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Cardiovascular response to a graded hypergravity load in patients with neurodegenerative diseases

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1. Introduction

Based on basic physiological principles, our cardiovascular system has adapted throughout human evolution to help our body's function while standing or lying down. Research in aerospace fields has shown that this evolution has been largely attributed to the effects of gravity [1, 2].

In healthy astronauts, exposure to the microgravity environment causes physiological alterations in the cardiovascular, among other systems. Following spaceflight, the change from weightlessness to Earth's gravity results in a drop in blood and stroke volume, as well as cardiac and vascular remodeling designed to keep blood pressure stable. These physiological changes ultimately lead to a decrease in cardiac output and vasoconstrictor reserve, which are the two primary causes of orthostatic intolerance following spaceflight [3].

Space research has used bed rest as a model to mimic the physiological impact of spaceflight, through the study of the consequences of postural change, immobilization, and inactivity. Although only a few people are exposed to microgravity, the physiological changes that astronauts experience in Space and on return to Earth are much like those that physiotherapists regularly observe in patients after bed rest, elite athletes during detraining, hospitalization, and critically ill patients in intensive care units. Additionally, alterations observed following spaceflight or bed rest are comparable to the secondary deconditioning observed in individuals with neurological conditions [4]. Intermittent exposure to artificial hypergravity using a short-arm human centrifuge (SAHC), has been identified as a significant tool in improving orthostatic tolerance in ground-based bed rest studies [5–12].

Based on this experience on the underlying mechanism and consequences of deconditioning in bed rest in healthy subjects, we decided to investigate "patients" made similarly inactive in bedrest, to determine whether short-arm centrifugation would be similarly beneficial. We reasoned that their long-term physical deconditioning would be aggravated by the lack of exposure to gravity due to their restricted mobility

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from the disease, and would benefit by introducing "gravity", the main thing that they lack and that aggravates their condition.

As an analogy to astronauts returning from the microgravity environment of space, we included patients with neurodegenerative diseases in the study. They were free from any other diseases but were subsequently confined to bed for extended periods of time and had limited mobility, making it impossible for them to exercise. We first examined the impact of using gravity on their cardiovascular system. We then applied graded gravity load on a short-arm human centrifuge to study their cardiovascular response, enabling us to achieve an individualized rehabilitation program, which would provide reciprocal knowledge and experience [13].

The autonomic "stress" response to acceleration, particularly hypergravity exposure of greater than 1g at the feet, may be necessary to maintain the cardiovascular control mechanisms during a long-duration spaceflight [14]. The primary reason for increased heart rate and blood pressure during high g-levels is that, with greater pressure in the legs and a resulting orthostatic challenge, greater compensation is needed via increased cardiac output and vasoconstriction to aid in venous return and return blood pressure to nominal levels at baroreceptors. Stepping, however, may act as a mechanical pump to aid venous return and reduce blood pooling in the legs and the effect of the orthostatic challenge.

Little has been reported on the effects of hypergravity on autonomic circulatory regulation. One way to study these effects of hypergravity is by using a human centrifuge to achieve greater acceleration forces [15]. The effects of Artificial Gravity (AG) training are comparable to those of natural gravity for both humans and animals. It works by applying a centrifugal force to a body that is centripetally accelerated in a spinning apparatus. Like the acceleration caused by gravity on Earth, the acceleration created via SAHC puts loads on the bones and muscles. Additionally, AG causes a fluid shift toward the lower limbs with significant positive effects on the cardiovascular system [1,16]. The effects of short-arm human centrifuge on cardiovascular activity have been studied in the past in a variety of case-control studies [17–19].

The study population that we selected, mainly patients with neurodegenerative diseases, regardless of the pathophysiology of the underlying disease, would benefit from the effects of such moderate intensity of physical activity [20–22]. These patients exhibit compromise of both the sympathetic and parasympathetic branches of the autonomic nervous system, impacting them in daily activities, as evident from orthostatic hypotension episodes or sweating dysfunction, making physical activities even more challenging. Apart from that, studies show that autonomic nervous system involvement could be responsible for cardiovascular complications, further deteriorating overall their prognosis. The short-arm human centrifuge has been rarely adopted so far to provide a better quality of care for these patients, and it has certainly not been included in recent systematic reviews of the literature [17–23]. Future long-duration spaceflight will require artificial gravity, multi-system countermeasures, and treatment equipment for spaceflight-related consequences. So far, this is the most promising space countermeasure for future space missions [19]. In addition, other ground-based disorders similarly may benefit from such hypergravity treatment implemented with the SAHC [19,24,25].

To answer the question of whether artificial gravity may reverse the effects of inactivity secondary to diseases or the physiological deconditioning caused by autonomic dysfunction, we aim to examine the status of the cardiovascular system of the patients with neurodegenerative diseases and their reaction to graded gravity load, generated by artificial gravity on a SAHC.

2. Materials and methods

2.1. Participants

The study included 24 individuals, ages 18 to 70, who were divided into two groups: healthy and patients. Of them, 12 patients (8 men and 4 women) had neurodegenerative disorders, and 12 volunteers (8 men and 4 women) were healthy (Table 1). The patient's type and stage of their neurodegenerative disease were also presented (Table 3). Eight distinct gravity conditions were applied to them, and throughout centrifugation, eight cardiovascular parameters were continually assessed non-invasively.

The participants should not have any history of chronic illness, not engaged in physical activity, no history of neurological, metabolic, or cardiovascular conditions, mental illness, vertigo, nausea, or persistent pain. Prior to being enrolled in the study, female volunteers had to have a negative pregnancy test result. Among the exclusion criteria were also the height of the individuals which should not exceed the 2 m, and some conditions as if they had a recent surgery, not controlled arrhythmia, severe migraines, epilepsy, cholelithiasis or kidney stones, acute pain or inflammation, or recently placed metal pins or plates inserted, and newly implanted stents.

2.2. Ethics

The participants were given the opportunity to ask any questions they had concerning their involvement in the study, as well as information about its goals and the impending measurements. After that, they signed a formal informed consent form that had been previously authorized by the Aristotle University of Thessaloniki School of Medicine's Bioethics Committee (179/March 19, 2020). NCT04369976 was the Clinical Trials Repository registration number for the intervention.

2.3. Experimental design

2.3.2. The suggested infrastructure

The Short Arm Human Centrifuge device (SAHC) used to generate acceleration (patent #1009812/September 13, 2019) is housed at the "Joan Vernikos Aerospace and Rehabilitation Applications Laboratory. It can attain a +3.5-Gz load at the foot and has a 4 m diameter, as shown in Fig. 1. It is made up of a support base, and the center axis is coupled to motion and rotation devices such as a motor, reducer, drive gear, spin gear, shaft, and two beds.

2.3.1. Pre-participation

The participants completed a 10-min familiarization centrifugation trial at 1 g at the feet, and if no symptoms like nausea or vertigo or any

Table 1
Participants' demographics for gender, age, height, weight and BMI.

Demographics	Classes	Frequency	Percentage (%)
Gender	Patients (8 Male+4Female)	12	50
	Healthy (8 Male+4Female)	12	50
	Total	24	100
Age	20–32	20	83.3
	33–45	3	12.5
	46+	1	4.2
	Total	24	100
Height	1.57–1.66	7	29.2
	1.67–1.76	10	41.7
	1.77–1.86	4	16.6
	1.87–1.96	2	8.3
	1.97+	1	4.2
	Total	24	100
Weight	49–60	5	20.8
	61–72	7	29.2
	73–84	7	29.2
	85–96	2	8.3
	97–108	3	12.5
	Total	24	100
BMI	Underweight (<18.5)	1	4.2
	Normal (18.5–25)	15	62.5
	Overweight (25–30)	6	25
	Obese (30–35)	2	8.3
	Total	24	100

pathological findings appeared, they were enrolled in the study. They were all instructed to avoid caffeine on training days, to abstain from alcohol and pharmaceuticals for 12 h before the training session, to avoid eating for the next 2 h, and to avoid strenuous exercise for the 24 h before the training session.

When centrifugation is used to create artificial gravity, as shown in Fig. 1, the rotating environment creates a cross-coupled Coriolis force that acts perpendicular to the axis of rotation and the direction of the moving subject mass's velocity. This force is known to cause discomfort and nystagmus. To lessen the Coriolis side effect, the participant was placed with the head close to the centrifuge's main axis of rotation and secured with safety straps.

The participants received a thorough explanation of the procedure, potential feelings, and any negative effects of the acceleration (dizziness, nausea, etc.). Before the initiation of the study, every participant received a refresher presentation on every facet of the study, including the personnel and equipment used, and they attended a centrifuge orientation session. Participants had the possibility to stop the centrifuge at any moment by pressing a "panic button." Every participant had direct verbal communication with a specialized medical doctor.

After being made aware of any possible side effects, each participant provided their signed consent. To meet eligibility requirements, they were also required to fill out participation questionnaires.

2.3.3. Protocol design

Once the participants lie down on the bed, one on each side, they are attached safely with safety harnesses on the beds to protect them from moving their body and are instructed also not to move their head during centrifugation to avoid being dizzy. An eye cover was used to cover their eyes to ensure that they were not watching the ceiling during acceleration and the details of the process were repeated to them once again. They were connected to the Edwards Clear Sight device for non-invasive cardiovascular parameters measurement and once the system was calibrated, their blood pressure was within acceptable limits, and they felt comfortable, the centrifugation protocol started with the Lying condition recording first.

The onset and offset acceleration/deceleration rates were 0.1 g/s, and this was critically important to ensure safety and minimize discomfort. Especially for patients with central nervous system involvement, higher than 0.1 g/s is not well tolerated, and sometimes even slower ramps might be necessary as low as 0.05 g/s.

The level of the first gravity load started with moderate acceleration in 0.5 g for 5 min, followed by a 6-min break and continued progressively with 0.7 g, 1.0 g, 1.2 g, 1.5g, 1.7 g, and 2 g for 5 min each, with a 6-min rest in between g loads and moderate deceleration after the last gravity load. The total number of sessions was 7, and the whole procedure lasted one and a half hours, including preparation and recuperation procedures. The ramp rate was approximately 0.1 g/s, as controlled by the centrifuge motor system. Participants underwent stepwise gravitational loading (0.5 g–2 g) with 5-min exposures interleaved with 6-min rest periods. The ramp up and down was set to 0.1 g/s as depicted in Fig. 2.

The cardiovascular parameters consisted of Cardiac Output (CO), Cardiac Index (CI), Stroke Volume (SV), Stroke Volume Index (SVI), Heart Rate (HR), Systolic Blood Pressure (SYS), Diastolic Blood Pressure (DIA), and Mean Arterial Pressure (MAP) were continuously recorded during centrifugation.

2.4. Statistical analysis

Data analysis was performed in SPSS statistical processing software and the R programming language using a minimum significance level of 5 %. To investigate the effect of condition (lying position and different levels of gravity) and group (healthy vs patient) on the parameters CO, CI, SV, SVI, HR, SYS, DIA, and MAP a mixed-design ANOVA was conducted. The condition was defined as a within-subject factor with eight levels, and the group was defined as a between-subject factor with two levels. Mixed-design ANOVA assessed the main effect of condition on parameters, the main effect of group on parameters, and the interaction of group and condition on parameters The mixed-design ANOVA was based on the Greenhouse-Geisser correction as in all cases the assumption of sphericity was violated based on Mauchly's Test of Sphericity ($p < .05$). Additionally, effect size was estimated based on partial eta squared (η^2). In cases where a statistically significant effect was recorded a post-hoc analysis was performed using Bonferroni's statistical criterion modifying the level of significance to $\alpha = .002$ as a total of 28 comparisons were made (we have a total of eight conditions, excluding standing, producing a total of 28 comparisons each). Finally, the correlation between the eight parameters was investigated using the repeated measures correlation (rmcorr) methodology and the corresponding 95 % Confidence Interval (95 % C.I.) in the R programming language. The repeated measures correlation method is suitable for finding the relationship between variables when they are evaluated in different conditions/situations [26].

3. Results

The results for the eight parameters (CO, CI, SV, SVI, HR, SYS, DIA, and MAP) in both groups in the eight different conditions are presented in Table 2. Mixed design ANOVA indicated a significant main effect of condition on SV (F (4.4, 168) = 4.868, $p = .001$, $\eta^2 = 0.169$), SVI (F(3.9, 168) = 5.856, $p < .001$, $\eta^2 = 0.196$) and HR (F(4.9, 168) = 3.965, $p = .002$, $\eta^2 = 0.142$). From the post-hoc analysis, it emerged that a significant difference in SV was recorded between 0.7 g and 1.7 g (Mean Difference = 7.2, $p < .002$, 95 % C.I. = [0.3, 14.0]) and between 0.7 g and 2 g (Mean Difference = 1.24, $p < .002$, 95 % C.I. = [4.3, 20.5]).

Fig. 1. Experimental setup showing participants positioned on a short-arm human centrifuge (SAHC). Participants are securely strapped in a supine position on opposite arms of the centrifuge, which enables the application of graded gravitational loads along the head-to-foot axis.

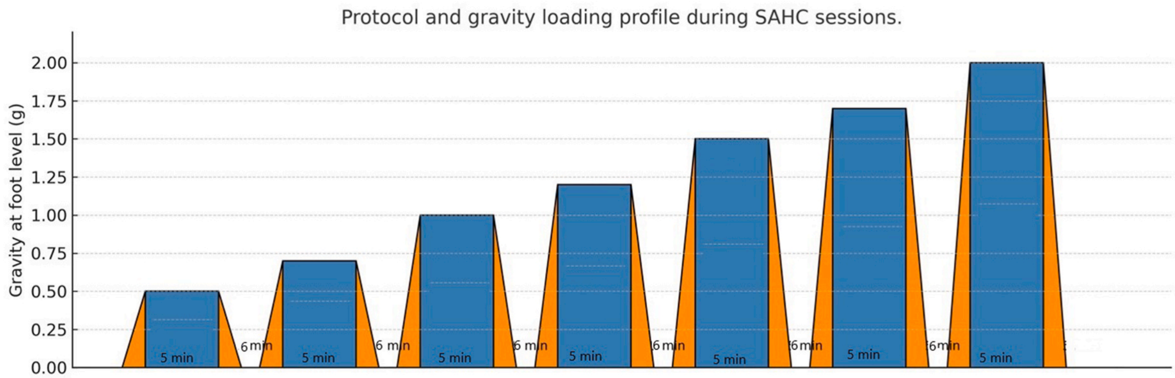

Fig. 2. Protocol and gravitational loading profile during short-arm human centrifuge (SAHC) sessions. Participants underwent stepwise gravitational loading (0.5g–2g) with 5-min exposures interleaved by 6-min rest periods. The diagram shows the actual g-profile, including smooth transitions (ramp-up/down), reflecting a gradual and safe adaptation process for participants.

Furthermore, a significant difference of SV is recorded between 1 g and 2 g (Mean Difference = 9.7, $p < .002$, 95 % C.I. = [0.8, 18.7]) and between 1.2 g and 2 g (Mean Difference = 6.9, $p < .002$, 95 % CI = [1.2, 12.6]). The findings indicate that in 2 g it is significantly lower SV compared to 0.7 g, 1 g, and 1.2 g. Also, the findings indicate that at 1.7 g it recorded a significantly lower SV compared to 0.7 g. Moreover, from the post-hoc analysis it emerged that a significant difference in SVI was recorded between 0.7 g and 1.7 g (Mean Difference = 4.3, $p < .002$, 95 % C.I. = [0.6, 8.0]) and between 0.7 g and 2 g (Mean Difference = 7.1, $p < .002$, 95 % C.I. = [1.6, 12.6]). Furthermore, a significant difference of SVI is recorded between 1 g and 2 g (Mean Difference = 5.9, $p < .002$, 95 % C.I. = [2.1, 9.8]) and between 1.2 g and 2 g (Mean Difference = 4.3, $p < .002$, 95 % CI = [0.6, 7.9]). The findings indicate that in 2 g a significantly lower SVI was recorded compared to 0.7g, 1 g and 1.2 g. Also, findings indicate that in 1.7 g a significantly lower SVI was recorded compared to 0.7 g.

Moreover, a significant difference in HR is recorded between lying position and 2 g (Mean Difference = −6.8, $p < .002$, 95 % C.I. = [−13.6, −0.04]) and between 0.5 g and 2 g (Mean Difference = −6.7, $p < .002$, 95 % CI = [−12.7, −0.6]). The findings indicate that in lying position and in 0.5 g condition recorded significantly lower HR compared to 2 g.

From the interaction analysis, a statistically significant interaction between condition and group on HR was recorded (F (4.9, 168) = 5.748, $p < .001$, $\eta^2 = 0.169$). From the analysis, it emerged that in the healthy group, the HR increased significantly as gravity increased, on the contrary, the HR measurements for the patients show a U shape distribution. More specifically, for the patients, a significant decrease in HR was recorded from the lying position up to 1.2 g, while from 1.2 g to 2 g an increase in HR was recorded (Fig. 3).

From the repeated measures correlation analysis, significant correlations between the research parameters were recorded. The results show a significant correlation between the CO parameter and the parameters CI ($r = 0.955$, $p < .01$), SV ($r = 0.782$, $p < .01$), SVI ($r = 0.745$, $p < .01$) and SYS ($r = 0.340$, $p < .01$). Also, significant correlation observed between the CI parameter and the parameters SV ($r = 0.781$, $p < .01$), SVI ($r = 0.778$, $p < .01$) and SYS ($r = 0.299$, $p < .01$). Moreover, significant correlation recorder between the SV parameter and the parameters SVI ($r = 0.956$, $p < .01$), HR ($r = -0.322$, $p < .01$), SYS ($r = 0.307$, $p < .01$) and DIA ($r = -0.287$, $p < .01$). Also, significant correlation recorder between the SVI parameter and the HR ($r = -0.321$, $p < .01$), SYS ($r = 0.303$, $p < .01$) and DIA ($r = -0.307$, $p < .01$). Finally, significant correlations were recorded between HR and SYS ($r = 0.216$, $p = .038$), HR and DIA ($r = 0.470$, $p < .01$), HR and MAP ($r = 0.409$, $p < .01$), SYS and DIA ($r = 0.680$, $p < .01$), SYS and MAP ($r = 0.878$, $p < .01$) and between DIA and MAP ($r = 0.922$, $p < .01$) (Fig. 4).

4. Discussion

The objective of our study was to determine whether using a Short-Arm Human Centrifuge (SAHC) could prove beneficial to patients with long-term deconditioning, how their cardiovascular system would respond to graded gravity levels in comparison to healthy individuals, and what level would be best for their rehabilitation. As an analog population for astronauts' post-space deconditioning, we included individuals with neurodegenerative disorders in this case.

As the body responded to the detected signal to maintain homeostasis, the main finding of the current study was that the gravity stimulus produced statistically significant differences in all outcomes across the various hypergravity settings, supporting the initial hypothesis that SAHC loading elicits cardiovascular responses similar to moderate-intensity supine exercise, such as cycling or recumbent stepping, as reported in bedrest analog studies. In fact, Diaz et al. [27] suggested that the addition of AG to exercise can provide a greater cardiovascular benefit than exercise alone. To compensate for the rapid fluid shift into the legs and return arterial blood pressure at the level of the baroreceptors to nominal levels, the primary sympathetic response triggers compensatory mechanisms (increased heart rate and vasoconstriction) when a subject stands up from a supine position. As g-levels increase, a further decrease in pressure is expected at the level of the carotid baroreceptors, and redistribution of blood to the lower part of the body, thus decreasing cardiac output. To compensate, the heart rate will increase, and blood vessels will constrict. Pressure at the level of the carotid baroreceptors will be brought back to nominal levels, and pressure at the level of the heart will be increased. As a result, we expected an increase in both heart rate and blood pressure with increasing g-levels [27].

The patients' slower reaction time to the acceleration stress and their lower performance compared to the healthy individuals were the main differences between the responses of the two groups. With inactivity, the cardiovascular system deconditions and results in reductions in muscle mass, metabolic enzyme levels, and the size and quality of capillary beds and mitochondria. Decreases in circulating blood volume and ventricular stroke volume are also prevalent [28]. Decreases in maximal aerobic capacity, elevated heart rate for any given amount of exertion, and orthostatic intolerance are also the principal consequences of such deconditioning during spaceflight if exercise CM is sub-optimal [29]. However, the International Space Station Countermeasures (ISS CM) program appears to be relatively effective in preventing significant in- and post-flight changes in cardiovascular stability under low-intensity physical conditions [30].

Table 2
Mean (SD) and range of parameters at lying position and different levels of gravity between healthy and patients.

	Healthy		Patient		*F*	*p*	η^2
	M (SD)	Range	M (SD)	Range			
CO					$F_c(3.6, 168) = 2.155$	0.088	0.082
Lying	6.7 (1.9)	3.3–9.4	6.3 (1.8)	3.2–9.6	$F_i(3.6, 168) = 1.073$	0.371	0.043
0.5g	7.3 (2.5)	3.3–11.5	6.6 (1.7)	3.7–9.3			
0.7g	7.8 (2.2)	3.1–10.7	6.5 (1.8)	3.1–9.1			
1g	7.8 (2.6)	3.2–11.0	6.3 (1.7)	2.4–8.6			
1.2g	7.4 (2.1)	3.2–11.3	6.2 (2.0)	1.3–9.6			
1.5g	7.1 (2.1)	3.2-0.9.7	6.3 (1.7)	2.8–9.4			
1.7g	7.2 (2.2)	3.3–9.9	6.2 (1.8)	2.6–8.8			
2g	7.1 (2.3)	3.2–10.7	5.8 (1.7)	2.0–9.0			
CI					$F_c(3.8, 168) = 2.401$	0.058	0.091
Lying	3.6 (1.2)	1.7–5.6	3.2 (1.0)	1.6–5.1	$F_i(3.8, 168) = 0.998$	0.411	0.040
0.5g	3.8 (1.5)	1.8–7.3	3.4 (0.9)	1.8–5.0			
0.7g	4.2 (1.4)	1.7–6.9	3.3 (0.9)	1.7–4.9			
1g	4.0 (1.4)	1.7–6.9	3.3 (0.9)	1.3–4.6			
1.2g	3.9 (1.3)	1.8–5.9	3.2 (1.0)	1.1–5.1			
1.5g	3.7 (1.2)	1.7–5.7	3.2 (0.9)	1.5–5.0			
1.7g	4.0 (1.1)	1.8–5.8	3.2 (0.9)	1.4–4.7			
2g	3.7 (1.1)	1.8–0.56	3.0 (0.9)	1.1–4.8			
SV					$F_c(4.4, 168) = 4.868$	0.001	0.169
Lying	82.6 (16.1)	56.5106.5	83.1 (22.2)	42.3–116.0	$F_i(4.4, 168) = 0.626$	0.660	0.025
0.5g	90.7 (17.8)	60.8–114.7	90.0 (20.2)	50.0–114.3			
0.7g	92.4 (17.2)	56.5–119.0	90.6 (22.3)	49.2–127.0			
1g	89.6 (24.3)	38.7–123.7	88.1 (22.3)	40.3–123.0			
1.2g	86.4 (18.3)	57.8–118.8	85.8 (24.9)	32.2–124.5			
1.5g	82.0 (17.9)	51.8–117.5	87.0 (22.7)	45.5–124.3			
1.7g	81.7 (16.4)	57.0–108.2	87.0 (24.5)	41.0–132.5			
2g	80.1 (21.6)	49.8–113.5	78.2 (23.5)	31.8–115.8			
SVI					$F_c(3.9, 168) = 5.856$	<0.001	0.196
Lying	42.9 (10.5)	29.3–68.0	42.8 (11.2)	20.8–61.7	$F_i(3.9, 168) = 0.945$	0.440	0.038
0.5g	47.1 (10.1)	32.5–62.3	46.4 (10.2)	24.2–61.0			
0.7g	48.0 (7.5)	30.8–58.0	46.5 (11.0)	23.5–61.2			
1g	46.2 (11.1)	20.5–59.8	46.0 (11.9)	21.8–60.3			
1.2g	44.8 (88)	31.5–61.8	44.1 (13.3)	17.5–63.0			
1.5g	43.1 (9.4)	23.0–59.2	45.0 (11.8)	23.2–63.3			
1.7g	40.8 (7.6)	28.8–54.2	45.2 (11.7)	22.5–64.2			
2g	39.8 (11.4)	15.8–54.7	40.5 (12.2)	17.3–61.8			
HR					$F_c(4.9, 168) = 3.965$	0.002	0.142
Lying	76.4 (12.5)	52.3–197.2	75.1 (6.8)	59.8–84.3	$F_i(4.9, 168) = 5.748$	<0.001	0.193
0.5g	79.0 (14.5)	55.5–118.5	72.8 (6.1)	58.2–81.3			
0.7g	85.5 (18.3)	54.8–121.7	71.4 (7.0)	59.2–81.5			
1g	86.8 (17.2)	57.7–126.2	70.8 (7.0)	56.5–77.3			
1.2g	85.0 (15.2)	55.5–118.3	70.5 (10.0)	41.3–81.2			
1.5g	84.7 (16.6)	55.8–116.0	70.6 (6.8)	60.5–79.0			
1.7g	91.3 (17.8)	57.0–123.7	71.9 (4.9)	63.7–78.5			
2g	90.2 (17.4)	65.2–132.0	74.9 (7.0)	61.8–90.8			
SYS					$F_c(3.5, 168) = 1.223$	0.307	0.048
Lying	118.1 (20.5)	80.7–172.2	125.1 (13.5)	102.5–147.8	$F_i(3.5, 168) = 1.058$	0.378	0.042
0.5g	126.3 (19.8)	80.2–169.0	125.0 (11.1)	106.2–144.7			
0.7g	131.8 (11.8)	114.2–160.0	124.9 (10.4)	103.3–140.3			
1g	127.9 (21.8)	71.2–153.7	124.2 (11.5)	102.7–140.2			
1.2g	123.4 (14.8)	94.2–148.7	121.8 (18.6)	72.0–137.7			
1.5g	121.4 (13.3)	91.7–140.3	125.2 (10.4)	110.2–139.7			
1.7g	125.1 (13.4)	103.8–146.8	125.6 (10.6)	105.2–145.0			
2g	123.5 (15.3)	98.7–143.8	120.4 (9.0)	104.8–133.5			
DIA					$F_c(4.5, 168) = 1.244$	0.295	0.049
Lying	77.7 (11.4)	59.2–103.7	76.6 (9.4)	58.2–95.3	$F_i(4.5, 168) = 1.275$	0.282	0.050
0.5g	81.7 (10.8)	59.0–99.2	73.5 (7.2)	57.5–83.7			
0.7g	81.2 (10.3)	65.8–99.5	73.2 (6.5)	61.7–82.8			
1g	77.1 (12.6)	56.7–94.8	73.2 (8.3)	59.3–86.5			
1.2g	78.7 (9.7)	67.5–101.2	72.6 (11.1)	45.7–87.5			
1.5g	79.5 (9.8)	67.5–97.7	75.7 (8.6)	60.3–90.2			
1.7g	81.1 (7.7)	68.0–93.7	75.4 (7.3)	63.5–87.5			
2g	80.8 (8.2)	66.8–91.2	75.9 (7.5)	62.0–91.0			
MAP					$F_c(4.1, 168) = 1.080$	0.371	0.043
Lying	94.0 (12.7)	77.2–125.0	95.4 (11.4)	72.0–116.0	$F_i(4.1, 168) = 1.167$	0.330	0.046
0.5g	99.8 (9.9)	82.0–115.7	93.5 (8.2)	75.5–105.5			
0.7g	100.2 (11.3)	83.2–123.7	93.0 (7.8)	77.7–104.7			
1g	94.8 (15.7)	63.2–115.7	92.4 (9.0)	76.2–105.7			
1.2g	95.2 (10.2)	83.0–117.7	90.3915.3)	47.7–105.0			
1.5g	94.9 (10.3)	80.2–111.3	94.2 (8.1)	78.5–107.0			
1.7g	97.3 (8.3)	82.8–111.5	94.1 (7.8)	79.2–109.5			
2g2	96.5 (9.2)	81.3–108.0	92.6 (6.8)	77.2–104.5			

Table 3
Type and stage of the neurodegenerative diseases.

Patient #	Disease	Disability scale (EDSS)	Sex	Height (cm)	Weight (Kg)	Age
P1	MS	5.5	M	170	78	32
P2	MS	7	M	179	84	47
P3	MS	5.5	M	198	115	33
P4	MS	7	F	179	70	28
P5	MS	7	F	180	82	45
P6	MS	6	F	157	57	32
P7	MS	7	M	174	70	30
P8	MS	5.5	M	172	80	27
P9	MS	5.5	M	176	70	29
P10	MS	6.5	F	166	56	31
P11	ALS	7	M	167	67	45
P12	ALS	8	M	183	85	47

4.1. Stroke volume, heart rate and cardiac output

A significant main effect on SV, SVI, and HR was the study's primary findings. The post hoc analysis revealed that there was a significant difference in SV between 0,7 g and 1.7 g and between 0,7g, 1 g, and 1.2 g in comparison to 2 g. Fluid shifts are known to have a major impact on cardiovascular regulation. Fluid displacements can be seen during gravitational changes (microgravity or hypergravity) or when the direction of action changes with respect to the body (relative gravitational vector), such as orthostasis during postural adjustments or acceleration sports [31]. The statistically significant difference between SV and SVI at 2 g and the other gravity levels, may be explained by the fact that at 2 g, the pooling and redistribution of fluids was greater at this gravity load, resulting in a smaller stroke volume. This caused the heart to pump more quickly to return blood pressure and cardiac output to normal. This accounts also for the notable rise in heart rate between lying and 2 g, as well as between 0.5 g and 2 g. Since cardiac output is dependent on the other two, we think of these results as interconnected.

Although there was a significant difference in cardiac output between the 0.5 g and lying condition in the patients' group (mean CO changed from 6.3 l/min to 6.55 l/min), this trend was not similar for heart rate or stroke volume. As the subjects moved from the lying setting (mean HR = 75.10 bpm) to the 1.5 g setting (mean HR at 1.5 g = 70.58 bpm, p = .04), their heart rates gradually dropped and only toward the end of the study, they increased, but still not being able to return to their starting heart rates, even in the 2 g setting (mean HR at 2 g = 74.88 bpm).

When comparing the two groups, we found that, although the HR of healthy individuals increased significantly as the level of gravity increased, the pattern for the patient group was different. Rather than showing a gradual increase in HR, we first showed a decrease between the conditions lying and 1.2 g, followed by a gradual increase. Fig. 3 shows a U-shaped curve for patients, which might be interpreted as a typical pattern brought on by prolonged bed rest and the muscular atrophy response to increased exercise or gravity load. Conversely, the 0.7 g setting had the highest mean stroke volume (mean SV = 90.62 ml/min). This pattern demonstrates that hypergravity activates the autonomic nervous system while simultaneously putting stress on the cardiovascular system.

However, higher levels of hypergravity may not necessarily result in greater advantages for the cardiovascular system and patients. Individualized gravity therapy and simultaneous measurement of other variables like sEMG, VO2max, and blood parameters may be more prudent before applying higher hypergravity levels to induce a better response from the autonomic nervous system, since subjects may not be able to handle them due to side effects. With all the advantages of exercise, both groups reacted to acceleration stress by increasing heart rate and cardiac stroke volume, finally increasing cardiac output, and raising mean arterial blood pressure, results similar to other researchers [32]. The direction and strength of the relationships between the cardiovascular parameters are indicated by correlations among them that were found during the statistical analysis.

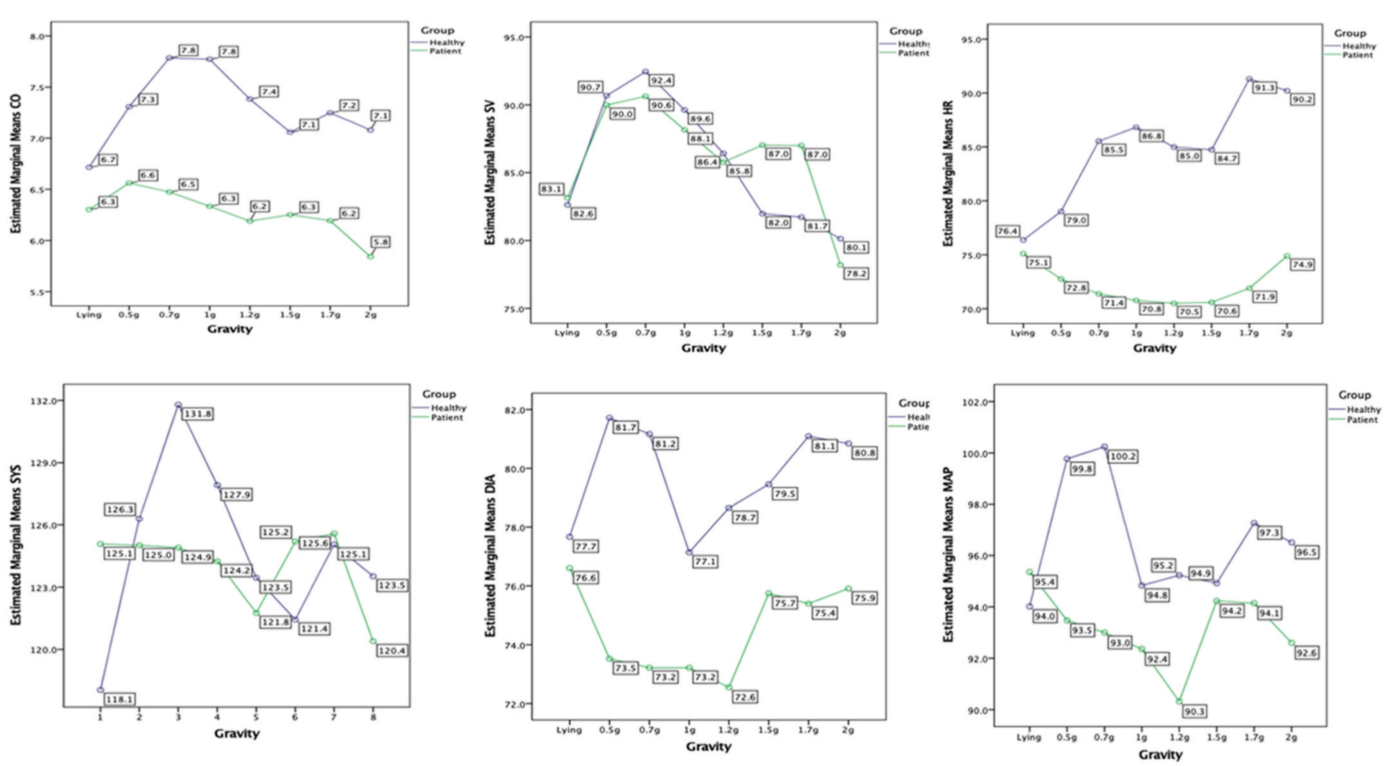

Fig. 3. Estimated marginal means of cardiovascular parameters across gravity levels in healthy participants (blue) and patients (green). Distinct differences in cardiovascular response profiles are observable between healthy controls and patients throughout the gravity exposure. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

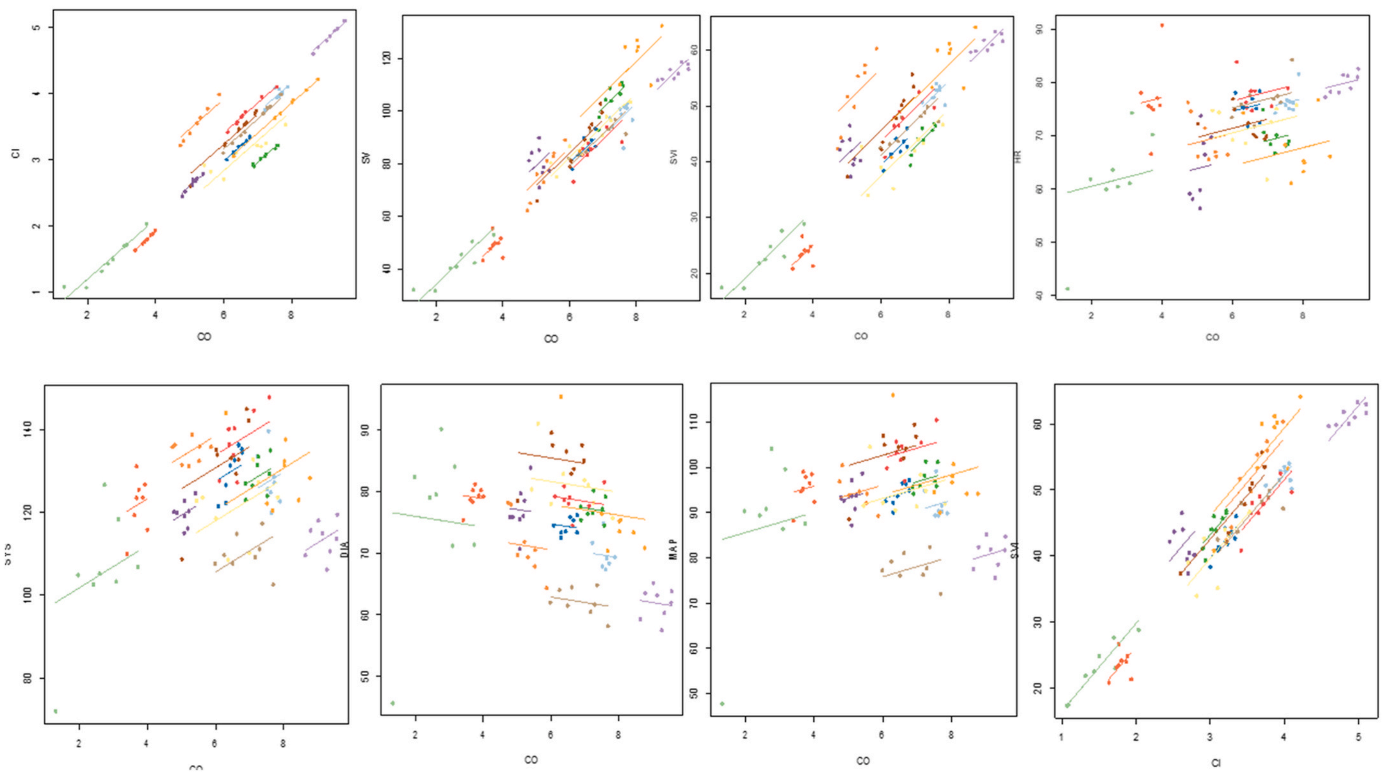

Fig. 4. Correlation plots showing inter-relationships between cardiovascular variables (CO, SV, HR, SYS, DIA, MAP, etc.) across gravity levels. Scatter plots with fitted trend lines illustrate pairwise correlations among key physiological variables. Each colored set represents a different gravity condition or participant subgroup, highlighting functional associations and regulatory coupling under artificial gravity stress.

People with neurological disorders have a well-defined response to exercise [33–36]. However, little is known about the cardiovascular and perceptual exercise response and adaptation in individuals with neurodegenerative diseases, primarily multiple sclerosis. High levels of variability in perceived exertion during a maximal exercise test have been reported in relation to Multiple Sclerosis (MS) and dysfunctional cardiovascular response, such as labile blood pressure (BP) and attenuated heart rate (HR) response, during functional activities [37–40]. As a result, it may not only disrupt autonomic dysfunction in the patient group, but it may also contribute to the disparities through muscle atrophy and inactivity. Our patients showed reduced CO, CI, and HR levels (Fig. 4) compared to healthy individuals, who did not fully follow the same trend. Even while their total cardiac output tends to increase, this tendency is maintained at higher hypergravity levels. On the other hand, they showed the same trend in terms of stroke volume, but their heart rates increased rather than decreased, which is consistent with the fact that they have an intact autonomous nervous system.

4.2. Systolic, diastolic, and mean arterial pressure

Results for arterial blood pressure and cardiac output parameters were similar. Both groups' systolic and diastolic blood pressure patterns were identical, except the patient's group was at a lower level. In particular, the systolic blood pressure decreased to 1.2 g and subsequently began to rise, reaching its optimal level at 1.7 g, while healthy individuals showed a sudden increase in blood pressure at 0.7 g. Both groups saw a drop in blood pressure at 2 g; however, the healthy individuals maintained a higher blood pressure than at the start, whereas the patient group followed an increase, but it was unable to return to their initial level. This could be attributed to the fact that higher AG levels generate higher sympathetic activity to counteract gravitational stress and maintain blood pressure at appropriate levels, as well as to the required time and stress associated with exercise for plasma catecholamines to increase and control the arterial blood pressure [41].

MAP and diastolic blood pressure decreased instantly in the patient group compared to the healthy individuals, reaching 1.2 g and 1.5 g, respectively. Following that, they increased BP and MAP to 2g, with the best values for the patients' group at 1.7 g and for the healthy group at 2 g. This suggests that 1.7 g may elicit autonomic control of blood pressure comparable to the pre-centrifugation level, making it a potential training tool to lessen orthostatic intolerance in astronauts upon their return to Earth. The results for healthy volunteers were comparable to those of the study conducted by A. Verma et al. [42]. Space reconditioning may also benefit from neurological rehabilitation techniques.

Although the disease process itself is not altered by this type of exercise, it can alter the deconditioning that results, reverse some of its consequences, and help avoid additional comorbidities that are linked to it [43]. Similarly, in healthy people, the two most severe forms of inactivity—bed rest and spaceflight—strongly promote cardiac remodeling. In fact, -6° head-down tilt bed rest (HDBR) is commonly used in research that mimics the cardiovascular deconditioning associated with spaceflight [44]. Similar age-related issues in long-duration spaceflight crew members mimic those in elderly people and potentially all patients with difficulty exercising or living a sedentary life [14]. These studies also provide strong evidence about the potential harm to the heart caused by sedentary behavior or immobility brought on by hospitalization. Exercise training can counteract the harmful effects of bed rest [45] or inactivity during spaceflight [46] and has good effects on heart size and function [47]. Similarly to other researchers, we concluded that increased gravitational forces could simulate physical exercise and alleviate the effects of inactivity [48], with the level of gravity load needed for rehabilitation, depending on the activity or inactivity level of the individual.

4.3. Limitations of the study

The relatively small number of participants, the borderline age differences between the groups, the inability to examine the gender effect due to the small number of female participants, and the inter-individual differences in artificial gravity tolerance were the main limitations of the study regarding the participants' response on cardiovascular regulation in altered gravity. Additionally, no orthostatic tolerance test was performed before or after centrifugation, due to the clinical fragility of our patient group and ethical approval limitations during the COVID-19 pandemic (study approved March 2020), we chose not to perform a pre- or post-centrifugation stand test to avoid adverse events. A follow-up study with pre- and post-testing is now being planned. Future studies should include more subjects and more female participants, as well as other factors to be examined, such as respiratory and muscular activity.

5. Conclusion

Artificial gravity for people with deconditioning due to inactivity or bedrest with physical disabilities or low gravity environment would be a wholistic rehabilitation tool which with a supervised and individualized exercise program, may improve fitness, functional capacity, and quality of life as well as modifiable impairments in patients.

Patients with neurodegenerative diseases who experience chronic deconditioning and immobility may serve as a suitable analog population for future studies on prolonged hypergravity exposure and cardiovascular adaptation.

In the future, during planetary exploration missions, there will be several changes in gravity. Physiological adaptation will begin in response to these gravitational shifts [14]. More research is needed into the physiological impacts of prolonged exposure to microgravity and hypergravity and an analogue population of patients would be a good start.

CRediT authorship contribution statement

Chrysoula Kourtidou-Papadeli: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Stavros Moschonas:** Formal analysis, Data curation. **Sofia Kourtidou:** Project administration, Methodology, Data curation. **Sotiria Gylou:** Methodology, Formal analysis, Data curation. **Eleni Dafli:** Resources, Data curation. **Kalliopi Galanopoulou:** Resources, Methodology. **Gerasimos Terzopoulos:** Resources. **Panagiotis D. Bamidis:** Writing – review & editing, Supervision, Project administration, Investigation. **Joan Vernikos:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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