EXTENDED DURATION ORBITER MEDICAL PROJECT COUNTERMEASURE TO REDUCE POST SPACE FLIGHT ORTHOSTATIC INTOLERANCE (LBNP) - STS-50/USML-1

John B. Charles* and Sheila W. Boettcher+

*NASA JSC, Houston, Texas
+KRUG Life Sciences, Houston, Texas

ABSTRACT

During the STS-50/USML-1 mission and 5 other Shuttle flights, decompression of the legs and lower abdomen ("lower body negative pressure," LBNP) was used (1) to apply a standardized stress to the cardiovascular system, to document the loss of orthostatic function during an extended period in weightlessness, and (2) to test its efficacy as a treatment which may be used to protect astronauts from gravitationally-induced fainting during and after reentry on Space Shuttle flights.

The loss of orthostatic tolerance (as determined by LBNP) occurred even earlier than indicated by similar testing on Skylab (1973-1974). The treatment was shown to be effective in reversing some of the effects of extended weightlessness on the cardiovascular system for at least one day after treatment.

NOMENCLATURE

ABPM	Automatic Blood Pressure Monitor
AERIS	"American Echocardiograph Research Imaging System", a modified commercial cardiac ultrasound device
BP	Blood pressure, the result of the ejection of blood from the heart into the elastic arteries, especially the aorta
Bradycardia	Slow heart rate
CO	Cardiac output, the volume of blood ejected during one minute
Diastolic	During the relaxation phase of the heart beat
Dysrhythmia	Abnormal heart beat

Joint "L+1" Science Review for USML-1 and USMP-1 with the Microgravity Measurement Group, September 22-24, 1993, Huntsville, Alabama, USA.

ECG	Electrocardiogram, also known as EKG
JSC	Johnson Space Center, Houston, Texas
LBNP	"Lower body negative pressure", the decompression of the legs and lower abdomen to allow blood pooling mimicking that in the upright posture
MSFC	Marshall Space Flight Center, Huntsville, Alabama
Orthostatic	Relating to the upright posture on Earth's surface
Plethysmograph	A device for measuring the volume of a limb
SV	Left ventricular stroke volume, the volume of blood ejected with each heart beat
Systolic	During the contraction phase of the heart beat
Tachycardia	Rapid heart rate
TPR	Total peripheral resistance, the result of the constriction of the small arteries throughout the circulatory system

INTRODUCTION

A candidate countermeasure against orthostatic intolerance after space flight was evaluated for its efficacy and operational practicality. This countermeasure, lower body negative pressure (LBNP) combined with salt, and fluid ingestion, is intended as a single-application, end-of-mission treatment to pre-adapt the cardiovascular system to exposure to orthostatic stress during and after Space Shuttle reentry, landing and cabin egress. The countermeasure evaluation involved 12 crew members as in-flight participants on six Shuttle flights of 9-14 days duration.

Exposure to weightlessness, even for short periods, induces significant changes in the cardiovascular system which are proposed to be secondary to headward fluid shifts, subsequent plasma volume contraction, and ensuing adaptations in cardioregulatorory function (1). The resulting cardiovascular state is inappropriate for orthostasis on Earth as manifested by the clinical findings of tachycardia, decreased exercise capacity and orthostatic intolerance (demonstrated by symptoms of dizziness) and presyncope or syncope (loss of consciousness) on return to Earth.

These findings prompted operational concerns for Space Shuttle crew members, due to their upright posture during Shuttle reentry and landing maneuvers and to the high degree of pilot involvement in the Shuttle landing process (2). These concerns have become especially pertinent as

Shuttle flight durations are extended, presumably predisposing the astronauts to an even greater risk of orthostatic intolerance during this critical mission phase (2).

Development of appropriate countermeasures to this cardiovascular change has been a priority of NASA's in-house directed medical research. One candidate countermeasure under investigation since the 1960s (6) involves lower body decompression (LBNP). This technique, which typically decompresses the legs and abdomen by up to 50 mm Hg, provides a cardiovascular stress similar to standing upright (orthostasis) by allowing blood to pool in the legs and abdomen (14). Brief decompression is used as a gravity-independent test of orthostatic capacity; longer decompression, either alone or in combination with salt and water ingestion, has been used as a countermeasure to restore orthostatic tolerance in bedrested subjects and astronauts. LBNP has been used in both of these capacities during Russian and U.S. manned space flights.

The first in-flight assessment of orthostatic tolerance was performed on the Soviet Union's Salyut 1 space station in 1971 (4). Two of the three crewmen were tested once in flight, on day 13 of their 24-day flight, using a prototype of the now-standard "Chibis" pneumatic vacuum suit. Two years later, the Skylab program allowed U.S. investigators to determine the time course of the development of orthostatic dysfunction in weightlessness (11, 12, 13). During all three Skylab missions (28, 59, and 84-day durations), crew members' heart rate (HR) and blood pressure (BP) responses to the standardized graded stress provided by the onboard LBNP device were recorded at approximately 3-4 day intervals. During the initial in-flight tests, which were performed on the 4th, 5th, and 6th days of flight, HR responses to the stress were already exaggerated compared to preflight tests. Resting HR plateaued after about 10 days of weightlessness; stressed HR plateaued after 20 days of weightlessness. BP was generally maintained throughout those LBNP studies that did not end in presyncope or bradycardia. The greater increase in HR during flight than before flight could reflect compensation for a reduction in blood volume early in flight. Calf volume increases with LBNP were greater during flight than before flight, probably because greater volumes of blood were required to fill the relatively empty leg veins during flight.

LBNP testing of cardiovascular function has been performed during all but one of the missions to the Russian Salyut and Mir space stations. In agreement with the U.S. Skylab data, testing of the crews of the 49-day and 17-day missions to Salyut 5 indicated that individual responses to in-flight LBNP tests were predictive of postflight responses to orthostatic stress (5).

The development of LBNP-based countermeasures proceeded independently in Russia and the U.S. Soviet researchers developed an LBNP countermeasure for use on long duration space missions (7). Since the mid-1970s, a routine multi-week course of LBNP treatments has gradually been developed for use by the crews of the Salyut and Mir space stations in preparation for landing.

This now typically includes brief, step-wise decompressions over 20-30 minutes at 4 day intervals beginning 3-4 weeks before landing, and culminates with 1-hour sessions of graded decompressions on the last two full days in flight. Extra salt is taken with meals on those days.

In the U. S., a variety of LBNP protocols were developed which were effective in preventing or reversing orthostatic intolerance during bedrest but which were also prohibitively long (several days) at the end of the bedrest (6). The breakthrough came in 1977 when Hyatt and West (9) demonstrated that a single application of only 4 hours of LBNP, when combined with the ingestion of one liter of a bouillon solution, restored plasma volume and orthostatic tolerance to pre-bedrest levels for at least 18 hours, even after seven days of bedrest. This result was confirmed in six subjects after two weeks of bedrest (10). The effective treatment period could not be reduced below 4 hours using the same protocol (one liter of isotonic solution and 30 mm Hg decompression).

These investigations formed the basis for the combined treatment countermeasure for orthostatic intolerance that has been tested during Shuttle flights.

I. METHODS

A collapsible LBNP device developed for use on-board the Space Shuttle was used for all in-flight decompressions (Figure (1)). A modified ambulatory blood pressure monitor measured HR and BP and provided analog electrocardiogram and BP signals for telemetry to MSFC and JSC. Cardiac ultrasound measurements of left ventricular end-diastolic volume) were performed in-flight on 4 Shuttle flights (STS-32, 43, 47, and 50). Ultrasound Doppler measurements of aortic blood flow (for calculation of stroke volume, cardiac output and total peripheral resistance) were performed for the first time in-flight on STS-50 (USML-1) using the AERIS device. In-flight leg volume measurements using the stocking plethysmograph were performed on STS-47 and STS-50 only.

On the USML-1 mission, LBNP was performed in-flight as tests ("ramps") of cardiovascular response, a treatment ("soak") and follow-up ramp tests to determine the effectiveness of the treatment after 24-hours and 48-hours. This time frame was selected to simulate a nominal landing 24-hours after the soak and a 1- day delay in landing (48-hours after the soak). The in-flight ramp and soak protocol are outlined in Figures (2) and (3) respectively.

The ramp tests consisted of 10 minutes of baseline data collection at 0 mm Hg of LBNP device decompression, 5 minutes of data collection at each step of decompression (10, 20, 30, 40 and 50 mm Hg), and 5 minutes of recovery data collection after recompression to ambient pressure. The soak treatment began with a step-wise decompression to 50 mm Hg followed by about 3.5 hours of LBNP at 30 mm Hg below ambient pressure. The total time of decompression of at least

30 mm Hg was 4 hours. One liter of water or artificially sweetened fruit drink and 8 grams of salt (NaCl in 1 gram tablets) were ingested during the first hour at 30 mm Hg decompression. The treatment was evaluated by comparing HR and BP responses to test decompressions on days before and after treatment.

Test termination criteria for LBNP testing included: achieving a HR equal to the maximum HR seen in preflight LBNP testing; one-minute decreases in HR of 15 beats/minute, in systolic BP of 25 mm Hg, and /or in diastolic BP of 15 mm Hg; a variety of clinically significant cardiac dysrhythmias; loss of signal at levels of decompression greater than 30 mm Hg,; and subject request at any time. Some tests were terminated on STS-50 for the maximum HR criterion; this represented a normal physiological response to space flight, and did not imply an increased risk to any subject.

II. RESULTS

The typical HR and BP response to LBNP is shown in Figure 4. Twenty four hours after the combined countermeasure of salt and water ingestion during LBNP at 30 mm Hg below ambient pressure, the HR response to 40-50 mm Hg lower body decompression was not statistically different from the preflight value. However, two days after the combined countermeasure, the HR response to decompression was not statistically different from the last pre-treatment ramp test. Thus, the cardiovascular effect of the soak treatment was present in crew members for at least one day after treatment.

Neither systolic nor diastolic BP responded significantly to the submaximal levels of LBNP tested in-flight.

Leg volume showed no greater increase after the 4-hour soak than after the 25-minute ramp tests.

Cardiac ultrasound measurements documented the expected decrease in left ventricular end-diastolic volume and stroke volume at rest and under LBNP stress. Cardiac output was maintained by an increase in HR. BP was maintained at preflight levels throughout in-flight testing by an appropriate increase in total peripheral resistance. Measurements of SV, CO and TPR responses to the soak treatment were not possible after the AERIS failed on flight day 9.

III. DISCUSSION

The loss of orthostatic tolerance (as reflected by heart rate response to 40-50 mm Hg decompression) occurs even earlier in flight than indicated by the Skylab data. The cardiovascular adaptations to weightlessness are thus shown to be rapid, implying that even short Shuttle flights

invoke nearly the full cardiovascular risk of orthostatic intolerance heretofore expected only on long flights.

The candidate treatment has been shown to be effective in restoring HR response to LBNP stress to its preflight value for at least one day after treatment, but not for two days. Thus, any operational application of this treatment must be planned for the day before landing; last-minute delays in landing, such as occurred on STS-50, will require re-treatment for maximum crewmember safety.

The capability for simulating the effects of orthostatic stress on the cardiovascular system during Space Shuttle flights has been developed and demonstrated. This capability can be used for basic and applied research as well as for the application of countermeasures.

ACKNOWLEDGMENTS

The EDOMP team would like to thank the crew members of USML-1 who participated in this study. LBNP required a substantial commitment on their part, with a certainty of inconvenience if not outright discomfort. We also thank the personnel of Marshall Space Flight Center whose efforts on this investigation have contributed to the future of long duration space flights.

REFERENCES

1. Blomqvist, C. G., and H. L. Stone. Cardiovascular adjustments to gravitational stress. *In: Handbook of Physiology*, Volume III. Edited by: Shepherd, J. T., and F. M. Abboud, Bethesda, MD: American Physiological Society, pp. 1025-1063, 1983.

2. Bungo, M. W., J. B. Charles, and P. C. Johnson, Jr. Cardiovascular deconditioning during space flight and the use of saline as a countermeasure to orthostatic intolerance. *Aviation Space Environmental Medicine* 56: 985-990, 1985.

3. Charles, J. B., and C. M. Lathers. Cardiovascular adaptation to space flight. *Journal of Clinical Pharmacology* 31: 1010-1023, 1991.

4. Degtyarev, V. A. and V. M. Khayutin. Condition of the human cardiovascular system in true and simulated weightlessness. NASA Technical Translation, 1971.

5. Degtyarev, V. A., V. G. Doroshev, Z. A. Kirillova, N.A. Lapshina, S. I. Ponomarev, and O. B. Kulikov. Hemodynamics and phase structure of the cardiac cycle in members of the first crew of Salyut-5 at rest. *Kosm. Biol. Aviakosm. Med.* (English Translation) 14(4): 11-16, 1980.

6. Fortney, S. M. Development of lower body negative pressure as a countermeasure for orthostatic intolerance. *Journal of Clinical Pharmacology* 31: 888-892, 1991.

7. Grigoriev, A. I. Correction of changes in fluid-electrolyte metabolism in manned space flights. *Aviation Space Environmental Medicine* 54(4): 318-323, 1983.

8. Hoffler, G. W. Cardiovascular studies of U. S. space crews: an overview and perspective. In: *Cardiovascular Flow Dynamics and Measurements.* Edited by: Hwang, N. H. C., and N. A. Normann, Baltimore, MD: University Park Press, 1977.

9. Hyatt, K. H., and D.A. West. Reversal of bedrest-induced orthostatic intolerance by lower body negative pressure and saline. *Aviation Space Environmental Medicine* 48: 120-124, 1977.

10. Johnson, P.C., Jr. Fluid volume changes induced by space flight. *Acta Astronautica* 6: 1335-1341, 1979.

11. Johnston, R. L., G. W. Hoffler, A. E. Nicogossian, and S. A. Bergman. Skylab experiment M-092: results of the first manned mission. *Acta Astronautica* 2: 265-296, 1975.

12. Johnston, R. L., A. E. Nicogossian, S. A. Bergman, and G. W. Hoffler. Lower body negative pressure: the second manned Skylab mission. *Aviation Space Environmental Medicine* 47(4): 347-353, 1976.

13. Johnston, R. L., G. W. Hoffler, A. E. Nicogossian, S. A. Bergman, and M. M. Jackson. Lower body negative pressure: third manned Skylab mission. *In*: *Biomedical Results From Skylab* (NASA SP-377). Edited by Johnston, R. S. and L. F. Dietlein, Washington, DC, U. S. Government Printing Office, pp. 284-312, 1977.

14. Wolthius, R. A., S. A. Bergman, and A. E. Nicogossian. Physiological effects of locally-applied reduced pressure in man. *Physiology Review* 54: 566-595, 1974.

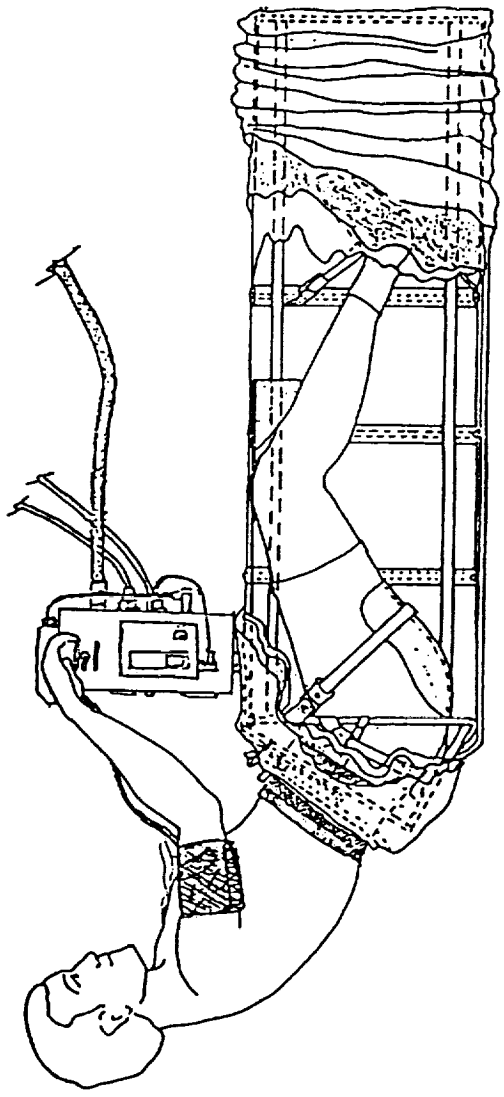

Figure 1 In-flight LBNP hardware configuration.

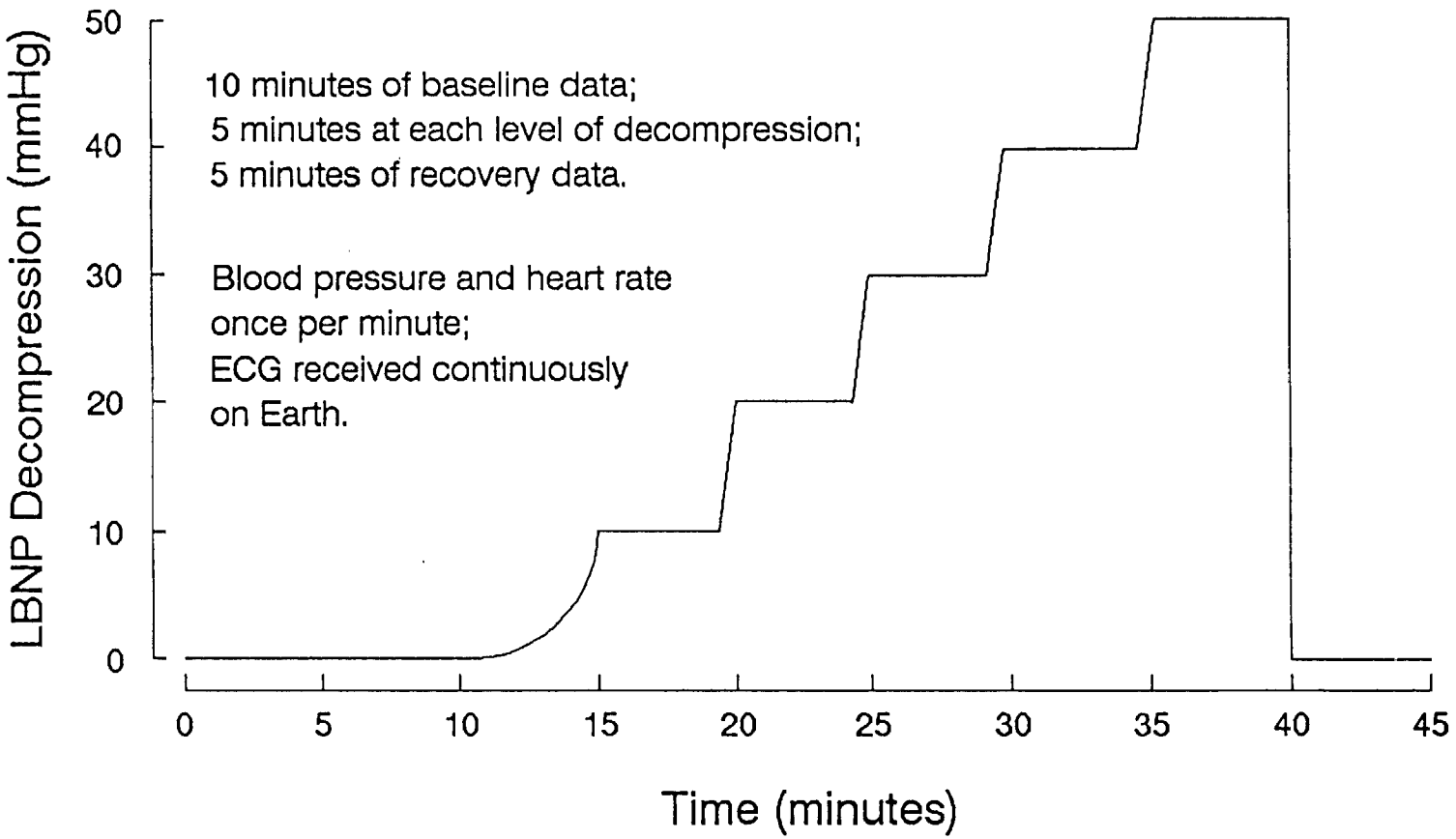

Figure 2 LBNP ramp protocol.

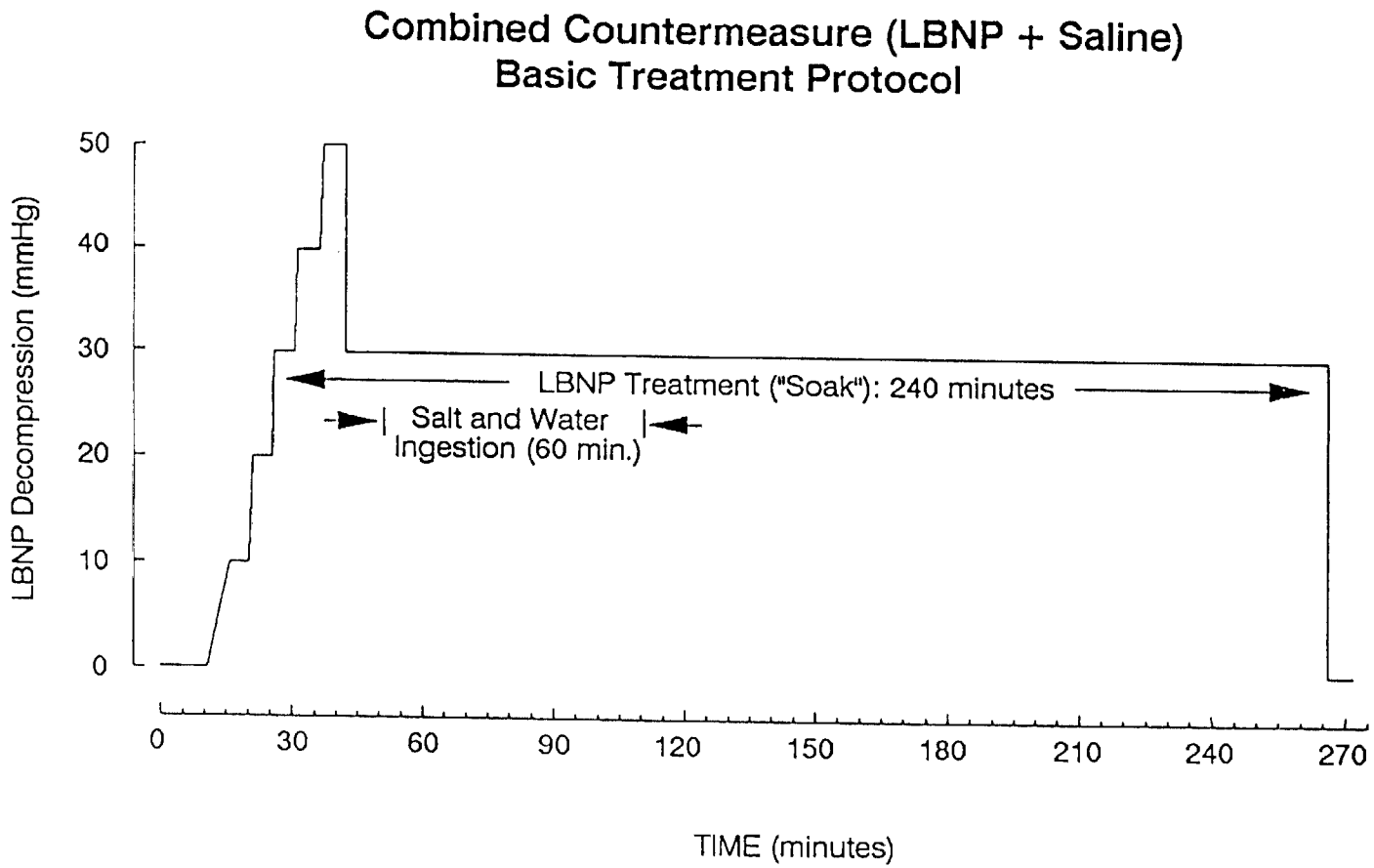

Figure 3 LBNP soak protocol.

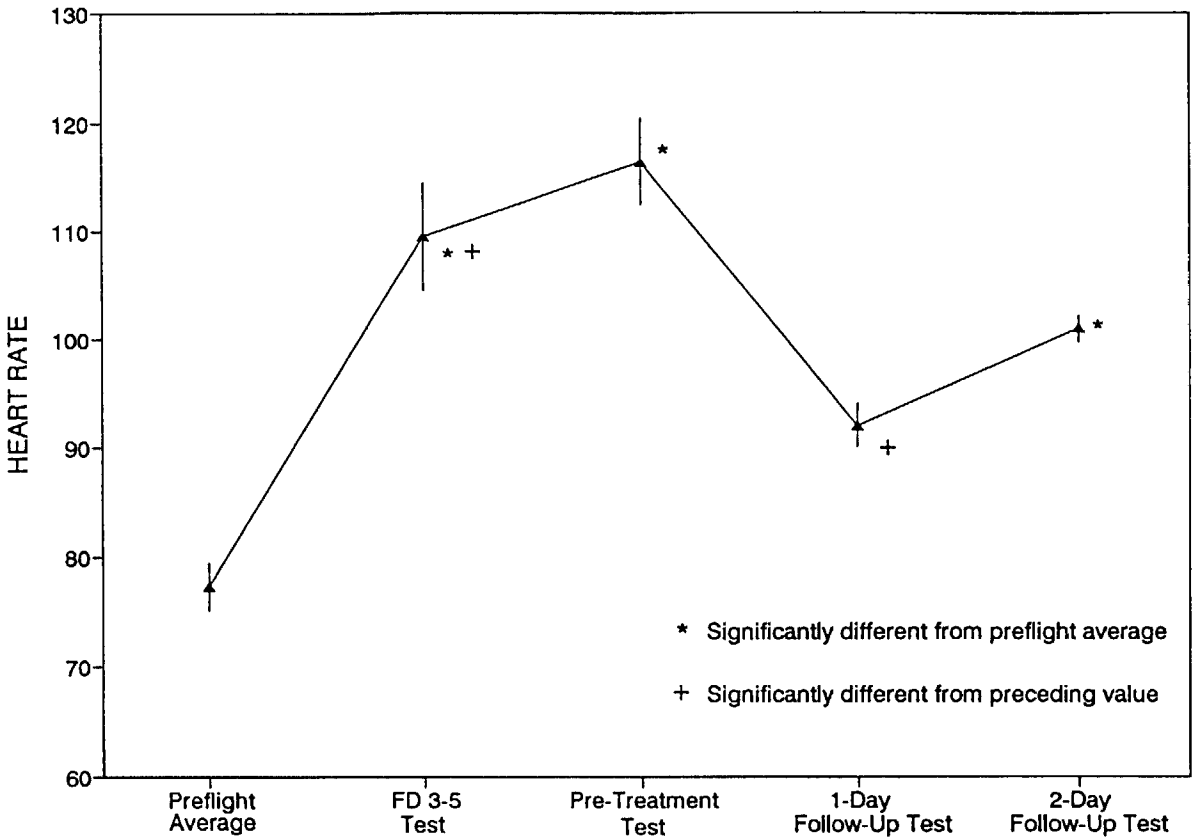

Figure 4 Heart rate during maximum level of the LBNP ramp test before and after soak treatment for 4 astronauts.

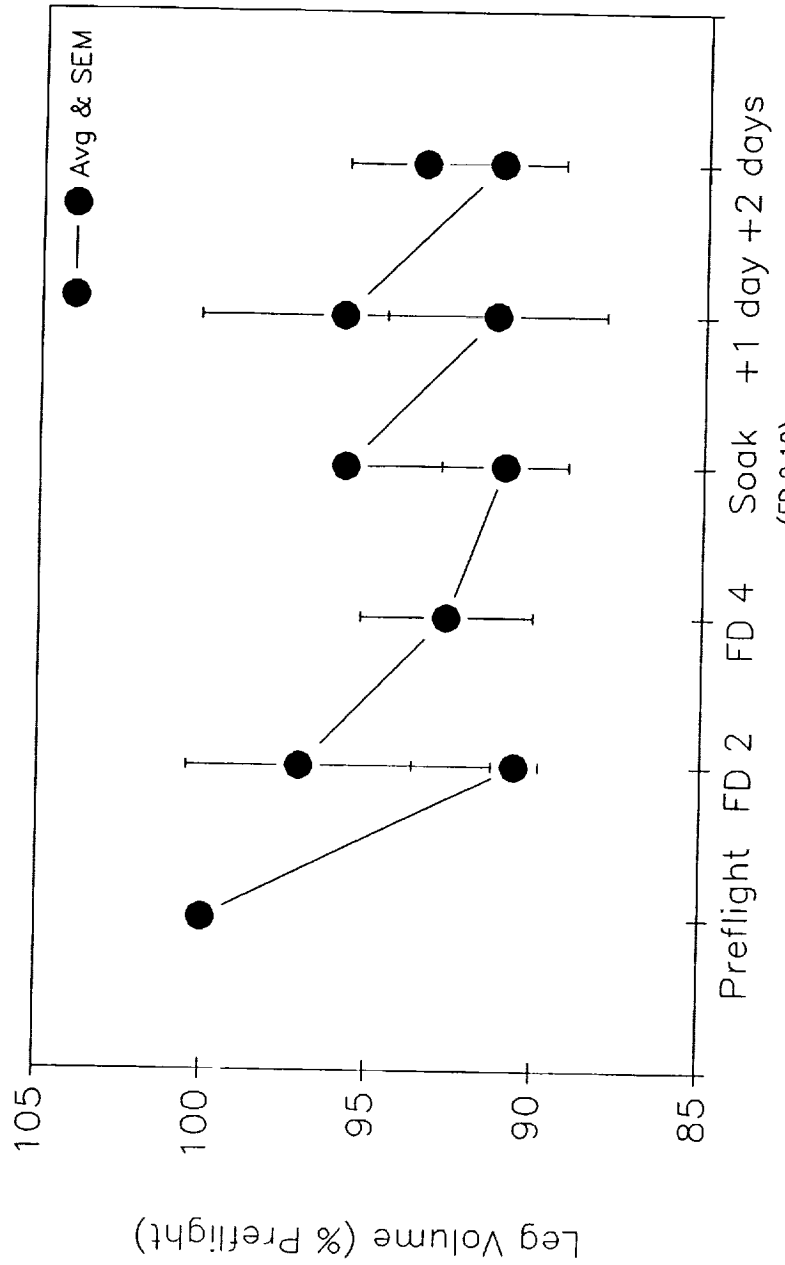

Figure 5 Leg volume responses to in-flight LBNP on STS-50/USML-1; n = 2.

Discussion

Questions: *What causes the blood volume loss you talked about ?*

Answers: The blood volume loss is believed to be caused by the fact that the normal hydrostatic pressure gradient which I am feeling at this moment disappears in 0 g. The blood volume which is normally sequestered in the legs or at least pools in the veins in the legs, then has no reason to pool in the veins in the legs. Those normal physiological mechanisms that squeeze it back up, act unopposed, squeezing the blood back up to the thorax and the upper part of the body, the head. In fact, if you look at photographs of the astronauts in flight, you see sometimes fairly puffy faces and some of the neck veins and head veins stand out. You will also see what some people call the bird legs of space flight which is when the legs on the flight get very small. Those mechanisms act unopposed and squeeze the fluid to the upper part of the body and it just so happens the reflexes which control blood volume are in the upper part of the body. So as far as the sensors that are built in the cardiovascular system are concerned, it is not fluid volume shifted, it is too much fluid volume and so they act through a complex series of mechanisms to reduce the blood volume in the body to an appropriate state. I should stress that all the data we have indicates the appropriate adaptation of normal, healthy people to space flight, and this is fine as long as they stay in space flight. If they are brash, as in to try to land and come to 1-g, then it is not an appropriate adaptation to life at 1-g post flight.

Question: *So the ratio of the red cells to water in the blood goes up ?*

Answer: It goes up briefly in flight, by briefly I mean a few weeks. As you excrete the watery portion of the blood you leave behind the red cells and the fraction increases and so the ratio increases. The body seems to have sensors for this as well, and seems to decrease the production of red cells to bring the ratio back down to normal. That is the adaptation, that is the anemia that you will sometimes hear about in space flight.

Question: *If the baro receptors are being fooled because you have a shift, because you have a shift in your fluid, why is it that the longer you stay in space the thought is, the worse off you will be in terms of this hypertension effect ?.*

Answer: Well in fact, we physiologists and medical researchers have made some fairly naive assumptions about the effect of prolonged space flight. My current thinking is the stress in the cardiovascular system changes fairly quickly in orbit, within hours to days within reaching orbit. I think the cardiovascular stresses, especially the change stimulation of the baro receptors in the body occurs quickly in flight, and probably doesn't increase too much beyond the first few days to weeks in flight. II

think the evidence from Skylab, the Shuttle, the Salyut and Mir flights, all experiments from pre and post flight show that the effect of a 4 or 5 day flight probably is not going to differ dramatically from a 14 day flight. What that means and it sounds good, it sounds like we are flying 4 and 5 day flights routinely with no problem so there is no problem flying longer missions, but I am here to tell you that is not the case. We have problems out there with shorter flights that need to be paid attention to.

Question: *Is it possible that as they sit in an environment where there is not much fluctuation, they somehow lose the ability to monitor the situation and so when you return to Earth, they don't work as well?*

Answer: That is our hypothesis. That was the hypothesis of the experiment that was done on the blue shift with the blood pressure variability. I still believe in the hypothesis, I just don't think we have the right technology to demonstrate that.

Question: *There are other counter measures, some we used on our flight (USML-1). Has there now been enough data accumulated to start to compare them and see which one is more effective ?*

Answer: The other counter measures that were used on your flight included an intense bout of exercise. I believe one or two people on your crew did it the day before landing, the idea there being, to follow up on bed rest study which may show that an intense bout of maximal exercise has the effect of restoring the plasma volume as we discussed here a few moments ago, and thereby hopefully increasing other static tolerance. Another counter measure was the application of a synthetic version of a normally occurring hormone. The hormone is called aldosterone which forces the body to retain salt and thereby retain water. That was used in a couple of individuals as well. Both of these investigations have occurred on other flights and the results are equivocal from those investigations. I do not have a high level of confidence in the hormone as an effective counter measure based on the data we have. Because they are attractive in terms of taking a pill versus 4 hours of LBNP, we continue to investigate, making sure we are making the right measurements in bed rest and in space flight, to demonstrate that it does or does not work effectively.

Question: *Could you comment on the amount of variability in cardio-vascular changes among different crew members in flight ?*

Answer: There is a depressing amount of variation among individuals. There are some people who fly 10 and 14 day missions, who are immune, who have no difficulty at all and there are some folks that fly 4 day missions who are in fairly sorry states after landing. I can qualify that with two episodes. One of the treatments for orthostatic intolerance and for a general physiological depressed state is to reinfuse some

fluid volumes. You have all seen the bags of saline that physicians will put through a vein and restore some blood volume. That has occurred on two incidences that I know of on shuttle flights. One after a 10 day flight and one after a four day flight. Based on just that little evidence alone, there is not an appreciable agreement in the cardiovascular or the static effects of 4 to 10 day flights and, like I say, it is not good news for the long flights, but it is bad news for the short flights.

Question: *Is there any correlation between the amount of changes in an individual and the tendency to sea sickness ?*

Answer: Well by the term sea sickness we relate that to space motion sickness and I don't think there is a good correlation. I am told there is not a good correlation between any kind of motion sickness on the ground and motion sickness in flight, but there is no doubt that there is motion sickness. And there is an incidence, depending on how you quantify it, of 25-50% plus of motion sickness in flight. We have shown that the folks that have the most trouble standing up post flight are also the folks that were the sickest on flight. There was a strong correlation between being sick in flight and having this apparently unrelated cardiovascular problem on landing day. Now what that tells me is two things. If you are sick in flight, either you are not eating or drinking and keeping yourself well hydrated and well nourished and you are putting yourself at physiological risk or maybe it is folks that are sick in flight are doomed to be sick in flight and are doomed to have cardiovascular problems post flight because a lot of the reflexes are common in both syndromes. We cannot differentiate between those, but we do encourage crew members to eat, hydrate and nourish themselves properly and to get as much rest as we, the investigators, will allow them to have. I have to wear two different hats because as a physiologist who is doing research, I have to say rest is for the wimps and lets get on with some more LBNP studies, but as someone who is charged with providing the astronauts well being there is no doubt that properly eating and resting are vital to continued safe function and flight.

Question: *How do you choose the pressure levels selected during LBNP and are you likely to change them ?*

Answer: I am not likely to change them. We have modified them a little bit. The pressure levels that you are thinking of 0, 10, 20, 30, 40, 50 mm-mercury decompressions are based actually on a long history of LBNP work preceding in fact Skylab. The investigators that did the work on Skylab established the -50 millimeters mercury as being a physiological analog to standing upright. So it seemed like a logical thing to investigate, if you are interested in the ability of astronauts to stand upright post-flight. It has become enshrined in literature. So if I want to maintain comparability between Skylab data and my

data in the literature base, I need to maintain comparability to those levels of decompression. But briefly -50 roughly approximates standing upright at 1-g.

Question: *Could you comment on the soaking parameters.*
Answer: The soaking is done with the -30 mm of mercury pressure because nobody wants to stand upright for 4 hours or longer. It was decided to pick a level that was tolerable for 4 hours but still a significant stress to exercise the cardiovascular system.

Question: *Is there any reason that we can't do the soaks during crew sleep period ?*
Answer: That is an excellent question. At first brush I am reluctant to do that because part of our monitoring of crew assurance and crew health is that the crew members don't faint during LBNP crew testing. And if someone is asleep you can't tell if they have fainted or not because they are unconscious. That would possibly eliminate a first line of protection in a very conservative medical monitoring situation. However, if we choose the appropriate level of LBNP, for example, say 15 millimeters of mercury for 8 hours instead of 30 millimeters of mercury for 4 hours, we might be able to circumvent with the appropriate medical monitoring equipment for heart rate and blood pressure that I showed you on the first view graph, there may be ways to go around that. I am not saying that 15 mm x 8 hours is equivalent to 30 mm x 4 hours. The only treatment that has been tried and is effective is 30 mm for 4 hours. A lot of investigators spent a lot of time back in the 60's and 70's looking at other combinations and that was the one that worked, really worked, with the addition of salt and water. So one of the tasks as we move in to the Space Station era and as we move further into the Space Shuttle era, is to try to optimize these kind of measures. If we can optimize it, by applying it during the sleep period, we will do so enthusiastically, but that has not been shown yet.

Question: *Are the baro receptors localized or distributed in the body ?*
Answer: The baro receptors are essentially nerve endings which wrap around the blood vessels. So if this is my artery, the baro receptors sort of wrap around and as your artery expands each time your heart beats those receptors stretch and with the influx of sodium across the membrane trigger additional activity along that nerve's fibers that is interpreted at the brain as whatever is supposed to be occurring at that location. The baro receptors are located preferentially in the carotid sinuses and the aortic arch. The aorta is the large artery that comes off the heart and carries blood throughout the body. In the arch of the aorta there are some baro receptors. Those are the two major areas of baro receptors. Baro meaning pressure, receptors meaning receptors or sensors. Those are the two areas that we are interested in the cardiovascular business. Now how those signals change at the sensor level, how the

mediation of those signals back to the brain and the brain stem changes and how the activity from the brain affects the effective organ changes, those questions all remain to be answered in space flight. They are going to be fairly invasive and fairly complex questions to answer, so we are trying to move in the other direction by applying essentially a black box as a cure to a very complex problem and sort of a stop gap solution to a problem.