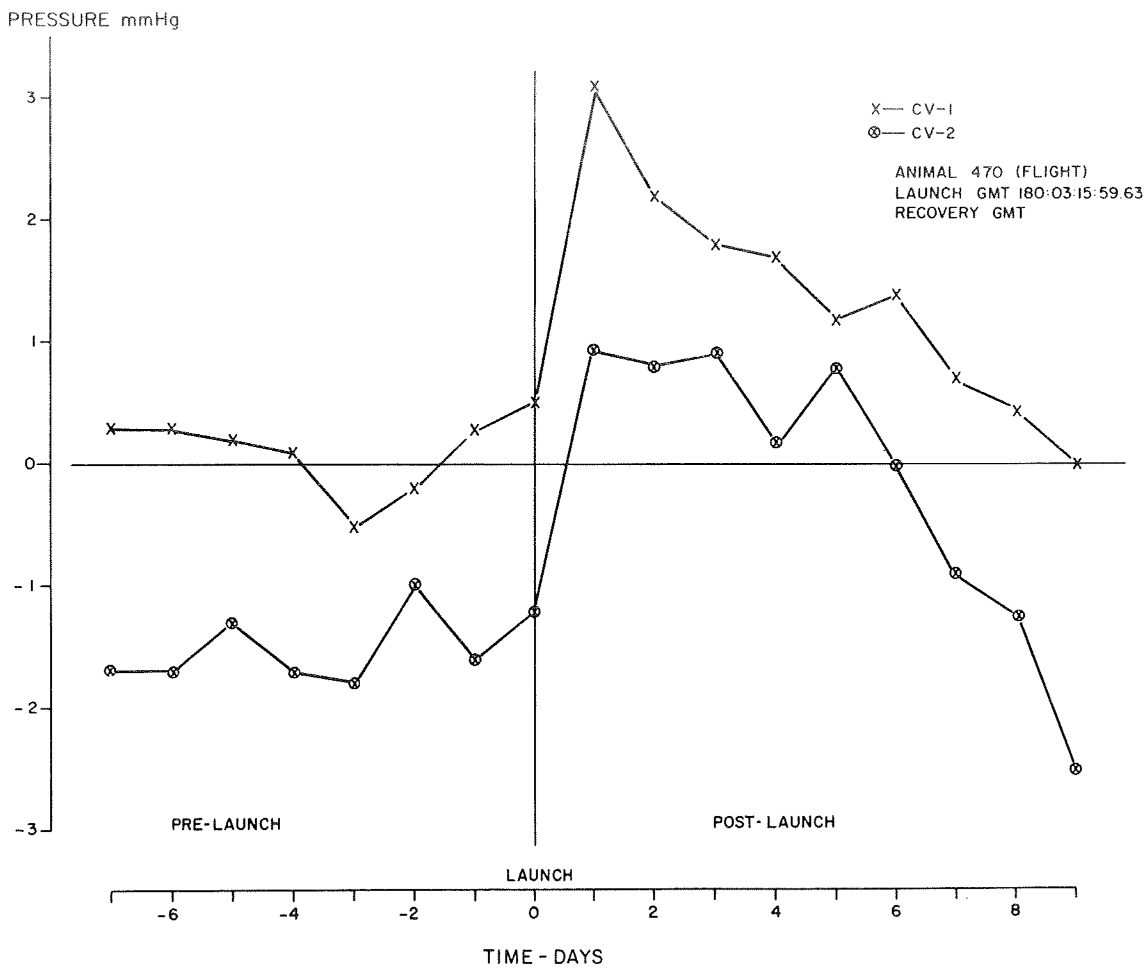


FIGURE 23: VENOUS PRESSURE DATA FROM THE TWO VENOUS CATHETERS

Flight data is presented in Figs. 22 through 32. Figure 22 shows the dynamics of the animal's reaction to the launch. The monkey faced the direction of acceleration with the long axis of the body perpendicular to the direction of acceleration. The increase in heart rate several seconds before ignition to the initial lift-off was apparently a reaction to vehicle motion and noise. After the main engine cutoff (lift-off +223.5 seconds) both the heart rate and respiration rate declined until the second engine cutoff, at which time the heart rate increased.

Initial orbital values of central venous pressure showed a marked increase relative to the ground levels. This was predicted on the basis of a reduction in gravitational effects on the long axis of the body and a consequent decreased pooling of blood in the extremities. Figure 23 illustrates this response: The upper curve shows the pressure measured near the right heart and the lower curve the pressure measured essentially in the right atrium. The pressure difference between the two catheters of approximately 2 mm Hg is reasonable. The dynamic response of each tracing substantiates their placement. The increase in pressure of approximately 2 mm Hg upon achieving orbit is on the same order of magnitude as that produced by changing position from day to night on the ground-test animal. Figure 24 illustrates the venous pressure response obtained when the position of the flight animal was altered

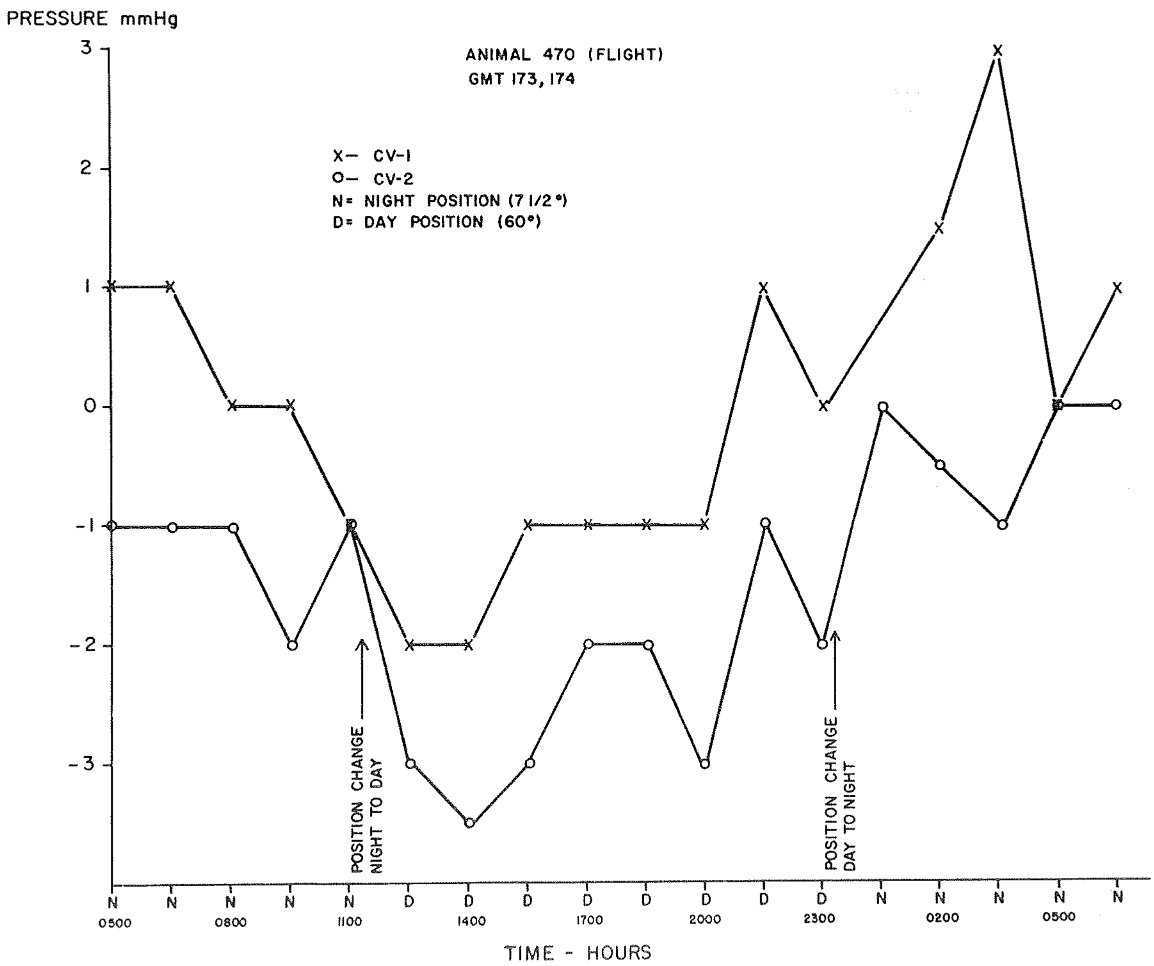


FIGURE 24: CYCLIC VARIATION IN CENTRAL VENOUS PRESSURE INDUCED BY POSITION

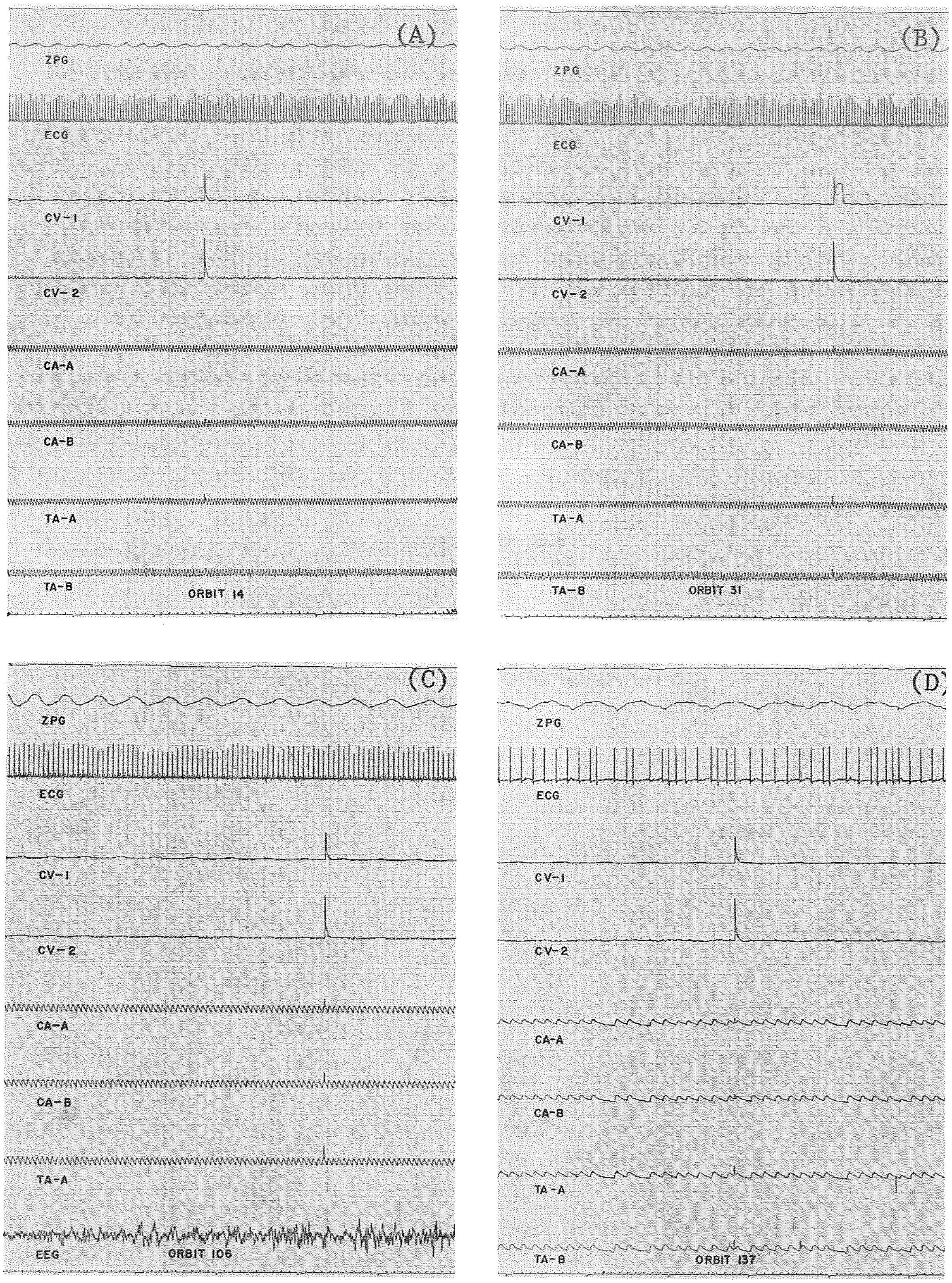


FIGURE 25: SAMPLES OF CARDIOVASCULAR DATA OBTAINED THROUGHOUT THE FLIGHT

according to prescribed schedules before launch. The pressure level is approximately 2 mm Hg higher in the night position than the level in the day position. These pressure levels agree with the concept that blood pools in the extremities when the subject is in a more upright position, causing a lowering of pressure in the chest region.

Samples of data received at the Goddard Space Flight Center during the flight are shown in Fig. 25. The upper channel on each chart is respiration; the second is electrocardiogram; the third and fourth are central venous pressure; and the fifth, sixth, seventh and eighth are arterial pressures. Channels 6 and 8 are samples at slower

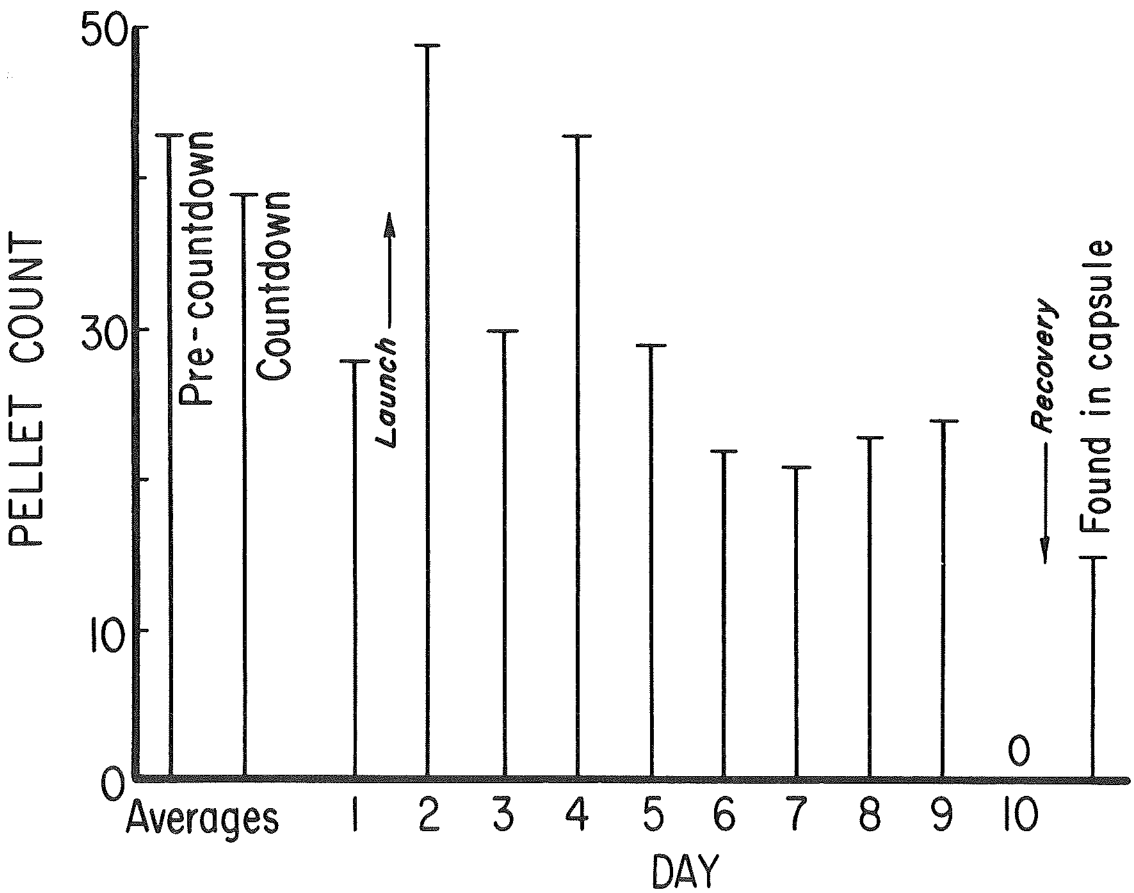


FIGURE 26: FOOD PELLETS DISPENSED.
DAY 1, THE MONKEY IS IN THE CAPSULE.
DAY 2, IS THE FIRST DAY OF FLIGHT.
(UCLA DATA)

rates, producing the rather blocked waveform. The pulse appearing on all pressure measurements results from heparin infusion. The quality of the data received throughout the flight remained very good. The heart rate in Fig. 25 (D) is considerable slower than in Fig. 25 (A), thus permitting a better inscription of the arterial pressure curves.

Figure 26 shows the number of food pellets dispensed before and during the flight. The number of food pellets taken on the first flight day exceeded precountdown averages. After the third day of flight, the number of pellets taken fell to approximately half the number taken during the precountdown control period.

Brain and body temperatures are plotted in Fig. 27. At the end of the third day the temperatures began to drop to a point below the lower end of the available temperature range on the amplifier.

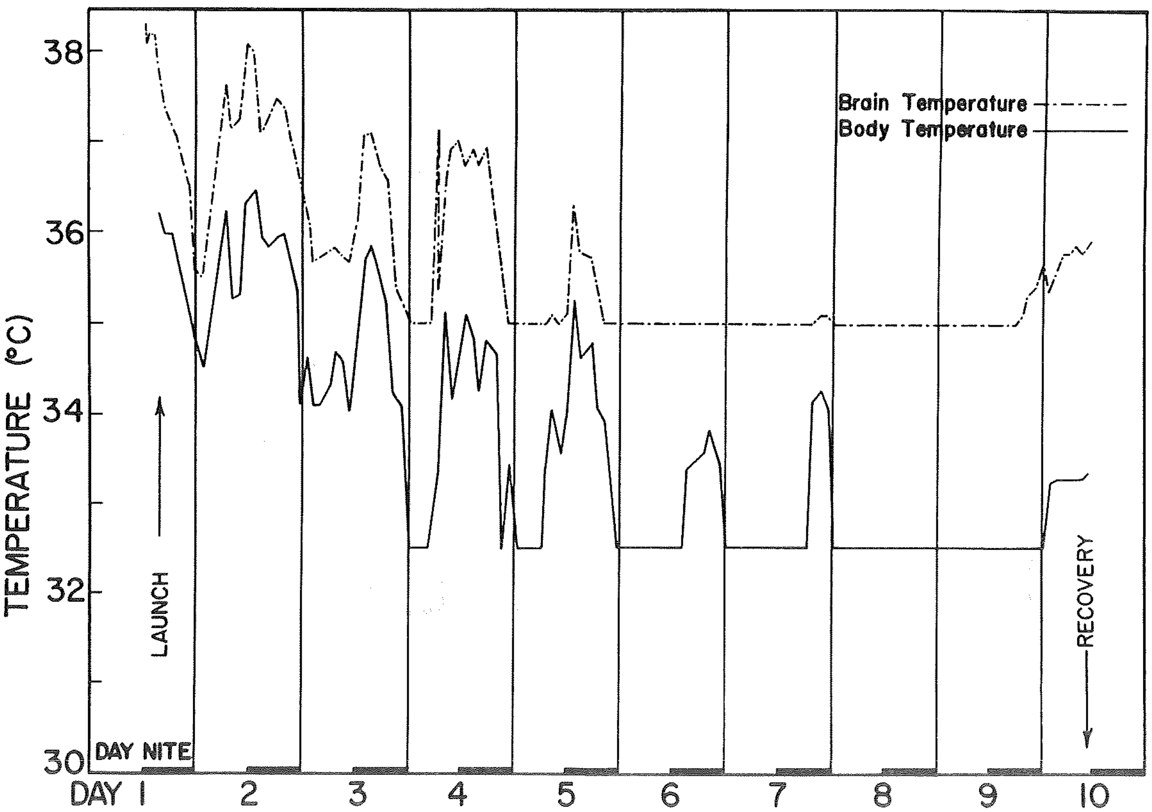


FIGURE 27: BRAIN AND BODY TEMPERATURES OF THE FLIGHT ANIMAL (UCLA DATA)

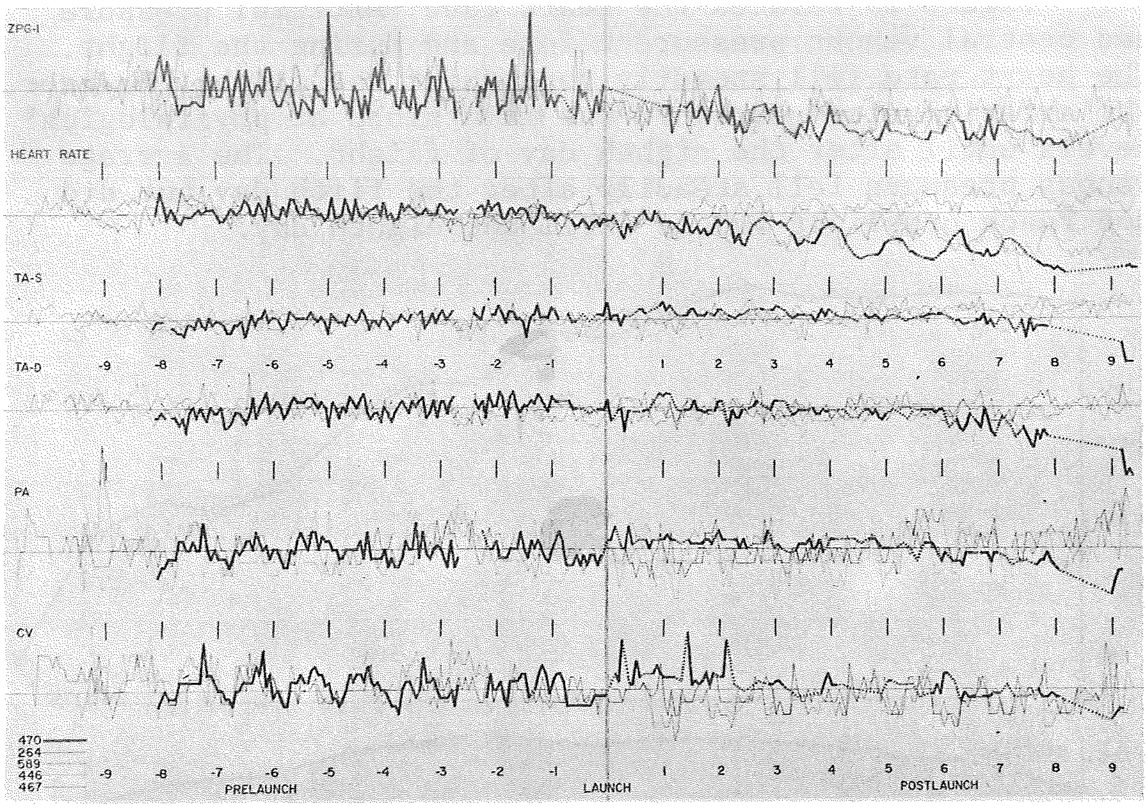


FIGURE 28: COMPILED CARDIOVASCULAR DATA. THE DATA IS NORMALIZED OVER THE PRELAUNCH PERIOD SUCH THAT THE DATA IN THE POST LAUNCH PERIOD INDICATES DEVIATIONS FROM THE PRELAUNCH DATA. TRACES FROM TOP TO BOTTOM ARE AS FOLLOWS:

ZPG-1:	RESPIRATORY RATE
HEART RATE:	
TA-S:	SYSTOLIC ARTERIAL PRESSURE
TA-D:	DIASTOLIC ARTERIAL PRESSURE
PA:	CENTRAL VENOUS PRESSURE
CV:	CENTRAL VENOUS PRESSURE

Figure 28 records the cardiovascular data for the flight animal plus the four that were instrumented and held as ground controls. Both the respiratory rate and the heart rate of the flight monkey showed progressive shifting of the 24-hour rhythm when compared with the data for the ground-control animals.

Figure 29 relates the heart rate, arterial pressure and central venous pressure before and during the flight. The heart rate fell steadily throughout the flight, however, the arterial blood pressure was maintained at physiological levels until after the eighth day of flight. The average venous pressure fell steadily after the fifth day but did not reach preflight values until the eighth day.

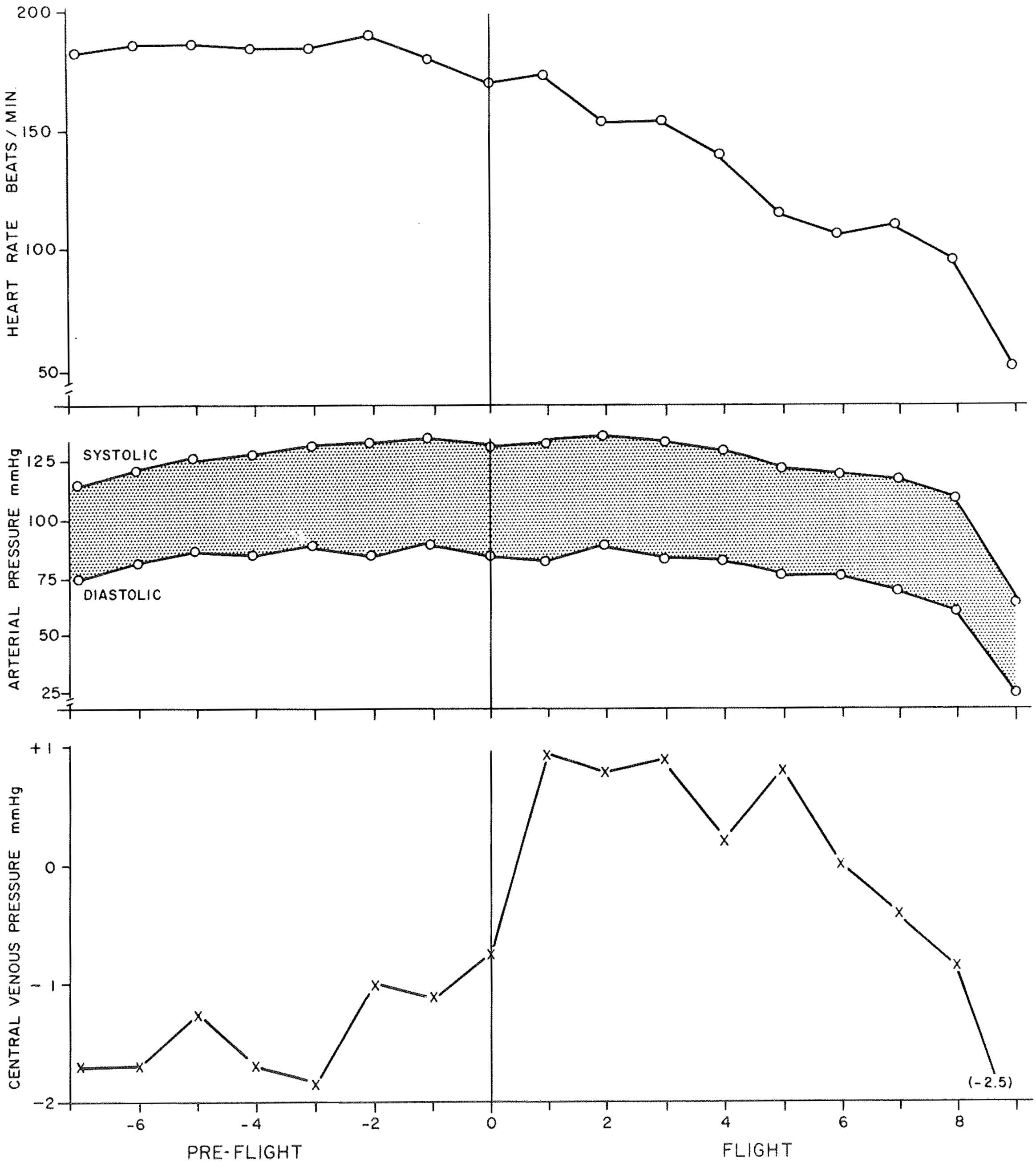


FIGURE 29: HEART RATE, BLOOD PRESSURE AND CENTRAL VENOUS PRESSURE PRIOR TO AND DURING THE FLIGHT.

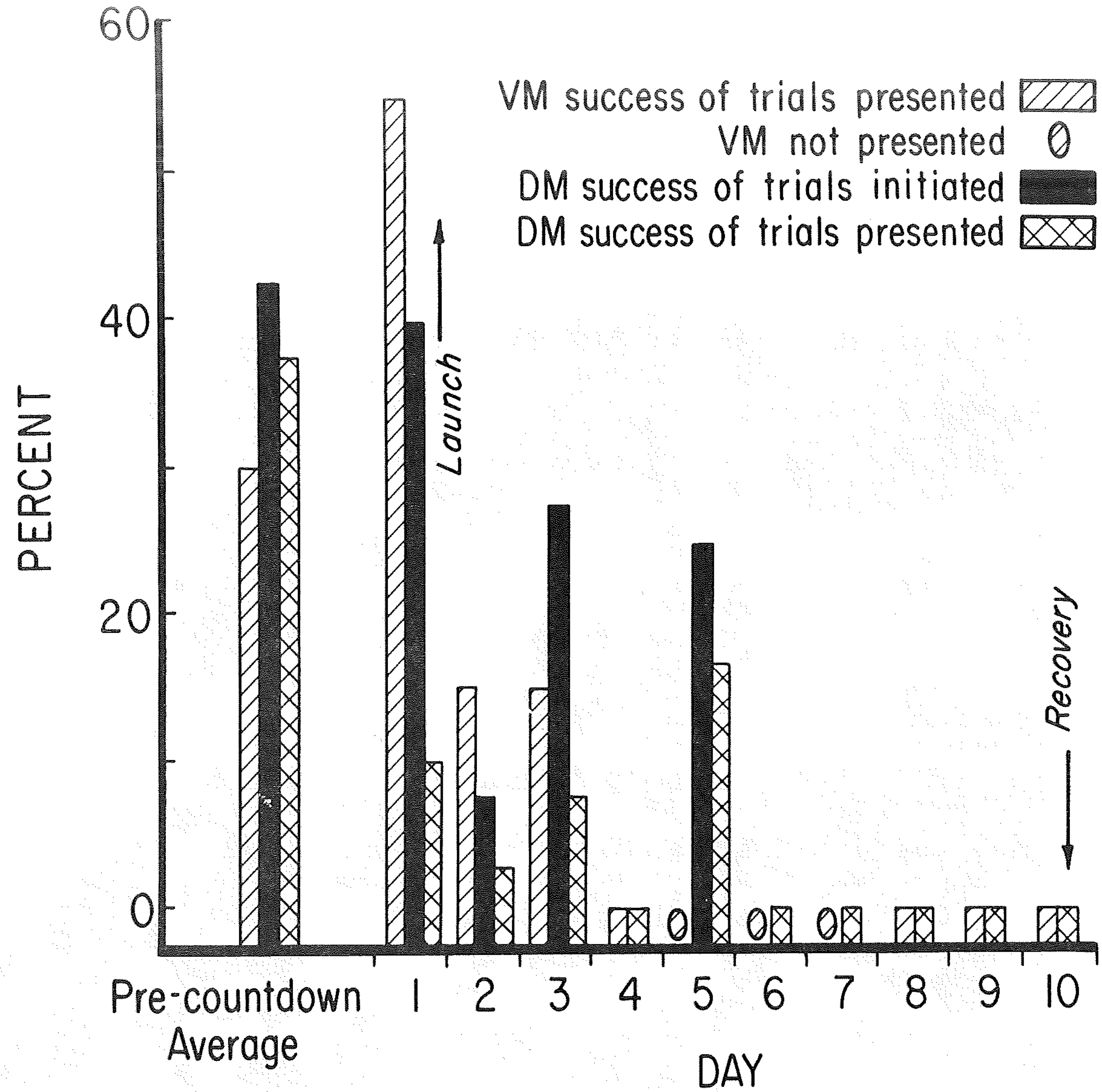
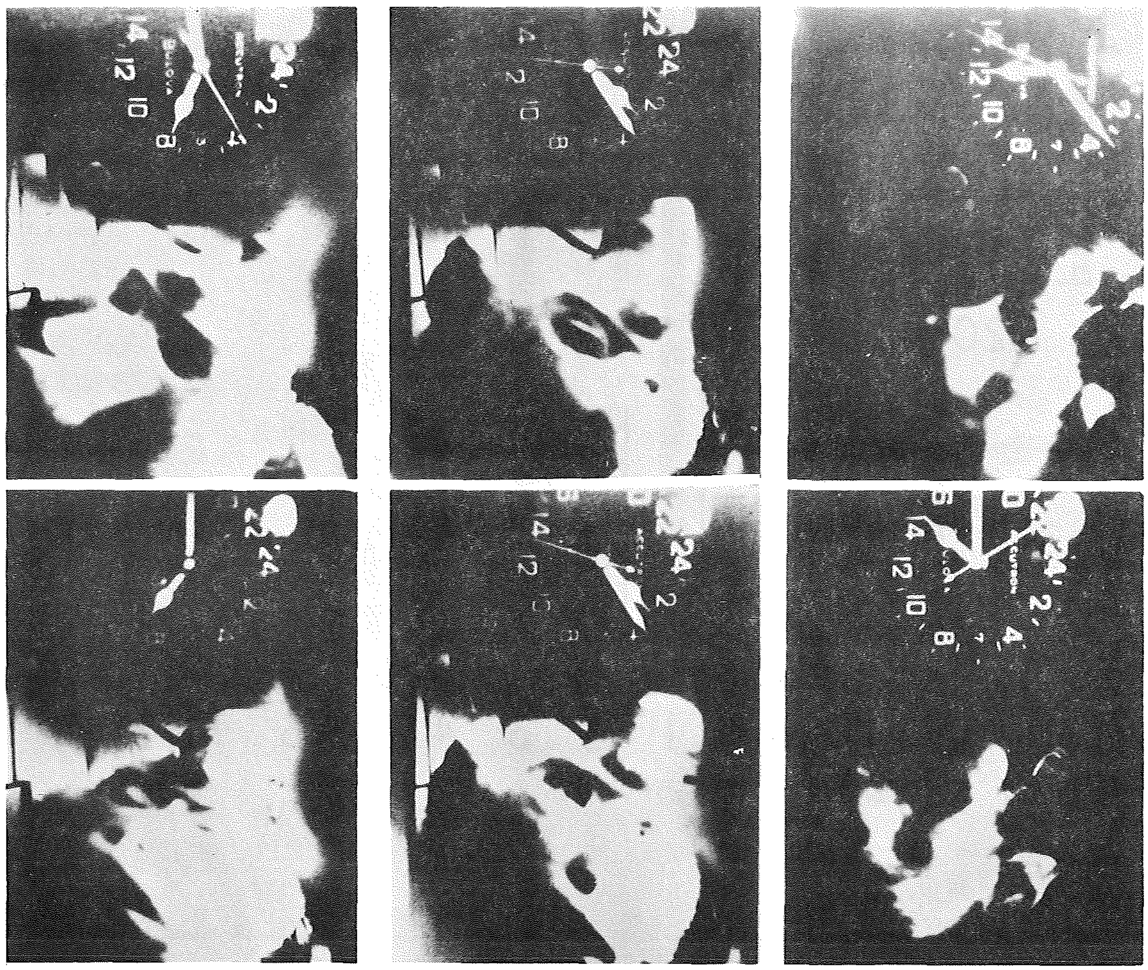


FIGURE 30: THE PERFORMANCE ON THE PSYCHOMOTOR TASKS (UCLA DATA)

The psychomotor tasks data are shown in Fig. 30. The VM task was performed better than 50% on the day preceding the launch and gradually stopped after two days of flight. The DM task performance dropped markedly on the first day of flight, recovered somewhat on the second day, showed negligible response on the third day and almost equalled the second day's record on the fourth day; however, the task performance essentially failed after this and the monkey then obtained all food pellets ad lib. Even on the seventh flight day, the monkey was able to fill his cheek pouches with food pellets and eat them as shown in the pictures obtained with the on-board camera (Fig. 31).



3 DAYS 5 DAYS 7 DAYS

FIGURE 31: SIX FRAMES FROM THE ON-BOARD CAMERA:
DAY 3: TWO PHOTOS, ONE AWAKE AND ONE ASLEEP
DAY 5: DURING DM TASK SESSION
DAY 7: CHEEK POUCHES FILLED AND TWO HOURS LATER, POUCHES EMPTY

V. TEST COMPARISON

In the process of preparing for and conducting this experiment, essentially four classes of experimental tests evolved: (1) The 601 and 602 tests, consisting mainly of restraint with a mild degree of isolation and a partial simulation of the expected capsule environmental parameters. (2) The endurance and thermal vacuum tests having a relatively high degree of isolation and a more exact simulation of expected flight capsule environmental parameters. (3) The KCS ground and post flight tests involving a reasonable degree of isolation and simulating environmental parameters. (4) The flight tests imposing weightlessness and a maximum degree of isolation.

The results of the four types of experiments are summarized in Table 2. The parameters listed are heart rate change in beats per minute per day, and central venous and arterial pressure change in mm Hg per day. Heart rate change was neutral or perhaps slightly positive for the two animals used in the 601 and 602 tests; slightly negative in the KSC and post flight ground tests and negative in the closed capsule test and in the flight test. On the basis of the heart rate change, it appears that there is a difference of response between the closed capsule tests and the simulated capsule tests.

The 601 and 602 tests did not yield valid central venous pressure data. However, central venous pressure decreased in the majority of the other tests. The difference in response between the KSC ground test animals and either the ground-based 203 and 501 closed-capsule test animals, or the flight animal, is quite evident.

Arterial blood pressure results presented a somewhat different story for the flight subject. The level change during the total flight was greater than 50 mm Hg. The value for eight full days in orbit was approximately 25 mm Hg or a rate of change of nearly -3 mm Hg per day. No ground test animal shows this degree of response.

TEST	AVERAGE HEART RATE CHANGE BPM/DAY	CENTRAL VENOUS PRESSURE CHANGE mmHg/DAY	SYSTOLIC PRESSURE CHANGE mmHg/DAY	DIASTOLIC PRESSURE CHANGE mmHg/DAY	AVERAGE DURATION DAYS
601 & 602 2 Animals 208, 223	+0.5	- - - -	- - - -	- - - -	- - - -
KSC Ground Tests 3 Animals 467, 446, 264	-3.5	+.04	+1.6	+0.30	9
Post Flight Ground Tests 1 Animal - 581 First 8 Days	-3.0	-.28	0.0	0.00	8
G.E. Capsule Tests 3 Animals 453, 479, 478	-8.7	-.33	+0.1*	-0.45*	7
Flight Test** 1 Animal - 470	-9.6 -13	-.25 -.39	-3.0 -7.5	-2.60 -6.30	Partial Flight 8 Total Flight 9

* Average of two animals due to loss of information on the third animal.
** These parameters were measured from shortly after launch and prior to recovery.

TABLE 2: TEST COMPARISON. The tests are listed in order of increasing isolation with the minimum isolation at the top. The average heart rate change in beats per minute per day, central venous pressure change in mmHg per day and systolic and diastolic pressure changes in mmHg per day were determined by the difference between the numbers on the first and last day of each test. An attempt was made to select tests or portions of tests which were of approximately the same duration as the flight experiment.

VI. DISCUSSION

The rapid physiological deterioration of the flight animal was not expected, especially in view of the history of successful manned flights for as long as 14 days. There are, however, many differences between the manned flights and the flight of the monkey, so that the sum total of stress factors operating on the monkey were much higher than for the astronauts. Thus it was necessary to have the monkey in close restraint because of the various catheters and other instrumentation; and even though the animal subjects were conditioned to the type of restraint required, the experience frustrated their normal drives.

The astronauts were confined also, but they did have some freedom of movement in the early flights and indeed considerable movement during the later flights in larger spacecraft. Furthermore, the astronauts in addition to being highly experienced pilots, had a very clear understanding and appreciation of their mission: the picture of restraint, then, is clearly a different matter for the astronaut.

A continuing drop in the animal's body temperature was observed during the flight, yet the spacecraft temperatures of 68^{o} to 72^{o}F were as planned. However, since there was a considerable velocity of air movement over the animal, there is the possibility that significant body cooling may have resulted from this air movement, especially if moisture was being evaporated from the surface of the animal. Thus the matter of restraint and isolation as contributing factors to the hypothermia must also be considered. It is a well known fact that some animals exhibit the physiological processes of temperature regulation accomplished by the hypothalamus, and, as a consequence, body temperature falls. This is usually a limited process however, and body temperature is restored after a few hours. Thus it is entirely possible that the central mechanisms responsible for this phenomenon were operating in the case of the monkey. There was very little evidence of shivering as judged by examination of all of the electrophysiologic data collected, suggesting suppression of this thermogenic mechanism.

The weightless state is associated with abnormal vestibular stimuli, and symptoms of motion sickness were experienced by five of the six crew members in Apollo 8 and 9 (3). The monkey did initially work the VM task which was designed to further stimulate the vestibular apparatus, since the animal moved his head in a circular path when tracking the target on the co-rotating disks. It may be relevant that this task was abandoned by the animal after two days, even though the on-board camera revealed him to be alert into the eighth flight day (Fig. 31). Hence the abnormal vestibular inputs which were undoubtedly experienced by the monkey were another stress factor; and an associated autonomic disturbance of the sweat glands may have played a role in stimulating the excessive evaporative fluid loss.

The voluntary water intake of the flight animal as well as that of the ground controls was quite variable and did not bear any particular relationship to the physical environment. It was usual to observe a marked increase in water consumption at times when the animals were handled or manipulated as, for example, following implantation of catheters. The urine volume is correspondingly high and the specific gravity low under such circumstances. Although this excessive water intake certainly has a psychogenic component, it does require specific physiologic adjustments of kidney function.

It is generally assumed that the recumbent individual or the individual in the weightless environment experiences a shift of blood volume toward the heart. The rise in central venous pressure in the monkey indicated that this indeed does happen. The observed increase in atrial pressure of 2-3 cm H_2O was of an order of magnitude sufficient to provide a stimulus for the loss of body fluid as described by Gauer and Henry (5).

As seen in Fig. 29, this pressure remained above preflight levels until the eighth day of flight. The hypothermia experienced by the animal would further enhance the shift of blood volume centrally and perhaps help to maintain the observed increase in central venous pressure.

An unexpected dividend to the biologists from the accurate observation of humidity and water absorbed, which was feasible in the flight capsule, is the useful data which was available concerning the evaporative water loss during the flight; this was not available for the ground control animals during their simulated flight in their mock-ups for these were not closed systems. Fig. 32 clearly shows that the animal realized close to the maximum fluid deficit after 3 to 4 days of flight. The relatively high urine volume in the face of a progressively increasing loss of body fluids strongly suggests that the animal encountered serious electrolyte problems. As shown by water immersion studies, the fluid loss will be hypotonic in the well hydrated subject. However, when hydration is limited, the increased volume elimination is accomplished by an increase in osmolar

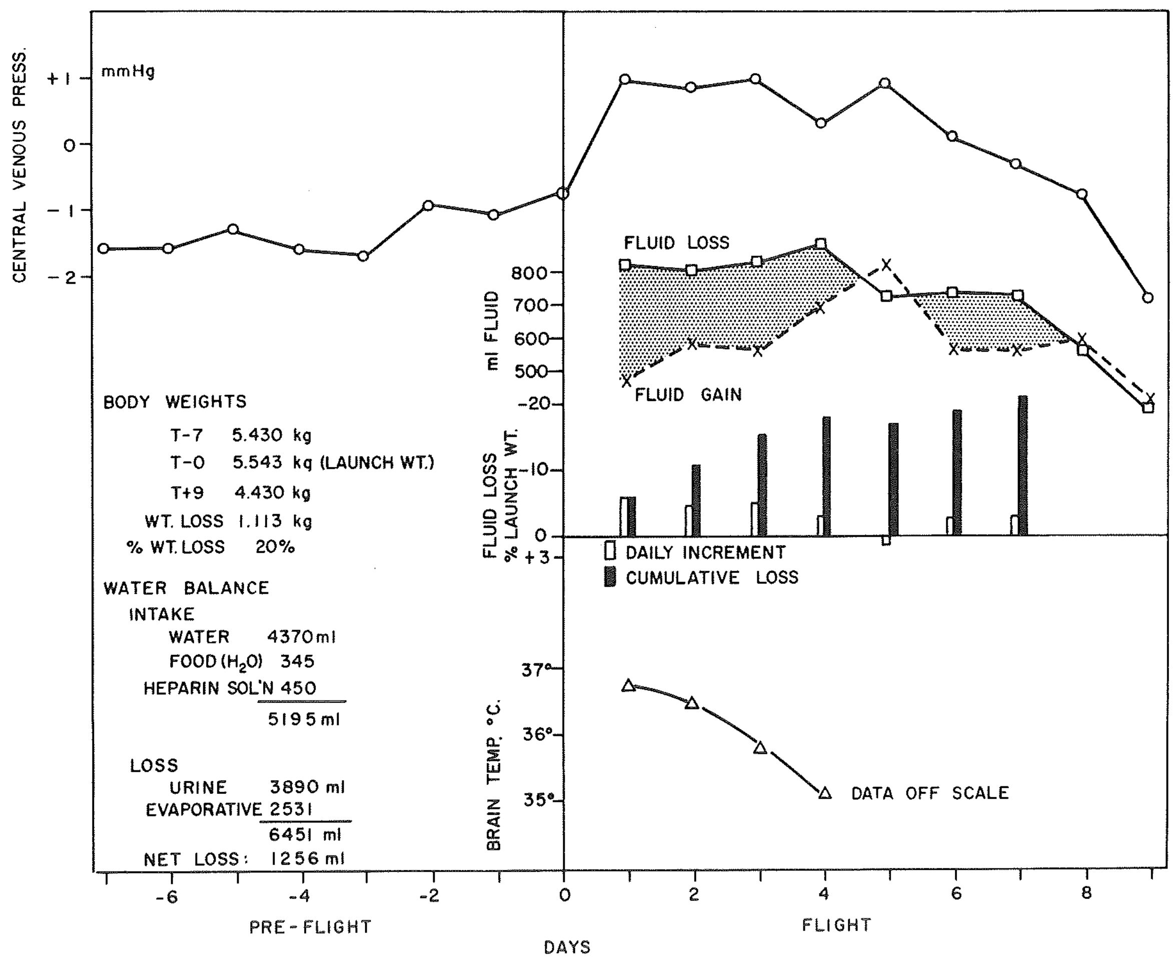


FIGURE 32: SUMMARY OF FLUID BALANCE, BODY WEIGHT CHANGES AND BRAIN TEMPERATURE DURING THE FLIGHT

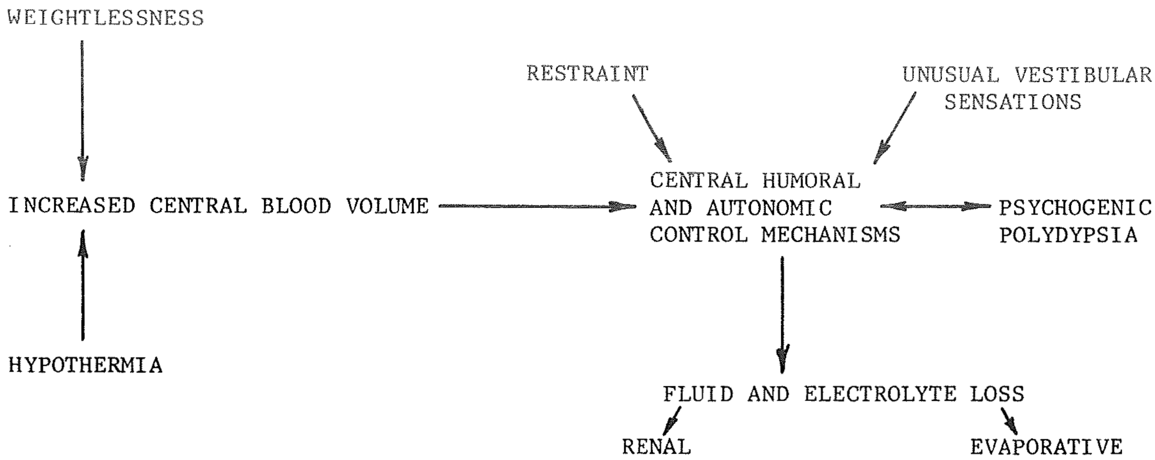


FIGURE 33: SUMMARY DIAGRAM OF STRESS FACTORS OPERATING IN THE BIOSATELLITE III FLIGHT

clearance only (6,8), and the experiments of Gauer, Henry and Behn (6), show that excessive sodium loss can actually occur. It was their impression that this loss was more marked in subjects who are anxious. It seems, then, that there is reasonable evidence to support the hypothesis that the monkey was considerably disturbed by his environment. In fact, the irrevocable physiologic derangements probably occurred early in the flight; thereafter adaptation may not have been possible in view of the multifaceted stress factors affecting fluid and electrolyte metabolism.

Such was probably not the case with the astronauts. The striking observations of Lutwak et al (7), of a decrease rather than an expected increase in the urinary secretion of 17-hydroxycorticoids is compatible with the view that astronauts Borman and Lovell were, in fact, quite at ease during the 14-day Gemini 7 flight. Their verbal reports further support this contention.

The length of time required for the cardiovascular changes to weightlessness to approximate their full effect is probably longer than 3 or 4 days. If the blood volume data of the Gemini flights is any indicator, it would appear that perhaps as long as 14 days or longer are required.

Neither the command pilot nor the pilot of the 14-day Gemini 7 flight had decreased blood volumes; such was not the case in flights of a shorter duration. It is possible that, in time, the venous tone is reduced -- probably as a consequence of the absence of gravitational loading. As this occurs, the venous system becomes more distensible thus permitting a return of the blood volume to its original more peripheral distribution. As this redistribution takes place, the central venous pressure should fall toward preflight values. One may speculate that in normal circumstances, as the venous pressure falls, the receptor drive from the atria will be reduced, thus allowing the regulatory mechanisms affecting the kidneys to return toward more usual levels of activity. In the case of the monkey, the central venous pressure remained elevated until almost the end of the flight when the rapid fall of systemic arterial pressure confirmed that he was in serious trouble.

Fig. 33 summarizes the various factors and mechanisms operating in the flight of the monkey. Weightlessness and hypothermia acted to shift blood volume centrally: this provided a strong drive for the reduction of blood volume. Restraint, unusual vestibular sensations and the continuing polydipsia, all acted to disturb the central mechanisms which might have restored normal control and regulation of salt and water metabolism. It is highly probable that the function of the kidney was significantly affected and that an excessive amount of salt was lost. We can speculate that a serious electrolyte disturbance was superimposed on the growing dehydration. Unpleasant vestibular sensations may have contributed to the high evaporative loss by autonomic disturbance -- the whole problem being compounded and reinforced by the unnatural restraint to which the monkey was subjected.

Thus, there were a number of factors all operating in concert which may have prevented the effective adaptation of the monkey to the environment. For the first time, the astronauts have been subjected to a similar series of profound stresses during the recently completed Apollo 13 flight. It will indeed be of great interest to study the data from that flight when they become available.

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