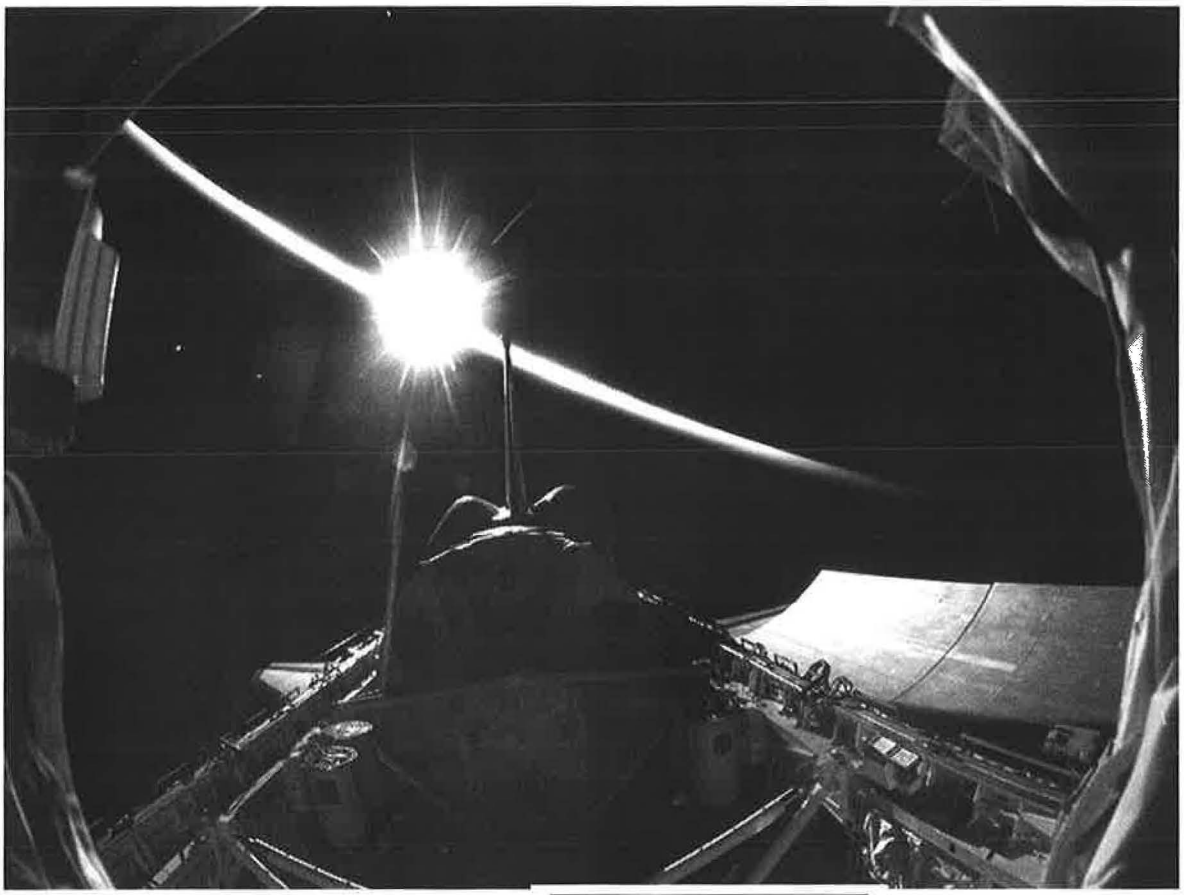
2004: A Space Odyssey –
Implications of Space Medicine for Life and Health on Earth



Benjamin D. Levine, M.D.

Director, Institute for Exercise and Environmental Medicine, Presbyterian Hospital
Professor of Medicine
University of Texas Southwestern Medical Center at Dallas

This is to acknowledge that Benjamin D. Levine, M.D. has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Levine will not be discussing off-label uses in his presentation

[Medical Grand Rounds, September 23, 2004]

Isaac Asimov once suggested that the landing of humans on the moon 35 years ago this summer was the greatest advance in human evolution since the origins of modern terrestrial life first crawled out of the ocean. Although he was specifically talking about the importance of making the first steps off planet earth, his words have hidden meaning – the transition from water to land based life ultimately led to the upright posture, freeing the hands for complex tasks and accelerating/facilitating human cultural as well as physical evolution. This required the development of multiple systems to support life in a gravitational environment: a hard skeleton to provide structure, muscles to raise the skeleton off the floor and exert force against gravity, a vestibular system to determine body position in gravitational (i.e., 3-dimensional) space, and a cardiovascular control system that enabled blood to flow uphill to the brain despite gravity's efforts to draw it into the feet.


Laika, the first living being in space

Exactly the opposite transition occurs in the microgravity environment of space. Humans are so adapted to life on earth with gravity that early scientists predicted physiological catastrophe should space flight be attempted. Laika the Russian "cosmonaut" immortalized in Ingmar Bergmann's film, "My Life as a Dog", demonstrated that indeed, the absence of gravity was not catastrophic. Followed quickly by Yuri Gagarin in Vostok 1, in April 1961, and then by Alan Shepard, Gus Grissom, and John Glenn from the US Mercury Program, it became immediately clear that mammals in general and humans in particular could survive in space. Although the US Space program has drifted somewhat aimlessly in the years since the end of the Apollo program, recent direction from the White House has suggested that a new goal may be at hand.

Mission to Mars

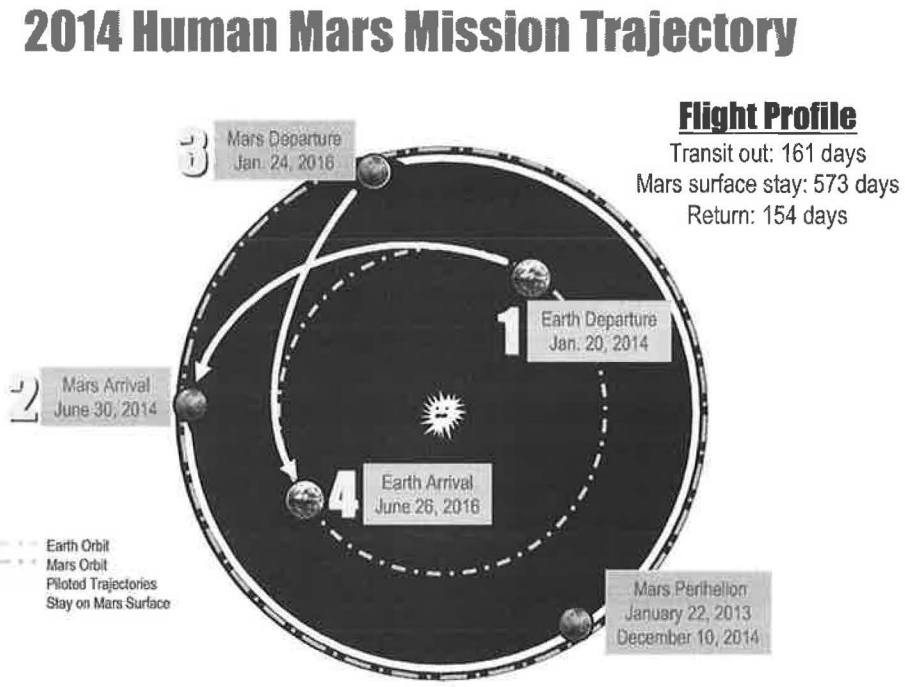
On January 14, 2004, President Bush announced a renewed and vigorous effort "to explore space and extend a human presence across our solar system." He focused on 4 main goals:

- to complete the International Space Station by 2010. "We will develop the skills and techniques necessary to sustain further space exploration."
- to develop and test a new spacecraft, the Crew Exploration Vehicle, by 2008, and to conduct the first manned mission no later than 2014, with the main purpose of this spacecraft to carry astronauts "beyond our orbit to other worlds."
- to return to the moon by 2020, as the launching point for missions beyond. "We will undertake extended human missions to the moon as early as 2015, with the goal of living and working there for increasingly extended periods."
- to take the next steps of space exploration: human missions to Mars and to worlds beyond. The human thirst for knowledge ultimately cannot be satisfied by

even the most vivid pictures, or the most detailed measurements. "We need to see and examine and touch for ourselves. And only human beings are capable of adapting to the inevitable uncertainties posed by space travel."

Fig 2: Putative Mars Mission beginning January 20th, 2014

A



mission to Mars would take an extraordinary logistical, scientific, and fiscal effort. First of all, a mission to Mars would take a long time. Because of the differences in both Earth and Mars orbits, the actual time window in which such a mission could be accomplished is relatively narrow. Because the Earth and Mars must be as close together as possible during arrival and departure, opportunities for a Mars mission only occur every 2 years or so. Figure 2 shows a potential scenario laid out by NASA in 2000 for launch in 2014. After 161 days traveling, the space craft would arrive on Mars in June. The crew would then have to remain on the Mars surface for about 1.5 years, before another opportunity would arise for return to Earth at the end of June, 2016. However since the break-up of Columbia, this specific scenario has become untenable. NASA currently "projects" a possible moon landing by 2020, and a Mars mission by 2030 at the earliest. Based simply on orbital configurations, and assuming current launch and power capabilities, potential dates over the next quarter century might include: May 2018, July 2020, Sep. 2022, Oct. 2024, Oct. 2026, Dec. 2028, Feb. 2031

Besides the extraordinary engineering concerns required to accomplish such a task, there are many effects of space flight on the human body that must be considered.

I. Physical Effects of Space

There are a number of key features of the space environment that influence how humans are able to live and function in space:

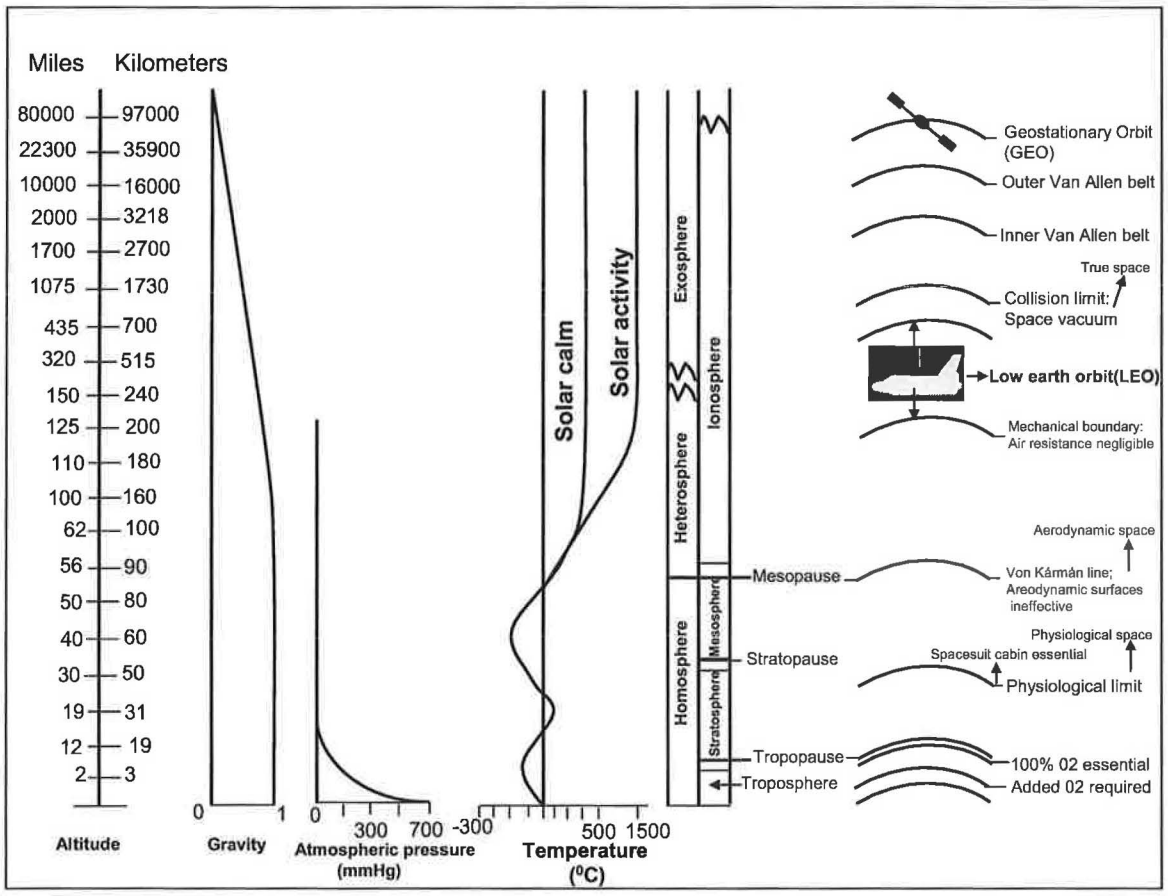
1). Absence of gravitational force – although gravity can never be completely eliminated, the gravitational pull toward the earth is exactly matched by the acceleration required to remain in orbit, so that gravity is effectively eliminated. The best term for this situation is "microgravity". Microgravity can be induced on earth for brief periods in vehicles such as the KC-135, which during parabolic flight accelerate toward the ground at the same acceleration as gravity's pull (9.8 m/s/s), similar to "free fall" in an elevator. For about 30 seconds, there is effectively no gravity, and brief experiments can be accomplished. The absence of gravity results in a number of other consequences:

- No up or down – results in disorientation, and conflict between visual and neurovestibular input (see more below). Astronauts can sleep in any position they choose, including "upside down". It is interesting that different individuals seem to have more or less trouble with this type of conflict. Some astronauts are very visually oriented and associate "up" with the "top" of the spacecraft as would be seen on the ground. Others are more internally oriented, and describe "up" as anything directed toward the top of their heads;
- No convection currents – the absence of convection, which requires a differential density between air of different temperatures, results in significant problems with temperature regulation. It also prevents the use of normal cooking (convection oven), or refrigeration (which requires convection of the primary coolant, Freon).
- No air/fluid interfaces – since air is no longer "heavier" than water, there are no typical air fluid interfaces, particularly in the body. For example, this may cause substantial problems with gastrointestinal gas, which in space is expelled mixed with fluid and particulate matter…

2). Absence of atmosphere – the absence of gravity results in the absence of earth's atmosphere, so there is effectively a vacuum. Thus survival depends on astronauts bringing an atmosphere with them. The exact nature of what this atmosphere should be has led to lots of debate within NASA and the space community. For structural reasons, early vehicles used relatively low barometric pressure with high oxygen concentrations. For example, the environment in Skylab was at one third of an atmosphere (5 PSI), with an environment containing 70% oxygen. However the fatal fire aboard Apollo 1 emphasized the danger of this approach.

Since the advent of the shuttle era, all space vehicles have been at 1 atmosphere pressure (i.e., 760 Torr) with a normal 20-21% O2 concentration. However because survival is not possible outside of the self-contained environment, EVERYTHING must be carried with the crew: fuel, food, air, water (though the latter is usually generated as a waste product of fuel cell use…).

Because of this absolute dependence on an artificial environment, the isolation associated with prolonged space travel is profound and potentially mission limiting. At least 3 Soviet missions have had to be terminated early because of psychological


Miles
Kilometers
80000
97000
22300
35900
10000
16000
2000
3218
1700
2700
1075
1730
435
700
320
515
150
240
125
200
110
180
100
160
62
100
56
90
50
80
40
60
30
50
19
31
12
19
2
3
Altitude
0
1
Gravity
0
300
700
Atmospheric pressure
(mmHg)
-300
500
1500
Temperature
(°C)
Solar calm
Solar activity
Exosphere
Ionosphere
Heterosphere
Homosphere
Mesosphere
Stratosphere
Mesopause
Stratopause
Tropopause
Troposphere
Geostationary Orbit
(GEO)
Outer Van Allen belt
Inner Van Allen belt
True space
Collision limit:
Space vacuum
Low earth orbit(LEO)
Mechanical boundary:
Air resistance negligible
Aerodynamic space
Von Kármán line;
Areodynamic surfaces
ineffective
Physiological space
Spacesuit cabin essential
Physiological limit
100% 02 essential
Added 02 required

issues. This area has been grossly understudied in space flight research, and may be one of the central limitations to long duration space flight. The absence of normal earth rotation also leads to the elimination of normal day-night cycles, which contributes to sleep disorders, and complicates issues associated with confinement.

Another consequence of the absolute dependence on engineering and equipment for survival is that when problems arise, they may be catastrophic. For example to date, all mortality in spaceflight has been due to equipment failure:

- **Apollo 1 fire 1967**
- **Soyuz 1 landing 1967**
- **Soyuz 11 decompression 1971**
- **STS-25 Challenger explosion 1986**
- **STS-107 Columbia re-entry disintegration 2003**

Thus just like test pilot work, or expeditions into demanding environments (Everest, Antarctica) the task itself is the main risk.

Moreover, similar to such terrestrial expeditions, Mars travelers must bring all their supplies with them, and be prepared for multiple medical emergencies. Based on experience with Antarctica expeditions, nuclear submarines, and previous Russian and American aviation and space experience, the incidence of *significant* illness or injury occurring is **0.06 per person-year** as defined by U.S. standards requiring emergency room (ER) visit or hospital admission; about a third of such injuries would likely need intensive care (ICU) support or about **0.02 person per year.** Thus for a crew of 6, on a Mars mission lasting 2.5 years, the odds that a crew member would need medical care equivalent to that of an ER visit or hospital admission is 0.9, with about one every three missions requiring ICU level care. This risk has led to many discussions about preventative procedures, such as prophylactic appendectomies for any potential Mars crewmember,

Exposure Table : Fig 4 (source: National Space Biomedical Research Institute)

A comparison of different types of human radiation exposures and their corresponding dose levels.

Types of Exposures (1 Sv = 100 rem)	**mSv**
Transcontinental round trip by jet	0.04
Chest X-ray (lung dose)	0.1
Living one year in Dallas, Texas	1.0
Living one year in Denver, Colorado	2.0
Living one year in Kerala, India	13.0
Highest skin dose, Apollo 14 {9-day mission to the Moon)	11.4*
Highest skin dose, Skylab 4 (87 day mission orbiting Earth at 272 miles)	178.0*
Highest skin dose, shuttle mission 41-C 18-day mission, orbiting Earth at 286 miles]	5.59*
Maximum allowable in I year to terrestrial worker with maximum of 100 mSv in any 5-year interval	50.0
Average maximum allowable to the public in 1 year (average over a 5-year interval)	1.0

* The differences in exposure values for the various space missions shown here are due to mission characteristics as altitude, duration, and quality of radiation shielding

and other screening efforts such requiring all Mars crew members to have no coronary calcium on electron beam CT scanning.

3). Excessive Radiation Exposure – the absence of an atmosphere exposes space travelers to excessive solar and cosmic radiation, unfiltered by the earth's atmosphere. Table 1 give doses of ionizing radiation for a variety of terrestrial and space activities. Solar flares, which create very high energy photons over periods of 1-2 days provide particularly intense radiation exposures, on a background of solar wind (continuous low energy particles) and cosmic rays. To put this exposure in perspective, an astronaut participating in a mission to Mars lasting approximately 2.5 years, assuming a similar exposure as experienced in Skylab, would be exposed to the equivalent of nearly 18,000 chest X-rays. The risk to human health from this level of radiation is not certain, but is considered one of the most important impediments to long duration space flight and exploration class missions.

II. Physiological Effects of Space

A. Neurovestibular – The vestibular system is the primary organ in the body which has as its principal function, the sensing of gravity i.e., the detection of position and acceleration within a gravitational environment. When the head moves in any single or combination of directions, normally, the fluid within the semicircular canals lags behind the structure of the canals, putting a slight bend on the hair cells which send signals back to the brain via the vestibular nerve. The three semicircular canals, located in the vestibular organ of each inner ear, are positioned roughly at right angles to each other. This set up allows exquisitely sensitive ability to detect pitch (up and down), roll (tilting the head toward either shoulder), and yaw (side to side movement), or rotational movement of the head. The otolith organs (the utricle and saccule) contain small, flat layers of calcium carbonate crystals imbedded in a gel like substance, which allows the detection of position and linear motion of the head. It is the otoliths that are primarily responsible for determining "up" and "down" and which are most acutely affected by the absence of gravity.

With acute entry into space, the sudden change in the stimulus to the vestibular system is one of the most dramatic physiological expressions of the absence of earth's gravity. The otolith organs no longer experience a "downward" acceleration, and a disconnect develops between visual cues, and the sense of body position. Although the exact mechanism remains unknown, the clinical

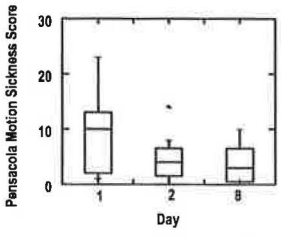


Fig 6: Data from National Space Biomedical Research Institute, Larry Young, Ph.D. A score of >5 is considered to be significant motion sickness[2]

expression of this disconnect seems to be the development of a syndrome called space motion sickness (SMS). This syndrome consists primarily of nausea, and occasionally intense vomiting, as well as a feeling of "being sick", like motion or acute mountain sickness. Probably the most well known sufferer of this condition was Utah senator Jake Garn, who flew in space as a political boondoggle on STS 51D in 1985. It is reported that Senator Garn, who has since been known among the astronaut corps as "Barfin Jake" had a particularly severe and intense bout of SMS, and a large unit of vomit is now known as a "Garn."

Most astronauts experience SMS at least to some degree, though it is most intense at the beginning of flight, and then appears to lessen as adaptation within the neurovestibular system progresses.

B. Bone demineralization and Risk of Nephrolithiasis -- The problem of progressive and potentially irreversible bone demineralization is one of the most important impediments to long duration spaceflight[6]. Virtually all space flight studies demonstrate a prominent loss of bone structure, which does not seem to recover even after prolonged re-exposure to gravity. Exposure to microgravity produces a number of physiological changes of both metabolic and environmental origin that promote bone loss and simultaneously increase the risk for renal stone formation. These include most prominently, the loss of skeletal loading, which is the primary stimulus to both inhibit bone resorption, as well as stimulate bone deposition. Most of our current data is based on observations made during the Gemini, Apollo, and Sky-lab missions [7-9] although there are some data for crewmen following 4 to 10 day [10] and 11 to 16 day [11] shuttle missions. These findings, which have also been observed during short term [12,13] and long-term bed rest studies [14,15], suggest that several key urine alterations (as a result of fluid shifts and bone demineralization) increase stone forming risk. The most important of these changes are a reduction in urine volume, urine citrate (a potent inhibitor of renal stone formation), increases in urinary calcium, phosphorus, and a fall in urinary pH. Overall, these changes could promote the formation of calcium oxalate or uric acid stones due to such changes in the urinary environment.

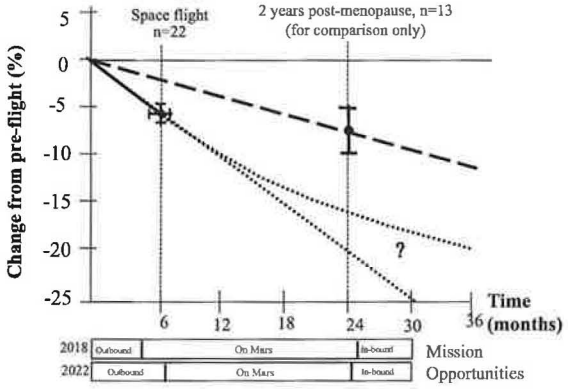


Fig 7: Data with permission from John Charles, Ph.D., NASA, Johnson Space Center

The Mineral Metabolism division, led by Drs. Charlie Pak, Joe Zerwekh, and Khashayar Sakhaee at UT Southwestern has extensive experience with both space flight and the bed rest model of skeletal unloading . For example, in two space missions, they demonstrated that urinary saturations of calcium oxalate and undissociated uric

acid were increased in-flight[10,11]. These results suggested an increased risk of stone formation in space.

During bed rest this increased risk appears to be primarily metabolic in origin (from hypercalciuria and hyperphosphaturia of bone loss). For example, urine from 8 normal subjects during 5 wk of bed rest showed increased saturation of calcium oxalate and calcium phosphate by raising urinary excretion of calcium and phosphate [12]. Recently, during 12 wk of bed rest, weekly 24-hour urine samples showed a significant and sustained increase in urinary calcium, phosphorus and saturation of calcium oxalate, compared with pre- & post-bed rest specimens[16]. In this same study, there was a rapid, sustained increase in urinary calcium (5.3 mmol/day to 7.3 mmol/day) and phosphorus as well as a significant increase in serum calcium [15]. Parathyroid hormone and serum 1,25-dihydroxyvitamin D de-clined significantly during bed rest although the mean values remained within normal limits. Intestinal calcium absorption decreased slightly but not significantly [15]. Moreover even within 3-weeks of bed rest in our laboratory, there was a significant rise in fasting urinary calcium, and a non-significant decrease in serum PTH, calcitriol concentration and G.I. Ca absorption [13]. The results are compatible with the hypothesis that bone loss from bed rest suppresses parathyroid function, calcitriol synthesis and intestinal calcium absorption.

In order to determine the effect of these metabolic changes on bone structure, two transcortical iliac crest bone biopsies were obtained from each volunteer before and after 12 wk of bed rest[15]. Significant changes in bone histology included a suppression of osteoblastic surface for cancellous bone (3.1 ± 1.3% to 1.9 ± 1.5%) and increased bone resorption for both cancellous and cortical bone. Cortical eroded surface doubled (3.5 ± 1.1% to 7.3 ± 4.0%), and active cortical osteoclastic surface tripled (0.2 ± 0.3% to 0.7 ± 0.7%). Cancellous eroded surface increased from 2.1 ± 1.1% to 4.7 ± 2.2%, while mean active osteoclastic surface doubled (0.2 ± 0.2% to 0.4 ± 0.3%, p=0.02). This increase in bone resorption during prolonged weightlessness was further supported by the changes observed for urinary biochemical markers of bone turnover (hydroxyproline, deoxypyridinoline, and N-telopeptide of type I collagen) as well as a serum marker of bone resorption (type I collagen carboxytelopeptide), all of which increased during bed rest and declined toward normal during reambulation. Thus, during bed rest, the skeleton appears to respond by a rapid and sustained increase in bone resorption and a more subtle decrease in bone formation.

Although various methods and devices exist for measuring bone structure and function, a novel device was developed at UT Southwestern for these studies based on the principles of UCR (Ultrasound Critical-angle Reflectometry) [17-20]. In 10 patients who underwent bed rest for 12 weeks, there was a significant decrease in the cancellous bone velocity along the transverse axis while the cortical bone velocity increased significantly in both directions (transverse and longitudinal). However, the values of the velocities were strongly site-dependent, as were their responses to the absence of gravity. Thus, there were significant differences between the lower, middle, and upper skeleton, consistent with a redistribution of bone elasticity between cancellous and cortical bone. Bed rest resulted in profound changes in the elastic properties of cancellous and cortical bone, which affected the two bone types differently and altered the values of the elasticity and its dependence on orientation. Similar to previous findings following spaceflight, the present findings suggest that the greatest changes in

bone strength occur at load-bearing bone sites. Based on our past work and our current understanding of UCR, this response to skeletal unloading indicates an overall reduction in material and structural bone strength, driven primarily by a loss in cancellous bone elasticity and secondarily by the differing responses of cortical and cancellous bone.

C. Muscle atrophy – The effects of prolonged disuse atrophy involve decrements in most every subsystem associated with skeletal muscle. Although some of these data come from ground-based and spaceflight experiments in humans[21,22], much has been collected from animal models, primarily tail suspended rats[23,24, 25]. Disuse atrophy induces a wide range of effects including: 1) loss of overall muscle size, contractile proteins and strength; 2) loss of metabolic capacity, mediated by loss of mitochondrial volume; 3) conversion of muscle fibers from slow to fast twitch; and 4) loss of capillarity. The mechanisms mediating these effects are less clear.

Prolonged disuse atrophy causes profound loss of muscle size, opposite in magnitude and direction to resistance strength training. In rats, while exercise training causes a doubling of the size of the trained muscles [26], prolonged unweighting, whether by hind-limb suspension or spaceflight can cause muscle to shrink to less than 50% of the original size [23, 27]. Since unweighting is opposite in effect to training, the use of exercise as a countermeasure is intuitive & effective [28].

In contrast to animals, the data describing the response of human muscle to prolonged spaceflight is much less abundant, and considerable questions remain about the ability of skeletal muscle to withstand the effects of long term spaceflight without undergoing so much atrophy that functional incompetence presents a grave risk [29,30]. Although it is clear that there is atrophy, the details of this atrophy remain incomplete. However, it is known that unloading causes reductions in the size of both slow and fast twitch muscle fibers [31] and that there are overall shifts from slow to fast isoforms [23,27,32,33].

This muscle atrophy, most prominent in slow-twitch muscles, is hypothesized to relate to loss of myofibril protein. While decreased muscle protein synthesis followed by increased protein degradation is thought responsible for this atrophy in rats [22,34], the mechanisms are not resolved in humans. Evidence for a decline in protein synthesis as the predominant mechanism in humans comes primarily from tracer studies during bed rest[35] and spaceflight[36] whereas evidence for a role of enhanced protein breakdown is lacking.

However the cellular and molecular mechanisms for how protein balance is handled in humans during unloading is less clear. The ubiquitin-proteasome pathway, studied extensively by Drs. George DiMartino and George Ordway here at UT Southwestern, clearly plays a significant role in protein breakdown in animals in response to both increases and decreases in activity, and has been well-characterized[37]. For example, several studies have examined relative contributions of various proteolytic pathways to muscle atrophy in the hindlimb suspension model. Soleus muscles of rats suspended for 3-9 days lose significant tissue protein and demonstrated markedly increased rates of protein degradation [38,34,39]. While lysosomal and calpain-dependent pathways of protein degradation are upregulated in these muscles, the vast majority of proteolysis is the result of increased activity of the

ubiquitin-proteasome pathway [38,40,34,39]. Alterations in the ubiquitin-proteasome pathway due to microgravity or bed rest have not been studied in humans.

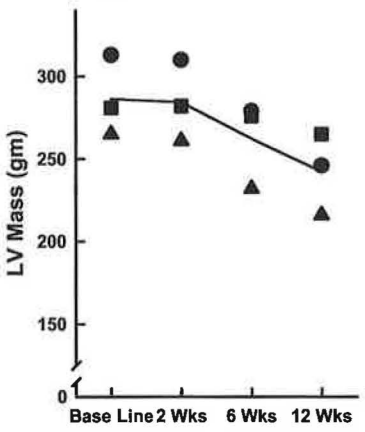
The effects of prolonged disuse atrophy on metabolic indices are also not clear [24]. In the rat, there are reports of a variety of changes, including increases, no change, or decreases in the capacity of atrophied muscle for oxidative metabolism [41,42,43]. Finally, there are other, less obvious, effects of chronic unloading, which could just as easily have serious functional consequences. These include, but are not limited to regulation of neuromotor control, torque, speed of contraction, and contraction induced muscle injury[23].

It is clear that exercise countermeasures are required to attenuate, if not offset, the effects of microgravity [21]. Moreover, such exercise countermeasures are indeed functional [28] and can limit atrophy. On the Mir Space Station, Russian cosmonauts reportedly exercised up to 2 hours/day in an attempt to prevent skeletal muscle atrophy (among other systems).

D. Cardiovascular deconditioning – Since the beginning of the manned space program, one of the most prominent observations was that returning astronauts developed orthostatic intolerance, termed "cardiovascular deconditioning" by early Russian scientists. This "deconditioning was manifest by a prominent increase in upright heart rate, even in flights such as John Glenn's lasting only 4 hours.

Overview: Gravitational and hydrostatic gradients play an essential role in determining the distribution of pressure and volume within the cardiovascular system[44]. When these gradients are removed or minimized, such as during spaceflight or its ground-based simulations (bed rest), a central fluid shift occurs, initiating a neurohumorally mediated reduction in both blood/plasma[45] and ventricular volume. Diastolic wall stress is thereby decreased and the volume load of the left ventricle is reduced compared to the supine position at 1G [46]. Compounding these hemodynamic changes is a reduction in physical activity associated with confinement, which minimizes chronotropic and pressure work compared to more freely ambulatory periods. Within a few weeks of real or simulated microgravity, the heart appears to atrophy, presumably in response to reduced myocardial work [47-49]. In ground based models, this adaptation results in impaired diastolic function characterized by decreased ventricular distensibility, and possibly by loss of diastolic suction leading to reduced ventricular filling[50]. The combination of atrophy and hypovolemia results in a prominent reduction in stroke volume in the upright position at 1G, which is the essential stimulus for microgravity induced orthostatic hypotension[50].

fig 1

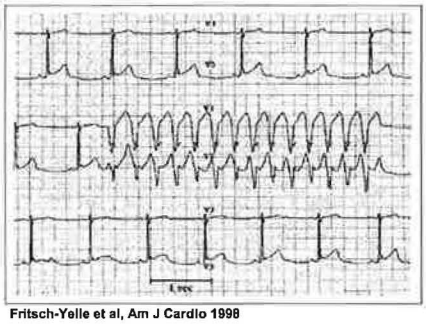


Although the hypovolemia of spaceflight or bed rest appears to stabilize after 24-48 hours of real or simulated microgravity[51,52], preliminary data by our research group in 3 subjects who have completed 12 weeks of bed rest has failed to identify a plateau in the loss of cardiac mass measured by MRI over this time period (fig 1)[48]. Similar data

are not available for prolonged spaceflight, and the clinical implications of cardiac atrophy for systolic and diastolic function after extended spaceflight are unknown. If severe or progressive, cardiac atrophy would represent an important limitation for prolonged human presence in space.

Structural changes in the heart with prolonged spaceflight may have other functional implications. For example, although cardiac arrhythmias do not appear to be increased during short term space flight[53], concern has been raised recently over an apparent increase in ventricular arrhythmias after prolonged exposure to the Mir space station, including one published case of non-sustained ventricular tachycardia[54].The potential mechanism for an increased susceptibility to life threatening arrhythmias in astronauts with normal hearts is unclear. However, if left and/or right ventricular atrophy is severe, then apoptosis, or a change in the distribution of conductive tissue may be at least one of the factors pre-disposing to arrhythmias during long term space flight.

Ventricular Tachycardia on Mir



Fritsch-Yelle et al, Am J Cardio 1998

The Hemodynamics of Microgravity

Head down tilt bed rest (HDT) is used to simulate spaceflight on earth by eliminating all head-to-foot gravitational (Gz) gradients. With assumption of the head down tilt (HDT) position, there is a cephalad fluid shift, increasing central venous pressure (CVP), LV dimensions, stroke volume (SV) and cardiac output [51,52]. Within 24 hours, there is a salt and water diuresis, reducing CVP and SV below supine values, similar in magnitude to that observed after more prolonged periods of bedrest or spaceflight [52].

A recent study by our group elaborated the time course of this adaptation, showing a gradual decrease in SV to below supine values, reaching a nadir at 48 hours, with no further reduction over the next 2 weeks[1] (fig 1). This value was about one-half between the supine and upright values suggesting that the "regulated" cardiac volume is equivalent to approximately 0.5G. Heart rate and total peripheral resistance followed similar trends [1]. Thus within a few days, the acute response to HDT bed rest ultimately leads to a smaller heart with lower filling pressure. The acute hemodynamic response to spaceflight appears very similar (despite a decrease in CVP referenced to atmospheric pressure[55]), with an acute increase in LV end diastolic volume and SV due to similar increases in transmural cardiac filling

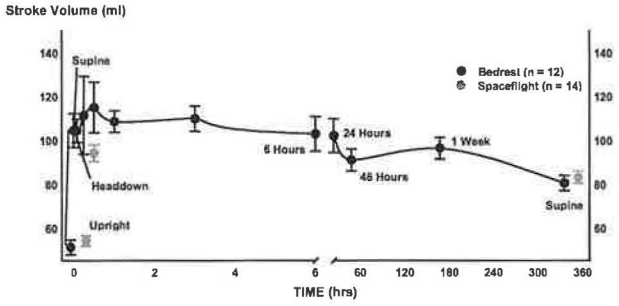


Fig 9: Acute response to HDT bed rest (n=12) shown in black (from ref 2: note after initial HDT, all values are head down except for 2 week mark which is supine), with comparison values from SLS-1, SLS-2, and D-2 space missions in gray[3-5]. Note remarkable similarity between HDT bed rest and spaceflight.

pressure [55,56,57]. This acute response is followed by a more chronic reduction in cardiac filling that is remarkably similar to HDT bed rest (Fig 9).

Echocardiographic data have been inconclusive regarding whether the heart atrophies after bed rest [1] or spaceflight[58] in part because of large variability in measurements of cardiac mass by echo [59]. More convincing data documenting cardiac atrophy have been obtained recently by our group after both spaceflight (2 wk) and bed rest (6 wk) [48] using magnetic resonance imaging (MRI), which has excellent precision in measuring cardiac mass, [60,48]. Moreover this atrophy was accompanied by a reduction in mean wall thickness,[48] suggesting that it was a normal adaptive response to maintain wall stress.

The Importance of Stroke Volume

In animal models, cardiac atrophy is associated with increased chamber stiffness [61]. Because of the curvilinear nature of the LV pressure-volume relationship, cardiac stiffness is dynamic with the instantaneous stiffness, dP/dV, dependent on LV volume [62]. These changes may occur **acutely:** with either an alteration in intravascular volume, or a sudden change in extracardiac influences (e.g., pericardial constraint); or more **chronically** via a specific cardiac adaptation. Not only is SV easily altered by mechanical and hydrostatic effects, but it serves as the primary stimulus to baroreflex regulation of arterial pressure during an orthostatic stress as part of the "triple product" of blood pressure control: BP = HR x **SV** x TPR [63]. Orthostatic hypotension thus will ensue if the fall in SV is of sufficient magnitude to overwhelm normal compensatory mechanisms[64] or if the reflex increase in HR and/or TPR is impaired by disease, or by a specific adaptation of the autonomic nervous system [65].

After adaptation to real or simulated microgravity, virtually all individuals studied have an excessive fall in stroke volume in the upright position [3-5]. Although there are conflicting data regarding changes in baroreflex regulation of heart rate and vascular resistance that may limit the compensatory response to orthostasis [66-73], it is this excessive fall in stroke volume that is the *sine qua non* of microgravity induced orthostatic hypotension. Recently our group, led by Dr. Blomqvist, has suggested that individuals who are prone to orthostatic hypotension after spaceflight have a reduced ability to augment TPR during standing after flight[3]. NASA investigators subsequently noted a smaller increase in plasma norepinephrine in susceptible individuals [4]. Studies in Dallas using intra-arterial infusion of phenylephrine however, showed that micro-gravity does not impair the peripheral vascular response to α-adrenergic vasoconstriction [74].

More recently, in a landmark series of investigations, our research team and colleagues demonstrated normal sympathetic neural function during and after short term space flight, with an increase in sympathetic activity that appeared appropriate for the reduction in cardiac filling and SV observed post flight[5,75 76,77]. These studies confirmed observations made by us previously after bedrest[78]. Thus rather than developing impaired neural control of vascular resistance after bed rest or spaceflight, reflex compensatory mechanisms appear to be challenged by an excessive fall in stroke volume. A corollary to this argument is that if this excessive fall in stroke volume could be eliminated, then orthostatic intolerance could be improved[79].

We recently completed an extensive investigation into the mechanisms

responsible for this excessive fall in SV, which has been published [1,49]. In brief, HDT led to a significant reduction in plasma volume, pulmonary capillary wedge (PCW) pressure, SV, LVEDV, and LBNP tolerance. The slope of the Starling curve increased, resulting in nearly twice the fall in SV for the same fall in PCW after bed rest. For any given PCW below baseline, there was a smaller SV after, compared to before bedrest (i.e., a different Starling curve), without a change in contractility.

Pressure-volume curves demonstrated a parallel leftward shift after HDT, with a decrease in equilibrium volume (the volume at which pressure = 0 mmHg), consistent with decreased chamber size. Therefore the principal mechanical adaptation to bedrest appeared to be decreased distensibility (smaller volume for a given pressure). Because supine LVEDV also decreased (due to a decrease in plasma volume), dP/dV at baseline after bedrest was only half the dP/dV at baseline before bedrest, leading to a greater decrease in SV during orthostatic stress and orthostatic intolerance. This remodeling was not observed after acute reduction in plasma volume with pharmacologic diuresis alone[49].

Together, these data argue strongly that there is a unique cardiac adaptation to bed rest deconditioning that is distinct from simple loss of plasma volume. Such data are not available for long duration bed rest, when cardiac atrophy is most prominent.

Long Term Microgravity

In contrast to the extensive data base examining the short term response to microgravity, data describing long term exposure are much rarer, particularly with regard to the cardiovascular system [80]. Of interest during Skylab, which included 3 missions of increasing duration from 29 to 84 days, there was no greater loss of exercise capacity, nor any greater degree of orthostatic intolerance after the longer missions, compared to the shortest [81]. Part of the explanation for this observation may be the prominent degree of exercise training the astronauts performed during the longer missions. Russian cosmonauts exhibited little evidence of a progressive deterioration in the cardiovascular system with long term space flight in the majority of crew members [82,83]. However the methods used in these small studies may not have been sensitive enough to detect meaningful alterations in cardiac structure or function.

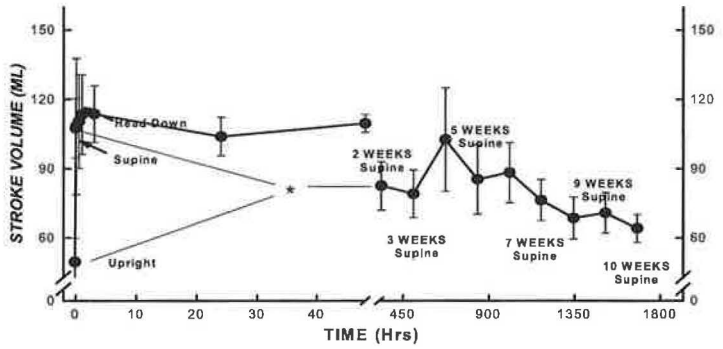
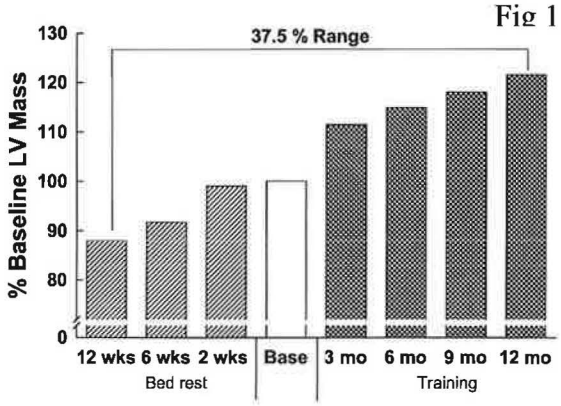


Fig 10. Changes in SV acutely, and then weekly for 12 weeks of supine bed rest. SV is significantly different (*=p<0.05) from both supine and upright after 2 weeks of bed rest, and then does not change from 2-10 weeks (n=5).

Ground based studies have suggested that during 17 weeks of supine bed rest, HR and BP responses to LBNP were remarkably stable, after the first week of bed rest [84]. Studies by our group, in collaboration with Dr. Zerwekh show similar findings for SV[48] (figure 10). However, poorly described Russian studies involving very long (370 days) bed rest have shown more labile hemodynamics with delayed (2 months) recovery.[85] In contrast to the hemodynamics, MRI measures raise the possibility of either progressive cardiac atrophy, or at least delayed stabilization of LV mass during prolonged

microgravity. [48] Together, these observations suggest that long duration microgravity may be quantitatively different from short duration microgravity. Because the future of space exploration will depend on longer flight exposures, it is critical that the physiological significance of cardiac atrophy be carefully defined. This focus is the overall objective of our new flight experiment called the C.A.R.D.I.A.C. (Cardiac Abnormalities in Rhythm and Diastolic function due to Inactivity, Atrophy, and Confinement) Study, E377, to be performed aboard the International Space Station.

Fig 11



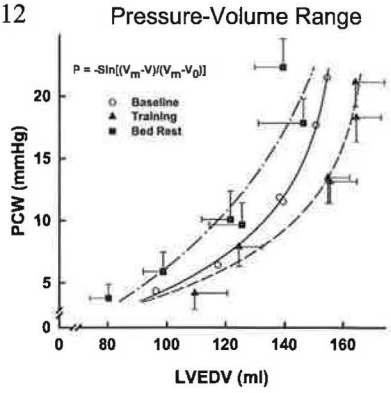
All subjects who have undergone either prolonged bed rest or prolonged training displayed together as a function of the change in LV mass (MRI) from baseline.

The Importance of Physical Activity

Physical activity is another critical factor which regulates the LV mass. Our research group has been involved intensively in an effort to examine the specific role of physical activity and exercise conditioning or deconditioning on cardiovascular function over the past decade [1,63,86-90]. For example, recently we have completed an ambitious training study in which 12 young men and women (including 5 subjects from the short term bed rest study) underwent a year long progressive endurance training program designed to enable them to run a marathon. In response to this training, LV mass increased greatly (163±38g to 205±44g).

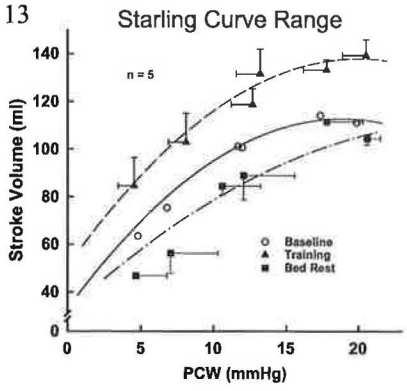
Taken together, these data suggest that the physiological hypertrophy" of exercise training appears to be the converse of the "physiological atrophy" of bed rest or space flight, both of which appear to be related to hemodynamics and physical activity. Thus over a large range of physical activity, the heart is remarkably plastic with a 38% variation in LV mass (fig 11), and a 25% variation in LV distensibility (fig 12). This plasticity leads to a 40% variation in the ability to increase SV via the Starling mechanism [91] (fig 13).

Fig 12



P/V and Starling curves for the 5 subjects who completed both 2 wk bed rest, and 1 yr training

Fig 13



Effect of Training During Bed Rest

A number of investigators have used exercise training to prevent "cardiovascular deconditioning" associated with bedrest. These studies have employed dynamic (generally supine cycling) vs static exercise[92], large muscle mass dynamic exercise vs relatively smaller muscle mass isokinetic exercise (knee flexion/extension)[93-95], and even supine treadmill walking during simultaneous

LBNP [96]. The small muscle mass exercise had no effect on either plasma volume or orthostatic tolerance. Cycling blunted the loss of plasma volume and maintained supine exercise capacity during bed rest up to 30 days. It also was modestly protective against orthostatic intolerance (50% relative risk reduction). Supine treadmill walking with LBNP was the only intervention to preserve upright exercise capacity[96], though orthostatic intolerance was not prevented.[97] Of particular note, no studies have used a comprehensive training program as typically followed by competitive endurance athletes incorporating submaximal intensity base training, higher intensity intervals, and regular strength training [98,99,100,101]. When such training is performed over very prolonged periods of time (25 yrs), recent studies by the PI have demonstrated that even cardiac stiffening from aging can be prevented [102]. Intriguingly, a single bout of maximal exercise appeared to minimize the reduction in LBNP tolerance in one study[103]. This model is unlikely to affect cardiac compliance and probably acts to acutely increase plasma volume [103-105].

The Dallas Bed Rest Countermeasure Study

Based on the direct relationship between cardiac work and LV mass, we speculated that with bed rest deconditioning, the reduction in wall stress combines with the reduction in physical activity leading to cardiac atrophy [1,48]. Preliminary calculations support this notion. Based on ambulatory and lab measurements, we measured a decrease in stroke work during bed rest by approximately 18% compared to normal ambulation[1]. We further estimated that it would take about 90 min of dynamic exercise/day at 75% of maximum HR to normalize stroke work between bed rest and ambulatory periods and maintain LV mass.

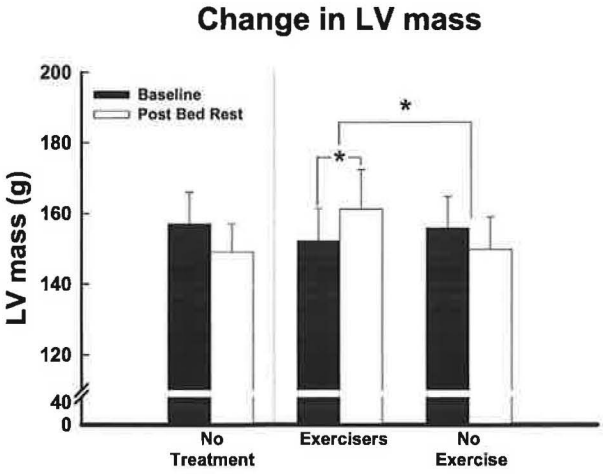
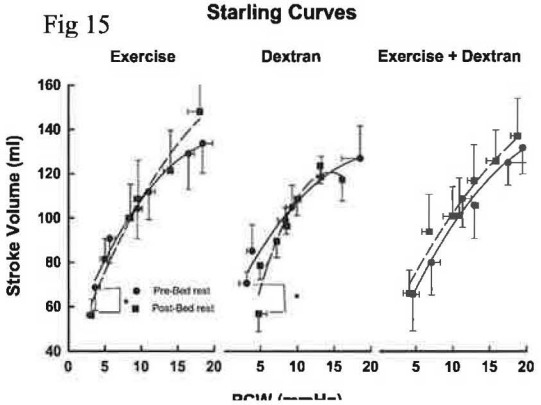


Fig 14: "No treatment" data by echo from ref [1]; "no exercise" by MRI from new study.

This hypothesis has been tested directly in a preliminary study funded by NASA and performed in our GCRC to examine whether exercise training, with or without volume loading is sufficient to prevent the cardiac atrophy during short term bed rest, and the associated orthostatic intolerance. 14 subjects completed bed rest with –6° HDT for 18 days and trained on a supine ergometer at 75% HRmax, 90 min/day to normalize cardiac work . 7 subjects completed HDT with no exercise (Dextran). LV mass, measured with MRI, increased by 10 % in the exercise group (fig 14) and decreased by 4 % in the no exercise group. In addition, 7 of the 14 exercising subjects also received an infusion of IV Dextran sufficient to normalize plasma volume and supine

Fig 15



pulmonary capillary wedge pressure, just prior to maximal LBNP testing. This strategy normalized the Starling curves for these subjects (fig 15). Most importantly, orthostatic tolerance was entirely preserved in these subjects despite 18 days of HDT bed rest (fig 16). The no exercise control group received the same Dextran infusion, but still had impaired cardiac filling during LBNP and reduced LBNP tolerance; the exercise only control had maintenance of LV mass, but still were orthostatically intolerant with a reduced SV during LBNP (fig 15). Finally, the Dextran plus exercise group had no change in upright VO_2max after bed rest, while the sedentary control group had a 22% decrease. Thus increasing physical activity during short term HDT bed rest not only prevents cardiac atrophy but if severe enough, may lead to LV hypertrophy. When combined with "optimal" IV volume loading, this strategy eliminated orthostatic intolerance after bed rest, and normalized upright exercise tolerance.

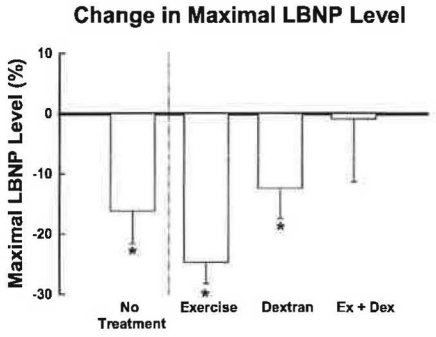


fig 16. "No treatment" data from ref[1] ; other 3 groups from new study with interventions as described in text.

Clinical Implications: Relationship Between Spaceflight and Aging

In 1966, one of the most important studies in exercise science was performed here in Dallas, led by Jere Mitchell, Gunnar Blomqvist, Bob Johnson, and Bengt Saltin. Five young men were put to bed for 3 weeks, then trained for 2 months to examine the cardiovascular response to bedrest and training. One of the key observations made from this study was that bed rest markedly reduced the maximal oxygen uptake, or the maximal ability of the cardiovascular system to transport oxygen and perform work[106] (fig 17).

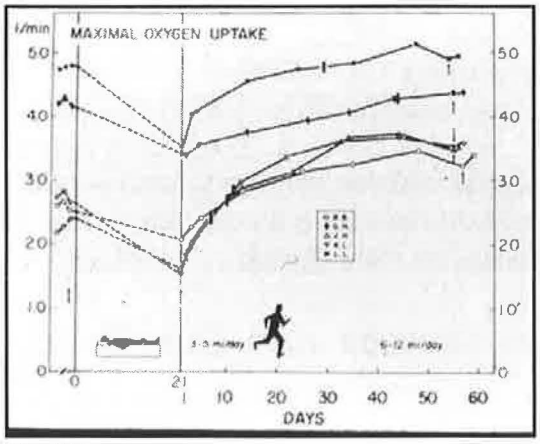


Fig 17

Eight years, ago, in an effort led by Dr. Darren McGuire[107,108], these same 5 men were located and brought back to Dallas now thirty years later, and the studies repeated. One of the most striking observations from these studies was that not a single subject was in worse shape 30 years later, then they were after 3 weeks of bedrest in their 20s (fig 18). In other words, 3 weeks of bedrest was worse for the body's ability to perform physical work, than 30 years of aging.

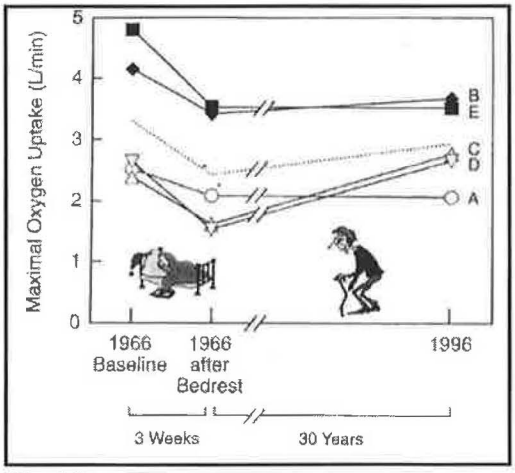
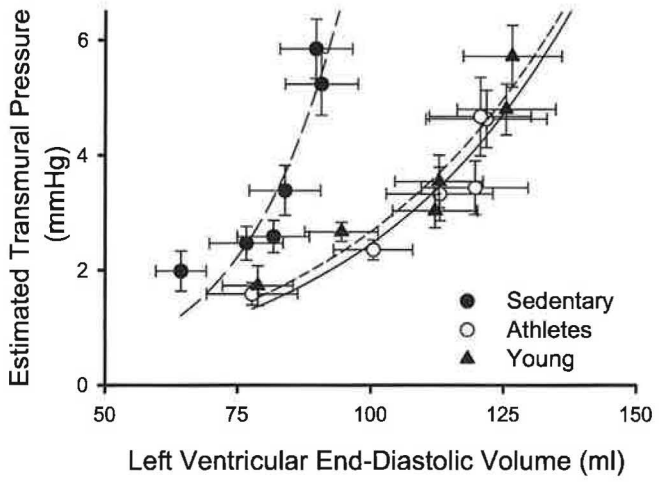


Fig 18

This parallel between aging and bedrest (or spaceflight) has been particularly intriguing for NASA, and led to a special mission for the 40th anniversary of the first orbital flight, both of which included now Senator John Glenn. For example, bed rest deconditioning leads to many of the apparent manifestations of the aging process, such as decreased work capacity[94], increased sympathetic nerve activity[109], and muscle atrophy[96].

Recently, we reasoned that if exercise while in bed prevents the atrophy and stiffening of the heart which appears to be at the root of cardiovascular deconditioning, then possibly life-long exercise training could prevent the cardiac stiffening that was presumed to occur with aging. A recent publication by Dr. Arbab-Zadeh published this week in Circulation, demonstrated quite convincingly that cardiac compliance of a group of Masters athletes was indistinguishable from a group of healthy young controls, while healthy but sedentary seniors had hearts that appeared similar to an exaggerated form of bedrest deconditioning[102] (fig 19).



Concluding Thoughts

Although it is common to speak in hyperbole when discussing space and its role in human endeavor, I thought that I would share with the department an excerpt from one of my favorite books by the scientist/philosopher Carl Sagan. In his masterpiece entitled The Pale Blue Dot, he wrote:

The Cosmos and Our Place in It

While almost anyone is taught that the Earth is a sphere with all of us somehow glued to it by gravity, the reality of our circumstance did not really begin to sink in until the famous frame-filling *Apollo* photograph of the whole Earth--the one taken by Apollo 17 astronauts on the last journey of humans to the Moon.

It has become a kind of icon of our age. There's Antarctica at what Americans and Europeans so readily regard as the bottom, and then all of Africa stretching up above it: You can see Ethiopia,

Tanzania, and Kenya, where the earliest humans lived. At top right are Saudi Arabia and what Europeans call the Near East. Just barely peeking out at the top is the Mediterranean Sea, around which so much of our global civilization emerged. You can make out the blue of the ocean, the yellow-red of Sahara and the Arabian desert, the brown-green of forest and grassland.

And yet there is no sign of humans in this picture, not our reworking of the Earth's surface, not our machines, not ourselves. We are too small and our statecraft is too feeble to be seen by a space-craft between the Earth and the Moon. From this vantage point, our obsession with nationalism is nowhere in evidence. The *Apollo* pictures of the whole Earth conveyed to multitudes something well known to astronomers: *On the scale of worlds--to say nothing of stars or galaxies-- humans are inconsequential*, a thin film of life on an obscure and solitary lump of rock and metal.

It seemed to me that another picture of the Earth, this one taken from a hundred thousand miles farther away [beyond the orbit of Neptune], might help in the continuing process of revealing to ourselves our true circumstance and condition. It had been well understood by the scientists and philosophers of classical antiquity that the Earth was a mere point in a vast encompassing Cosmos, but no one had ever *seen* it as such. Here was our first chance (and perhaps also our last for decades to come). [...]

From this distance the planets seem only points of light-- even through the high-resolution telescope aboard Voyager. They are like the planets seen with the naked eye from the surface of the Earth-- luminous dots, brighter than most of the stars. This is how the planets would look to an alien spaceship approaching the Solar System after a long interstellar voyage. You cannot tell merely by looking at one of these dots what it's like, what's on it, what its past has been, and whether, in this particular epoch, anyone lives there. [...]

But for us, it's different. Look again at that dot. That's here. That's home. That's us. On it everyone you love, everyone you know, everyone you ever heard of, every human being who ever was. lived out their lives. The aggregate of our joy and suffering, thousands of confident religions, ideologies, and economic doctrines, every hunter and forager, every hero and coward, every creator and destroyer of

civilization, every king and peasant, every young couple in love, every mother and father, hopeful child, inventor and explorer, every teacher of morals, every corrupt politician, every "superstar", every "supreme leader", every saint and sinner in the history of our species lived there--on a mote of dust suspended in a sunbeam.

The Earth is a very small stage in a vast cosmic arena. Think of the rivers of blood spilled by all those generals and emperors so that, in glory and triumph, they could become the momentary masters of a fraction of a dot. Think of the endless cruelties visited by the inhabitants of one corner of this pixel on the scarcely distinguishable inhabitants of the other corner, how frequent their misunderstandings, how eager they are to kill one another, how fervent their hatreds.

Our posturings, our imagined self-importance, the delusion that we have some privileged position in the Universe, are challenged by this point of pale light. Our planet is a lonely speck in the great enveloping cosmic dark. In our obscurity, in all this vastness, there is no hint that help will come from elsewhere to save us from ourselves. [...]

It has been said that astronomy is a humbling and character-building experience. There is perhaps no better demonstration of the folly of human conceits than this distant image of our tiny world. To me, it underscores our responsibility to deal more kindly with one another, and to preserve and cherish the pale blue dot, the only home we've ever known.

Excerpt from Carl Sagan (1994)
Pale Blue Dot: A Vision of the Human Future in Space
New York: Random House

References

1. Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance. *Circulation.* 1997;96:517-25.
2. Kennedy RS, Fowlkes JE, Berbaum KS, Lilienthal MG. Use of a motion sickness history questionnaire for prediction of simulator sickness. *Aviat Space Environ Med.* 1992;63:588-93.
3. Buckey JC, Jr., Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Moore WE, Gaffney FA, Blomqvist CG. Orthostatic intolerance after spaceflight. *J Appl Physiol.* 1996;81:7-18.
4. Fritsch-Yelle JM, Whitson PA, Bondar RL, Brown TE. Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight. *J Appl Physiol.* 1996;81:2134-41.
5. Levine B, Pawelczyk J, Ertl A, Cox J, Zuckerman J, Diedrich A, Biaggioni I, Ray C, Smith M, Iwase S, Saito M, Sugiyama Y, Mano T, Zhang R, Iwasaki K, Lane L, Jr. JB, Cooke W, Baisch F, Robertson D, Eckberg D, Blomqvist C. Human muscle sympathetic neural and haemodynamic responses to tilt following spaceflight. *Journal of Physiology.* 2002;538:331-340.
6. Whalen R. Musculoskeletal adaptation to mechanical forces on Earth and in space. *Physiologist.* 1993;36:S127-30.
7. Leach CS, Rambaut PC. Biochemical responses of the Skylab crewmen. In: Rummel JA, S.Deutsch, eds. *Biospex: Biological Space Experiments, A Compendium of Life Sciences Experiments Carried on U.S. Spacecraft.* Washington D.C.: NASA; 1979:55.
8. Nicogossian AE. Overall physiological responses to space flight. In: Nicogossian AE, Huntoon CL, Pool SL, eds. *Space physiology and medicine.* Philadelphia: Lea & Febiger; 1989:139-153.
9. Whedon G, Lutwak L, Rambaut P, Whittle M, Smith M, Reid J, Leach C, CRStadler, Sanford D. DD Mineral and nitrogen metabolic studies, experiment M071. In: Johnston R, Dietlein L, eds. *Biomedical Results from Skylab.* Washington DC: National Aeronautics and Space Administration; 1977:64-174.
10. Whitson PA, Pietrzyk RA, Pak CY, Cintron NM. Alterations in renal stone risk factors after space flight. *J Urol.* 1993;150:803-7.
11. Whitson PA, Pietrzyk RA, Pak CY. Renal stone risk assessment during Space Shuttle flights. *J Urol.* 1997;158:2305-10.
12. Hwang TI, Hill K, Schneider V, Pak CY. Effect of prolonged bedrest on the propensity for renal stone formation. *J Clin Endocrinol Metab.* 1988;66:109-12.
13. Ruml LA, Dubois SK, Roberts ML, Pak CY. Prevention of hypercalciuria and stone-forming propensity during prolonged bedrest by alendronate. *J Bone Miner Res.* 1995;10:655-62.
14. Leblanc AD, Schneider VS, Evans HJ, Engelbretson DA, Krebs JM. Bone mineral loss and recovery after 17 weeks of bed rest. *J Bone Miner Res.* 1990;5:843-50.
15. Zerwekh JE, Ruml LA, Gottschalk F, Pak CY. The effects of twelve weeks of bed rest on bone histology, biochemical markers of bone turnover, and calcium homeostasis in eleven normal subjects. *Journal of Bone & Mineral Research.* 1998;13:1594-601.

16. Ruml L, Hill K, Pak C. The effect of prolonged bed rest on the urinary saturation of stone-forming salts. In: Pak C, Preminger G, Resnick M, eds. *Urolithiasis 1996 -- VIIIth International Symposium on Urolithiasis*. Dallas, Texas: Millet the Printer; 1996:34-35.
17. Antich PP, Pak CY, Gonzales J, Anderson J, Sakhaee K, Rubin C. Measurement of intrinsic bone quality in vivo by reflection ultrasound: correction of impaired quality with slow-release sodium fluoride and calcium citrate. *J Bone Miner Res*. 1993;8:301-11.
18. Antich PP. Ultrasound study of bone in vitro. *Calcif Tissue Int*. 1993;53 Suppl 1:S157-61.
19. Antich PP, Anderson JA, Ashman RB, Dowdey JE, Gonzales J, Murry RC, Zerwekh JE, Pak CY. Measurement of mechanical properties of bone material in vitro by ultrasound reflection: methodology and comparison with ultrasound transmission. *J Bone Miner Res*. 1991;6:417-26.
20. Mehta SS, Antich PP, Daphtary MM, Bronson DG, Richer E. Bone material ultrasound velocity is predictive of whole bone strength. *Ultrasound Med Biol*. 2001;27:861-7.
21. Convertino VA. Physiological Adaptations to weightlessness: Effects on exercise and work performance. *Exerc. Sport Sci. Rev*. 1990;18:119-166.
22. Fitts RH, Riley DR, Widrick JJ. Physiology of a microgravity environment invited review: microgravity and skeletal muscle. *J Appl Physiol*. 2000;89:823-39.
23. Baldwin KM. Effect of spaceflight on the functional, biochemical, and metabolic properties of skeletal muscle. *Medicine & Science in Sports & Exercise*. 1996;28:983-7.
24. Booth FW, Gollnick PD. Effects of disuse on the structure and function of skeletal muscle. *Medicine and Science in Sports and Exercise*. 1983;15:415-420.
25. Stein TP, Gaprindashvili T, Thomason DB, Booth FW. Atrophy of the soleus muscle by hindlimb unweighting. *Journal of Applied Physiology*. 1990;68:1-12.
26. Saltin B, Gollnick PD. *Skeletal muscle adaptability: significance for metabolism and performance*. Section 10 ed. Bethesda, MD: American Physiological Society; 1983.
27. Caiozzo VJ, Baker MJ, Herrick RE, Tao M, Baldwin KM. Effects of spaceflight on skeletal muscle: mechanical properties and myosin isoform content of slow muscle. *Journal of Applied Physiology*. 1994;76:1764-1773.
28. Convertino VA. Exercise and adaptation to microgravity environments. In: Blatteis C, Fregly M, eds. *Handbook of Physiology: Adaptation to the Environment*. Bethesda, MD: American Physiological Society; 1996:815-843.
29. Riley DA. Is skeletal muscle ready for long-term spaceflight and return to gravity? *Advances in Space Biology and Medicine*. 1999;7:31-48.
30. Stein TP, Gaprindashvili T. Spaceflight and protein metabolism, with specific reference to humans. *American Journal of Nutrition*. 1994;60:806S-819S.
31. Greenisen MC, Edgerton VR. Human capabilities in the space environment. In: Nicogossian AE, Huntoon CL, Pool SL, eds. *Space Physiology and Medicine*. 3rd ed. Philadelphia: Lea dn Feiberger; 1993:194-210.
32. Caiozzo VJ, Haddad F, Baker MJ, Baldwin KM. Influence of mechanical loading on myosin heavy-chain protein and mRNA isoform loading. *Journal of Applied Physiology*. 1996;80:1503-1512.
33. Hideka RS, Gollnick PD, Dudley GA, Convertino VA, Buchanan P. Structural and metabolic characteristics of human skeletal muscle following 30 days of simulated microgravity. *Aviation, Space, and Environmental Medicine*. 1989;60:664-670.

34. Thomason DP, Booth FW. Atrophy of the soleus muscle by hindlimb unweighting. *Journal of Applied Physiology*. 1990;68:1-12.
35. Ferrando AA, Lane HW, Stuart CA, Davis-Street J, Wolfe RR. Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. *Am J Physiol*. 1996;270:E627-33.
36. Stein TP, Leskiw MJ, Schluter MD, Donaldson MR, Larina I. Protein kinetics during and after long-duration spaceflight on MIR. *Am J Physiol*. 1999;276:E1014-21.
37. DeMartino GN, Ordway GA. Ubiquitin-proteasome pathway of intracellular protein degradation: implications for muscle atrophy during unloading. *Exerc Sport Sci Rev*. 1998;26:219-52.
38. Taillandier D, Aurousseau E, Meynial-Denis D, al. e. Coordinate activation of lysosomal, Ca2+-activated and ATP-ubiquitin-dependent proteinases in the unweighted rat soleus muscle. *Biochemical Journal*. 1996;316:65-72.
39. Thomason DP, Booth FW, Tischler ME, Rosenberg S, Satarug S, al. e. Different mechanisms of increased proteolysis in atrophy induced by denervation or unweighting of rat soleus muscle. *Metabolism*. 1990;39:756-763.
40. Templeton GH, Padalino M, Manton J, al. e. The influence of suspension hypokinesia on the rat soleus muscle. *Journal of Applied Physiology*. 1984;56:278-286.
41. Diffee GM, Caiozzo VJ, Herrick RE, Baldwin KM. Contractile and biochemical properties of rat soleus and plantaris after hindlimb suspension. *American Journal of Physiology*. 1991;260:C528-C534.
42. Fitts RH, Brimmer CJ, Heywood-Cooksey A, Timmerman RJ. Single muscle fiber enzyme shifts with hindlimb suspension and immobilization. *American Journal of Physiology*. 1989;256:C1082-C1091.
43. Michel RN, Gardiner PF. To what extent is hindlimb suspension a model of disuse? *Muscle and Nerve*. 1990;13:646-653.
44. Blomqvist CG, Stone HL. Cardiovascular adjustments to gravitational stress. In: Shepherd JT, Abboud FM, eds. *Handbook of Physiology: The Cardiovascular System*. Bethesda, MD: American Physiological Society; 1983:1025-1063.
45. Alfrey CP, Udden MM, Leach-Huntoon C, Driscoll T, Pickett MH. Control of red blood cell mass in spaceflight. *J Appl Physiol*. 1996;81:98-104.
46. Blomqvist CG, Levine, B.D., Lane, L.D. Space Medicine and Physiology. In: Braunwald EC, M.H., ed. *Heart Disease in the Presence of Disorders of Other Organ Systems*. Philadelphia: Mosby Inc.; 1996:10.1-10.29.
47. Goldstein MA, Edwards RJ, Schroeter JP. Cardiac morphology after conditions of microgravity during COSMOS 2044. *J Appl Physiol*. 1992;73:94S-100S.
48. Perhonen MA, Franco F, Lane LD, Buckey JC, Blomqvist CG, Zerwekh JE, Peshock RM, Weatherall PT, Levine BD. Cardiac atrophy after bed rest and spaceflight. *J Appl Physiol*. 2001;91:645-53.
49. Perhonen MA, Zuckerman JH, Levine BD. Deterioration of left ventricular chamber performance after bed rest : "cardiovascular deconditioning" or hypovolemia? *Circulation*. 2001;103:1851-7.
50. Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning - A nonneural mechanism for orthostatic intolerance. *Circulation*. 1997;96:517-525.

51. Nixon JV, Murray RG, Bryant C, Johnson RL, Jr., Mitchell JH, Holland OB, Gomez-Sanchez C, Vergne-Marini P, Blomqvist CG. Early cardiovascular adaptation to simulated zero gravity. *J Appl Physiol.* 1979;46:541-8.
52. Gaffney FA, Nixon JV, Karlsson ES, Campbell W, Dowdey AB, Blomqvist CG. Cardiovascular deconditioning produced by 20 hours of bedrest with head- down tilt (-5 degrees) in middle-aged healthy men. *Am J Cardiol.* 1985;56:634-8.
53. Charles JB, Yelle J, Sawin CF. Lessons from operational cardiovascular studies in space. *Med Sci Sports Exerc.* 1996;28:S18-22.
54. Fritsch-Yelle JM, Leuenberger UA, D'Aunno DS, Rossum AC, Brown TE, Wood ML, Josephson ME, Goldberger AL. An episode of ventricular tachycardia during long-duration spaceflight [see comments]. *Am J Cardiol.* 1998;81:1391-2.
55. Buckey JC, Jr., Gaffney FA, Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Yancy CW, Jr., Meyer DM, Blomqvist CG. Central venous pressure in space. *Journal of Applied Physiology.* 1996;81:19-25.
56. White RJ, Blomqvist CG. Central venous pressure and cardiac function during spaceflight. *J Appl Physiol.* 1998;85:738-46.
57. Videbaek R, Norsk P. Atrial distension in humans during microgravity induced by parabolic flights. *J Appl Physiol.* 1997;83:1862-6.
58. Henry WL, Epstein, S.E., Griffith, J.M., Goldstein, R.E., Redwood, D.R. Effect of prolonged space flight on cardiac function and dimensions. In: Johnston RS, Dietlein, L.F., ed. *Biomedical Results From Skylab.* Washington, D.C.: National Aeronautics and Space Administration; 1977:366-371.
59. Germain P, Roul G, Kastler B, Mossard JM, Bareiss P, Sacrez A. Inter-study variability in left ventricular mass measurement. Comparison between M-mode echography and MRI. *Eur Heart J.* 1992;13:1011-9.
60. Katz J, Milliken MC, Stray-Gundersen J, Buja LM, Parkey RW, Mitchell JH, Peshock RM. Estimation of human myocardial mass with MR imaging. *Radiology.* 1988;169:495-8.
61. Zile MR, Tomita M, Ishihara K, Nakano K, Lindroth J, Spinale F, Swindle M, Carabello BA. Changes in diastolic function during development and correction of chronic LV volume overload produced by mitral regurgitation. *Circulation.* 1993;87:1378-88.
62. Mirsky I. Assessment of diastolic function: suggested methods and future considerations. *Circulation.* 1984;69:836-41.
63. Levine BD, Buckey JC, Fritsch JM, Yancy CW, Jr., Watenpaugh DE, Snell PG, Lane LD, Eckberg DL, Blomqvist CG. Physical fitness and cardiovascular regulation: mechanisms of orthostatic intolerance. *Journal of Applied Physiology.* 1991;70:112-22.
64. Fu Q, Witkowski S, Levine B. Vasoconstrictor Reserve and Sympathetic Neural Control of Orthostasis. *Circulation.* 2004;110:xxx - xxx *(in press).*
65. Robertson D, Convertino VA, Vernikos J. The sympathetic nervous system and the physiologic consequences of spaceflight: a hypothesis. *Am J Med Sci.* 1994;308:126-32.
66. Fritsch JM, Charles JB, Bennett BS, Jones MM, Eckberg DL. Short-duration spaceflight impairs human carotid baroreceptor-cardiac reflex responses. *J Appl Physiol.* 1992;73:664-71.
67. Fritsch-Yelle JM, Charles JB, Jones MM, Beightol LA, Eckberg DL. Spaceflight alters autonomic regulation of arterial pressure in humans. *J Appl Physiol.* 1994;77:1776-83.

68. Convertino VA, Doerr DF, Eckberg DL, Fritsch JM, Vernikos-Danellis J. Head-down bed rest impairs vagal baroreflex responses and provokes orthostatic hypotension. *J Appl Physiol.* 1990;68:1458-64.
69. Convertino VA, Doerr DF, Ludwig DA, Vernikos J. Effect of simulated microgravity on cardiopulmonary baroreflex control of forearm vascular resistance. *Am J Physiol.* 1994;266:R1962-9.
70. Crandall CG, Engelke KA, Convertino VA, Raven PB. Aortic baroreflex control of heart rate after 15 days of simulated microgravity exposure. *J Appl Physiol.* 1994;77:2134-9.
71. Hughson RL, Maillet A, Gharib C, Fortrat JO, Yamamoto Y, Pavy-Letraon A, Riviere D, Guell A. Reduced spontaneous baroreflex response slope during lower body negative pressure after 28 days of head-down bed rest. *J Appl Physiol.* 1994;77:69-77.
72. Zuckerman JH, Zhang R, Pawelczyk JA, Levine BD. Heart rate and blood pressure variability after bedrest deconditioning. *Med Sci Sports Exerc.* 1996;28:S173.
73. Zuckerman JH, Zhang R, Pawelczyk JA, Levine BD. Plasma volume effects on bed rest deconditioning related baroreflex impairment. *Circulation.* 1996;94:I-490.
74. Pawelczyk JA, Levine BD. Limb vascular responsiveness to adrenergic agonists followingphysical deconditioning. *Med Sci Sports Exer.* 1995;27:S31.
75. Cox J, KTahvanainen, Kuusela T, Levine B, Cooke W, Mano T, Iwase S, Saito M, Sugiyama Y, Ertl A, Biaggioni I, Diedrich A, Robertson R, Zuckerman J, Layne L, Ray C, White R, Pawelczyk J, Buckey J, Baisch F, Blomqvist C, Robertson D, Eckberg D. Influence of microgravity on astronaut's sympathetic and vagal responses to Valsalva's manoeuvre. *Journal of Physiology.* 2002;538:309-320.
76. Ertl A, Diedrich A, Biaggioni I, Levine B, Robertson R, Cox J, Zuckerman J, Pawelczyk J, Ray C, Buckey J, Lane L, Shiavi R, Gaffney F, Costa F, Holt C, Blomqvist C, Eckberg D, Baisch F, Robertson D. Human muscle sympathetic nerve activity and plasma noradrenaline kinetics in space. J Physiol, 538: 2002. *Journal of Physiology.* 2002;538:321-329.
77. Fu Q, Levine BD, Pawelczyk JA, Ertl AC, Diedrich A, Cox JF, Zuckerman JH, Ray CA, Smith ML, Iwase S, Saito M, Sugiyama Y, Mano T, Zhang R, Iwasaki K, Lane LD, Buckey JC, Jr., Cooke WH, Robertson RM, Baisch FJ, Blomqvist CG, Eckberg DL, Robertson D, Biaggioni I. Cardiovascular and sympathetic neural responses to handgrip and cold pressor stimuli in humans before, during and after spaceflight. *J Physiol.* 2002;544:653-64.
78. Pawelczyk JA, Zuckerman JH, Blomqvist CG, Levine BD. Regulation of muscle sympathetic nerve activity after bed rest deconditioning. *Am J Physiol Heart Circ Physiol.* 2001;280:H2230-9.
79. Ludwig DA, Convertino VA. Predicting orthostatic intolerance: physics or physiology? *Aviat Space Environ Med.* 1994;65:404-11.
80. Nicogossian AE, Garshnek, V. Historical Perspectives. In: Nicogossian AE, Huntoon, C.L., Pool, S.L., ed. *Space Physiology and Medicine.* 2 ed. Philadelphia: Lea and Febiger; 1989:3-44.
81. Buderer MC, Rummel JA, Michel EL, Mauldin DG, Sawin CF. Exercise cardiac output following Skylab missions: the second manned Skylab mission. *Aviat Space Environ Med.* 1976;47:365-72.
82. Atkov OY, Bednenko, V.S. *Hypokinesiaand weightlessness: clinical and physiologic aspects.* Madison, Connecticut: International Universities Press; 1992.

83. Atkov O, Bednenko VS, Fomina GA. Ultrasound techniques in space medicine. *Aviat Space Environ Med.* 1987;58:A69-73.
84. Lathers CM, Charles, J.B., Schneider, V.S., Frey, M.A. Fortney, s. Use of lower body negative pressure to assess changes in heart rate response to orthostatic-like stress during 17 weeks of bed rest. *J. Clinical Pharmacology.* 1994;34:563-70.
85. Turbasoc VD, Artamonova, N. P., Golubchikova, Z.A.. Saikina, G.P., Nechaeva, E.I., Antenenko , L.V. Cardiac bioelectrical activity in healthy men during 370-day head-down tilt hypokinesia [Russian]. *Aviakosmicheskaia I Ekologicheskaia Meditsina.* 1992;26:39-41.
86. Levine BD, Lane LD, Buckey JC, Friedman DB, Blomqvist CG. Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance. *Circulation.* 1991;84:1016-23.
87. Levine BD, Lane LD, Watenpaugh DE, Gaffney FA, Buckey JC, Blomqvist CG. Maximal exercise performance after adaptation to microgravity. *J Appl Physiol.* 1996;81:686-94.
88. Morrow MJ, Zuckerman JH, Franco F, Levine BD. Myocardial hypertrophy is the primary cardiovascular adaptation to endurance training in sedentary men. *Med Sci Sports Exerc.* 1997;29:S139.
89. Franco FF, Peshock RM, Morrow MJ, Zuckerman JH, Zhang R, Levine BD. Left ventricular hypertrophic rsponse to long term endurance training. *Circulation.* 1998;98:I-85.
90. Franco F, Morrow MJ, Zuckerman JH, Zhang R, Peshock RM, Levine BD. Right ventricular enlargement precedes left ventricular enlargement during long term endurance training. *Circulation.* 1998;98:I-85.
91. Levine BD, Zuckerman JH, Zhang R. Plasticity of the Frank-Starling Mechanism. *Circulation.* 1999;100:I-859.
92. Stremel RW, Convertino VA, Bernauer EM, Greenleaf JE. Cardiorespiratory deconditioning with static and dynamic leg exercise during bed rest. *J Appl Physiol.* 1976;41:905-9.
93. Greenleaf JE, Wade CE, Leftheriotis G. Orthostatic responses following 30 day bed rest deconditioning with isotonic and isokinetic exercise training. *Aviat. Space Environ. Med.* 1989;60:537-542.
94. Greenleaf JE, Bernauer EM, Ertl AC, Trowbridge TS, Wade CE. Work capacity during 30 days of bed rest with isotonic and isokinetic exercise training. *J. Appl. Physiol.* 1989;67:1820-1826.
95. Greenleaf JE, Vernikos J, Wade CE, Barnes PR. Effect of leg exercise training on vascular volumes during 30 days of 6° head-down bed rest. *J. Appl. Physiol.* 1992;72:1887-1894.
96. Watenpaugh DE, Ballard RE, Schneider SM, Lee SM, Ertl AC, William JM, Boda WL, Hutchinson KJ, Hargens AR. Supine lower body negative pressure exercise during bed rest maintains upright exercise capacity. *J Appl Physiol.* 2000;89:218-27.
97. Schneider SM, Watenpaugh DE, Lee SM, Ertl AC, Williams WJ, Ballard RE, Hargens AR. Lower-body negative-pressure exercise and bed-rest-mediated orthostatic intolerance. *Med Sci Sports Exerc.* 2002;34:1446-53.

98. Levine BD, Stray-Gundersen J. "Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance. *Journal of Applied Physiology*. 1997;83:102-12.
99. Chapman RF, Stray-Gundersen J, Levine BD. Individual variation in response to altitude training. *Journal of Applied Physiology*. 1998;85:1448-56.
100. Banister EW, Morton RH, Fitz-Clarke J. Dose/response effects of exercise modeled from training: physical and biochemical measures. *Annals of Physiological Anthropology*. 1992;11:345-56.
101. Vigil JI. *Road To The Top*. Albuquerque, New Mexico: Creative Designs, Inc.; 1995.
102. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Zhang R, Thomas JD, Palmer D, Levine BD. Effect of aging and physical activity on left ventricular compliance. *Circulation*. 2004;110:1805-1811.
103. Engelke KA, Doerr DF, Crandall CG, Convertino VA. Application of acute maximal exercise to protect orthostatic tolerance after simulated microgravity. *Am. J. Physiol.* 1996;271:R837-R847.
104. Convertino VA, Doerr DF, Guell A, Marini JF. Effects of acute exercise on attenuated vagal baroreflex function during bed rest. *Aviat Space Environ Med.* 1992;63:999-1003.
105. Engelke KA, Doerr DF, Convertino VA. A single bout of exhaustive exercise affects integrated baroreflex function after 16 days of head-down tilt. *Am. J. Physiol.* 1995;269:H614-H620.
106. Saltin B, Blomqvist G, Mitchell JH, Johnson RL, Jr., Wildenthal K, Chapman CB. Response to exercise after bed rest and after training. *Circulation*. 1968;38:VII1-78.
107. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the Dallas Bedrest and Training Study: II. Effect of age on cardiovascular adaptation to exercise training. *Circulation*. 2001;104:1358-66.
108. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the Dallas Bedrest and Training Study: I. Effect of age on the cardiovascular response to exercise. *Circulation*. 2001;104:1350-7.
109. Pawelczyk JA, Zuckerman JH, Levine BD. **Regulation of muscle sympathetic nerve activity following bed rest deconditioning**. *Am. J. Physiol.* 2001;in press.