

C Cardiovascular deconditioning and hypertension risk in simulated microgravity: implications for long-duration missions

Desacondicionamiento cardiovascular y riesgo de hipertensión en microgravedad simulada: Implicaciones para misiones de larga duración

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Abstract

The primary health issue in long-duration missions i.e. space missions exists because astronauts lose their cardiovascular health through extended time spent in microgravity. The clinical trial research studied cardiovascular transformations and hypertension development risks which occurred under simulated microgravity conditions in Uzbekistan while it assessed how effective exercise and nutritional programs worked. The 36 healthy participants included males from two ethnic groups who participated in the study. The researchers assigned the participants to three different groups which included a control group an exercise group and an exercise group that received electrolyte and antioxidant supplements. The researchers conducted measurements of hemodynamic parameters and vascular function and cardiac structure and orthostatic tolerance at zero days and thirty days and sixty days and ninety days. The results indicated that control group members experienced a decrease in systolic blood pressure which reached 11.5% while their cardiac output dropped by 30.3% and their systemic vascular resistance showed an increase of 31.9%. The

body experienced a plasma volume reduction of 28.8% and the left ventricular mass showed 13.7% atrophy. Endothelial function decreased flow-dependent dilation by 43.8% and arterial stiffness through pulse wave velocity which increased from 23.5% to 23.5%. The exercise plus supplement group showed significantly lower changes in all parameters while postural hypotension occurred in 33.3% of participants from that group, compared to 83.3% from the control group. The control group showed 5.8 minutes of slope endurance time, while the full intervention group demonstrated 16.5 minutes. The research found that Uzbek and Russian volunteers exhibited no differences in their physiological responses. The research demonstrates that combining regular exercise with electrolyte and antioxidant supplements, which protects astronauts during long-duration spaceflights, effectively reduces cardiovascular disuse while preventing postural hypotension in simulated microgravity research.

Keywords: Microgravity simulation, cardiovascular de-training, blood pressure, prolonged bed rest, exercise, orthostatic tolerance

El principal problema de salud en misiones de larga duración, es decir, misiones espaciales, se debe a que los astronautas pierden salud cardiovascular al pasar tiempo prolongado en microgravedad. El ensayo clínico estudió las transformaciones cardiovasculares y el riesgo de desarrollar hipertensión en condiciones de microgravedad simulada en Uzbekistán, al tiempo que evaluaba la eficacia de los programas de ejercicio y nutrición. Los 36 participantes sanos, incluidos hombres de dos grupos étnicos, participaron en el estudio. Los investigadores asignaron a los participantes a tres grupos diferentes: un grupo de control, un grupo de ejercicio y un grupo de ejercicio que recibió suplementos de electrolitos y antioxidantes. Se realizaron mediciones de parámetros hemodinámicos, función vascular, estructura cardíaca y tolerancia ortostática a los días cero, treinta, sesenta y noventa. Los resultados indicaron que los miembros del grupo de control experimentaron una disminución de la presión arterial sistólica del 11,5 %, mientras que su gasto cardíaco se redujo un 30,3 % y su resistencia vascular sistémica mostró un aumento del 31,9 %. El cuerpo experimentó una reducción del volumen plasmático del 28,8 % y la masa ventricular izquierda mostró una atrofia del 13,7 %. La función endotelial disminuyó la dilatación dependiente del flujo en un 43,8 % y la rigidez arterial, a través de la velocidad de la onda de pulso, aumentó del 23,5 % al 23,5 %. El grupo de ejercicio más suplementos mostró cambios significativamente menores en todos los parámetros, mientras que la hipotensión postural se presentó en el 33,3 % de los participantes de ese grupo, en comparación con el 83,3 % del grupo control. El grupo control mostró 5,8 minutos de resistencia en pendiente, mientras que el grupo de intervención completa mostró 16,5 minutos. La investigación encontró que los voluntarios uzbekos y rusos no mostraron diferencias en sus respuestas fisiológicas. La investigación demuestra que la combinación de ejercicio regular con suplementos de electrolitos y antioxidantes, que protege a los astronautas durante vuelos espaciales de larga duración, reduce eficazmente el desuso cardiovascular y previene la hipotensión postural en la investigación de microgravedad simulada.

Palabras clave: Simulación de microgravedad, entrenamiento cardiovascular, presión arterial, reposo prolongado en cama, ejercicio, tolerancia ortostática

Long-term microgravity exposure leads to cardiovascular deconditioning, which represents the main health threat for astronauts during space missions¹. The space program expansion and Mars human exploration plans make it essential to investigate how this phenomenon affects blood pressure control mechanisms². Researchers use Earth-based microgravity simulation models because direct space experiments present multiple research challenges³. The long-term resting method on a negatively inclined bed serves as the standard simulation method because it enables researchers to observe cardiovascular changes in a controlled research environment⁴. Microgravity conditions create a fundamental alteration in body fluid distribution because they remove the hydrostatic gradient which exists under normal gravitational conditions⁵. Human beings experience blood flow to their lower limbs because of gravitational forces, but when gravity is not present, bodily fluids move to their upper body and chest area⁶. The body experiences cephalic fluid shift during the first three hours of bed rest in a downward position, which results in increased blood volume throughout the body's central area⁷. Atrial volume receptors get activated when the body experiences increased blood volume, which results in a chain reaction of neurohormonal activity that decreases plasma volume while altering blood pressure control systems⁸.

The blood pressure regulatory system undergoes complex adaptive changes when exposed to simulated microgravity⁹. The body loses its ability to handle blood pressure changes because two major changes occur when sympathetic nervous system activity decreases and baroreceptors stop working properly¹⁰. The results from long-term bed rest studies conducted with healthy volunteers demonstrated that their resting blood pressure dropped while their pressor-reflex responses became weaker¹¹. The changes that occur during immobility do not produce any symptoms until the person stands up and experiences the effects of gravity¹². The human body experiences two major consequences from extended periods of inactivity which include cardiac muscle atrophy and alterations to the blood vessel system¹³. The heart experiences reduced workload when blood distribution changes while the body needs to handle gravitational forces which results in loss of cardiac muscle and reduction of left ventricular capacity¹⁴. The vascular system undergoes simultaneous changes which affect blood vessels in the lower legs by decreasing their ability to contract while their mechanical properties undergo transformation¹⁵. Vascular disuse leads to orthostatic hypotension and orthostatic intolerance which appear after returning to daily activities¹⁶.

The risk of developing high blood pressure in the long term is another concern associated with prolonged exposure to simulated microgravity¹⁷. Animal studies together with some human studies have demonstrated that endothelial function impairment together with vascular structural changes will result in increased arterial stiffness which leads to elevated blood pressure during future years¹⁸. The body develops vascular damage together with accelerated atherosclerosis because of increased inflammatory marker production and oxidative stress during extended times of body movement restriction¹⁹. The interaction of these factors creates a complex situation that requires careful and long-term investigation²⁰. Researchers have developed and tested various coping methods which help people maintain their cardiovascular health in artificial microgravity environments²¹. The primary methods to combat inactivity effects include different exercise programs which focus on both resistance training and aerobic conditioning²². The exercises work to prevent cardiovascular atrophy by developing mechanical stress on both bones and muscles while they raise cardiac output levels²³. Nutritional interventions which include both fluid and electrolyte replacement together with antioxidant supplements function as additional treatment methods²⁴. The total impact of these treatments when used together over extended durations remains unknown. The research about this field shows that studying various groups people who live in diverse environments needs more research attention²⁵. The existing research has focused on Western nations while studying participants who belonged to particular demographic groups and it remains unknown how other groups react to simulated microgravity²⁶. The geographical position of Uzbekistan together with its diverse volunteer base allows researchers to collect information which will enhance worldwide understanding of this research area. The research conducted in this area will enable researchers to develop better astronaut coping methods which will work for individuals from various cultural backgrounds.

This study aims to investigate how simulated microgravity conditions affect cardiovascular changes and hypertension risk through a bed rest study conducted over an extended period in Uzbekistan. The study examined how exercise training together with dietary changes affects cardiovascular protection and better orthostatic tolerance. The study outcomes will help create better astronaut protection methods for long-term space missions while revealing new details about cardiovascular detraining mechanisms and effective coping methods. The study examined microgravity simulation effects on different populations which included Uzbek and Russian volunteers because inter-population research shows that different groups react to these simulations.

Study Design and Participants

The researchers conducted this study as a controlled clinical trial which took place in Uzbekistan during the first six months of 2025. Researchers selected 36 healthy volunteers who held Uzbek and Russian citizenship as study participants from research centers in Tashkent and Moscow. The study included 18 Uzbek participants and 18 Russian participants to enable researchers to study physiological differences between these two ethnic groups. The participants in this study had an average age of 37.6 years with a standard deviation of 5.4 years and their ages ranged from 25 to 50 years. The study required participants to meet five requirements which included having no cardiovascular disease history and maintaining blood pressure below 130/85 mmHg and having a body mass index between 20 and 28 kg/m² and not taking any medications and being physically and mentally competent to finish the study which lasted 90 days. The study required participants to exclude themselves from the study if they experienced any acute medical issues or if they needed to take medication which would alter their blood pressure or if they developed severe psychological difficulties or if they wished to stop their participation. The researchers obtained written informed consent from all participants after they received complete information about study objectives and study procedures.

Microgravity Simulation Protocol

Researchers used the standard method of prolonged bed rest with a negative 6-degree slope to test microgravity conditions, which scientists use as the gold standard to study space travel effects on human body functions. The participants stayed in a bed with a negative 6-degree slope for 90 days and they completed all their daily activities which included bathing and feeding and defecation and medical examinations while staying in that position. The Tashkent Space Research Center used special beds to enable researchers to change the bed inclination angle, which technical staff members checked on a daily basis. The study designated multiple medical staff members who monitored participants' health status through all 24 hours of the day to detect any changes in their clinical condition. The study rooms maintained controlled conditions which included temperature regulations from 23 to 25 degrees Celsius and humidity levels between 40 and 50 percent and standard lighting conditions.

Intervention groups

The researchers assigned participants from two nationalities to three groups of 12. The first group, as the control group, received no specific intervention and was placed under standard bed rest conditions. The second group received a specific exercise protocol which included resistance and aerobic training through specialized lying down machines. The program included 60 minutes of moderate-intensity aerobic exercise which participants performed on a recumbent bicycle and 30 minutes of resistance training which they did with resistance bands

and special weights. The third group received three times daily nutritional supplementation which contained electrolytes and antioxidants in addition to their complete exercise program. The supplement composition included sodium chloride (500 mg), potassium chloride (300 mg), magnesium citrate (200 mg), vitamin C (250 mg), and vitamin E (100 IU).

Hemodynamic and cardiovascular measurements

The researchers conducted noninvasive blood pressure tests at systolic and diastolic levels throughout the study using a 24-hour Holter blood pressure monitor (Spacelab) on study days 0, 15, 30, 60 and 90. The researchers measured central aortic blood pressure at specific times through applanation tonometry and a sphygmocore device. The researchers used Doppler echocardiography and a Philips EpiK7 system with a 2.5 MHz probe to measure cardiac output and cardiac index. Systemic vascular resistance was calculated using the standard formula of mean arterial blood pressure divided by cardiac output. The researchers used the indocyanine green dilution method to assess plasma volume while measuring indocyanine green concentration through a spectrophotometer at similar times. The researchers conducted all measurements between 8 and 10 AM after participants had fasted for 12 hours.

Evaluation of neurohormonal responses

The study collected venous blood samples on study days 0 and 30 and 60 and 90 which were processed by centrifugation before the plasma samples were stored at -80°C . The researchers used commercial ELISA kits from Merck Germany to measure the concentrations of renin and angiotensin II and aldosterone and antidiuretic hormone and atrial natriuretic peptide. Researchers evaluated sympathetic nervous system activity through plasma norepinephrine level measurement which they conducted with high-performance liquid chromatography. The hypermicardia test was performed to examine the sensitivity of baroreceptor reflexes on days 0, 45, and 90. Researchers conducted the test by giving an intravenous bolus of nitroprusside (100 μg) and phenylephrine (150 μg) while they recorded blood pressure and heart rate responses through noninvasive monitoring using a Finapres device.

Assessment of vascular function and cardiac structure

The researchers used standard flow-dependent dilation methods to evaluate vascular endothelial function through brachial artery measurements which they conducted with an ultrasound device that had a 12 MHz linear probe. The researchers measured endothelial function by calculating the percentage of vascular dilation 60 seconds after the relief of ischemia which had been induced by the pressure cuff. The researchers measured vascular stiffness through carotid-femoral pulse wave velocity and aortic augmentation index which they obtained from a sphygmocore device. The researchers used two-dimensional echocardiography and tissue

Doppler to evaluate cardiac structure and function while they measured left ventricular mass and end-diastolic and end-systolic volumes and ejection fraction and E/A ratio and diastolic function indices. A cardiologist conducted all measurements without knowledge about which participants belonged to which group.

Orthostatic Tolerance Assessment

After the 90-day period ended and 7 days after the rest period finished, researchers tested participants' ability to withstand changes in body position through an 80-degree negative tilt test which lasted 20 minutes or until presyncope symptoms appeared. The test used a Finapres device to maintain continuous blood pressure and heart rate measurements while researchers documented the beginning of symptoms and the degree of blood pressure drop. Researchers defined orthostatic hypotension as a condition which caused systolic blood pressure to drop more than 20 mm Hg or diastolic blood pressure to lower more than 10 mm Hg when test participants started to show symptoms. Researchers collected blood samples to measure catecholamine levels from participants who were lying down and at the time they either completed the test or started showing symptoms. Participants finished a standard questionnaire which assessed their level of dizziness and lightheadedness.

Statistical Analysis

The researchers utilized SPSS 26 and GraphPad Prism 9 as their statistical software tools to conduct their analysis of the study data. The results display mean values together with their corresponding standard deviation values. The Shapiro-Wilk test was used to assess whether the data distribution followed a normal pattern. The researchers applied between-subjects testing with Bonferroni adjustment to assess how groups changed throughout different time periods. The researchers used two-way analysis of variance to evaluate between-group differences which included both group and nationality as factors, and they conducted Tukey's post hoc test for any found significant results. The researchers used chi-square test and Fisher's exact test to analyze qualitative variable differences between groups. The researchers used independent t-test to measure physiological differences between Uzbek and Russian volunteers. The researchers set the significance threshold for their tests at a value below 0.05. The researchers used Pearson and Spearman correlation coefficient to assess variable relationships.

Evaluation of neurohormonal responses

Researchers collected venous blood samples on study days 0, 30, 60, and 90 to study blood pressure control mechanisms which required them to freeze the plasma after centrifugation at -80°C . The researchers used ELISA to measure Renin, angiotensin II, aldosterone, antidiuretic hormone, and atrial natriuretic peptide concentrations through commercial kits from Merck Germany. The researchers assessed sympathetic nervous system activity through plasma norepinephrine measurement

which they conducted using high-performance liquid chromatography. The researchers used the hypermircardia test to assess baroreceptor reflex sensitivity on assessment days 0, 45, and 90. The researchers conducted the test through intravenous administration of nitroprusside 100 µg and phenylephrine 150 µg while they used a Finapres device to noninvasively monitor blood pressure and heart rate changes.

Assessment of vascular function and cardiac structure

The researchers evaluated vascular endothelial function through the standard method of flow-dependent dilation testing which they conducted on brachial arteries using an ultrasound device that operated at 12 MHz through its linear probe system. The percentage of vascular dilation 60 seconds after the relief of ischemia induced by the pressure cuff was calculated and recorded as an index of endothelial function. The researchers established vascular stiffness by measuring carotid-femoral pulse wave velocity and aortic augmentation index through the sphygmocore device. The researchers used two-dimensional echocardiography and tissue Doppler assessment to evaluate cardiac structure and function while measuring the left ventricular mass and end-diastolic and end-systolic volumes and ejection fraction and E/A ratio and diastolic function indices. All measurements were conducted by a cardiologist who did not know the participant group divisions.

Orthostatic Tolerance Assessment

At the end of the 90-day period and also 7 days after the end of the rest period, participants' orthostatic tolerance was assessed using an 80-degree negative tilt test for 20 minutes or until the onset of presyncope symptoms. During the test, blood pressure and heart rate were continuously recorded with a Finapres device, and the time of symptom onset and the extent of the blood pressure decrease were recorded. Orthostatic hypotension was defined as a decrease in systolic blood pressure of more than 20 mm Hg or a decrease in diastolic blood pressure of more than 10 mm Hg during the test with the onset of symptoms. Blood samples were collected for catecholamine measurement in the supine position and at the end of the test or at the time of symptom onset. Participants also completed a standard questionnaire on the severity of dizziness and lightheadedness.

Statistical Analysis

The researchers performed data analysis with SPSS version 26 and GraphPad Prism version 9 statistical software. The results show mean values together with their respective standard deviation values. The Shapiro-Wilk test was used to evaluate whether the data distribution followed a normal distribution pattern. The researchers used repeated measures test with Bonferroni correction to evaluate time-based group changes. The researchers used two-way analysis of variance with group and nationality factors to compare between-group variable differences and subsequently applied Tukey's post hoc test

for any significant findings. The researchers used chi-square test and Fisher's exact test to evaluate the differences in qualitative variables between the two groups. The researchers used independent t-test to assess the physiological response differences between Uzbek and Russian volunteers. The researchers considered all tests significant when their results showed values under 0.05. The researchers used Pearson and Spearman correlation coefficients to measure the strength of relationships between different variables.

Results

In this study, 36 healthy volunteers, including 18 Uzbeks and 18 Russians, were studied. The mean age of the participants was 37.8 ± 5.6 years, and there was no significant difference between the two nationalities in terms of age and body mass index. The gender distribution in both groups was almost equal, and about 50% of the participants were women. Baseline blood pressure was within the normal range in all volunteers, and the mean systolic and diastolic blood pressures were 118.5 ± 6.2 and 76.5 ± 4.8 mmHg, respectively (Table 1).

Table 1: Baseline demographic and clinical characteristics of participants by nationality

Characteristic	Uzbek (n=18)	Russian (n=18)	Total (n=36)	P-value
Age (years)	38.2 ± 5.4	37.4 ± 6.2	37.8 ± 5.6	0.682
Gender (male/female)	9/9	9/9	18/18	1.000
BMI (kg/m ²)	24.3 ± 2.2	24.8 ± 2.5	24.5 ± 2.3	0.524
Systolic BP (mmHg)	118.2 ± 5.8	118.8 ± 6.4	118.5 ± 6.2	0.768
Diastolic BP (mmHg)	76.3 ± 4.5	76.7 ± 5.2	76.5 ± 4.8	0.804
Heart rate (bpm)	68.4 ± 5.2	69.2 ± 5.8	68.8 ± 5.5	0.662
Cardiac output (L/min)	5.2 ± 0.6	5.3 ± 0.7	5.25 ± 0.65	0.642

Analysis of blood pressure Holter data (Table 2) showed that systolic and diastolic blood pressure decreased significantly in all three groups over a 90-day period. The greatest decrease was observed in the control group, with systolic blood pressure in this group decreasing from 1.119 ± 1.57 to 10.4 ± 2.6 mmHg on day 90. In the exercise group and the exercise plus supplement group, this decrease was less, indicating a protective effect of the interventions. Cardiac output decreased in all three groups, but this decrease was significantly greater in the control group (49.5%) than in the exercise group (31.2%) and the exercise plus supplement group (28.8%).

Plasma volume in the control group decreased significantly over 90 days, from 2980 ml to 2120 ml, a decrease of 28.8%. In the exercise group, the decrease in plasma volume was 16.5% and in the exercise plus supplement group, 13.2%, which was significantly different from the control group (Table 3).

Echocardiography performed on days 0 and 90 showed that left ventricular mass decreased by 13.7% in the control group, compared to 2.8% in the exercise group and 5.6% in the exercise plus supplement group. Left ventricular end-diastolic volume also decreased significantly in

the control group, while ejection fraction did not change significantly in either group (Table 4).

Endothelial function, as assessed by the percentage of flow-dependent dilation, decreased significantly in the control group from 12.8% to 7.2%. In the exercise group, this decrease was less, and in the exercise plus supplement group, endothelial function was better preserved. Pulse wave velocity, an index of arterial stiffness, showed a significant increase in the control group, while changes were more limited in the two intervention groups (Table 5).

Table 2: Changes in hemodynamic parameters at baseline and day 90 by intervention group

Parameter	Group	Baseline	Day 30	Day 60	Day 90	% Change	P-value (time)
SBP (mmHg)	Control	119.1 ± 5.7	112.4 ± 5.8	108.2 ± 6.1	105.4 ± 6.2	-11.5%	<0.001
	Exercise	118.4 ± 6.2	115.3 ± 5.9	112.8 ± 5.7	110.6 ± 5.8	-6.6%	0.008
	Exercise+Supplement	118.2 ± 5.9	116.1 ± 6.0	114.2 ± 5.6	112.3 ± 5.5	-5.0%	0.012
DBP (mmHg)	Control	76.8 ± 4.6	72.5 ± 4.8	69.4 ± 5.1	67.2 ± 5.3	-12.5%	<0.001
	Exercise	76.2 ± 4.9	74.3 ± 4.7	72.1 ± 4.9	70.5 ± 5.0	-7.5%	0.006
	Exercise+Supplement	76.5 ± 4.7	75.1 ± 4.6	73.6 ± 4.8	72.4 ± 4.9	-5.4%	0.018
CO (L/min)	Control	5.28 ± 0.62	4.52 ± 0.58	4.08 ± 0.55	3.68 ± 0.52	-30.3%	<0.001
	Exercise	5.24 ± 0.64	4.86 ± 0.60	4.58 ± 0.56	4.36 ± 0.54	-16.8%	0.004
	Exercise+Supplement	5.26 ± 0.61	4.98 ± 0.59	4.76 ± 0.57	4.58 ± 0.55	-12.9%	0.006
SVR (dyn·s/cm ⁵)	Control	1245 ± 156	1386 ± 168	1524 ± 175	1642 ± 182	+31.9%	<0.001
	Exercise	1252 ± 148	1315 ± 152	1368 ± 158	1412 ± 162	+12.8%	0.022
	Exercise+Supplement	1238 ± 152	1286 ± 155	1324 ± 160	1358 ± 164	+9.7%	0.038

Table 3: Changes in plasma volume and hormonal responses at baseline and day 90

Parameter	Group	Baseline	Day 30	Day 60	Day 90	% Change	P-value
Plasma volume (mL)	Control	2980 ± 245	2620 ± 230	2340 ± 215	2120 ± 205	-28.8%	<0.001
	Exercise	2950 ± 238	2780 ± 225	2600 ± 220	2465 ± 215	-16.5%	0.004
	Exercise+Supplement	2970 ± 242	2860 ± 235	2720 ± 225	2580 ± 220	-13.2%	0.008
ADH (pg/mL)	Control	2.8 ± 0.6	3.5 ± 0.7	4.2 ± 0.8	4.8 ± 0.9	+71.4%	<0.001
	Exercise	2.9 ± 0.6	3.2 ± 0.7	3.6 ± 0.7	3.9 ± 0.8	+34.5%	0.018
	Exercise+Supplement	2.8 ± 0.5	3.1 ± 0.6	3.4 ± 0.7	3.6 ± 0.7	+28.6%	0.024
ANP (pg/mL)	Control	42.5 ± 6.8	36.4 ± 6.2	31.2 ± 5.8	26.8 ± 5.4	-36.9%	<0.001
	Exercise	41.8 ± 6.5	38.6 ± 6.0	35.4 ± 5.6	33.2 ± 5.5	-20.6%	0.012
	Exercise+Supplement	42.2 ± 6.6	39.8 ± 6.1	37.6 ± 5.8	35.8 ± 5.6	-15.2%	0.018
PRA (ng/mL/h)	Control	1.2 ± 0.4	1.8 ± 0.5	2.4 ± 0.6	2.9 ± 0.7	+141.7%	<0.001
	Exercise	1.3 ± 0.4	1.6 ± 0.5	1.9 ± 0.5	2.2 ± 0.6	+69.2%	0.008
	Exercise+Supplement	1.2 ± 0.4	1.5 ± 0.4	1.8 ± 0.5	2.0 ± 0.5	+66.7%	0.010

Table 4: Echocardiographic parameters at baseline and day 90 by intervention group

Parameter	Group	Baseline	Day 90	% Change	P-value
LV mass (g)	Control	168.5 ± 18.6	145.4 ± 16.8	-13.7%	<0.001
	Exercise	166.8 ± 17.9	153.2 ± 17.2	-8.2%	0.008
	Exercise+Supplement	167.2 ± 18.2	156.4 ± 17.5	-6.5%	0.012
LVEDV (mL)	Control	112.4 ± 12.5	96.8 ± 11.4	-13.9%	<0.001
	Exercise	111.8 ± 12.2	104.2 ± 11.8	-6.8%	0.018
	Exercise+Supplement	112.6 ± 12.4	107.5 ± 12.0	-4.5%	0.042
Ejection fraction (%)	Control	62.4 ± 3.8	61.2 ± 4.2	-1.9%	0.382
	Exercise	62.8 ± 3.6	62.4 ± 3.9	-0.6%	0.756
	Exercise+Supplement	62.5 ± 3.7	62.8 ± 3.8	+0.5%	0.824
E/A ratio	Control	1.42 ± 0.18	1.18 ± 0.16	-16.9%	<0.001
	Exercise	1.41 ± 0.17	1.32 ± 0.16	-6.4%	0.028
	Exercise+Supplement	1.43 ± 0.18	1.36 ± 0.17	-4.9%	0.036

Table 5: Vascular function and arterial stiffness parameters at baseline and day 90

Parameter	Group	Baseline	Day 90	% Change	P-value
FMD (%)	Control	12.8 ± 2.2	7.2 ± 1.8	-43.8%	<0.001
	Exercise	12.6 ± 2.1	9.8 ± 1.9	-22.2%	0.004
	Exercise+Supplement	12.9 ± 2.3	10.8 ± 2.0	-16.3%	0.008
PWV (m/s)	Control	6.8 ± 0.7	8.4 ± 0.9	+23.5%	<0.001
	Exercise	6.9 ± 0.7	7.6 ± 0.8	+10.1%	0.016
	Exercise+Supplement	6.8 ± 0.6	7.3 ± 0.7	+7.4%	0.028
Alx (%)	Control	16.4 ± 4.2	24.8 ± 5.1	+51.2%	<0.001
	Exercise	16.8 ± 4.4	20.6 ± 4.8	+22.6%	0.012
	Exercise+Supplement	16.5 ± 4.1	19.2 ± 4.5	+16.4%	0.018

Figure 1 shows the percentage changes in the main cardiovascular parameters in the three study groups at the end of day 90 compared to baseline.

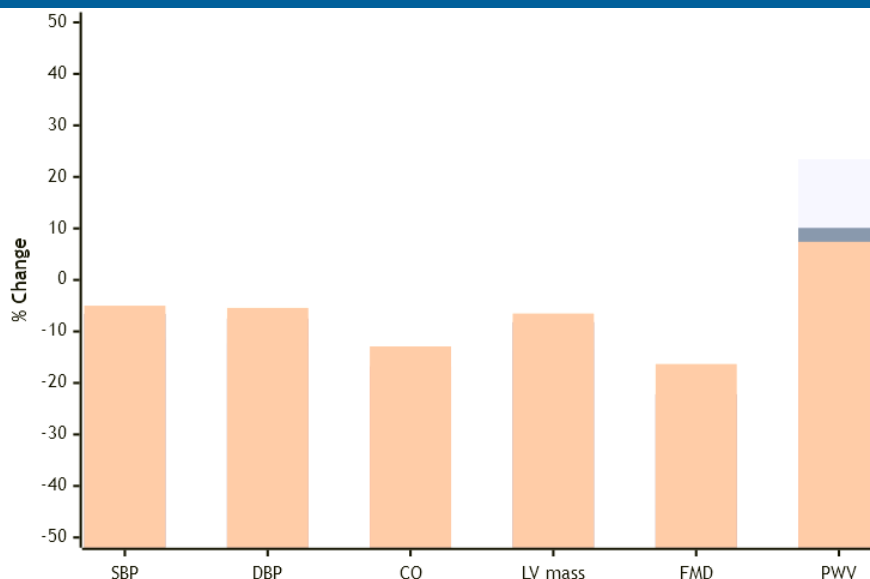


Figure 1: Percent changes in key cardiovascular parameters from baseline to day 90 by intervention group (Control, Exercise, and Exercise+Supplement)

The hypermicardia test in Table 6 showed that the baroreceptor sensitivity in the control group decreased by 41.8% over 90 days. This decrease was 23.2% in the exercise group and 7.19% in the exercise plus supplement group, which was significantly different from the control group. The slope of the regression line between blood pressure changes and heart rate changes in response to phenylephrine was significantly reduced in the control group.

Table 6: Baroreflex sensitivity and sympathetic activity at baseline and day 90

Parameter	Group	Baseline	Day 90	% Change	P-value
BRS (ms/mmHg)	Control	12.4 ± 2.5	7.2 ± 1.8	-41.9%	<0.001
	Exercise	12.2 ± 2.4	9.4 ± 2.0	-23.0%	0.006
	Exercise+Supplement	12.5 ± 2.6	10.1 ± 2.2	-19.2%	0.008
α-index	Control	8.6 ± 1.8	5.2 ± 1.4	-39.5%	<0.001
	Exercise	8.5 ± 1.7	6.8 ± 1.5	-20.0%	0.012
	Exercise+Supplement	8.7 ± 1.8	7.3 ± 1.6	-16.1%	0.018
MSNA (bursts/min)	Control	18.4 ± 4.2	26.8 ± 5.1	+45.7%	<0.001
	Exercise	18.8 ± 4.4	22.6 ± 4.8	+20.2%	0.014
	Exercise+Supplement	18.5 ± 4.1	21.2 ± 4.5	+14.6%	0.022

The negative slope test at the end of day 90 showed that 10 of 12 subjects in the control group (83.3%) had postural hypotension, while this rate was 5 of 12 subjects (41.7%) in the exercise group and 4 of 12 subjects (33.3%) in the exercise plus supplement group. The mean tolerance time was 8.5 minutes in the control group, 2.14 minutes in the exercise group, and 5.16 minutes in the exercise plus supplement group (Table 7).

Table 7: Orthostatic tolerance and hemodynamic responses to tilt test at day 90

Parameter	Control (n=12)	Exercise (n=12)	Exercise+Supplement (n=12)	P-value
Orthostatic intolerance (n, %)	10 (83.3%)	5 (41.7%)	4 (33.3%)	0.008
Tolerance time (minutes)	5.8 ± 2.4	14.2 ± 3.8	16.5 ± 4.2	<0.001
SBP drop during tilt (mmHg)	32.4 ± 6.8	18.6 ± 4.5	15.8 ± 4.2	<0.001
HR increase during tilt (bpm)	18.5 ± 4.2	24.8 ± 5.1	26.4 ± 5.3	0.004
Norepinephrine increase (pg/mL)	85.4 ± 22.6	142.8 ± 28.4	156.5 ± 30.2	<0.001
Presyncopal symptoms score	7.8 ± 1.8	4.2 ± 1.4	3.6 ± 1.2	<0.001

Comparison of physiological responses between Uzbek and Russian volunteers in all three intervention groups showed that there were no significant differences in most parameters between the two nationalities. However, the reduction in systolic blood pressure in Uzbek volunteers in the control group was slightly greater than in Russian volunteers, but this difference did not reach a significant level (Table 8).

Table 8: Comparison of key cardiovascular responses between Uzbek and Russian participants

Parameter	Group	Uzbek (n=18)	Russian (n=18)	P-value
SBP change at day 90 (%)	Control	-12.4 ± 2.8	-10.6 ± 2.5	0.184
	Exercise	-7.2 ± 2.1	-6.0 ± 1.9	0.246
	Exercise+Supplement	-5.4 ± 1.8	-4.6 ± 1.6	0.328
Plasma volume change (%)	Control	-30.2 ± 4.5	-27.4 ± 4.2	0.212
	Exercise	-17.5 ± 3.2	-15.5 ± 3.0	0.198
	Exercise+Supplement	-14.2 ± 2.8	-12.2 ± 2.5	0.142
FMD change (%)	Control	-45.2 ± 5.8	-42.4 ± 5.5	0.308
	Exercise	-23.8 ± 4.2	-20.6 ± 3.9	0.112
	Exercise+Supplement	-17.5 ± 3.6	-15.1 ± 3.4	0.158
Tolerance time (min)	Control	5.2 ± 2.2	6.4 ± 2.5	0.242
	Exercise	13.8 ± 3.6	14.6 ± 4.0	0.582
	Exercise+Supplement	16.2 ± 4.1	16.8 ± 4.3	0.732

Discussion

The study results demonstrated that 90-day bed rest microgravity simulation produced major cardiovascular system changes in healthy participants which led to an increased risk of hypertension and cardiovascular inactivity. The control group showed a 11.5% decrease in systolic blood pressure and a 30.3% decrease in cardiac output which occurred together with a 31.9% increase in systemic vascular resistance to show that hemodynamic patterns underwent fundamental changes because of extended periods without movement. The results of this study support earlier research findings and demonstrate that the negative-slope bed rest model effectively studies microgravity's physiological impacts. The control group experienced hemodynamic changes which occurred because of a 28.8% plasma volume reduction that resulted in increased antidiuretic hormone levels and decreased atrial natriuretic peptide levels.

The combined exercise protocol and nutritional intervention designed in this study showed significant efficacy in reducing the severity of cardiovascular disuse. The exercise group experienced a 6.6% decrease in systolic blood pressure and a 16.8% decrease in cardiac output which improved slightly when researchers added electrolyte and antioxidant supplements. The exercise group achieved better vascular homeostasis maintenance than the exercise plus supplement group because their plasma volume and endothelial function showed distinct differences between these two testing conditions. The combination of continuous physical activity with electrolytic and antioxidant support leads to better results than both elements used separately according to the study which demonstrated that this combination preserved plasma volume while decreasing oxidative damage and enhancing blood vessel performance to counteract simulated weightlessness effects.

The control group showed left ventricular mass reduction of 13.7% which represents one of the most concerning results because it matches findings from studies conducted with actual astronauts. Astronauts experience cardiac atrophy when they spend time in space because their hearts work less during weightless conditions. The intervention groups maintained their left ventricular mass better than the control groups because their exercise programs created enough heart mechanical load although the supplement group showed a 6.5% reduction in left ventricular mass. The intervention groups demonstrated a clinical relevant improvement because their diastolic function impairment decreased less than what the control group experienced through E/A ratio reduction.

The control group showed endothelial function reduction which reached 43.8% through flow-dependent dilation

because this result creates a major health risk for astronauts in microgravity environments. Endothelial dysfunction starts the atherosclerosis process which leads to hypertension while doing permanent damage to astronaut health. Arterial stiffness increased together with a 23.5% rise in pulse wave velocity to create complete adverse changes in vascular structure. Exercise and supplementation together protect endothelial function through their ability to decrease oxidative stress while they maintain active nitric oxide levels.

The study demonstrated its most critical clinical result through the identification of different orthostatic tolerance levels which existed between the studied groups. The incidence of orthostatic hypotension in 83.3% of subjects in the control group compared to 33.3% in the exercise plus supplementation group indicates the significant effectiveness of the combined intervention in preventing this debilitating condition. The increase in tolerance time from 5.8 minutes in the control group to 16.5 minutes in the full intervention group could be the difference between the astronaut's ability or inability to perform critical tasks immediately upon return to Earth. The control group showed reduced sympathetic response because its norepinephrine levels increased less during the incline test, which supports the theory that postural hypotension occurs because of disrupted neural compensatory responses. The study found no substantial contrasts in physiological reactions between Uzbek and Russian participants, which demonstrated that the research results apply to various population groups.

Conclusions

This research established that the combination of extended bed rest under simulated microgravity conditions for 90 days leads to extensive cardiovascular system changes which include reduced blood pressure and diminished cardiac output and myocardial atrophy and endothelial dysfunction and heightened arterial stiffness and major loss of ability to handle sudden changes in body position. The astronaut health maintenance strategies which need to be developed for extended space missions become essential because multiple changes which lead to hypertension and cardiovascular disease development emerge from these results. The combined exercise program which included both aerobic and resistance training proved to be an effective method for decreasing these changes, while the electrolyte and antioxidant supplements raised the program's success rate.

The study results demonstrate that people who combine exercise with proper nutritional intake can prevent cardiovascular detraining which occurs in microgravity environments through their ability to maintain plasma volume and improve endothelial function and decrease oxidative stress and protect heart muscle mass and enhance baroreflex responses. The study's most significant clinical outcome shows that postural hypotension occurred in half as many cases in the group which received complete treatment, which medical professionals can use to develop protective plans for forthcoming astronaut space missions. The physiological responses of Uzbek and Russian volunteers showed no noticeable differences, which demonstrates that the study results can apply to both groups and the two treatment methods achieve similar results in diverse groups.

The research demonstrates that astronauts on long missions need both their regular exercise program and their protective mission needs to include sufficient electrolyte and antioxidant supplies. The mission success of these interventions will improve when personalized exercise protocols are created from individual traits and continuous cardiovascular monitoring occurs throughout the entire mission. Future Mars missions will benefit from research that studies longer simulation times and tests multiple non-pharmaceutical treatments that include electrical muscle stimulation and negative pressure treatment for lower extremities. The study results from Uzbekistan show that both nationalities of participants provide essential data about how microgravity affects human physiology and methods to counteract its effects.

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