Historical Review of Lower Body Negative Pressure Research in Space Medicine

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Cephalad redistribution of intravascular and extravascular fluid occurs as a result of weightlessness during spaceflight. This provokes cardiovascular, cardiopulmonary, and autonomic nervous system responses. The resulting altered functional state can result in orthostatic hypotension and intolerance upon landing and return to a gravity environment. In-flight lower body negative pressure (LBNP) transiently restores normal body fluid distribution. Early in the U.S. space program, LBNP was devised as a way to test for orthostatic intolerance. With the development of the Skylab Program and longer duration spaceflight, it was realized that it could provide a method of monitoring orthostatic intolerance in flight and predicting the post-landing orthostatic response. LBNP was also investigated not only as an in-flight cardiovascular orthostatic stress test, but also as a countermeasure to cardiovascular deconditioning on Soviet space stations, Skylab, and the Shuttle. It is still being used by the Russian program on the International Space Station as an end-of-flight countermeasure.

KEYWORDS: weightlessness, microgravity, Apollo program, Skylab program, International Space Station, shuttle program, orthostatic intolerance, spaceflight countermeasures.

In 1964, it was demonstrated that following 4 wk of bed rest, the same duration as the planned USAF Manned Orbiting Laboratory (MOL) missions, orthostatic intolerance was present that was less intense and more variable than water immersion. During the Gemini Program (1965–1966), pre- and postflight 70° tilt table tests for orthostatic tolerance became a standard protocol and showed consistently elevated heart rates (increased by 17–105%), reduced pulse pressure, and increased pooling of fluids in the lower extremities in the early postflight period which returned to normal after 50 h. There was one case of tilt test syncope out of 16 subjects.

Given that headward fluid shifts are associated with the development of orthostatic intolerance, it follows that prevention or reversal of headward fluid shifts might reduce or eliminate orthostatic intolerance. Intermittent venous occlusion with extremity tourniquets simulating hydrostatic pressure effects was effective in maintaining cardiovascular adaptability during water immersion and bed rest subjects as well.

Early Development of Lower Body Negative Pressure

Lower body negative pressure (LBNP) is the application of subatmospheric pressure to the lower portion of the body to pool blood in the lower extremities. The level of negative pressures covers a wide range, from 5 mmHg to 100 mmHg and the duration of negative pressure can be from minutes to hours. Essentially there is a shift of fluid volume from the upper body to the lower body. The fluid deficit is detected by the upper body vascular pressure and stretch receptors, and triggers an integrated systemic-wide response and is a test for orthostatic intolerance. LBNP hardware provides only a small pressure change to the systemic-wide response and is a test for orthostatic intolerance.

Following is a discussion by Dr. Graveline on his development of the first LBNP device:

“My extremity tourniquet countermeasures for fluid redistribution during water immersion weightlessness were an adaptation from Dietrick, Whedon and Schor’s oscillating bed. The LBNP device that I developed at SAM was just an adaptation of my extremity tourniquet concept. When I developed the original LBNP prototype, I had the shop people build me “half a casket” with a rubber waist seal at one end connected to a simple vacuum pump. The shop foreman would not get inside it so I got into it myself. I determined that the waist seal was sufficiently tight, put a blood pressure cuff on my arm, and started applying vacuum at 5 mmHg pressure while recording serial blood pressure and heart rate. That seemed safe enough so I increased the vacuum to 10 mmHg and could feel a physiologically significant response with an increased diastolic pressure and slight drop in the systolic pressure. After a good deal of experimentation, I finally settled on 30 mmHg negative pressure as the setting that best mimicked standing erect in a one-G field, with values roughly the same as my normal baseline tilt test. I believed that it had the potential to prevent the loss of orthostatic responsiveness by incorporating it into a sleep chamber during spaceflight, but I never had a chance to work on this. I was then ordered by Lt. Col. Daniel B. Smith to turn it over to Dr. Larry Lamb in research cardiology” (Dr. Duane Graveline. Personal communication; 2010).

The first paper describing the cardiovascular effects of LBNP was published in 1965 by Stevens and Lamb at the SAM, who apparently received Graveline’s prototype and further developed it. They showed that LBNP was an excellent test for orthostatic intolerance and had advantages over tilt testing in that it was more controlled and did not directly affect cerebral blood flow. Data obtained using a LBNP device (studying the effects of sudden volume overload with the termination of LBNP) had been presented earlier at the American Physiological Association meeting in August of 1963 by Greenfield et al. and later published. Their original LBNP device was similar to the later Soviet LBNP devices in that there was no saddle support. Gilbert and Stevens showed that 60 mmHg LBNP was very similar in cardiac response to 90° tilt-table testing and so was an equivalent method of testing for orthostatic intolerance. One important difference was that tilt testing decreased cerebral blood pressure, which increased the baroreceptor response and increased venous tone as compared to LBNP. They also showed that LBNP was a potent stimulus to water and sodium retention in supine patients and so potentially could be used as a future countermeasure to orthostatic intolerance. Water immersion and 500 cc venesection was found to give similar LBNP responses and was an indication of similar orthostatic intolerance. Musgrave et al. showed that the lower extremity volumetric changes that occurred with the use of 40 mmHg LBNP was equivalent to the upright posture. However, higher levels of LBNP were necessary to obtain the same level of heart rate response as upright tilt testing due to the nonstimulation of the carotid baroreceptors with LBNP. Although some researchers found individual variances with LBNP testing, it
was found that 70° tilt testing correlated well with 40 mmHg LBNP.\textsuperscript{55} Further research demonstrated that LBNP (30 mmHg for 8-10 h/d) maintained plasma volume and prevented orthostatic intolerance in bed rest (duration of 1 to 4 wk) subjects.\textsuperscript{48,59} This was true even if only used during the last 2 d of prolonged bed rest.\textsuperscript{45,60} It was found that even brief LBNP exposure increased the levels of renin, angiotensin I, ADH, and catecholamines.\textsuperscript{24}

**Apollo Program**
LBNP testing with a final pressure of 50 mmHg in a ramped up protocol over 15 min was used routinely pre- and postflight during the Apollo Program (on Apollo 7, 8, 9, 15, 16, and 17) as it was felt to be easier to standardize than tilt testing and could be applied incrementally (Fig. 1). There was also a desire to generate data to compare to the upcoming Skylab Program. The Apollo crewmembers all showed decreased body weight (average of 5%), decreased plasma volume, decreased leg volume, and increased but variable orthostatic intolerance by LBNP and tilt testing. Average heart rate response to 50 mmHg LBNP was 109 bpm postflight as compared to 70 bpm preflight.\textsuperscript{4} Interestingly, cardiothoracic ratio postflight was decreased except for in the crewmembers that had performed lunar extravehicular activities (EVA), indicating that the brief exposure to lunar gravity was protective of cardiac deconditioning.\textsuperscript{34,35}

**Skylab Program**
There were tentative plans to deploy an in-flight LBNP device on the MOL missions, so a prototype was developed at Brooks AFB in 1966. However, the MOL program was canceled in 1969. The Skylab Program (1973-74) made use of preflight, in-flight, and postflight LBNP using the same 50 mmHg ramped up protocol over 15 min as in the Apollo Program. In-flight LBNP was performed on each crewmember every 3-4 d (Fig. 2).

Skylab also measured body mass for the first time in flight using a spring-mass oscillator.\textsuperscript{62} The 28-d Skylab 2 mission (the first manned mission) found that a large volume of fluid was shifted out of the legs (decreased leg circumference) and body mass decreased early in the flight. Orthostatic intolerance was reflected by early termination of LBNP (for termination parameters see Fig. 3), which was present on some of the LBNP trials during the first week. In-flight heart rate increases plateaued at 5-10 d and adaptation to the stress of LBNP occurred after 4 wk. In-flight LBNP predicted the degree of postflight orthostatic intolerance for each individual crewmember.\textsuperscript{39,40}

The 59-d Skylab 3 mission found that in-flight orthostatic intolerance paralleled the findings on Skylab 2, but stabilized at 6-8 wk and that postflight orthostatic intolerance recovery was actually shorter than on Skylab 2. In-flight orthostatic intolerance for each individual accurately predicted their postflight response.\textsuperscript{40,41} Systolic time interval abnormalities measured postflight during LBNP indicated that there was a small decrease in cardiac contractility.\textsuperscript{3}

**Fig. 1.** LBNP hardware used during the Apollo Program. This is the earliest known photograph showing LBNP Research. LBNP testing was used routinely pre- and postflight during the Apollo Program. The Apollo crewmembers showed increased but variable orthostatic intolerance by both LBNP and tilt testing. (NASA photograph from Biomedical Results of Apollo, SP-368, 1975.)

**Fig. 2.** NASA artist concept of Skylab LBNP hardware being used in flight. The Skylab Program made use of preflight, in-flight, and postflight LBNP. In-flight LBNP was performed on each crewmember every 3-4 d. Orthostatic intolerance was found using LBNP during the first week. In-flight heart rate increases plateaued at 5-10 d and adaptation to the stress of LBNP occurred after 4 wk. In-flight LBNP predicted the degree of postflight orthostatic intolerance for each individual crewmember. (NASA, 1972.)

**Fig. 3.** Skylab “test continuation criteria” were inscribed on a small plaque mounted directly onto the side of the LBNP device for convenient reference by the operator.
The 84-d flight of Skylab 4 found that in-flight orthostatic intolerance began improving after 30 d and in one astronaut actually returned to preflight values. A feeling of fullness in the head, distended jugular veins, and decreased leg girth and leg volume remained unchanged for the duration of the flight. Body mass decreased by 2.5 kg (3.8%) and leg volume decreased by 12.5%. However, the magnitude of the decrease in leg volume measurements was the same as in Skylab 3. The first 2 mo of in-flight LBNP data from Skylab 3 and 4 indicate that the astronauts became adapted after 4 wk to the orthostatic stress provided by LBNP (Fig. 4).

**Soviet Experience**

Early Soviet spaceflight missions also showed evidence of fluid shifts in flight, which is critical to understanding the results of LBNP studies. The Soviets found a decrease in body mass post-flight (average loss of 2.5 kg) and significant postflight orthostatic intolerance. The last three Vostok cosmonauts had elevated heart rates on tilt testing postflight. Two of the three Voskhod cosmonauts showed decrease stroke volume and cardiac output (26–47% reduction) during postflight tilt testing. Out of 13 short duration Soyuz cosmonauts, 9 had elevated heart rates on postflight tilt testing. On the 18-d Soyuz-9 mission (1970), orthostatic intolerance was unexpectedly severe. Both cosmonauts had presyncopal symptoms and standing heart rates were increased by 63% and 65%. Pulse pressure was reduced by 71%. These exaggerated responses resolved after several days. The Soviet Salyut space station missions showed decreased body mass early in flight using an in-flight spring-mass oscillator. Ultrasound examination during Salyut-7 showed that jugular vein diameter was considerably increased in flight.

In-flight LBNP was first performed with the Veter LBNP device on Salyut-1 in 1971 (Fig. 5). The Soviets, therefore, were the first to use LBNP during spaceflight, fully 2 yr before the first manned Skylab mission. The Chibis LBNP suit was then developed (as was Veter) at IBMP by Oleg Gazenko and used on four Salyut flights, the Mir space station, and the Russian segment of the International Space Station (ISS). A newer version, Chibis-M, was developed in 2012 for use on the ISS. Chibis did not have a saddle to support the body (possibly designed for ambulation during LBNP) so that during decompression the feet pressed against the bottom of the collapsible corrugated chamber, which shortened and applied force against the feet proportional to the decompression level. This activation of the skeletal musculature of the legs counteracted the lower extremity venous pooling and acted as an additional countermeasure. Loading the lower extremities during LBNP increases muscle tone and decreases venous capacitance and so provides a protective effect to the fluid shifts that are induced by LBNP. In the American LBNP configuration, used aboard Skylab and the Space Shuttle, a saddle supports the astronaut so that the feet do not contact the bottom of the chamber, and vascular engorgement is not countered by muscular contraction. This minimizes skeletal muscle involvement and allows measurements of changes in leg volume and muscle sympathetic nerve activity for research purposes. Comparing data between the two LBNP devices shows that heart rate increases are less with the Chibis suit due to this lower extremity muscle activity.

The IBMP protocol was 2 min at 25 mmHg and then 3 min at 35 mmHg. Unaccountably, first reports were that heart rate and mean arterial blood pressure response to in-flight LBNP during the first 2 wk was not found to be significantly different than preflight responses. However, on the 30-d and 63-d Salyut-4 (1975) missions, in-flight LBNP was performed weekly and consistently found elevated heart rates. Salyut-6 (1977–1981) and Salyut-7 (1982–1986) hosted 11 long duration missions (over 65 d). In-flight LBNP showed increased heart rate, increased total peripheral resistance, and increased left ventricular ejection time as compared to
preflight values. However, there were no decrements noted with increasing flight duration and postflight orthostatic intolerance was not increased with longer duration flights as compared to short duration flights.\(^{20}\) In-flight individual response was predictive of postflight orthostatic intolerance. Reportedly, several individual crewmembers did not show an exaggerated response to in-flight LBNP and had no postflight orthostatic intolerance.

The Soviets used in-flight LBNP to evaluate other countermeasures for postflight orthostatic intolerance. The usual exaggerated heart rate response was not found with the last LBNP that was performed on the 1975 Soyuz-18/Salyut-4 flight (63 d) with the ingestion of 4 g NaCl and 1000 cc water as an additional countermeasure prior to landing day (Fig. 6). Beginning with Salyut-6, countermeasures were standardized to prevent orthostatic intolerance which included regular exercise, LBNP during the last 2-5 d before landing, and ingestion of salt water (6-9 g NaCl in 900-1200 cc water). At least subjectively, the Soviets were convinced that these countermeasures were beneficial and effective.\(^{11-13,71}\) In-flight rheography demonstrated that spaceflight causes a decrease in the total peripheral resistance that has regional variation.\(^{20,63}\) The use of in-flight LBNP appears to cause an increase in total peripheral resistance by rheography.\(^{23}\) The use of thigh level occlusion devices (“Bracelet”) by the Russians causes lower extremity fluid sequestration and exerts commensurate measurable effects on cardiac performance in microgravity,\(^{22}\) and prevents the subjective discomfort of initial fluid redistribution during spaceflight, but does not change the response to in-flight LBNP or post-landing orthostatic intolerance.\(^{15}\)

The new Russian “Chibis-M” suit (also called “PVK-2”) was developed to encompass a broader range of crewmember anthropometric parameters. It also has more reliable depressurization and contains a computer controller with preloaded programs. Like the original Chibis (“PVK-1”), the Chibis-M suit is designed with corrugated pants which enable the axial compression of the shell. The Russians continue to use a version of the LBNP protocol with the Chibis-M suit at the end of mission time frame onboard the ISS as a countermeasure for post-landing orthostatic intolerance.

### LBNP Bed Rest Studies

In 1976, Soviet bed rest studies showed that \(-12^\circ\) (as compared to \(-4^\circ\) and \(-8^\circ\)) head down tilt for 5 d exactly replicated the subjective symptoms and tilt test response of spaceflight.\(^{42}\) In the United States in 1979, \(-5^\circ\) head-down tilt for 24 h closely matched spaceflight data with regard to decrease in blood volume, leg volume, weight loss, and response to LBNP.\(^{5}\) U.S. ground studies revealed that LBNP resulted in decreased end diastolic volume and therefore decreased stroke volume, but did not influence cardiac contractility.\(^1\) Women were found to be less tolerant of LBNP at 60 mmHg than men.\(^{51}\) LBNP was found to be more reliable as an indicator of orthostatic intolerance as compared to 70° tilt or a stand test.\(^{26}\) In 1977, 4 h of LBNP at 30 mmHg and saline loading at the end of 1 wk of bed rest was found to restore the plasma volume deficit and to be completely protective of orthostatic intolerance.\(^{37}\) Prolonged bed rest (2-4 wk) and spaceflight (11-84 d) were found on analysis in 1979 to both result in decreased blood volume and plasma volume and show very similar post-study LBNP responses.\(^{38}\) One difference was that blood volume deficits occurred in spaceflight within several days, whereas bed rest deficits occurred gradually over a longer period of time. Again, 4 h of LBNP at 30 mmHg and saline loading at the end of the bed rest study was found to restore the volume deficits, to be protective of orthostatic intolerance, and was proposed as a future countermeasure. It was noted in this study that although the plasma volume deficit post-spaceflight was restored within 18 h, orthostatic intolerance lasted several days, indicating that there were other factors involved besides volume deficit. It is now known that at least some of these factors include a decrease in the total peripheral resistance post-landing due to a blunting of the cardiac baroreceptor reflex and a lack of responsiveness to catecholamines.

In 1999, Watenpaugh\(^{64}\) developed an LBNP prototype that self-generated the decreased pressure in a collapsible chamber during “leg-press” type exercise that prevented lower extremity venous pooling by leg muscle activity similar to the Chibis device. This simplified the LBNP device and again was oriented as an orthostatic countermeasure device and not as a research tool. This concept is now being flown on the Chinese space station.\(^{70}\) Exercise during LBNP in bed rest studies has been shown to reduce orthostatic intolerance and maintain exercise capacity.\(^{65,66}\) There is some evidence in bed rest studies that exercise with LBNP prevents the vascular deconditioning (decreased total vascular resistance) that was found on later Shuttle flights.\(^2\)

### Shuttle Program

The development of the Shuttle Program raised new concerns about postflight orthostatic intolerance as Shuttle landing exposed the pilot to as much as 2.0 g in the \(G_x\) (head to foot) axis. All previous spaceflights required minimal pilot function and forces that were in the easily tolerated \(G_x\) (chest to back).
axis. On the first four short duration Shuttle flights, two astronauts (the crew of STS-4) out of eight crewmembers ingested 1 L of isotonic saline and showed a marked difference in postflight orthostatic intolerance with less heart rate increase on stand testing.\(^\text{10}\) Out of 26 astronauts, 17 performed saline loading just prior to re-entry on the first 8 Shuttle flights and had a decrease in presyncope and a decreased heart rate response to stand testing by 29%.\(^\text{9}\) Thereafter, saline loading was adopted as standard protocol on all subsequent Shuttle flights. Detailed leg volume studies in flight showed that up to 2 L of fluid was lost from the lower extremities within 10 h of flight. This volume was replaced within 1.5 h of landing, although some volume loss was present 1 wk post-landing.\(^\text{52,61}\) There was found to be a rapid loss of plasma volume during the first day of spaceflight (17%), which caused an increase in the hematocrit, but did not cause an immediate diuresis. There was some adaptation that occurred which adjusted this to a 10% reduction at 12 d.\(^\text{14,46}\)

LBNP was used during the Shuttle Program during the Extended Duration Orbiter Project (1989-1995) both to investigate in-flight cardiovascular responses and as a countermeasure to postflight orthostatic intolerance. The hardware developed was a fabric cylinder with collapsible internal bracing that required minimal storage volume. A ramp protocol was used that gave stepwise decompression in 10 mmHg increments until 50 mmHg was reached, with a total LBNP time of 40 min. A soak protocol was tested as a potential countermeasure for application on the day before landing which used 30 mmHg for 4 h. The soak was first used in flight with concurrent saline ingestion and had a beneficial effect which was manifested by a diminished heart rate response to the LBNP ramp protocol the next day. However, this benefit was lost by 2 d after the soak treatment. The soak treatment concurrent with saline ingestion was then demonstrated as a countermeasure the day before landing and LBNP treated astronauts showed less heart rate increase and less decrease in systolic blood pressure as compared to the non-LBNP astronauts during stand testing. Although the LBNP soak treatment has a protective effect on post-landing orthostatic intolerance, the 5 h required to treat each individual makes it impractical to use.

Tolerance to ground-based LBNP was found to not be related to leg volume changes alone.\(^\text{57}\) It was found that the loss of plasma volume was not the sole cause of orthostatic intolerance post-spaceflight. In a study of Shuttle astronauts, 9 out of 14 (64%) developed presyncope after a 10 min stand test post-landing. Comparison of orthostatic tolerant and intolerant astronauts showed no differences in heart rate increases, cardiac output, or decreases in stroke volume. However, the tolerant astronauts had a more profound increase in total peripheral resistance with standing.\(^\text{8}\) Further biomedical research on the Shuttle discovered that short-term spaceflight resulted in blunting of the carotid baroreceptor-cardiac reflex, which did not return to normal until several days post-landing and that this contributed to orthostatic intolerance.\(^\text{16}\) Shuttle astronauts were found to have a lack of responsiveness to catecholamines post-landing. Although increased levels of norepinephrine were present with post-landing stand testing, total peripheral resistance was not increased as expected.\(^\text{68}\) It was also found that a hypoadrenergic response with decreased plasma norepinephrine and decreased peripheral vascular resistance occurred with orthostatic stress following spaceflight in a group of astronauts who were relatively more susceptible to presyncope post-landing.\(^\text{17}\) Women are more susceptible than men in that they have lower total peripheral resistance and a less pronounced adrenergic response to orthostasis.\(^\text{57}\)

**Future Research**

The intense research interest in Visual Impairment and Intracranial Pressure (VIIP) syndrome recently discovered during long duration ISS missions has created a new role for in-flight LBNP research to study physiological fluid shifts in weightlessness. A thorough investigation will be undertaken jointly by American and Russian investigators on ISS beginning in 2015, specifically to test the hypothesis that an acute reversal of the head-ward fluid redistribution using LBNP may prevent increases in intracranial pressure and visual impairment.\(^\text{72}\)

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