THE INTEGRATED IMPACT OF ARTIFICIAL GRAVITY AND VIBRATION EXERCISE TRAINING ON MUSCLE STRUCTURE AND FUNCTION

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Doctoral Dissertation
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Doctoral Dissertation

Integriran vpliv umetne gravitacije in vibracijske vadbe na mišično strukturo in funkcijo

Doktorska disertacija

Supervisor: Professor Igor B. Mekjavic

Co-supervisors: Professor Matej Supej
Dr. Andrej Vovk

Ljubljana, Slovenia, May 2025

"I say unto you: one must still have chaos in oneself to be able to give birth to a dancing star. I say unto you: you still have chaos in yourselves."

*Friedrich Nietzsche, "**Thus Spoke Zarathustra**"*

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Abstract

During space sojourns, astronauts experience musculoskeletal deconditioning caused by the lack of gravity. The adaptation of the musculoskeletal system to inactivity and unloading of the weight-bearing limbs may be countered by daily exercise. However, current exercise devices and strategies employed on the International Space Station (ISS) do not appear to be optimal. As a consequence, a new potential countermeasure has been proposed by the European Space Agency. This exercise countermeasure combines resistive exercise on a Short-Arm Human Centrifuge (SAHC) and whole-body vibration (WBV). This thesis investigated some key aspects of this exercise countermeasure. Additionally, the combined effects of centrifugation and WBV on muscular structure and function were investigated.

These objectives were achieved in a series of four studies:

Study 1: Comparison of joint kinematics between upright front squat exercise and horizontal squat exercise performed on a short arm human centrifugation. This study compared the kinematics of squat exercise conducted on the SAHC with upright squat exercise. In both conditions the exercise was conducted under two loading conditions: (g and 1.25g at the centre of mass (CoM). Twelve health young males participated in this repeated measures study.

Study 2: The effects of exercise on acute muscular activation: resistance exercise vs whole-body vibration resistance exercise.

Using magnetic resonance imaging, this study evaluated muscle activation in the thigh and calf muscles following body weight squat (resistance) exercise performed without and with WBV. Fifteen healthy young males participated in this repeated measures study.

Study 3: Whole-body vibration transmission during resistance vibration exercise

This study compared vibration transmission while performing URVE and AGRVE. Fifteen male participants were assigned to the URVE (N=7) and AGRVE (N=8) groups.

Study 4: Muscular adaptations following a 2-weeks artificial gravity resistance vibration exercise.

This study compared the muscle structure and performance adaptations after 2-weeks of daily resistance vibration exercise (RVE) performed under three conditions: a) URVE: upright RVE, b) HRVE: horizontal RVE conducted on a bespoke exercise device, and c) AGRVE: supine exercise conducted on the SAHC establishing a head-to-foot gravitational vector (i.e., artificial gravity, AG). Twenty-four healthy young male participants were assigned to the three exercise groups.

The main findings of these studies are that:

1) A two-axis cradle allows hips movement which is crucial to maintain muscular activity of those muscles involved into keeping a straight posture and which are the most affected during space exploration. New users cannot replicate their squat movement on the centrifuge, resulting in a diminished range of motion (ROM). However, participants do improve the movement efficacy already within a single session.
2) MRI can be effectively used to measure muscular activity. Vibrations do not promote any additional benefit on muscular water content and metabolite accumulation, which is the main physiological responses after exercise.
3) Vibration transmission is dampened by lower limbs in both URVE and AGRVE. In the latter, vibration transmission is further dampened compared to URVE due to technical factors which could have absorbed part of the vibration stimulus.
4) AGRVE resulted to be a feasible exercise and can be performed by new users. Exercising in AGRVE resulted to be more effective compared to two control exercises in short-term muscular adaptation.

Povzetek

Zaradi zmanjšane gravitacije astronavti med odpravami v vesolju doživljajo spremembe v mišično-kostnem sistemu, kot je izguba mišične in kostne mase. Najboljši način za preprečevanje teh sprememb je izvajanje vsakodnevnih treningov. Trenutne vadbene naprave in metode, ki se uporabljajo na Mednarodni vesoljski postaji (ISS), v celoti ne preprečijo omenjenih sprememb. Enega izmed možnih protiukrepov predstavlja izvajanje uporovne vadbe na človeški centrifugi s kratko ročico (SAHC) v kombinaciji z vibracijo celotnega telesa (WBV). V doktorski disertaciji so predstavljeni nekateri ključni vidiki glede SAHC in WBV. Poleg tega so predstavljeni integrirani učinki centrifugiranja in vibracije celotnega telesa na strukturo in funkcijo mišic.

Sledeči cilji so predstavljeni v štirih študijah:

Študija 1: Primerjava kinematike sklepov med izvajanjem pokončnega počepa in horizontalnega počepa, izvajanega na človeški centrifugi.
Namen te študije je bil preučiti kinematiko počepa na novi generaciji SAHC v primerjavi s pokončno različico vadbe pri dveh obremenitvenih pogojih (1 g in 1,25 g v središču mase). V študiji ponavljajočih se meritev je sodelovalo dvanajst moških udeležencev.
Študija 2: Učinki vadbe na akutno mišično aktivacijo: primerjava uporovne vadbe in uporovne vadbe v kombinaciji z vibracijo celotnega telesa.
Namen te študije je bil predlagati metodo za ocenjevanje mišične aktivacije z MRI, ki velja za zlati standard, ter s to metodo primerjati mišično aktivacijo pri tradicionalni vadbi z uporom ter isti vaji, izvedeni na vibracijski platformi. V raziskavi ponavljajočih se meritev je sodelovalo petnajst moških udeležencev.
Študija 3: Prenos vibracij med uporovno vibracijsko vadbo celotnega telesa.
Ta študija je preučevala prenos vibracij med izvajanjem uporovne vadbe pri dveh skupinah: URVE in AGRVE. Petnajst moških udeležencev je bilo razdeljenih v dve skupini (7 proti 8) za analizo z mešano zasnovo analize modela variance (ANOVA).
Študija 4: Adaptacija mišic po dveh tednih uporovne vadbe z umetno gravitacijo in vibracijo celega telesa: rezultati FAVE študije.

Ta študija je preučevala zgodnje spremembe v strukturi mišic in zmogljivosti po dveh tednih vsakodnevne uporovne vibracijske vadbe, izvedene v treh pogojih: pokončno (URVE), na horizontalni napravi (HRVE) in na človeški centrifugi (AGRVE). Študija je vključevala štiriindvajset udeležencev, ki so bili razdeljeni v tri skupine z mešano zasnovo analize modela variance (ANOVA).

Glavne ugotovitve navedenih študij so sledeče:
1) Dvoosna zibelka na horizontalni vadbeni napravi in na človeški centrifugi omogoča ustrezno gibanje kolkov, kar je ključno za ohranjanje aktivacije tistih mišic, ki so odgovorne za vzdrževanje ravne drže in so najbolj prizadete med vesoljskimi poleti. Med prvim poskusom izvedbe počepa na človeški centrifugi preiskovanci navadno ne zmorejo replicirati pokončnega počepa, kar vodi do zmanjšanega obsega gibanja (ROM). Vendar pa že znotraj enega seta ponovitev izboljšajo učinkovitost gibanja.
2) MRI je uporabna za merjenje mišične aktivnosti, če so upoštevani določeni koraki. Vibracija ne povzroča dodatnih koristi pri kopičenju vode in metabolitov v mišicah, kar je eden glavnih fizioloških odzivov na vadbo.
3) Prenos vibracij v spodnjih okončinah je zmanjšan tako pri URVE kot pri AGRVE. Pri AGRVE je prenos vibracij še dodatno zmanjšan zaradi tehničnih dejavnikov, ki bi lahko absorbirali del vibracijskega dražljaja.
4) Vadba na AGRVE se je izkazala za enostavno izvedljivo. Vadba z AGRVE se je v kratkoročnih mišičnih prilagoditvah izkazala za učinkovitejšo v primerjavi z drugima dvema kontrolnima vajama.

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Abbreviations

AGRVE	Artificial Gravity Resistive Vibration Exercise
ANOVA	Analysis of Variance
BR	Bed Rest
BRAVE	Bed Rest Artificial Gravity Vibration Exercise
CSA	Canadian Space Agency
CSAr	Cross-sectional Area
DEXA	Dual-energy X-Ray Absorpiometry
DLR	Deutsches Zentrum für Luft- und Raumfahrt
ES	Effect Size
ESA	European Space Agency
EVA	Extravehicular Activity
HDT	Head Down Tilt
HDTBR	Head Down Tilt Bed Rest
HRE	Human and Robotic Exploration
HRVE	Horizontal Resistive Vibration Exercise
IMU	Inertial Measurement Unit
IPS	International Postgraduate School
ISS	International Space Station
JAXA	Japan Aerospace Exploration Agency
JSI	Jozef Stefan Institute
LAHC	Long Arm Human Centrifuge
LK	Left Knee
MBRSC	Mohammed Bin Rashid Space Center
MLKT	Mediolateral Knee Travel
MME	Mixed-Model Effect
MRI	Magnetic Resonance Imaging
NASA	National Aeronautics and Space Administration
PLANHAB	Planetary Habitat
RK	Right Knee
RE	Resistance Exercise
RM	Repetition Maximum
SAHC	Short-Arm Human Centrifuge
SD	Standard Deviation
UAE	United Arab Emirates
USA	United States of America
URVE	Upright Resistive Vibration Exercise
WBV	Whole-Body Vibration

Chapter 1

Statement of the Problem and Thesis Structure

"The beginning of wisdom is the definition of terms." (Plato, "Thereatetus")

Humans and other mammals adapt phenotypically to extreme environments through physiological changes that mitigate harmful effects and enhance performance. Well-known examples include increased blood oxygen-carrying capacity at altitude and improved heat loss in hot climates. In contrast, removing the head-to-foot gravitational vector (Gz), such as in microgravity, induces widespread but generally detrimental adaptations, such as muscle atrophy, bone demineralization, and cardiovascular deconditioning. Similar effects occur on Earth during prolonged inactivity or limb unloading due to injury, aging, or osteoporosis. In space, microgravity leads to unloading of the weight-bearing limbs and reduced activity, causing loss of muscle and bone mass and reduced aerobic capacity.

With the advent of longer duration space missions on the International Space Station, and particularly in preparation for future missions to Mars, two avenues of research were initiated. One investigating the processes of adaptation of physiological systems to microgravity, and the other developing strategies to counteract these adaptations (so-called countermeasures). The former investigations have concluded that the observed adaptations to microgravity, do not necessarily pose a problem to the astronauts during their sojourn in space. However, upon return to Earth's gravity they can have serious consequences to the health and well-being of the astronaut (Sibonga et al. 2007; Vico et al. 2000, 2017).

It is for this reason that prevention of microgravity-induced adaptations is now considered a novel strategy of interest. Ground-based studies have confirmed that this can be achieved with a variety and combination of countermeasures. In this regard, exercise remains the cornerstone of countermeasure strategies mitigating inactivity/unloading-induced adaptations of physiological systems (Alkner and Tesch 2004; D. L. Belavý et al. 2010; Berg and Tesch 1994; Rittweger et al. 2005; Trappe et al. 2004). Safe return to Earth's gravitational field relies on the prevention of these adaptations. While several countermeasures have shown partial effectiveness in mitigating musculoskeletal deterioration in terms of both structure and none have demonstrated clear superiority over the current exercise equipment used on the International

Space Station (ISS). Moreover, the long-term effects of microgravity on muscle and bone remain uncertain, particularly in the context of future lunar and Martian missions. Therefore, it is essential to develop an effective and ethically viable countermeasure to preserve astronauts' musculoskeletal health.

1.1 Problem Identification

Developing a new countermeasure is a complex challenge that requires balancing multiple factors: it must be scientifically effective, safe, and ethically applicable to users, while also being financially and logistically feasible. The countermeasures investigated so far have only been partially effective in mitigating musculoskeletal and overall bodily deconditioning. While the implementation of exercise-based countermeasures has allowed astronauts to extend their missions and reduce physical decline, these countermeasures remain insufficient for the long-term demands of extended space travel and future human exploration of Mars.

To address these challenges, the European Space Agency has launched a research program to evaluate the effectiveness of a novel countermeasure that combines artificial gravity, whole-body vibration, and resistance exercise—referred to as Artificial Gravity Resistive Vibration Exercise (AGRVE). The program aims to assess AGRVE's efficacy through two bed-rest campaigns conducted from September to December 2024 and April to July 2025. As a result, the project has been named BRAVE (**B**ed **R**est **A**rtificial Gravity **V**ibration Resistive **E**xercise). In preparation for this large-scale study, preliminary research was necessary to examine key aspects of AGRVE that required investigation before its full implementation. The centrifuge which will be used in the BRAVE study is a novel type of centrifuge. Participants are positioned supine on the nacelle of the short arm human centrifuge (SHAC), such that their head is near the axis of rotation, and their point to their feet are positioned towards the end of the nacelle. During centrifugation, their feet are positioned on a vibration platform mounted on the nacelle. The participants are positioned on a sled system which enables horizontal movement. A swivel at hip level allows the participant to execute a squat manoeuvre in same manner as in the upright position.

1.2 Thesis Structure

The evaluation of AGRVE as a potential countermeasure and its singular components was investigated in a series of studies. All the experiments received ethical approval by the Committee for Medical Ethics at the Ministry of Health of Republic of Slovenia and the Commission for Ethical Issues in Sports of the Faculty of Sport, University of Ljubljana (no. 033-10/2023-2; Appendix A), and conformed to the guidelines of the Helsinki Declaration.

The Introduction (Chapter 2) provides a brief overview of the key components of AGRVE, namely whole-body vibrations, artificial gravity, and resistance exercise. Additionally, it outlines the fundamental physiological processes underlying musculoskeletal adaptation to training, as well as the effects of immobilization and unloading in the context of space exploration

Study 1 (Chapter 3) examined knee and hip kinematics during the front squat exercise before, during, and after centrifugation using a next-generation short arm human centrifuge (SAHC) that allows hip movement. Additionally, the study investigated whether participants with no prior experience in centrifugation could improve their technique within a single session.

Study 2 (Chapter 4) explored the effects of whole-body vibrations on muscle activation using muscle functional magnetic resonance imaging (mfMRI). Two key parameters were assessed: T2 relaxation time, which indicates metabolite and water accumulation in tissues, and three-dimensional muscle reconstruction obtained through multiple segmentations. Additionally, the study evaluated the accuracy of these methods by comparing segmentations performed by different operators

Study 3 (Chapter 5) investigated the vibration transmission during AGRVE and compared it with URVE, in order to understand whether transmission mechanisms are similar to those already investigated in literature regarding traditional vibration exercise.

Study 4 (Chapter 6) examined the effects of resistive vibration exercise in three different conditions: upright position (URVE), a horizontal device simulating centrifugation (HRVE), and during centrifugation (AGRVE) following a two-week training protocol. Muscle structure and performance were assessed both before and after the training period. This study represents the first investigation into the application of AGRVE.

The conclusions and the future perspectives of the series of studies conducted are summarised in Chapter 7. The findings of this thesis will contribute to clarifying various challenges associated with implementing AGRVE as a possible space countermeasure, both by evaluating the effects of AGRVE as a training modality and by analysing its individual components. Given the novelty of this research, this work will serve as a foundation for future studies exploring this exercise approach.

1.3 Hypotheses

This thesis comprises four studies. Each study addressed a set of hypotheses. The null and alternative hypotheses are outlined below.

Study 1 (Chapter 3): The effects of centrifugation on knee and hip kinematics during and after centrifugation.

- Null hypothesis (H_0) 1.1: Participants can not replicate their knee and hip kinematics during centrifugation.
  Alternative hypothesis (H_A) 1.1: Participants can replicate their movement during centrifugation.
- H_0 1.2: Centrifugation does not affect exercise kinematics performed after centrifugation.
- H_A 1.2: Centrifugation does affect exercise kinematics performed after centrifugation.

- H_0 1.3: Participants cannot improve their technique within a single session of centrifugation.
- H_A 1.3: Participants can adapt to centrifugation exercise within a single session.

Study 2 (Chapter 4): The effects of resistance exercise with and without whole-body vibration on muscle activity measured with muscle functional MRI.

- H_0 2.1: Exercise does not increase T2 relaxation time and volume of muscles.
- H_A 2.1: Exercise increases T2 relaxation time and volume of muscles.

- H_0 2.2: Vibration does not enhance T2 relaxation time and oedema volume formation compared to resistance exercise.
- H_A 2.2: Vibration enhances T2 relaxation time and oedema volume formation over resistance exercise.

Study 3 (Chapter 5): Investigate vibration transmission during resistive vibration exercise with and without artificial gravity.

- H_0 4.1: Vibration stimulus is not dampened in both exercises.
- H_A 4.1: Vibrations are dampened in both exercise conditions.

- H_0 4.2: Vibration transmission does not differ between exercise groups.
- H_A 4.2: Vibration transmission would be dampened during AGRVE exercise compared to upright.

Study 4 (Chapter 6): The effects of two weeks of URVE, HRVE and AGRVE on muscle structure and performance in active males.

- H_0 3.1: Resistive vibration exercise does not promote any neuromuscular adaptation after 2 weeks daily training either performed with artificial gravity and in the horizontal device.
- H_A 3.1: Resistive vibration exercise promotes detectable neuromuscular adaptations after 2 weeks daily vibration training, either performed with artificial gravity and in the horizontal device.

- H_0 3.2: Artificial Gravity does not provide any additional stimulus for neuromuscular adaptation.
- H_A 3.2: Artificial Gravity enhances neuromuscular adaptation compared to URVE and HRVE.

- H_0 3.3: AGRVE could not be performed by participants due to its complexity.
- H_A 3.3: AGRVE was a feasible exercise that could be performed by participants.

Chapter 2

Physiological Adaptations to Microgravity and Possible Countermeasures: A Review

"…It is only thanks to these forays into the unknown that advances in technology, geography, cosmology and philosophy in European culture have taken place, advances that have allowed the expansion of the first modern era."

Schulz Raimond[1]

2.1 From the Earliest Concepts to the Latest Missions of Space Exploration: Achievements and Limitations

Space exploration has always represented a challenge and a milestone for mankind. Much before the modern era, the concept of space travel was deliberated by both scientists and fictional writers. Kepler in the 16th century, mentioned the concept of space travel in his *Somnium* where he imagined a journey to the moon. Three centuries later, Konstantin Tsiolkovsky discussed the idea of space colonization and laid the foundation of later rocket science, being the first one to mathematically describe the rocket equation, known also as Tsiolkovsky rocket equation. During the first half of the 20th century, the contribution of many scientists such as R. Goddard, H. Oberth, W. von Braun, to name a few, led to the launch in 1944 of the first rocket to reach the edge of space (~ 189 km altitude). One decade later, in 1957, the Soviet Union launched *Sputnik 1,* the first artificial satellite to orbit Earth. One month after the launch of Sputnik 1 they launched *Sputnik 2,* which contained the first living creature carried into space: a dog named Laika. Only three years later (1961), Yuri Gagarin became the first human to travel into space and he completed an orbit around Earth aboard *Vostok 1.* Eight years later, Neil Armstrong and Buzz Aldrin, during NASA's *Apollo 11* mission, became the first humans to land and walk on the Moon.

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[1] Schulz Raimond, "Adventurers in distant lands. The great exploratory journeys and the understanding of the world in antiquity." 2024, Oxford Press : UK.

The first extended space sojourn was achieved by the Soviet Union in 1971 with the Soyuz 11 Mission. The crew of Soyuz 11 spent 23 days in space. Despite the tragic accident during the re-entry process which led to the death of the whole crew, it was demonstrated that humans can live for prolonged periods of time in space. The U.S. maintained the *Skylab* space station, hosting three missions lasting 84 days. The next *Salyut* soviet stations (*Salyut 6 and 7*) extended human permeance in space, respectively of 185 and 237 days (1980 and 1986). A decade later, the cosmonaut Valeri Polyakov set a record for the longest duration space mission, by spending 437 days aboard the *Mir* Space Station (established by the Soviet Union and maintained by the Russian Federation).

To date, *ISS* is the only fully operational space station which is continuously inhabited (from 2000) by astronauts representing space partners NASA (USA), ESA (Europe), JAXA (Japan), CSA (Canada) and Roscosmos (Russia). Another space station which has been recently become operational (2021) is the Chinese *Tiangong* space station. Future plans forecast the launch of new space stations with several purposes. The *Lunar Gateway* is planned be the first space station to orbit the Moon. It is a multinational project supported by several space agencies, including the MBRSC (United Arab Emirates). It will support lunar exploration and will serve as a fundamental part of NASA's *Artemis program.* The vision is to establish a permanent base on the Moon, in order to facilitate human missions to Mars. Aside from governments' space programs, private companies are planning to establish a private station orbiting Earth. The *Axiom Space Station* is currently under Axiom$^{\text{tm}}$ plans. It will serve as a commercial space station and a hub for commercial activities and tourism, but also for scientific research. Several missions were already completed by Axiom and to date twelve private astronauts were sent to the ISS through Axiom's flights. Blue Origin$^{\text{tm}}$ in collaboration with Sierra Nevada Corporation, are planning to launch a commercial space station called *Orbital Reef*, with the aim of providing support for research, manufacturing and possibly tourism.

The space missions to date, particularly the activities on the ISS, demonstrate that humans can live and work in space. Launching new space missions and/or stations is a multi- and inter-disciplinary challenge. Factors which influence astronauts' health, include confinement, exposure to solar radiation, psychological stress, and microgravity. The human body along with all other life forms on Earth, developed under the influence of gravity. The removal of gravity provokes a series of adaptations which causes life forms to adapt the microgravity environment. For example, microorganisms change their gene expression affecting their metabolism, and stress response. A multitude of experiments are conducted on the ISS dealing with microbial behaviour; however, the results are still debated given the large variety of responses by microorganisms (Sharma and Curtis, 2022). Humans' physiological systems undergo several adaptations during space missions as depicted in Figure 1.

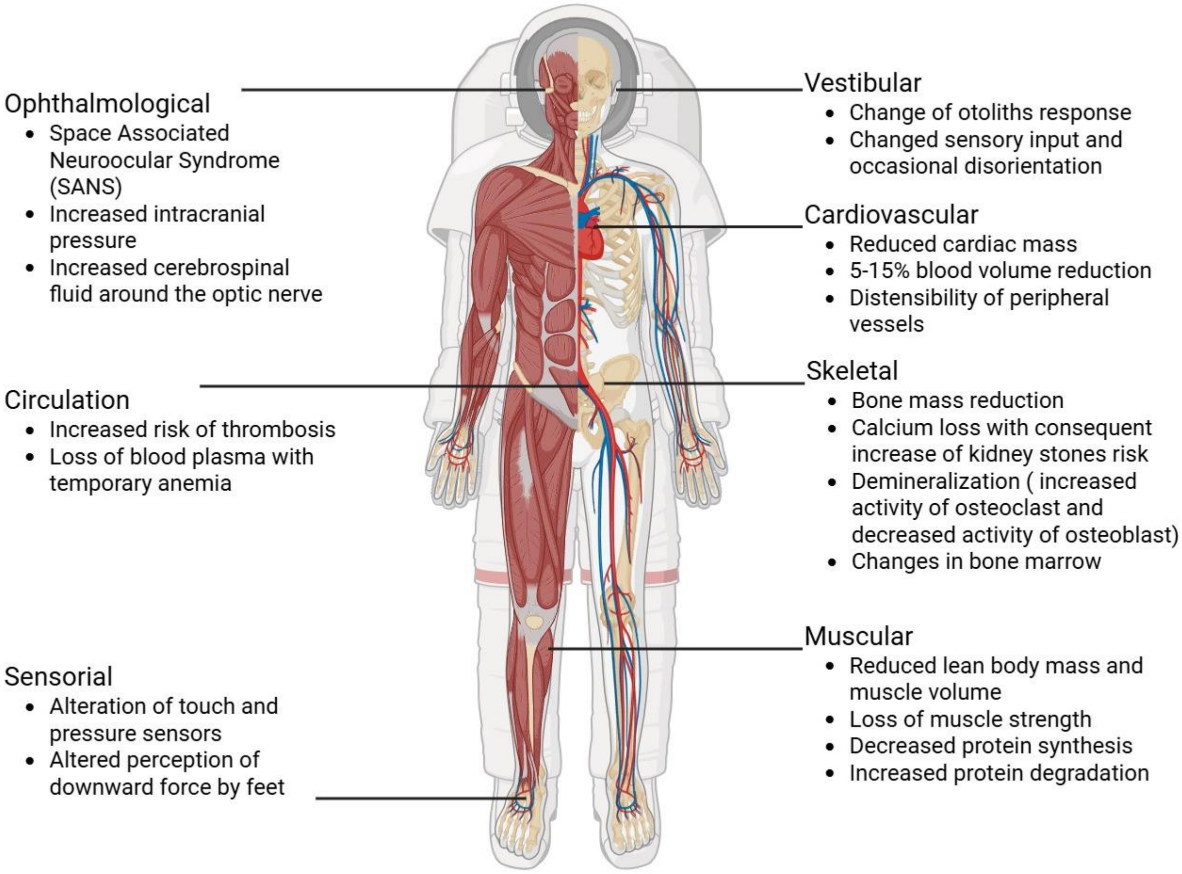

Figure 1: Graphical representation of some of the physiological adaptations to microgravity exposure (Clément 2011; Goswami et al. 2021).

During space missions, astronauts do not experience any gravitational vector, hence body fluids accumulate in the upper regions of the body (Aubert, et al., 2016; Goswami, et al., 2021). This leads to the phenomenon referred to as “puffy face”. This sign has been observed in astronauts whose faces appeared wider, due to the switch of fluid distribution. Astronauts can also experience disorientation due to the alterations of otoliths function. These small structures are calcium aggregate which are present in the inner ears of vertebrates, including humans, and play a crucial role in the sense of balance and spatial orientation (Smith, 2019). In normal conditions, otoliths respond to changes in the head’s position relative to gravity. During a movement, they shift and bend micro hair cells in the inner ear, which convey this information to the central nervous system where it is integrated and provides the perception of the body’s orientation and balance. In a microgravity environment, the stimulation provided by the otoliths to the hair cells is reduced, and the information received from the vestibular apparatus in the left and right ears may also provide conflicting information, which may cause space motion sickness (Carriot, Mackrous, and Cullen, 2021). All the above-mentioned adaptations can represent a risk to the astronauts’ wellbeing.

2.2 Musculoskeletal Adaptations During Space Missions

Muscle and bone together form what is called the musculoskeletal system, which its primary function is locomotion and performing physical efforts. The musculoskeletal system, whether human or animal, forms as a result of living in a 1 g environment and its mechanical stress exerted on the body. During space sojourns, muscles lose volume, strength and mass, while bones lose calcium which results in an increase in the interosseous spaces and can increases the risk of fractures upon return to Earth's gravity. These adaptations affect performance and motor function, which might jeopardize the work capability and performance during surface operations on Mars and the Moon.

2.2.1 Muscle anatomy and physiological adaptation

Skeletal muscles account for approximately 40–45% of total body weight and are among the tissues most affected by spaceflight. Each muscle is composed of muscle fibers, which are cylindrical in shape and approximately 50 micrometers in diameter. Each fiber contains several hundred myofibrils, with a diameter of around 1 micrometer. In addition to myofibrils, muscle fibers include mitochondria and a specialized membrane network known as the sarcoplasmic reticulum. This membrane system regulates calcium ion levels within the fiber, a critical factor in the muscle contraction process.

Myofibrils are composed of repeating units of protein filaments, primarily myosin (thicker) and actin (thinner), which form the structural basis for contraction. These filaments interact within the sarcomere, the fundamental contractile unit of each myofibril. Alongside myosin and actin, additional proteins, such as tropomyosin and troponin, are involved in the contraction process. The integrity of the sarcomere is maintained by smaller structural proteins essential for force transmission, including dystrophin, desmin, vinculin, talin, and α-actinin. Resistance training produces a variety of responses in muscles, which eventually lead to hypertrophy (DeFreitas, et al., 2011; Franchi, et al., 2018). The exact mechanisms behind hypertrophy remain unresolved. Many factors contribute to hypertrophy, both physical factors such as mechanotransduction and stretch of muscle fibers and cellular factors, such as the presence of free radicals, calcium turnover and cascades of hormones. Another important factor is the transcriptional regulation of transcription factors to the DNA, mechanisms triggering the transcription of several target genes. One known protein which exerts its effect at transcriptional level is myostatin. It is a down-regulator of muscle hypertrophy, decreasing muscle size. The inhibition of such protein would lead to an extensive increase of muscle size and strength, such as naturally observed in a case study in 2004 (Schuelke, et al., 2004). A review (Roberts, et al., 2023), identified the following factors which are currently considered the most pertinent regarding muscle hypertrophy: I) mTORC1 signalling (involved in translation, initiation and elongation of mRNA into protein synthesis), II) ribosome biogenesis (increased ribosomal RNA expands translational capacity through ribosome biogenesis), and III) satellite cells (proliferation, differentiation and fusion with myofibers contributing to the formation of new myonuclei).

Muscle atrophy is a process which occurs quickly after cessation of physical training. After just few days, there is a decline in muscle strength and mass with consequent decreases in performance (Hansen, et al., 2024; Mulder, et al., 2015). Given that muscular tissue is very plastic, it is indeed easier to recover from inactivity and to regain the same condition prior to the cessation of training. This phenomenon is usually referred as "muscle memory". Muscle atrophy is characterized by both structural (decrease in fiber size) and functional (i.e., increase in myostatin expression and protein's metabolism) adaptations (Wall, et al., 2014). Space related muscle atrophy is not equal for all muscles. It is more evident and considerably greater for postural muscles, supporting activities such as walking, running and standing. The main function of these muscles, as the name suggest, is to keep a straight posture. Living in a 1g environment, provides a constant load to the postural muscles, such that even a light activity as walking, activates many lower limb and pelvic muscles.

Upper body muscles undergo marginal or no changes during sojourns in microgravity. During short durations missions, astronauts lose 10-20% of muscle mass in the lower limbs, and as much as 50% during long duration missions in the absence of countermeasures. The decrease in size is not exclusive for muscular tissue, but fluid shift is also involved. As discussed previously, microgravity induces a caudal shift of fluids. This shift contributes to the overall decrement of cross-sectional area (CSA). The main cause of muscle mass loss is likely caused by changes in muscle metabolism. Experiments performed on the Mir station, revealed a decrease of 15% in the rate of protein synthesis in humans and an increased protein breakdown process (Dickerson, et al., 2023). The alteration of fluid flow, regards also blood flow and consequently, the nutrients delivery to muscles, hence, impaired blood flow affects muscle metabolism. Fluid shifts contribute to the initial decrease in muscle volume; however, these shifts are completed within the first week, while reductions in leg volume persist. This indicates that fluid shifts account for only a portion of the observed muscle volume loss. During spaceflight, there is also an increased loss of nitrogen, a key structural component of proteins. Since muscles serve as the primary container for proteins in the body, the majority of nitrogen loss is associated with muscle tissue, ultimately leading to muscle atrophy. Muscle adaptation is not exclusive of size and function, but is a process deep down to single muscle fibre biology. It was shown that microgravity, either during spaceflight or bed rest, affects type I fibres more than type II (Fitts, Riley, and Widrick, 2011; Trappe, et al., 2004). In addition, studies using animal models reveal that muscle fibre isoform, shifts from type I to type II fibres (Fitts, et al., 2011).

2.2.2 Bone anatomy and physiological adaptations

Bone tissue is often misconceived as an inert structure primarily serving as a point of attachment for muscles via tendons. However, this view is incorrect, as bone is a dynamic and living tissue that undergoes continuous cycles of renewal, similar to muscles. In addition, bone serves as the body's principal calcium reservoir, with approximately 99% of the total calcium stored in the bone matrix and only 1% present in soft tissues and extracellular fluid. Bone remodelling is mediated by specialized cells. Osteoblasts synthesize a new collagen matrix, which provides the framework for bone formation. Once the matrix becomes mineralized, osteoblasts transition into a quiescent state and differentiate into osteocytes. Osteocytes play a central role in maintaining bone homeostasis and are highly sensitive to mechanical stimuli, adapting bone structure in response to stress. Another key cell type involved in bone remodelling is the osteoclast, which mediates the resorption of bone tissue by secreting acidic enzymes that degrade the mineralized matrix. Bone remodelling is a lifelong process essential for maintaining skeletal integrity and calcium homeostasis. In adult humans, approximately 20–30% of bone tissue is replaced annually, underscoring its dynamic nature. This balance is quantified as Bone Mineral Density (BMD). Up to approximately the age of 30, the equilibrium between bone formation and resorption favours bone formation, leading to an increase in BMD. This period marks the attainment of peak BMD. After this point, the balance gradually shifts toward bone resorption, with a decline of approximately 1–2% per decade. In women, this process accelerates significantly following menopause. The resulting increase in intraosseous cavities reduces bone density, thereby elevating the risk of fractures as partially shown in Figure 1.

Resistance exercise is considered the gold standard mechanical mediator to increase bone mineral density. There is evidence that performing resistance-like exercises results in a greater stimulus for BMD compared to light exercise such as running (Dornemann, et al., 1997; Erickson, et al., 2020). Engaging in resistance exercise prior to reaching peak BMD has been shown to enhance bone mineral density, resulting in a less pronounced decline in bone mass due to osteoclast-mediated resorption when compared to individuals with sedentary or low activity levels.

During space exploration, the rate of bone resorption is dangerously higher compared to terrestrial conditions (Fig.2). After the age of 40, humans typically lose approximately 0.5% of bone mineral density (BMD) per year due to aging, even though the decrease is not linear and depends on the level of activity. In contrast, astronauts in microgravity conditions can lose between 1% and 2% of BMD per month, depending on individual factors. This equates to an annual loss of up to 19%, meaning that BMD loss in space can occur at a rate approximately 38 times faster—or around 3,700% higher—than on Earth. Therefore, the rate of bone loss in space is dramatically elevated compared to terrestrial conditions, posing significant health risks during extended space missions (Vico and Hargens, 2018).

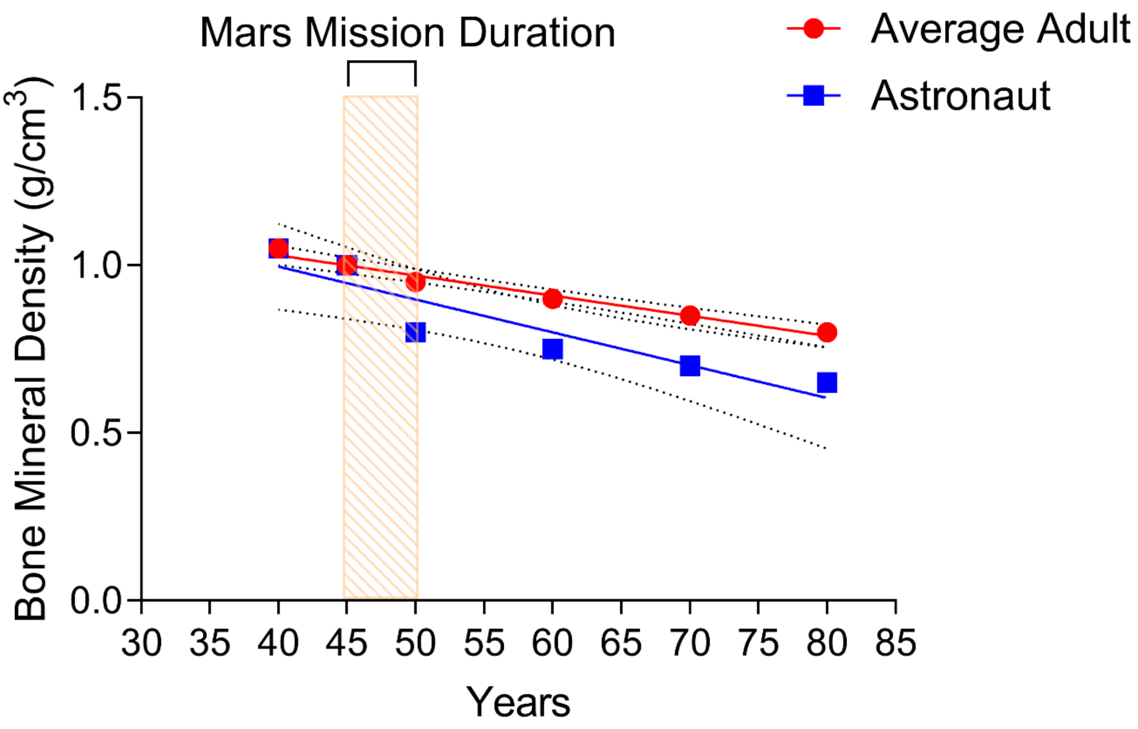

Figure 2: Simple non - linear regression of bone mineral density alteration after a theoretical mission to Mars (Winnard, et al., 2019).

2.2.3 The loss of muscle and bone mass during bed rest: a space analogue

It was observed that immobilization, such as in those individuals constrained in bed, produces almost the same responses observed in astronauts (LeBlanc, et al., 2007; Qaisar, Karim, and Elmoselhi, 2020). Dry immersion and bed rest models provide researchers with cost-effective methods for studying physiological adaptations induced by spaceflight (Bleeker, et al., 2005; Clément, et al., 2022; Fernandez-Gonzalo, et al., 2019; Ferrando, et al., 1996; Ganse, et al., 2021; Lipnicki and Gunga, 2009; McDonnell, et al., 2020; Moore, et al., 1994; Pavy-Le Traon, et al., 2007; Pišot, et al., 2008; Šarabon, et al., 2018; Strewe, et al., 2017; Trappe, et al., 2004). Conducting experiments of such scale and complexity aboard spacecraft is challenging, making these ground-based analogues valuable alternatives. Among these, bed rest, especially when performed 6° head-down tilt, is currently regarded as the gold-standard procedure for evaluating potential countermeasures to the effects of spaceflight (Belavý, et al., 2011; Dillon, et al., 2018; Miokovic, et al., 2014; Mulder, et al., 2015; Ogawa, et al., 2020; Rittweger, et al., 2005, 2010).

2.3 Physical Exercise as a Countermeasure to Deconditioning

More than two-thousand years ago, Hippocrates of Kos declared: "*Eating alone will not keep a man well; he must also take exercise*". With this statement he emphasised the importance of physical exercise not only as a sport activity, but as a remedy to many illnesses. Exercise promotes a series of acute and chronic physiological adaptations which depend on the type, frequency and intensity of exercise. The musculoskeletal system is particularly sensitive to resistance exercise. Resistance exercise produces a cascade of mechanisms which eventually results in stronger bones and muscles. It is known that the first muscular adaptations are neural adaptations; the main neural adaptations are: reduced antagonist activation, increased agonist activation, improvement of synergist activation and motor unit recruitment (Del Balso and Cafarelli, 2007; Del Vecchio, et al., 2019). It is widely believed that neuromuscular adaptations occur prior hypertrophic changes on a temporal scale. However, there is no compelling evidence to support the notion that these two adaptations are mutually exclusive or fail to occur concurrently (DeFreitas, et al., 2011). On the contrary, early signs of hypertrophy were observed already in the first weeks of training (DeFreitas, et al., 2011; Seynnes, De Boer, and Narici, 2007).Hypertrophy is a long-term physiological adaptation commonly expected following resistance exercise. It is characterized by an increase in muscle size and can be assessed through various methods, including measurements of individual fiber cross-sectional area (CSA), muscle thickness, volume, or CSA at the macroscopic level, and lean body mass, although the latter is less precise. Hypertrophic adaptations occur even in the absence of training specifically for hypertrophy or resistance exercises. Furthermore, research indicates that unilateral training (e.g., training exclusively on one limb, such as the left arm) can induce cross-education effects, promoting adaptations in the contralateral, untrained limb. The hypertrophic response is a complex physiological process involving the interplay of multiple systems in an action-reaction dynamic. As illustrated in Figure 3, exercise initiates a cascade of events that ultimately result in muscle growth. However, the precise mechanisms and the relative contributions of each component within this cascade remain a topic of ongoing debate. For instance, testosterone was long considered a fundamental driver of hypertrophic adaptation. Yet, studies on castrated animals have shown no significant differences in hypertrophic responses compared to those with intact testosterone systems, challenging this assumption. A review (Roberts, et al., 2023), highlighted the main mechanism which seem to be the key for skeletal muscle hypertrophy induced by resistance training: I) mTORC1 signalling (responsible for transducing RNA to protein synthesis), II) biogenesis of ribosome (increased availability of RNA content which can be transduced in protein synthesis) and III) *satellite cells* (cells which can fuse with myofibers in response to exercise, contributing to formation of new myonuclei.

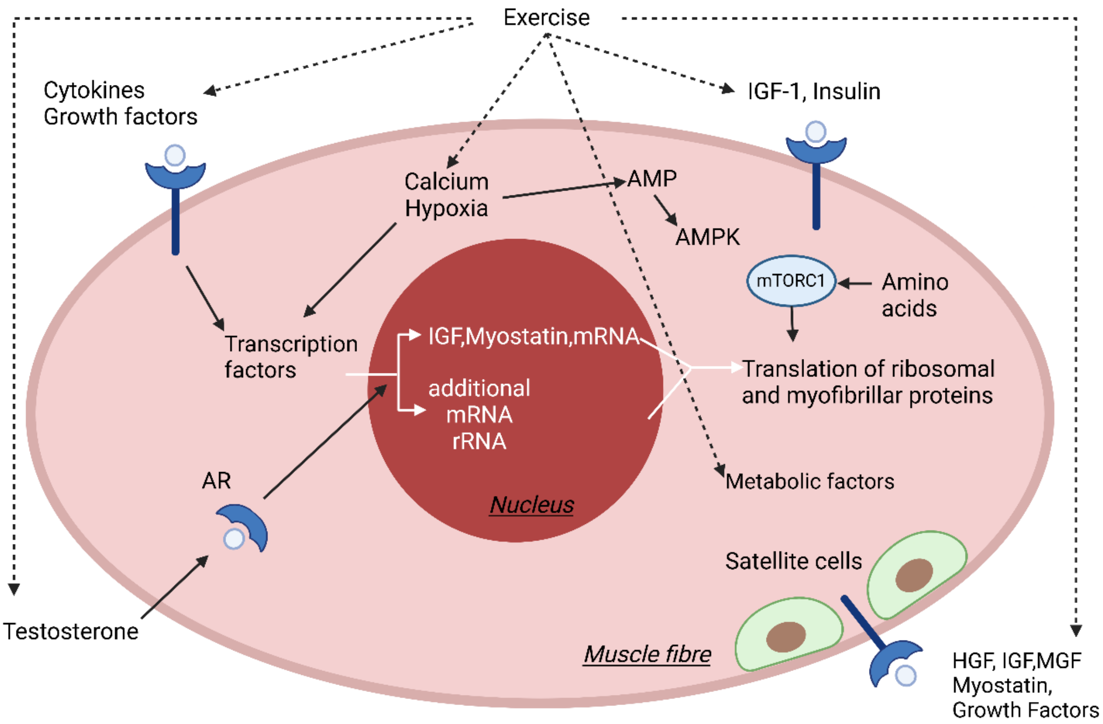

Figure 3: Graphical representation of some of the most important mechanisms for muscle hypertrophy (Jorgenson, Phillips, and Hornberger, 2020; Roberts, et al., 2023).

Exercise does not influence only muscular tissue, but directly affects also bone tissue. While bones are generally less metabolically responsive than muscles, they nonetheless undergo significant structural adaptations in response to mechanical loading, particularly through resistance training. As described in chapter 2.2.2, bone formation is mediated by the homeostatic action of three molecules: osteoblasts, osteoclasts and osteocytes. An article (Frost, 2003) suggested that the theory of a “mechanostat” can explain the mechanisms by which these molecules respond to training, especially involving load administration. This theory proposes that bone possesses an intrinsic biological mechanism to stimulate bone formation in response to elevated mechanical strains, hence enhancing its structural integrity. Central to this process are osteocytes, which act as mechanosensors capable of detecting and responding to mechanical loading. Osteocytes play a pivotal role in bone remodeling by sensing mechanical stimuli and mediating signals to osteoblasts and osteoclasts, which coordinate the maintenance of skeletal homeostasis. When a muscle contracts it generates a tension which is discharged with tendons to the underlying bone. Bone formation is enhanced in areas subjected to high mechanical strain, particularly along the periosteal surface, while bone turnover and porosity are concurrently reduced. Mechanical loading contributes to an increase in both the cross-sectional area and tissue density of bones. Moreover, this theory highlights the site-specific nature of skeletal adaptations to mechanical loading, with the most pronounced effects occurring at skeletal sites experiencing greater mechanical impact. Weight-bearing exercises predominantly load the lower limbs, as reflected in the observed positive skeletal effects on the hip region (Bolam, van Uffelen, and Taaffe, 2013).

2.3.1 Space agencies approach to exercise prescription

Each space agency follows a plan of exercise which must be adhered to by astronauts, prior, during and after a mission. For example, NASA's inflight exercise program was designed to maintain or minimize the loss of bone mineral density, aerobic and anaerobic capacity, muscle strength, muscle power, and local muscle endurance while also reducing neuromuscular dysfunction. The exercise regimen primarily targeted the lower body—focusing on movements such as squats, deadlifts, and heel raises—since most physiological adaptations during long-duration spaceflight affect the lower extremities. Treadmill exercise prescriptions were self-selected by astronauts, though they were encouraged to incorporate both steady-state and interval workouts. Training was conducted using both motorized and non-motorized treadmill modes, with astronauts wearing a harness to apply external load. Initially, the load was set at approximately 60% of body weight and gradually increased throughout the mission, with a target of reaching 100% body weight by mission end. Nevertheless, loads exceeding 85% were often too uncomfortable for most crew members to tolerate. Resistance exercise during Expeditions 1–18 was performed using the Interim Resistance Exercise Device (iRED) and followed a two-session cycle, alternating between upper-body exercises and a combination of double-leg and single-leg lower-body exercises. During the first two weeks, light to moderate intensity workouts were prescribed to allow astronauts to acclimate to exercising in microgravity. The iRED had a maximum load capacity of 136 kg (300 lb), which prevented the implementation of a fully periodized training program. For instance, a 90.9-kg (200-lb) astronaut in microgravity could only achieve a maximum external load of approximately 45.5 kg (100 lb) when accounting for body weight reduction. With the implementation of the new Advanced Resistance Exercise Device (aRED) it was possible to implement a structured periodized training protocol.

The Japanese Space Agency (JAXA) in-flight training program consisted in performing treadmill exercises three times per week and cycle-ergometer sessions three times per week, each lasting 30 to 45 minutes. Early in the mission, a greater emphasis was placed on cycle-ergometer training to help maintain aerobic capacity and physical strength through the mission's midpoint. In the later phases, treadmill running was performed daily to facilitate re-ambulation upon return to Earth's gravity. The in-flight exercise program was periodically updated throughout the mission based on monthly fitness evaluations, which assessed training load, exercise type, and duration. Cycle-ergometer sessions incorporated both steady-state and interval training, targeting 50–90% of maximum heart rate or a Borg scale rating of 13 ("somewhat hard"). During treadmill exercise, astronauts used a harness and loading system to apply 60–100% of body weight. Training included both steady-state and interval protocols, with speeds ranging from 5 to 14.5 kph (3.1 to 9 mph), targeting 60–80% of maximum heart rate or a Borg scale rating of 13. Resistance training was performed six days per week using the Advanced Resistance Exercise Device (ARED). The training regimen included bar exercises such as deadlifts, heel raises, squats, and bench presses, as well as cable exercises like biceps curls, triceps extensions, and bent-over rows. To prevent muscle and bone atrophy, the program utilized loads of 6, 8, and 12 repetition maximum (RM) for four sets across both upper- and lower-body exercises.

The European Space Agency (ESA) countermeasure plan implemented an intensive daily exercise program using various training modalities and methodologies, with crew compliance being a key factor in the program's success. The primary focus was on strength training and running to maintain gravity-stimulated neuromuscular function. The in-flight physical training (PT) program was designed to be high in intensity, fluctuating between high- and low-intensity sessions throughout the week. The training program was periodized over the mission and divided into three distinct phases:

I. Adaptation Phase (2 weeks) – Low-intensity general exercise to allow astronauts to adjust to microgravity training.
II. Progressive Training Phase – Gradual increase in training intensity, with an emphasis on strength and treadmill workouts, supplemented by cycle-ergometer sessions.
III. Pre-Return Phase (Final 2–3 weeks) – Increased training intensity, focusing exclusively on strength and treadmill exercises to prepare astronauts for reambulation upon return to Earth.

Strength training loads on the Interim Resistance Exercise Device (iRED) and Advanced Resistance Exercise Device (ARED) ranged from 60% to 90% of individual maximal capacity. Lower loads were used during Phase 1 and systematically increased every 1 to 2 weeks throughout Phases 2 and 3. While pre-flight training loads were used as initial estimates for in-flight resistance, differences in exercise environments and hardware often required adjustments. Key lower-body exercises, such as squats, heel raises, and deadlifts, were included in every session, while upper-body exercises varied. To maximize efficiency, exercise order was adjusted to prevent premature hand fatigue during bar exercises. Squats, heel raises, and deadlifts were typically performed at the beginning of each session. Additional exercises targeting the hands, arms, and shoulders were incorporated before extravehicular activities (EVA) to strengthen prime movers and reduce injury risk. Many astronauts using iRED reached its maximum load capacity of 136 kg (300 lb) by mid-mission, requiring intensity adjustments through increased exercise volume (sets and repetitions) rather than load. When training with ARED, exercises and intensity levels rotated between four distinct workout sessions and three repetition-based intensity levels (8, 12, or 15 reps) to ensure progressive overload and muscle adaptation. All these approaches helped in mitigating the physiological adaptations that occurs during spaceflight. As shown in a meta-analysis (Stavnichuk, et al., 2020) the implementation of countermeasures significantly mitigated bone loss in astronauts. Given the same percentage of bone loss observed, these countermeasures have allowed for extended durations of spaceflights. Nevertheless, they suggested that their results are affected by the fact that there was lack of data availability (189 out of 565 astronauts at the time of the review). Future space missions will require astronauts to spend much more time in microgravity future space missions will require astronauts to spend much more time in microgravity (Winnard, et al., 2019). Hypothetical future space mission will take from 210 to 954 days, respectively for Moon and Mars missions (Winnard, et al., 2019). Most of this period will be spent in microgravity, which as discussed above, leads to adaptations which may increase the risk of mission failure. Given the limited knowledge regarding long-term musculoskeletal adaptations in space, the development of effective countermeasures is crucial to maintaining pre-mission physical conditioning. Various countermeasures have been explored and continue to be of interest to multiple space agencies. This thesis will focus on the two primary countermeasures currently being investigated by the European Space Agency (ESA).

2.4 New Possible Countermeasures

Given the results from resistance training implementation on ISS, many space agencies are evaluating other countermeasures. Some examples include: i) the possibility of implementing bisphosphonate as a supplement to exercise to protect bone (LeBlanc, et al., 2013), ii) modification of astronauts' nutritional plan (Dakkumadugula, et al., 2023), iii) implementation of anabolic drugs to artificially control the metabolic changes due to microgravity. However, these countermeasures could also pose long-term risks to astronauts and their implementation may be ethically unacceptable. Currently, ESA is investigating the possibility of implementing artificial gravity training and whole-body vibrations as a possible exercise countermeasure, which will be hereby presented.

2.4.1 Whole-body vibration

Whole-body vibration (WBV) is a physical intervention that has been proposed as a method for delivering an exercise stimulus. Bosco and colleagues (Bosco, et al., 1999, 2000) were among the first to propose this modality as an exercise stimulus. However, the effects of vibration as an exercise intervention remain highly debated and inconsistent. This is primarily attributed to the numerous factors influencing its application and effectiveness. As described by Rittweger (Rittweger, 2010, 2020), the factors influencing the outcome are: time of exposure, amplitude of vibrations, frequency of vibrations, type of vibration platform, type of exercise performed and training status of the individual. The interaction of all these variables determines the efficacy of vibration both in training and rehabilitation (Rauch, et al., 2010; Rittweger, 2010). For example, vibrations delivered by rotational platform are more efficient to stimulate muscle activation, while vibrations delivered by vertical platforms stimulate more bones. Furthermore, low vibration frequencies (~15 Hz) may facilitate the rehabilitation process by providing an effect comparable to active massage, whereas higher frequencies have been associated with enhanced muscle activation.

Some studies fail to accurately report the characteristics of the applied vibrations, frequently misinterpreting amplitude as peak-to-peak amplitude and vice-versa, which complicates result replication (Rauch, et al., 2010). The most effective range of frequencies to stimulate musculoskeletal system is between 15 to 35 Hz (Cardinale and Bosco, 2003; Rittweger, 2020). Below 15 Hz vibrations become dangerous as they may coincide with critical frequencies of body organs and thus cause harm, while for vibrations beyond 35 Hz no added value was recorded for muscular activation (Cardinale & Lim ,2003; Pollock, et al., 2010). The type of vibration platform, although often overlooked, plays a crucial role in determining the effectiveness of the intervention and the effects on human body. Commercially, three types of vibration platforms are available (Rittweger, 2010): rotational, vertical, and three-dimensional platforms that combine both vertical and rotational components. the three-dimensional type has been rarely employed in scientific research, primarily due to challenges in protocol standardization and reproducibility. Transmission of vibrations through the body, and the consequent physiological responses of the user, will depend on the type of platform. Vertical plates oscillate in an up-and-down motion, whereas rotational plates move in a see-saw pattern, where one side rises as the other descends, as illustrated in Figure 4. Both types of platforms have advantages and disadvantages. Whereas, vertical oscillations might promote a higher anabolic stimulus for bone, rotational might be more effective for muscles (Oliveira, et al., 2019; Rittweger, 2010). Additionally, rotational platforms are generally better tolerated by participants over extended durations compared to vertical vibration platforms. From a musculoskeletal perspective, a primary limitation of vertical platforms is the challenge of increasing vibration frequency without reducing the contact time between the vibration source and the targeted body region.

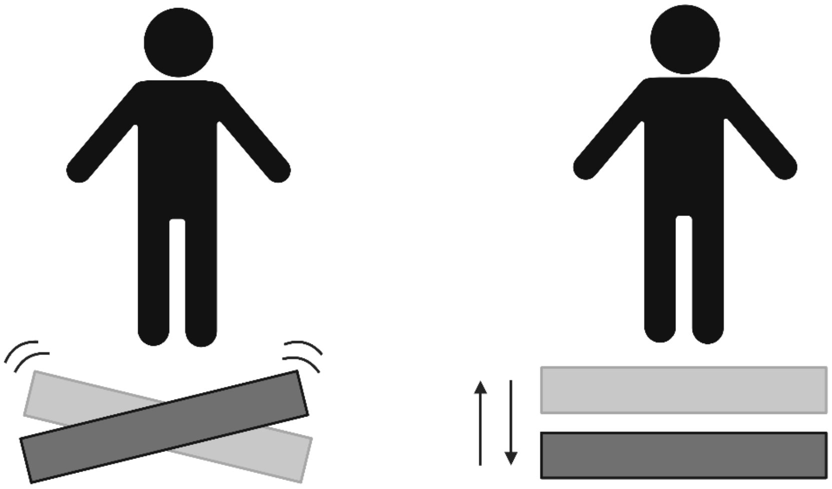

Figure 4: Graphical representation of rotational (left panel) and vertical (right panel) whole-body vibration platforms.

This phenomenon happens because higher frequencies, tend to increase the moment where users lose contact with the platform and in the long-term results in less vibrations delivered (Abercromby, et al., 2007; Pel, et al., 2009; Rittweger, 2010, 2020). To train the musculoskeletal system, rotational platforms seem to promote a higher response. Nevertheless, results are quite discordant, partially for the above-mentioned reasons. Evidence suggests that the stimuli generated by vibrations might increase neuromuscular activation thus leading to enhanced muscle recruitment and potentially enhanced training adaptation (Cochrane, et al., 2008; Hazell, Kenno, and Jakobi, 2010; Marín, et al., 2015, 2015b; Marín and Cochrane, 2021; Ritzmann, et al., 2010; Zange, et al., 2009). On the contrary, opposite evidence suggested (Arora, et al., 2021; Artero, et al., 2012; Celik, et al., 2022; Kvorning, et al., 2006; de Ruiter, et al., 2002, 2003) no added value by pairing or substituting resistance exercise with vibration exercise. It was noted that vibration does increase O_2 consumption, thus indirectly indicating an increase muscular activity (Cochrane, et al., 2008; Rosenberger, et al., 2019; Serravite, et al., 2013; Zange, et al., 2009). We recently compared (Sorrentino, et al., 2025b) the resistance exercise without (RE) and with vibration (RVE) on T2 relaxation time, reflecting the accumulation of water and metabolites within the muscles as a result of the muscular activity. We observed that RVE did not provided a higher stimulus compared to RE. Since vibration exercise is being considered as a potential countermeasure for future space missions, it has been evaluated together with resistance exercise in several bed rest (BR) studies (Armbrecht, et al., 2010; Belavý, et al., 2011; Belavý, et al., 2010; Miokovic, et al., 2011, 2014; Rittweger, et al., 2006, 2010). Whilst vibrations proved to be superior in preserving bone mineral density in tibia and lower spine, there appeared to be no additional benefit in mitigating loss of muscle mass. It would appear that the effect of vibrations on neuromuscular responses are quite heterogenous and dependent on the amplitude, frequency and trained population. For example, Torvinen and colleagues (Torvinen et al. 2002, 2002b) found increased jump performance and knee strength after vibration training, whereas De Ruiter and colleagues did not (de Ruiter, et al., 2002, 2003). Other evidence (Cardinale and Wakeling, 2005; Rittweger, 2010), suggest that without a common framework of vibration training namely controlling the variables that are known to influence the outcome of the vibration training, comparisons are difficult. In addition, there is also evidence that vibration training decreases muscle performance and tactile perception (Desmedt and Godaux, 1978). To understand the manner in which vibrations affects different organs and organs systems within the body, it is necessary to delve into the physics and mechanics of vibration transmission throughout the body. Namely, the manner in which the application of a vibration stimulus at the feet will affect organs and organ systems will depend on the transmission of this energy throughout the body, or rather the resultant vibration imposed on the tissues within the body.

2.4.1.1 Physiology of whole-body vibration and its transmission

Muscle contraction is a very complex process which involves the interaction of many signal pathways, both chemical and mechanical. It begins with a neural signal from the motor cortex, which triggers the release of acetylcholine at the neuromuscular junction. This depolarizes the muscle fibre, leading to calcium release from the sarcoplasmic reticulum. Calcium binds to troponin, activating the cross-bridge cycle between actin and myosin, resulting in muscle contraction (Figure 5).

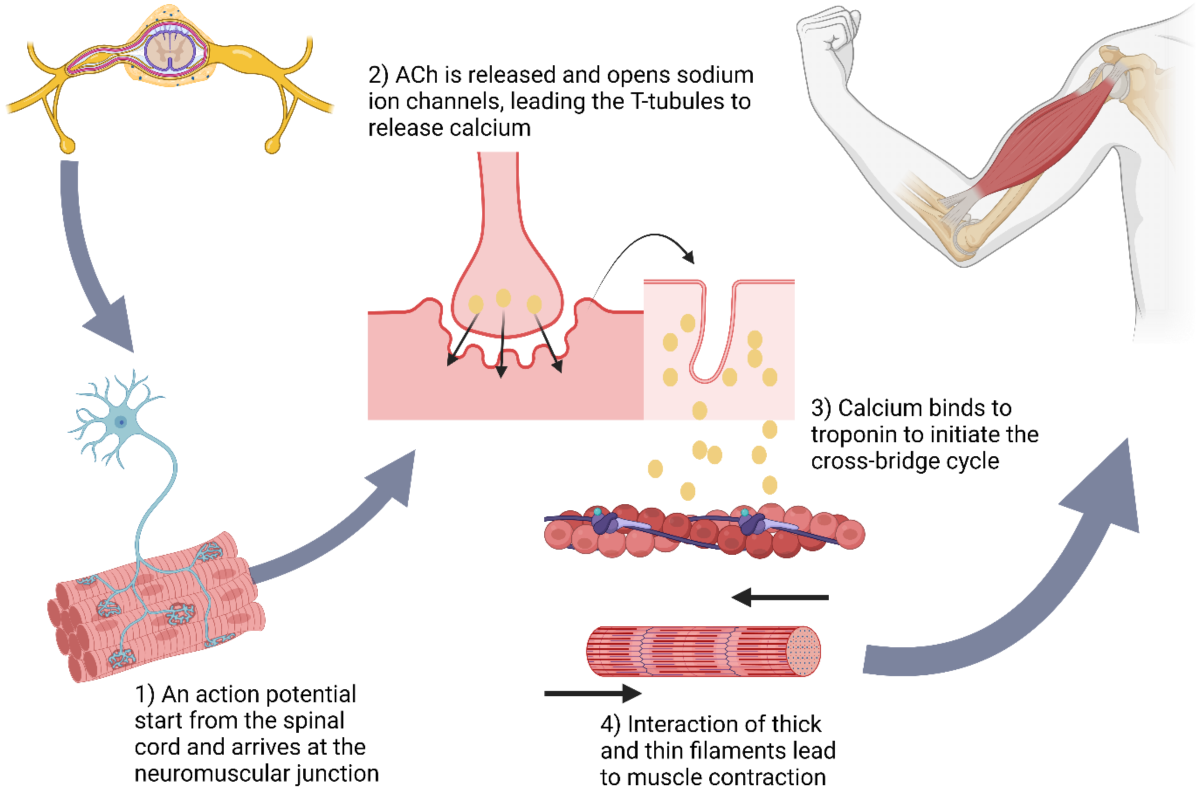

Figure 5: Diagrammatic representation of muscular contraction mechanism.

According to some evidence, vibration is meant to enhance muscular activation, however, the exact process of how and why this happens remains unresolved. According to Bosco and colleagues (Bosco, et al., 2000), vibrations increase neuromuscular activation by inducing a “tonic vibration reflex”. The forces produced by vibrations stimulate the primary endings of the muscle spindles and excite the α-motor neurons which in response increase the recruitment of motor units, resulting in a tonic contraction. As a result, this was termed the “tonic vibration reflex” (Delecluse, Roelants, and Verschueren, 2003; Hammer, Linton, and Hammer, 2018; Hortobágyi, et al., 2015; Jordan, et al., 2010; Lamont, et al., 2011). It is very unlikely that such a reflex might represent a higher anabolic stimulus, either alone or with resistance exercise, in healthy individuals (Aagaard, et al., 2002; Celik, et al., 2022; Hammer, et al., 2018; Hortobágyi, et al., 2015). Nevertheless, it might be sufficient in rehabilitation and conditioning in the elderly or frail individuals with lower exercise capacity (Bemben, et al., 2018; Rittweger, 2010).

When employing vibration training, it is also important to control the actual transmission of the vibrations during the exercise. There is evidence that vibrations paired with efforts producing high ground-reaction forces can increase the risk of back pain (Spitzenpfeil and Mester, 1997; Supej and Ogrin, 2019; Supej, Ogrin, and Holmberg, 2018) and cause discomfort. Vibration transmission is a widely studied topic, as it is significantly influenced by various biomechanical and environmental factors. Kiiski and colleagues (Kiiski, et al., 2008) investigated the effects of different vertical vibration frequencies and amplitudes on vibration transmission across multiple body regions (ankle, knee, hip, and spine). Their findings indicated that these regions exhibit distinct responses to vibration frequency. At frequencies beyond 10–40 Hz, the transmitted vibration power decreased to approximately 1/10th to 1/1000th of the peak power delivered by the platform, highlighting the body's ability to attenuate vibratory forces. Munera and colleagues (Munera, et al., 2016) reported that body position, whether static or dynamic, significantly influences vibration transmission by either amplifying or attenuating its effects. For instance, increased flexion at the knee and hip joints reduced vibration transmission to the hip and dynamic squats further attenuate transmission, indicating a greater protective effect compared to static postures. These results are strongly supported by other studies, further emphasizing the importance of posture in vibration-based interventions. (Caryn and Dickey, 2019; Marín, et al., 2009; Nawayseh, 2019; Pel, et al., 2009; Pollock, et al., 2010; Spain, et al., 2020; Tankisheva, et al., 2013; Zaidell, et al., 2019). In addition, it was demonstrated that external material, such as clothing or other equipment can influence vibration transmission (Marín, et al., 2009). Active movement involving joint flexion is the most effective strategy for dampening vibration transmission (Sorrentino, et al., 2025). This mechanism enhances the tolerability of resistive vibration exercise compared to vibration training alone. Similar observations were reported in a recent bed-rest study (Rittweger, et al., 2006).

The long-term efficacy of vibration training remains a topic of debate. While its benefits for bone health in elderly and frail populations are well-supported in the literature, its impact on muscle structure and function is less conclusive. This uncertainty is particularly evident in studies involving healthy and athletic individuals, where findings are inconsistent and often conflicting. Moreover, it is not known how the body would respond to daily whole-body vibrations (WBV), should this be implemented as a countermeasure in future space mission. Especially considering that vibrations also affect the circulation and histamine release. The European Space Agency has initiated a programme of research that is assessing the contribution of artificial gravity in enhancing the outcome of exercise. With regards to a countermeasure that would combine resistance vibration exercise and artificial gravity, the outcome of the training may be influenced by muscle perfusion and motion sickness, or rather the effects on the circulation and histamine release, respectively.

2.4.2 Artificial gravity

The concept of employing artificial gravity as a means to counteract human physiological adaptations to microgravity during space exploration has been a subject of scientific discussion for nearly a century. One of the earliest proposals was put forth by Herman Potočnik Noordung in 1929 in his seminal work, “The Problem of Space Travel” (Noordung, 1929). Potočnik hypothesized that artificial gravity could be generated through a rotating spacecraft, where centrifugal forces at the periphery would simulate Earth-like gravitational conditions for astronauts. While it is technically feasible to build such spacecraft today, significant engineering and cost-related challenges have so far prevented serious pursuit of these projects. In recent years, advancements in engineering have led to the development of smaller-scale systems based on the same physical principles. These systems utilize a rotating central pillar to generate centrifugal forces, thereby inducing artificial gravity at the extremities of the rotating arms, or nacelles. These devices are called "*human centrifuges*". Several trials have been conducted to develop a device capable of generating artificial gravity. A more recent study examined the ground-reaction forces of squat exercises performed on a human-powered centrifuge in comparison to traditional upright exercises. (Yang, et al., 2007). However, these devices were considered impractical, especially, and further development was abandoned.

Currently, two different systems exist: *long-arm human centrifuges* (LAHC) and *short-arm human centrifuges* (SAHC). LAHCs are commonly employed to train pilots, especially military pilots, to withstand the high g-forces experienced during flights. Conversely, SAHCs are being evaluated as a potential countermeasure.

2.4.2.1 Short-arm human centrifugation

The first deliberations regarding short-arm human centrifuges date to 1980 (Vil'-Vil'iams and Shul'zhenko, 1980). From 1994, the interest in SAHCs increased substantially with a major focus on the human cardiovascular responses (Vil'-Vil'iams, 1980; Vil'-Vil'iams and Shul'zhenko, 1980; Yajima, et al., 1994). In recent years, the focus of studies has shifted towards the effectiveness of SAHC exercise on the musculoskeletal system (Frett, et al., 2022; Kramer, et al., 2020).

Modern motor-powered centrifuges operate using a motor that drives the rotation of a central pillar, generating artificial gravity (AG) at the end of the nacelle. By adjusting the rotational speed, the G-force experienced by participants can be increased or decreased accordingly. The key physical distinction between long-arm human centrifuges (LAHCs) and short-arm human centrifuges (SAHCs), as their names suggest, lies in the length of the arm. This difference influences their functionality and the way the load is administered. In LAHCs, the gravitational load is evenly distributed across the participant's body, and they typically maintain a seated or partially inclined position. In SAHCs, the load is not constant but gradually increases toward the end of the nacelle. Moreover, participants in SAHCs are generally positioned in a supine posture, with their heads closer to the central pillar. This results in participants experiencing the lowest g-force generated at the head and the highest at the feet (Clément, 2011; Clément and Traon, 2004; Sorrentino, et al., 2024).

As previously mentioned, the earliest evidence of SAHC applications pertains to cardiovascular responses (Vil'-Vil'iams and Shul'zhenko, 1980). Even today, the majority of SAHC applications and significant findings stem from research on the cardiovascular system. For example, Goswami and colleagues (Goswami, et al., 2015) found that passive centrifugation with 0.75 g at heart level, provides similar cardiovascular responses to standing. Verma and colleagues obtained similar results (Verma, et al., 2018), observing that centrifugation at 2g at the feet elicited cardiovascular responses comparable to those in a standing position. However, when a centrifuge was used as a countermeasure in a bed rest study, it proved ineffective in maintaining aerobic exercise capacity and overall cardiovascular conditioning, instead, it primarily helped mitigate muscle strength loss (Kramer, et al., 2021). Increase of cardiac output, heart rate and decrease in muscle oxygenation in patient with multiple sclerosis, were observed in a recent study (Kourtidou-Papadeli, et al., 2022), suggesting the potential benefits of SAHC exercise also as therapy for some patients.

Centrifugation alone, though providing some degree of stimulus to the cardiovascular and musculoskeletal system, might not be sufficient in mitigating muscle and bone loss when applied on participants with a high degree of physical conditioning (Clément, et al., 2022; Kramer, et al., 2021; Kramer, et al., 2020). In contrast, there is mounting evidence that the outcome of artificial gravity is much more favourable, when exercise is conducted during the centrifugation. Trunk exercise performed while exposed to artificial gravity on the SAHC inducing a ground reaction force of 1g at the feet promoted comparable muscular activation as the same exercise conducted in an upright posture, thus exposed to the same head-to-foot acceleration as on the SAHC Many studies investigated the efficacy of pairing exercise and centrifugation (Frett, et al., 2022). Rowing exercise during centrifugation produced higher mean and peak ground reaction forces compared to ground rowing (Frett, et al., 2024). Pairing centrifugation with jump exercise was also demonstrated to be a feasible exercise (Frett, et al., 2020), however due to technical characteristics of the centrifuge, it results in reduced peak forces and prolonged ground contact compared to upright jumping (Kramer, et al., 2020). Finally, a study from Piotrowski and colleagues (Piotrowski, Rittweger, and Zange, 2018) reported that squat exercise performed on a SAHC was metabolically more challenging compared to upright squat.

The possibility of SAHCs targeting multiple physiological systems makes their application as a countermeasure highly promising.

Chapter 3

Comparison of Joint Kinematics Between Upright Front Squat Exercise and Horizontal Squat Exercise Performed on a Short Arm Human Centrifugation[2]

> *“To understand a thing is to understand the limits beyond it becomes something else”*
>
> *(Frank Herbert)*[3]

3.1 Foreword

New generation short arm human centrifuges (SAHC) allow participants to perform exercise during centrifugation (Frett, et al., 2014, 2022, 2024; Kramer, et al., 2012, 2017). The majority of exercises primarily target the lower limbs, as they are the most responsive to changes in gravitational stimuli and are particularly susceptible to deconditioning when this stimulus is absent, as described in Chapter 2. One of the latest advancements in centrifuge design is the integration of a two-axis sled system. This system enables the cradle to facilitate hip flexion-extension alongside knee and ankle flexion-extension (Figure 6). The structure of this system makes the movement more comparable to a squat than a leg press (Sorrentino, et al., 2024). The key distinction lies in the muscles recruited, as the leg press does not involve hip flexion-extension, which engages the hip musculature, gluteus, and abdominal muscles—critical for posture control. Existing literature offers limited insights into resistance exercise kinematics during centrifugation, with evidence focusing on fixed sled systems (Duda, Jarchow, and Young, 2012; Piotrowski, et al., 2018). To explore the application of these centrifuges, this study examined knee and hip kinematics during an upright front squat compared to a front squat

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[2] **Sorrentino R.G.**, Avila-Mirèles E., Babič J., Supej M., Mekjavic I.B., McDonnell A.C. (2024). Comparison of joint kinematics between upright front squat exercise and horizontal squat exercise performed on a short arm human centrifugation. Physiological Reports, 12.

[3] Frank Herbert “Dune”, 1965, Chilton Books : UK

performed in the centrifuge. Additionally, it assessed whether participants with no prior centrifugation experience could improve their movement kinematics within a single session.

3.2 Introduction

Astronauts participate in tailored exercise programs before, during and after spaceflight (Korth, 2015; Loehr, et al., 2015). Prior to missions, the exercise programme maintains their physical fitness, whereas during spaceflight the aim of the daily exercise programme is to mitigate the adaptation of the musculoskeletal and cardiovascular systems to weightlessness. Since exercise as a countermeasure to mitigate the deconditioning that occurs during longer sojourns in weightlessness is only been partially effective, exercise is also part of the astronauts' rehabilitation programme upon return to Earth. The implementation of exercise countermeasures on the International Space Station (ISS) has reduced, but not eliminated, the loss of muscle and bone mass (Stavnichuk, et al., 2020). The efficacy of the current exercise strategy on the ISS may not be optimal for deep space missions, and thus new concepts are being investigated. During future Mars and Moon missions, astronauts will be exposed to less than 0.5 g for 493 and 180 days, respectively (Winnard, et al., 2019). Implementing a strategy that could combine exercise with artificial gravity established with SAHC in future space habitats might provide an efficient countermeasure against microgravity-induced adaptations.

The possibility of creating and utilising artificial gravity (AG), an idea proposed by Herman Potočnik Noordung (1929), is being assessed as a potential countermeasure. Whereas Noordung (1929) proposed a rotating space station that would establish Earth's gravity at the perimeter of the circular station, the current strategy is to use short arm human centrifuges (SAHC) with radii varying from 2 to 5 m, to expose astronauts to artificial gravity for short durations daily (Clément, 2011; Clément, Paloski, et al., 2016; Frett, et al., 2014). Three strategies incorporating AG are currently being investigated by the European Space Agency (ESA). The first entails passive exposure to AG, and the remaining two incorporate either aerobic (Yang, et al., 2010) or strength (Yang, et al., 2007) exercise during exposure to AG. The unique feature of conducting exercise on a SAHC, is that it allows targeting all physiological systems during one exposure (Goswami, et al., 2015; Laing, et al., 2020; Yang, et al., 2010), instead of relying on several exercise devices. Centrifugation per se initiates cardiovascular responses akin to those observed in the upright position (Goswami, et al., 2015; Verma, et al., 2018). During squat exercise on the SAHC the acceleration vector acting on the body increases linearly from the axis of rotation, so that a participant lying on a SAHC with distal to the central axis, will experience more force at the feet than on the upper body. Furthermore, squat exercise on the SAHC compared to upright squat exercise, may be biomechanically different, resulting in different pattern of muscle activation. Yang et al. (2007) have reported that it is possible to generate high ground reaction forces (GRF) during squat exercise performed on a centrifuge compared to the GRF generated during upright exercise. This study demonstrated that both technique and muscular activation are similar between the two conditions. However, this study used a human-powered centrifuge, which is markedly different from motor-powered centrifuges, particularly short arm human centrifuges (SAHC). A more recent study (Duda, Jarchow, and Young, 2012) investigated squat biomechanics performed on a SAHC and reported that centrifugation increases mediolateral knee travel (MLKT), but confirmed that an exercise protocol can be completed. Piotrowski et al. (2018) compared the metabolic cost of upright squats and squats performed on a SAHC and reported that squats performed on the SAHC had a lower oxygen uptake, which they attributed to diminished activation of trunk muscles as participants were positioned supine on the sled, thereby avoiding the need for torso stabilization.

The SAHC utilized in these and numerous prior investigations employed a one-axis sled configuration, enabling movement solely along the frontal plane. Recently developed iterations of the SAHC feature an advanced 2-axes sled system, distinguished by its additional rotational capability within the frontal plane. Such a system allows the engagement of hip movement (flexion/extension), which enables the squat on the SAHC to better mimic the conventional squat rather than a leg press. This feature holds significant implications for astronauts, as conventional leg press exercises and single-axis sled systems typically restrict hip movement, resulting in isolation of leg muscles without engagement of the hip and abdominal musculature. Consequently, crucial stabilizing muscles of the hip and abdomen, which play a pivotal role in maintaining proper posture and are subjected to significant adaptations in microgravity environments, remain underutilized. The recruitment of these muscles as part of the countermeasure exercise would therefore be beneficial (Qaisar, et al., 2020; Vandenburgh, et al., 1999).

For this reason, the aims of the present study were: i) to assess the feasibility of conducting squat exercise on the SAHC with the novel 2-axes sled system allowing flexion/extension of the hip joint, ii) compare the kinematics of squat exercise performed on the SAHC with that of upright squat exercise, conducted at the same GRF, iii) assess the magnitude of adaptation that occurs when performing squat exercise on the SAHC during one training session.

3.3 Methods

The study was conducted at the European Space Agency (ESA) ground-based facility PlanHab (Rateče-Planica, Slovenia), which maintains ESA's SAHC (Fig. 1). The SAHC (Qinetiq, Belgium, now acquired by Redwire, Antwerp, Belgium) has two nacelles, one for the participant, and another acting as a counterweight. The SAHC nacelle cradle comprises side mounting blocks affixed on a sliding rail and a cushioned back board that provides support from the coccyx to the head. The unique feature of this cradle is that it rotates around the mounting block allowing for movement in both the horizontal and vertical direction (AMST, Austria). For this reason, this system is referred to as the 2-axis sled. The participant is positioned supine on the sled, and during centrifugation little input is required from the participant to maintain balance, however, when initiating a squat movement, the vertical displacement (up to 45°) allows the participants to flex their hips in a motion that would not be possible on a fixed sled. Fig. 6 illustrates the manner in which the subjects were able to conduct horizontal front squat exercise on the SAHC, mimicking the squat exercise conducted in the upright position.

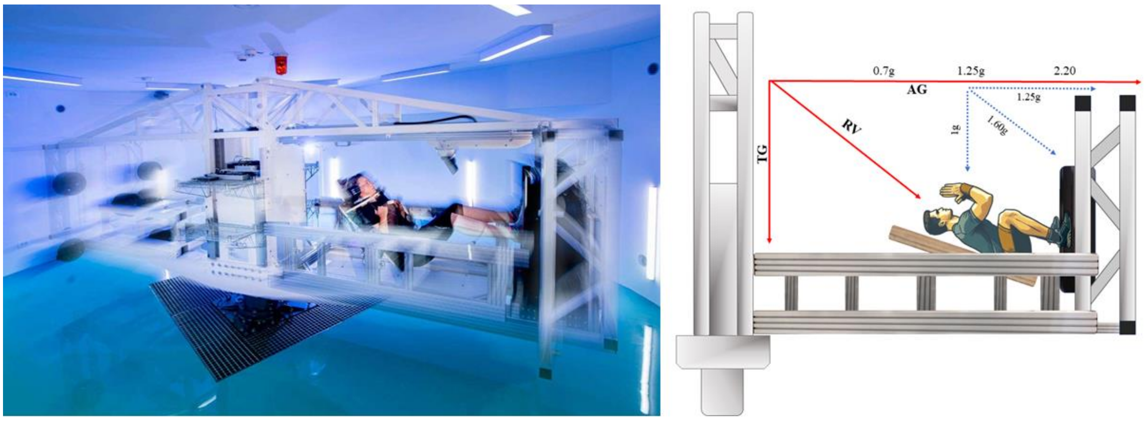


Figure 6: Left panel: European Space Agency (ESA) Short Arm Human Centrifuge (SAHC) in motion (photo credit: K. Bidovec and A. Hodalic). The SAHC has two nacelles. One for the participant and the other for the counterweights. The participant is positioned with the feet on a platform, which can be activated to provide vibration. The unique feature of the SAHC is the sliding gurney on which the subject is positioned. It allows for squats to be performed simulating upright squat exercise. Specifically, the swivel at the centre of mass allows hip flexion and extension during the squat exercise. Right panel: Establishing a ground reaction force of 2.2 g

at the feet (B) would result in a linear decrease in acceleration towards the head (see text for details). During the squat manoeuvre, the gravito-inertial force on the subject (resultant vector, RV) will be the result of the terrestrial gravity (TG) and artificial gravity (AG).

3.3.1 Participants

Healthy male subjects (N=12) participated in the study. Their mean ± SD age was 22.7±1.7 years, weight was 83.3±6.1 kg, and height was 183.1±6.1 cm. All participants met the inclusion criteria: age between 18 and 40, physical exercise at least thrice weekly, knowledge of how to perform squat exercise, non-smokers, height less than 195 cm and weight less than 95 kg. The latter two constraints were due to technical reasons associated with the SAHC. The study protocol was approved by the University of Ljubljana, Faculty of Sports' Committee for Ethical issues in the field of sport (Reference number: 033-10/2023-2). All participants provided their written informed consent to participate in the study, which was performed according to the guidelines of the Declaration of Helsinki, excluding clause 35 (i.e., the study was not registered in a publicly accessible database). A certified strength and conditioning coach gave final approval for participation of subjects in the study, once they were deemed capable of performing a front squat according to the criteria of Kritz et al. (Kritz, Cronin, and Hume, 2009). Specifically, the participants had to be capable of executing the squat movement by reaching a peak knee flexion of 90° while maintaining neutral (upright) spine position. The participants wore gym clothes and shoes sports clothing and footwear for this initial assessment and throughout testing.

3.3.2 Experimental protocol

The participants were requested to perform front squats in two exercise settings: 1) conventional upright squats (PRE and POST) and 2) squats on the SAHC under AG loading. The front squat was the chosen exercise instead of a back squat as this may more accurately simulate the position maintained by the participants during squatting on the centrifuge. Based on the guidelines set out by Myer et al. (Myer, et al., 2014) and Yavuz et al. (Yavuz, et al., 2015) the back squat allows further thoracic lean than that noted in the FS variant. This reduced lean is similar to that noted in novice users of the centrifuge and therefore a kinematic comparison between the two exercise modalities may be valid.

In each setting, the participants performed 3 sets of 6 squats with 1 minute of rest between sets under two different loads. The loads were either body weight (BW) or BW + 25 %. In the AG setting these loads corresponded to 1g or 1.25g at the centre of mass (COM). BW and BW+25 % from heretofore will be referred to as 1g and 1.25g Participants first conducted the exercise in an upright position (PRE), followed by squatting on the centrifuge (AG) and finally repeated the squats in an upright position after centrifugation (POST). There was a five-minute break between the exercise settings to allow the researchers to install the participant onto the centrifuge and remove them following AG. The conventional upright squat exercise was performed using a squat rack and barbell in a room adjacent to the SAHC, which minimised the transfer time between the exercise settings.

The order of exercise was always the same, however, the application of load was randomised in the PRE trials and then kept constant in the following conditions (AG and POST).

Once instrumented the participants performed 3 series of 6 squats with 2 minutes of rest in between, both unloaded (bodyweight squat) and loaded (1.25 x body weight achieved with a barbell) for a total of 36 repetitions of terrestrial squats before the exercise on the SAHC. This protocol was chosen because optimal squats were required for the analysis to have proper squat kinematics and fatigue needed to be avoided. Fatigue was monitored with the Borg scale for subjective ratings of perceived exertion (RPE). The pace of 3s per squat cycle (i.e., the down and up phase combined), was provided by using a metronome with vocal cues. Participants were given specific instructions and verbal feedback during upright exercises. This feedback related to maintaining proper chest posture and a neutral spine alignment while performing the front squat. After completing PRE squats, the participant was secured to the centrifuge. The harness worn by the participant was secured to the centrifuge's frame to avoid the participant shifting towards the side of the sled during spinning. Once centrifugation was initiated, one minute was required to reach the target acceleration in the head-to-foot direction of 1g, at which point the squat exercise commenced. During AG, participants were instructed to maintain a pace similar to that of upright exercise. Purposely, neither metronomes nor verbal cues were employed, as one of the study's objectives was to examine the performance of new users executing front squats on the centrifuge and to discern potential movement adaptations. Verbal cues and instructions were only provided in instances when the observed squat manoeuvre was inappropriate. During the trials the participants rested for 2 minutes between sets. After completing the 1g set on the SAHC (AG trial), the speed of the centrifuge speed was increased to simulate 1.25g. This process took one minute and after reaching the proper ground reaction force (GRF) of 1.25.

Upon completion of the AG trial, subjects performed repeated the same protocol in the upright position (POST trial).

The participants were equipped with a head-set and microphone on the SAHC, which provided continuous communication with the lead researcher during centrifugation. The foot board and thus the participants' feet were 2.4m from the centre of rotation of the SAHC and were spaced ~45 cm apart.

In order to generate the required loading, the SAHC was spun at an individualised speed, which was based on the height of each participant's COM and its distance from the central motor. The speed of rotation was then altered to provide a load of 1g and 1.25g.

3.3.3 Kinematics assessment

A wearable wireless motion capture system (MVN Awinda, Xsens, Enschede, Netherlands) was used to capture the participants movement during squatting. Data was sampled at 60 Hz. A full body configuration was used. Prior to the attachment of the sensors, pre-recorded anatomical measurements obtained from each participant were registered in the software. These anatomical measurements were height, shoulder height and width, elbow dimensions, wrist dimensions, arm span, hip dimensions, as well as knee and ankle measurements. The placement, orientation, and positioning of sensors were established according to the guidelines specified by the manufacturer and validated in prior research studies (see Appendix B, B1) (Schepers, Giuberti, and Bellusci, 2018). Subsequently, each participant underwent sensor calibration. The calibration procedure involved maintaining an upright standing posture with relaxed arms extended straight alongside the trunk with palms of the hands parallel to the thighs, followed by walking forward, returning to the initial position, and maintaining the original posture. If the software deemed the calibration satisfactory, the participant proceeded with the experiment; otherwise, the calibration process was repeated until it was deemed acceptable. The participants' movement data for the knee and hip angles were exported for further analysis. Participants were instrumented with 15 sensors, which were secured with Velcro® straps on specific anatomical locations. Single sensors were placed on the sternum, at the back of the head and on the lower back. Paired sensors were strapped on the scapula, at the base of the deltoids, wrists, on the vastus lateralis, on the surface of the shins and feet.

The Xsens MVN Awinda Analyze system was used to record the participants' movement and to extrapolate knee and hip flexion/extension angles. Data was sampled at 60 Hz. A full body configuration was used.

3.3.4 Data analysis

Four joints were chosen for the analysis, i.e., right/left hip and right/left knee. The minimum (MIN) and maximum flexion (MAX) and range of motion (ROM) i.e., the range of joint movement from the maximum to the minimum flexion point, were analysed for both the participants knee and hip joints during the squatting exercise. Initial analyses found no difference between the right and left selected joints and as such the data was combined and presented as simply knees and hips. Minimum flexion was defined as the angle when the participant was fully extended, and just prior to the onset of the down-phase of the FS. Maximum flexion was defined as the angle when participants reached the bottom position of the FS, and just prior to the up-phase of the FS. Data comparisons was performed between three conditions: front squats before centrifugation (PRE), front squats on the centrifuge (AG) and front squats after centrifugation (POST). To investigate the mediolateral knee travel, only the MAX was taken as value. Single joint data are available in the Supplementary data.

The first and the last repetition of the middle set was discarded and thereafter the average of the remaining repetitions (the middle sets under each load with 4 repetitions per set) were taken into account. These combined average values were then utilised for the subsequent statistical analyses. The selection of repetitions as described ensures a good degree of data analysis reliability for kinematic investigations, in accordance with previous literature findings (Frykberg, Grip, and Murphy, 2021). Data comparisons were performed between three exercise settings (PRE, AG and POST). All data were tested for normality distribution with a Shapiro-Wilk test due to the sample size.

The kinematic characteristics of both TS and AG exercises and the impact of varying loads were compared with a two-way repeated measures ANOVA. This analysis incorporated two factors: exercise (conditions: PRE, AG, POST) and load (loads: 1-1.25 g). Statistical significance for which the hypothesis would be accepted was set a priori as $p < 0.05$. Tukey's post hoc test was performed if a main effect was identified among the condition x load interaction and/ or its singular components.

A two-tailed paired t-test was performed between the first and the last repetition performed on the centrifuge; for this analysis, only the first and the last repetition of the full centrifugation session were analysed regardless of the load (1g and 1.25g). When an adaptation was observed, an additional 2-way repeated measures ANOVA was performed specifically within the AG session. This analysis considered the variables of repetitions (timepoint: first and last), and load levels (load: 1 to 1.25 g), in order to examine the precise location at which the adaptation took place. An analysis of effect size was also conducted using Hedges' G test. Given the relatively small sample size in this study (less than 20), this approach was chosen to mitigate potential bias, with the incorporation of a correction factor (Sullivan and Feinn, 2012). The statistical analysis and visual data representation was performed with GraphPad Prism 9 (Dotmatics) and Hedge'G calculations with a Microsoft Excel add in. Data comparisons were performed between three exercise settings (PRE, AG and POST). Moreover, whether an acute adaptation to centrifugation was evident was of interest and therefore a comparison was made between the very first squat on the centrifuge and the last squat for all mentioned parameters. Given that it was observed an acute adaptation within the centrifugation session, a 2/way ANOVA was performed between the first and last repetition in 1 and 1.25 g.

3.4 Results

All participants successfully completed all trials. During PRE and POST front squats, participants performed the exercise correctly, meeting the guidelines of a well-executed exercise (Kritz, et al., 2009).

3.4.1 Knee kinematics

No interaction of *load x condition* (F (2,22) = 1.002; p =0.38) was observed; however, a significant source of variation was identified within the *condition* factor (F (2,22) = 39.59; p < 0.001). The multiple comparison test revealed a decrease of knee range of motion (ROM) by 13% during the exercise on the AG with a GRF of 1g, compared to both PRE (G = -1.60; p < 0.001) and POST (G = -1.46; p < 0.001) trials during which the subjects were exposed to terrestrial gravity. A further reduction of 15% was observed in both PRE (G = -1.96; p < 0.001) and POST (G = -1.93; p <0.001) exposure states at 1.25g, when compared to the exercise performed at the same GFR (1.25 g) in the AG trial. This reduction in ROM is attributable to knees MAX flexion, given that for knees MIN flexion there were no statistically significant differences either for the main effect of *condition x load* (F (2,22) = 0.77; p = 0.47) or for its singular components (condition = F (2,22) = 0.33; p = 0.71; load = F (2,22) = 1; p =0.33; G = n.s.). On the contrary, the model for knees MAX reported no source of variation on *condition x load* interaction (F (2,22) = 1.65; p = 0.21), but on its singular components (condition = F (2,22) =28.61; p < 0.0001; load = F (2,22) = 8.99; p = 0.01) The multiple comparison test revealed a decrease of knee MAX flexion by 12% in AG compared to both PRE (G = -1.50; p < 0.001) and POST (G = -1.21; p < 0.001) exposure at terrestrial gravity (1g), and a further reduction of 16% in both PRE (G = -2.17; p < 0.001) and POST (G = -2.16; p < 0.001) at 1.25g, when compared to the exercise conducted at the same GRF during the AG trial. All multiple comparisons are depicted in Figure 7.

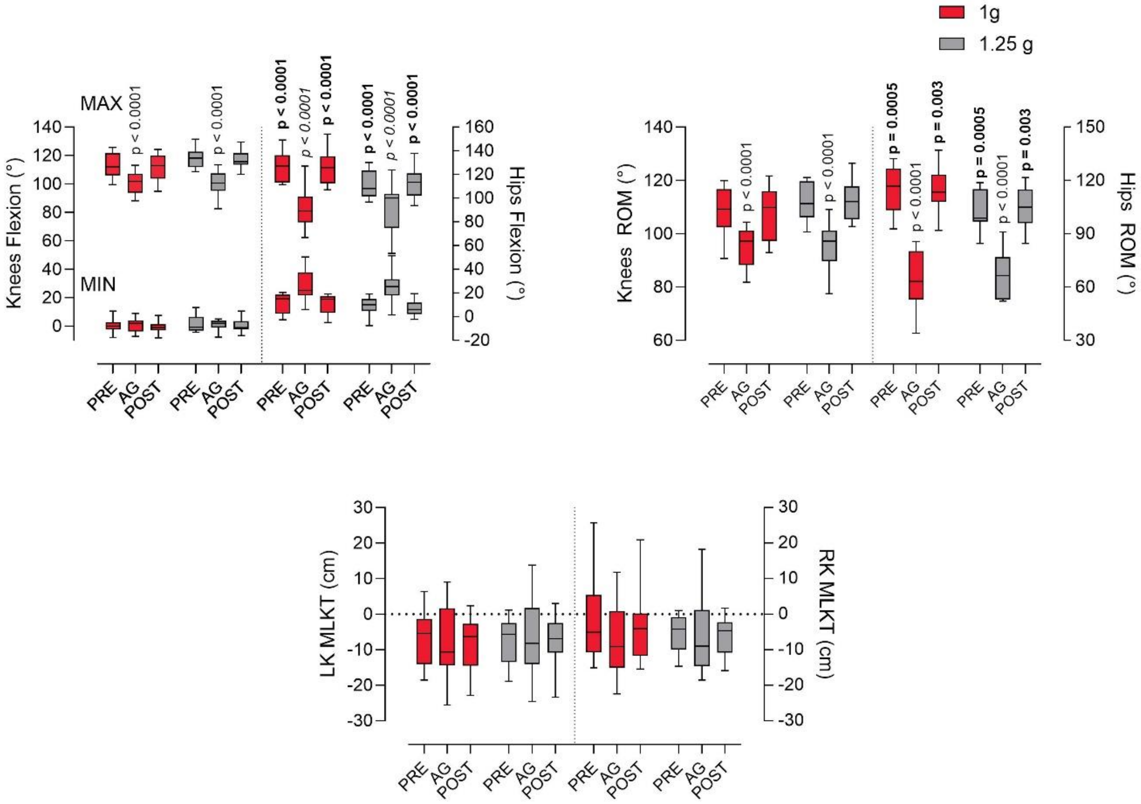


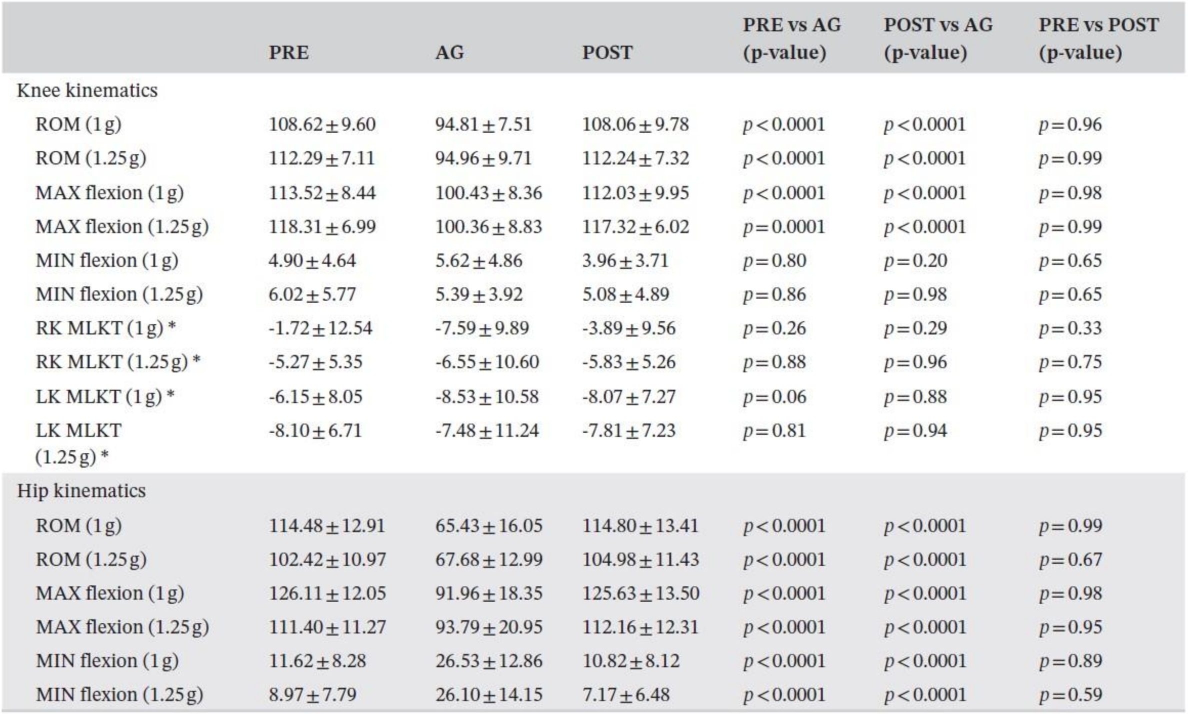
Figure 7: Minimum to maximum and mean values are represented in the box and whisker plots. Knees and hips flexion (top left panel) and range of motion (ROM, top right panel), and left (LK) and right knee (RK) medial lateral knee travel (MLKT) in trials conducted before (PRE), after (POST) and on the SAHC establishing a load at the center of mass (artificial gravity, AG) of 1.0g and 1.25g. For MLKT, a positive value signifies lateral knee deflection in the frontal

plane (outward), whereas a negative value signifies a medial deflection (inward). Regular font = differences between AG, and PRE and POST; bold font = indicates difference between loads in the same condition (PRE 1g vs. PRE 1.25g, and POST 1g vs. POST 1.25g); italic font = difference between AG, and PRE and POST for MIN flexion.

3.4.2 Hip kinematics

A statistically significant *condition x load* interaction was observed for the hip movements during the squat exercise (F (2,22) = 6.65; p = 0.005) as well on its singular components (*condition* = F (2,22) = 86.77; p < 0.0001; *load* = F (2,22) = 15.28; p = 0.002). Tukey's multiple comparisons test revealed a significant ROM decrement in AG of 42% compared to PRE (G = -3.25; p < 0.001) and POST (G = -3.23; p < 0.001) at 1 g, and of 33% compared to PRE (G = -2.78; p < 0.001) and POST (G = -2.94; p < 0.001) at 1.25. Moreover, a ROM reduction of 10 % occurred also between loads (1 g vs 1.25 g) in PRE (G = 1; p = 0.006) and POST (G = 0.78: p = 0.03).

Table 1: Kinematic data and multiple comparisons test results between conditions. All data are presented as: Mean± Standard deviation. Note: the asterisk (*) signifies that numbers are expressed as centimeters (cm) and not as degrees of flexion (°) as the other data.



	PRE	AG	POST	PRE vs AG (p-value)	POST vs AG (p-value)	PRE vs POST (p-value)
Knee kinematics						
ROM (1 g)	108.62 ± 9.60	94.81 ± 7.51	108.06 ± 9.78	$p < 0.0001$	$p < 0.0001$	$p = 0.96$
ROM (1.25 g)	112.29 ± 7.11	94.96 ± 9.71	112.24 ± 7.32	$p < 0.0001$	$p < 0.0001$	$p = 0.99$
MAX flexion (1 g)	113.52 ± 8.44	100.43 ± 8.36	112.03 ± 9.95	$p < 0.0001$	$p < 0.0001$	$p = 0.98$
MAX flexion (1.25 g)	118.31 ± 6.99	100.36 ± 8.83	117.32 ± 6.02	$p = 0.0001$	$p < 0.0001$	$p = 0.99$
MIN flexion (1 g)	4.90 ± 4.64	5.62 ± 4.86	3.96 ± 3.71	$p = 0.80$	$p = 0.20$	$p = 0.65$
MIN flexion (1.25 g)	6.02 ± 5.77	5.39 ± 3.92	5.08 ± 4.89	$p = 0.86$	$p = 0.98$	$p = 0.65$
RK MLKT (1 g) *	-1.72 ± 12.54	-7.59 ± 9.89	-3.89 ± 9.56	$p = 0.26$	$p = 0.29$	$p = 0.33$
RK MLKT (1.25 g) *	-5.27 ± 5.35	-6.55 ± 10.60	-5.83 ± 5.26	$p = 0.88$	$p = 0.96$	$p = 0.75$
LK MLKT (1 g) *	-6.15 ± 8.05	-8.53 ± 10.58	-8.07 ± 7.27	$p = 0.06$	$p = 0.88$	$p = 0.95$
LK MLKT (1.25 g) *	-8.10 ± 6.71	-7.48 ± 11.24	-7.81 ± 7.23	$p = 0.81$	$p = 0.94$	$p = 0.95$
Hip kinematics						
ROM (1 g)	114.48 ± 12.91	65.43 ± 16.05	114.80 ± 13.41	$p < 0.0001$	$p < 0.0001$	$p = 0.99$
ROM (1.25 g)	102.42 ± 10.97	67.68 ± 12.99	104.98 ± 11.43	$p < 0.0001$	$p < 0.0001$	$p = 0.67$
MAX flexion (1 g)	126.11 ± 12.05	91.96 ± 18.35	125.63 ± 13.50	$p < 0.0001$	$p < 0.0001$	$p = 0.98$
MAX flexion (1.25 g)	111.40 ± 11.27	93.79 ± 20.95	112.16 ± 12.31	$p < 0.0001$	$p < 0.0001$	$p = 0.95$
MIN flexion (1 g)	11.62 ± 8.28	26.53 ± 12.86	10.82 ± 8.12	$p < 0.0001$	$p < 0.0001$	$p = 0.89$
MIN flexion (1.25 g)	8.97 ± 7.79	26.10 ± 14.15	7.17 ± 6.48	$p < 0.0001$	$p < 0.0001$	$p = 0.59$

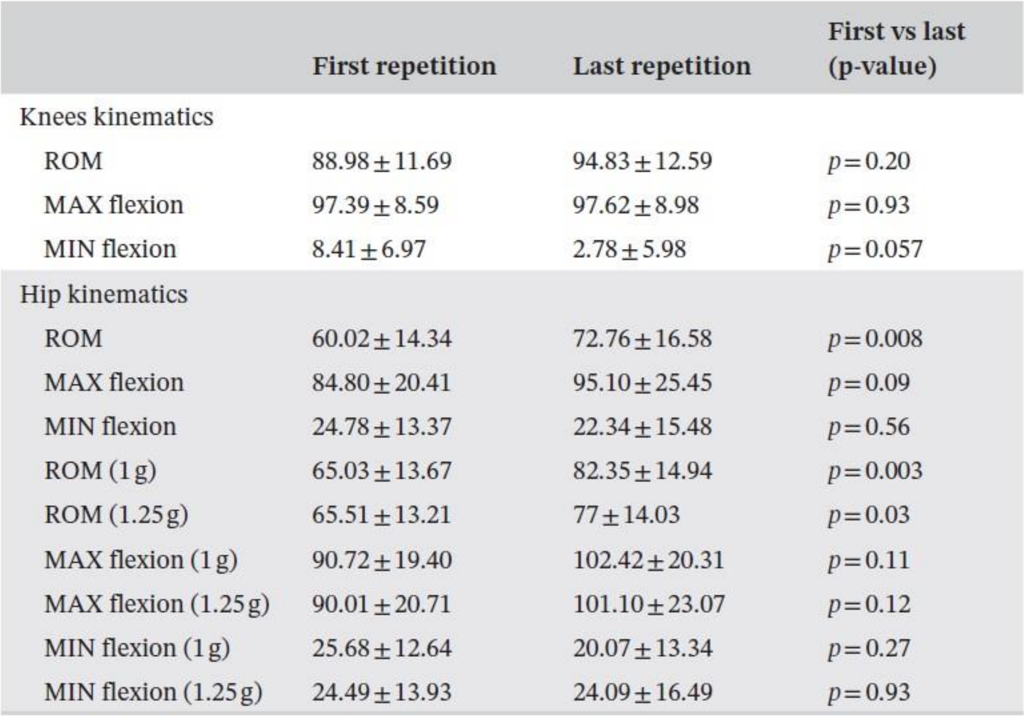
Unlike knees, hips ROM reduction is caused by both a reduction of hips MAX (*condition x load* = F (2,22) = 6.65; p = 0.005) and an increase of hips MIN (*condition* = F (2,22) = 0.82; p = 0.45). Tukey's post hoc analysis revealed a 27 % reduction of hips MAX in AG compared to PRE in 1 g (G = -2.12: p < 0.001) and POST (G = -2.01; p < 0.001) and of 15 % compared to PRE (G = -1.01; p < 0.001) and POST (G = -1.03; p <0.001) in 1.25 g. Hips MAX decreased of 13 % between loads within the same condition (1 g vs 1.25 g) both in PRE (G = 1.26; p = 0.003) and POST (G = 1.04: p = 0.009)

Hips MIN increased by 56% in AG compared to PRE (G = 1.33; p < 0.001) and POST (G = 1.41; p < 0.001) at 1 g, and by 65% at 1.25 g compared to PRE (G = 1.44; p < 0.001) and POST (G = 1.66; p < 0.001). No load effect was recorded for hips MIN.

3.4.3 Mediolateral knee travel

There was no main effect for either both knees (RK *condition x load* = F (2,22) = 0.19; p = 0.72; LK *condition x load* = F (2,22) = 2.41; p = 0.11), of for the singular components (*condition* and *load*). No differences were found between right and left knee during AG both in 1 and 1.25g. Moderate and small effect were recorded for RK in 1g for PRE (G = 0.51) and POST (G = 0.38).

Table 2: Acute adaptation kinematic data, t-test results and multiple comparisons results between conditions.



	First repetition	**Last repetition**	**First vs last (p-value)**
Knees kinematics			
ROM	88.98 ± 11.69	94.83 ± 12.59	$p=0.20$
MAX flexion	97.39 ± 8.59	97.62 ± 8.98	$p=0.93$
MIN flexion	8.41 ± 6.97	2.78 ± 5.98	$p=0.057$
Hip kinematics			
ROM	60.02 ± 14.34	72.76 ± 16.58	$p=0.008$
MAX flexion	84.80 ± 20.41	95.10 ± 25.45	$p=0.09$
MIN flexion	24.78 ± 13.37	22.34 ± 15.48	$p=0.56$
ROM (1 g)	65.03 ± 13.67	82.35 ± 14.94	$p=0.003$
ROM (1.25 g)	65.51 ± 13.21	77 ± 14.03	$p=0.03$
MAX flexion (1 g)	90.72 ± 19.40	102.42 ± 20.31	$p=0.11$
MAX flexion (1.25 g)	90.01 ± 20.71	101.10 ± 23.07	$p=0.12$
MIN flexion (1 g)	25.68 ± 12.64	20.07 ± 13.34	$p=0.27$
MIN flexion (1.25 g)	24.49 ± 13.93	24.09 ± 16.49	$p=0.93$

3.4.4 Acute adaptation

No significant differences between the first and the last repetition were observed through post-hoc analysis for knees ROM, MAX and MIN (Fig. 3). However, moderate to large effect sizes were recorded for knees MIN (G = 0.86) and knees ROM (G = 0.48). No significant differences were found for hips MAX and MIN, while a small effect size (G = 0.44) was observed for hips MAX. Hips ROM resulted to be higher during the last repetition compared to the first one of 17% (t =3.215, df = 11; p = 0.008).

With regards to hips acute adaptation, Tukey's post hoc analysis revealed no significant differences for MAX and MIN between first and last rep of both 1 and 1.25 g. A moderate effect (G = 0.58) was observed for hips MAX between the first and the last repetition in 1 g and a moderate effect (G = 0.50) for 1.25 g. A small effect was observed for hips MIN (G = 0.43) in 1g. On the contrary, hips ROM resulted to be 21% higher on the last compared to the first rep at 1g (G = 1.20; p = 0.003) and of 15% at 1.25 g (G = 0.84; p = 0.03). All data are depicted in Figure 8.

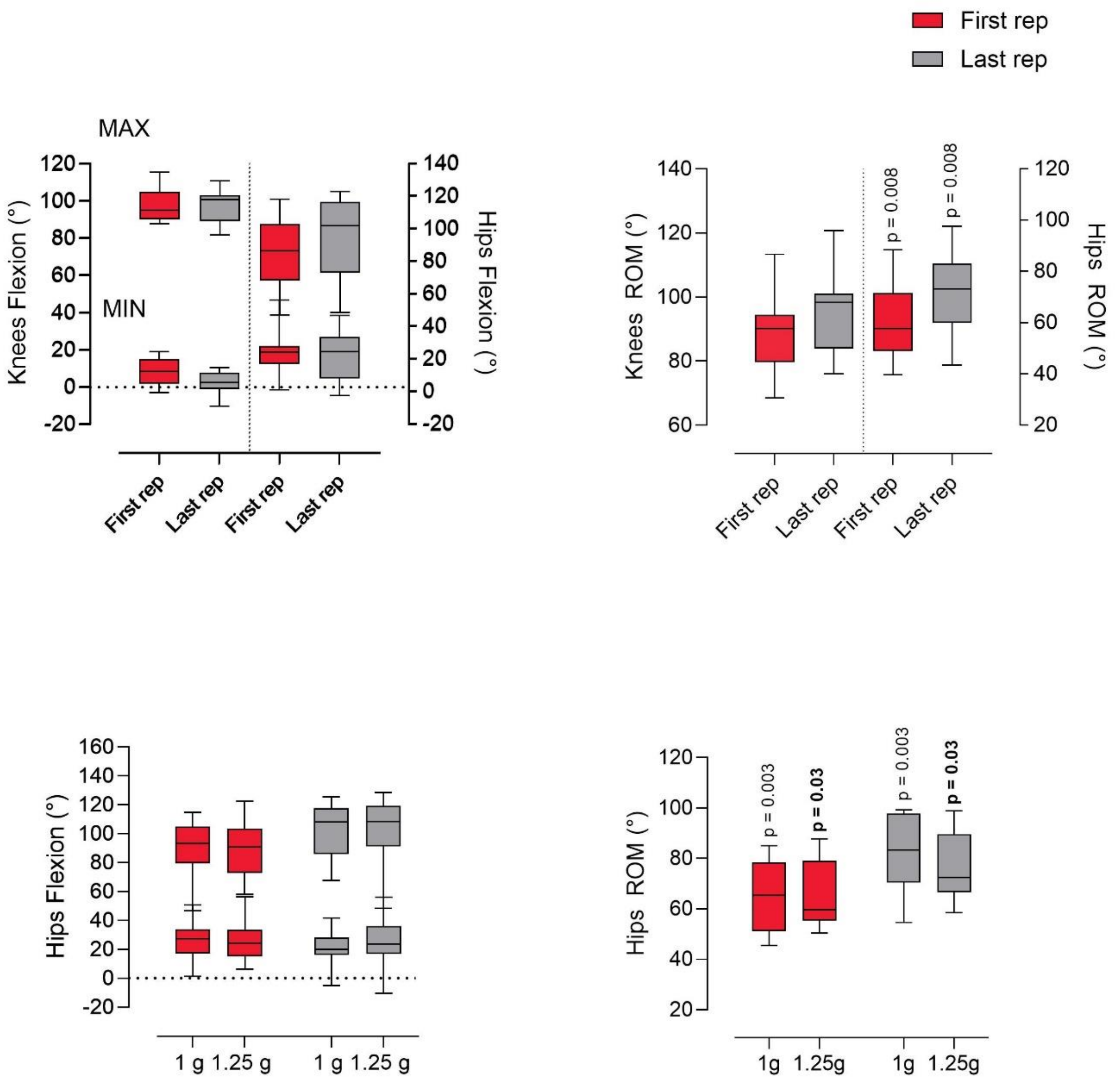


Figure 8: Minimum to maximum and mean values are represented in the box and whisker plots. Adaptation of knees and hips flexion (top left panel) and knees and hips range of motion (ROM, top right panel), as reflected in the difference between the first and last (rep) squat performed on the SAHC. Regular font = difference between the first and the last repetition. The lower panel presents the adaptation to the AG loads, specifically hips flexion (bottom left panel) and hips ROM (bottom right panel). Regular font = significant difference between first and last repetition at 1g; bold font = significant differences between first and last repetition at 1.25 g.

3.5 Discussion

The principal finding of the present study is that participants naïve to exercise on a short arm human centrifuge cannot replicate the kinematics of squat exercise performed in terrestrial settings, when the exercise is performed during AG on the SAHC. Moreover, a mild adaptation process occurs already within a single centrifugation session.

3.5.1 Kinematic response to centrifugation

During traditional front squats all participants conformed to the observed kinematics of a conventional squat movement, as documented in prior studies (Gullett, et al., 2009; Kritz, et al., 2009). The front squat exercise was selected in this study, because it is a multi-joint movement producing substantial internal forces, which has the potential to mitigate the muscle atrophy experienced by astronauts when conducted on regular basis in reduced gravity environments (Escamilla, 2001; Escamilla, et al., 1998, 2001). Compared to other well-established lower limb exercises, such as the leg press, the squat elicits higher levels of muscular activity and places increased stress on the knee joint (Escamilla, 2001). Furthermore, the squat necessitates the engagement of hip stabilization muscles and the posterior chain to a greater extent compared to the leg press.

In the context of the study, when participants repeated squats in AG, they were unable to replicate the movement pattern they exhibited during upright squats. Specifically, the ROM in both the hips and knees was found to be significantly reduced in AG. Upon further analysis of the ROM, which comprises maximum flexion (MAX) and minimum flexion (MIN), it was observed that the reduction in knee ROM occurred primarily at MAX flexion, while at MIN flexion, participants were able to fully extend their knees to the starting position with no discernible differences. The load did not have any effect on participants' response to centrifugation, since no differences were recorded between AG at 1 and 1.25 g.

In contrast, the reduction in hip ROM in the altered gravitational environment (AG) was attributed to a combination of decreased MAX and an increased in MIN. This reduction was the result of a failure to achieve complete flexion of hips as in TS and an inability to achieve full extension of the hips. Consequently, participants were unable to return their hips to a neutral position, resulting in each repetition starting from a partially flexed hip position. This adaptation can be explained by differences in the gravitational vectors exerting influence on the body during TS and in AG. In the context of TS exercises, whether loaded or unloaded, the sole acceleration vector impacting the participating subject is the unchanging force of Earth's gravity with or without the additional load.

Conversely, as described by Clement (Clément, 2011) and co-workers (Clément and Palowski, 2016), multiple acceleration vectors are present during centrifugation (see Fig. 6 on the SAHC: i) natural gravitational vector, ii) artificial gravity vector generated by the centrifugal force during the centrifugation, and iii) gravito-inertial force (GRIF) vector, which is the result of the interaction between the first and second vectors. The magnitude of this vector surpasses that of both vertical (natural gravitational vector) and horizontal vectors. The example in Fig. 6 presents a scenario of a participant lying supine on the SAHC with a rotational speed generating 1.25g at the Center of Gravity (COG), and 2.2g at the feet. The gravito-inertial force in this example amounts to 1.60g or 15.68 Newtons (N). The g_z values presented on the red arrow denote the gravitation load exerted on the participant in the supine position. During the down phase of the squat manoeuvre, the COG will move toward the feet, and the gravitational forces at the head and COG will increase. Thus, the dynamic interaction is not confined to a singular reference point; rather, at any point on the body, participants encounter a range of gravito-inertial forces throughout AG exercise. During the squat manoevre, the gravito-inertial force on the subject (resultant vector, RV) will be the result of the terrestrial gravity (TG) and artificial gravity (AG). The resultant vector (RV) generates a force that exerts a gravitational pull on the hips, a phenomenon distinctive to our experimental arrangement. Consequently, participants require multiple sessions to acquire the skill of activating their gluteal muscles in order to transition from a squatting position to a fully upright posture. The sled used in this study is similar to a system validated in previous research conducted under terrestrial conditions (Kramer, et al., 2012, 2017) and more recently within a centrifuge setting (Frett, et al., 2020). Such findings support the notion that this two-axis slide system enables the execution of jumping exercise, which involves the engagement of muscles activated during hip movement. It is important to note that an exact replication of the same movement could not be achieved, and kinematic distinctions were observed between exercises performed in the centrifuge and in the ground counterpart. The significance of utilizing a sled apparatus lies in its potential to engage a broader array of muscles during a single exercise.

The differences observed between TS and AG squats can be attributed to variations in the loads encountered by the participants. In TS, the load remains consistent throughout the entire range of motion, meaning that the load applied to the barbell during the squat remains constant and it is perceived by participants as such, during both the eccentric and concentric phases of the exercise. In contrast, during AG, there is a linear increase in acceleration along the length of the nacelle, minimal near the central rotor and maximal at the end of the nacelle. When a subject lies supine on the nacelle on the SAHC, the acceleration along the length of their body also increases linearly toward the feet. During the descent phase of the squat exercise on the SAHC, participants encounter an increasing load sensation. Conversely, during the ascent (concentric) phase of the squat, the load gradually diminishes, resulting in an actual and perceived reduced weight. In conventional upright squatting, biomechanical outcomes are influenced by variables such as the positioning of the barbell (high or low), the type of squat (front or back squat), the stance technique (wide or narrow) and the load. Therefore, the distinctly contrasting mechanics of load generation and perception during the ascending and descending phases of AG squats may play a contributory role in the modification of knee and hip kinematics when compared to those observed during TS squats. Given the low load of the exercise, it is unlikely that fatigue had an effect on the observed differences. As mentioned above, all participants were experienced in gym training, and the protocol was designed to minimize fatigue while providing a stimulus greater than body weight alone. Moreover, the rest intervals between sets and conditions were substantially longer than those typically recommended for resistance training with heavier loads. The highest reported rating of perceived exertion following an exercise, obtained with the Borg scale, was 12, indicating that the participants perceived the exercise to be light.

Our findings support those previously observed (Duda, Jarchow, and Young, 2012) that of an adaptation to centrifugation in a single artificial gravity (AG) set. Our data indicate that this adaptation extends beyond hip kinematics to include knee kinematics as well. Although no statistically significant differences were detected in knee kinematics, the effect sizes suggest an ongoing process of in the knees as well. It is possible that an additional set may have made these differences more evident.

3.5.2 Load effect

There was no effect of load on the kinematic outcomes for flexion-extension of knees (MAX, MIN and ROM between all conditions. In contrast, load influenced hip ROM and MAX flexion of PRE/POST squats, but not the AG squats.

Hip ROM and MAX flexion differences between PRE and POST squat loads can be explained by the increased load applied on the barbell. As reviewed by Schoenfeld (Schoenfeld, Ogborn, and Krieger, 2016), elevating the load within the range of 40-70% of the one-repetition maximum (1RM) prompts a greater degree of forward trunk inclination, and individuals with compromised hip mobility may exhibit diminished hip flexion mechanics. In the case of the front squat, where the load is positioned on the chest, this phenomenon becomes more pronounced in comparison to the back squat. Even loads below those recommended by Schoenfeld may accentuate restricted hip movement, given the heightened demand for flexibility in the posterior kinetic chain during front squats. It is worth noting that our study utilized only two loads. Future investigations should consider employing various levels of loading to assess whether differences emerge within AG at varying degrees of loads (i.e., 1.50 g, 1.75 g, etc.).

3.5.3 Mediolateral knee travel (MLKT)

This study investigated whether AG causes an increase in mediolateral knee travel (MLKT). Data were extrapolated within the same repetitions employed to investigate knee and hip movement. As pointed out by Duda (Duda, Jarchow, and Young, 2012) the knees internal deflection during the MLKT produce a torque, which can damage the knee joint, if repeated over a longer term. Continuous internal rotation or unwanted abduction of the knees can lead to long-term joint pathologies and the optimal kinematics would be to maintain a neutral position during squatting or jumping exercise (Han et al. 2013). The internal deflection of the knee is a problem during exercises involving lower limbs (Duda, Jarchow, and Young, 2012; Kramer, et al., 2020; Piotrowski, et al., 2018), especially during centrifugation. One of the main problems during centrifugation is represented by the Coriolis effect, which can exaggerate medial or lateral deflection of the knees during both the eccentric and concentric phases. In contrast to the findings of Duda (Duda, Jarchow, and Young, 2012), this study did not report any statistically significant differences in MLKT between conditions. Furthermore, no differences were observed between right and left knee in AG. A moderate and a small effect size between PRE/POST and AG were observed for RK only in 1 g. The disparities in findings between the current study and that of Duda (Duda, Jarchow, and Young, 2012) may be attributed to the differential cadence at which participants were instructed to perform squats. In the study of Duda, participants executed squats at a cadence of 2 seconds per repetition during upright and centrifugation squats. In the present study, participants were directed to adhere, as closely as possible, to the pace employed during the PRE and POST squats, which involved a descent and ascent phase of 3 seconds each. During AG squats, participants were allowed to perform squats at their preferred pace, resulting in a longer duration for each repetition of up to 6 seconds per repetition. The faster squatting pace in the study of Duda and colleagues may explain why they observed an increased mediolateral knee travel (MLKT) during AG squats, as higher speeds tend to amplify the Coriolis effect. The slower execution speed of squats in the current study could have contributed to enhanced control over knee positioning in relation to abduction/adduction movements during both descent and ascent phases, potentially preventing an escalation in MLKT when compared to PRE and POST front squats and decreasing the momentum.

3.5.4 Muscle activation

The goal of any exercise countermeasure is to induce sufficient activation of target skeletal muscles to mitigate the loss of muscle mass and function during space missions. The muscles of the thighs and calves are most affected by the inactivity/unloading experienced by astronauts on the International Space Station (Berg, et al., 2007; Clément, 2011), and by people involved in simulated microgravity environments (Berg, et al., 2007; McDonnell, et al., 2019; Pišot, et al., 2008) thus any exercise strategy should focus on these muscles. The difference in the kinematics observed between the PRE and AG conditions would suggest that SAHC with a 2-axes sled allows the performance of squat exercise safely, nevertheless, participants without any familiarization trials cannot recreate their upright front squat movement. This could result in a different pattern of muscle activation in AG compared to PRE and POST trials. Although, no data regarding muscle activation of the muscles involved in the exercise were recorded in this study. We suggest, in line with the findings that we have from upright typical squat and leg press exercise, that the squat, especially the front variant, is a superior exercise to elicit higher forces on lower limbs (Larsen, et al., 2022; Yavuz, et al., 2015). Furthermore, the squat necessitates the engagement of hip stabilization muscles and the posterior chain to a greater extent compared to the leg press (Schoenfeld, 2010). When coupled with the utilization of a SAHC featuring a 2-axes system, the effect of squat exercise on muscle activation may surpass those achievable with centrifuges employing only a single-axis system. Moreover, the gravito-inertial vector acting on the participant during AG squats most likely generates different torques on the joints between the two types of exercises and thus may result in differences in muscle activation.

3.6 Limitations and Future Perspectives

This is the first study monitoring the front squat exercise kinematics in a novel SAHC. In the present study, EMG data were not obtained, as the primary emphasis was on kinematics. Future investigations should contemplate the inclusion of EMG measurements during SAHC squats and their comparison with upright exercises to explore potential disparities in muscular activation and quantify such differences.

Chapter 4

Enhancement of Muscle Activation During Squat Exercise: Evaluation with Magnetic Resonance Imaging[4]

"Facts do not cease to exist because they are ignored"

(Aldous Huxley)[5]

4.1 Foreword

The consensus regarding the efficacy of vibration in promoting muscle use remains equivocal (Arora, et al., 2021; Artero, et al., 2012; Bemben, et al., 2018; Rittweger, 2010). Most studies investigating the effects of vibration on muscle activation use electromyography (EMG) which reflects neuromuscular activation (Di Giminiani, et al., 2015; Marín and Cochrane, 2021; Ritzmann, et al., 2010). Another factor of muscle activation is the accumulation of metabolites and water in the muscles. Metabolite accumulation during resistance exercise induces osmotic shifts, increasing intracellular and extracellular water in active muscles. This cellular hydration promotes anabolic signaling, including mTOR activation, growth hormone release and IGF-1 (DeFreitas, et al., 2011; Kirby and McCarthy, 2013; Roberts, et al., 2023; Schoenfeld, 2013). Muscle functional MRI (mfMRI) assesses muscle activity by measuring T2 relaxation time, which reflects the spin-spin decay of hydrogen nuclei in tissue water. Following a radiofrequency pulse, nuclei lose phase coherence, and this T2 signal increases with muscle activation, providing a non-invasive marker of muscular involvement. In MRI, T2 relaxation time reflects fluid shifts, intracellular acidification, and muscle recruitment, providing insight into metabolic and physiological changes (Cagnie, et al., 2011; Dickx, et al., 2010; Kinugasa, Kawakami, and Fukunaga, 2006; Shaikh, et al., 2023; Price, et al., 2003). It is generally thought that exercise promotes the accumulation of osmolytes (i.e., phosphates, lactate, sodium) in the cytoplasm and an influx of free-water in the active muscles which increase the volume of intracellular space. This results in a prolonged T2 following exercise, which is used as an indirect marker of muscle recruitment and workload (Cagnie, et al., 2011; Dickx, et al., 2010; Price, et al., 2003). For this reason, the following study aimed to provide insights about the of effects of WBV on T2

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[4] **Sorrentino, R.G.**, Vovk, A., Suput, D., Ioannou, L.G., Mekjavic, V., Fernandez-Gonzalo, R., Supej, M. & Mekjavic I.B. (2025). Enhancement of muscle activation during squat: evaluation with magnetic resonance imaging. European Journal of Applied Physiology (accepted pending revisions)

[5] Aldous Huxley, "Brave New World" 1932, Chatto & Windus Publisher: UK

relaxation time and acute metabolic responses from muscle rather than neuromuscular responses and compared it with an upright counterpart.

4.2 Introduction

Resistance exercise is considered the gold-standard for improving muscle structure and function (Aube, et al., 2022; Shaw, Shaw, and Brown, 2009). Enhancement of muscle activation by traditional exercises, such as squats, deadlifts and their variations, are well documented (Schoenfeld, et al., 2016). Performing consistent resistance exercise training, and consequently increasing muscle activation, promotes both neural and hormonal neuromuscular adaptations, concomitant with muscle hypertrophy (Paulsen, Myklestad, and Raastad, 2003), which eventually results in increased strength and muscle size (Del Balso and Cafarelli, 2007; DeFreitas, et al., 2011; Folland and Williams, 2007).

A variety of novel exercise modalities aimed at enhancing muscular training have been introduced and investigated, ranging from electrical stimulation (Doucet, Lam, and Griffin, 2012), blood flow restriction training (Lorenz, et al., 2021) and whole-body vibration (Rittweger, 2010). The latter consists of applying mechanical vibrations through a vibrating platform to the whole body, both with (Delecluse, et al., 2003) and without resistance exercise (Tankisheva, et al., 2013).

Evidence suggests that the stimuli generated by vibrations might increase neuromuscular activation, thus leading to enhanced muscle recruitment and potentially enhanced training adaptation (Hazell, et al., 2010; Marín, et al., 2015; Marín & Cochrane, 2021). However, the additional benefit of combining vibration with resistance exercise remains equivocal (Arora, et al., 2021; Artero, et al., 2012; Celik, et al., 2022). Methodological discrepancies, including variations in vibration type (vertical or rotational), intensity (frequencies and amplitudes), duration of exposure and population investigated, contribute to the lack of consensus in the literature, precluding definitive conclusions.

One of the main questions regarding whole-body vibration (WBV) is its effects on muscular activation. Several studies have investigated muscle activation following WBV protocol with electromyography (Di Giminiani, et al., 2013, 2015; Lienhard, et al., 2015; Cardinale & Lim, 2003). Concerns regarding EMG efficacy arise due to potential vibration interference with signal detection, addressable via bandpass filters (Pollock, et al., 2010) and also it is possible that the acute muscular activation is a reflex triggered by α and γ motor neurons which modulate muscle stiffness (Cardinale and Bosco, 2003; Celik, et al., 2022; Rittweger, 2020).

Magnetic resonance imaging (MRI) is widely regarded as a reliable technique for investigating muscle structure due to its ability to produce high-resolution images of muscle tissue. This non-invasive method offers detailed insights into muscle structure (Murphy, et al., 1986), activation patterns and alterations in response to exercise or other stimuli (Cagnie, et al., 2011; Dickx, et al., 2010; Fernandez-Gonzalo, et al., 2016; Hooijmans, et al., 2020). Notably, MRI can detect increases in the spin–spin T2 relaxation time of water within muscle tissue, which serves as an indicator of muscle activity. The nuclear magnetic resonance signal arises from the magnetic behaviour of hydrogen nuclei in tissue water and fat. When exposed to a strong magnetic field, these nuclei are excited by a resonant radio frequency pulse, causing synchronized oscillation and generating a detectable signal. Once the pulse stops, the nuclei gradually lose phase coherence, leading to signal decay, known as T2 relaxation. This spin-spin relaxation is independent of magnetic field strength and increases after muscle activity. In MRI, T2 relaxation time reflects fluid shifts, intracellular acidification, and muscle recruitment, providing insight into metabolic and physiological changes (Cagnie, et al., 2011; Dickx, et al., 2010; Kinugasa, et al., 2006; Shaikh, et al., 2023). It is generally thought that exercise promotes the accumulation of osmolytes (i.e., phosphates, lactate, sodium) in the cytoplasm and an influx of free-water in the active muscles which increase the volume of intracellular space. This results in a prolonged T2 following exercise, which is used as an indirect marker of muscle recruitment and workload (Gold, 2003; Cagnie, et al., 2011; Dickx, et al., 2010; Price, et al., 2003). The T2 effect is often still detectable 20-30 minutes after the exercise, hence osmotic water uptake solely due to lactate accumulation is insufficient to account for overall water uptake. In fact, the mechanisms which leads to water retention after muscle use are not fully understood. Along with T2 analysis, assessing muscle volume is crucial for understating structural adaptation in response to exercise. Changes in volume can provide insights about muscle use (Wilcox, et al., 2021). Measuring both volume and T2 relaxation time, provides a comprehensive view of both functional and morphological effects of acute exercise on muscles.

According to Fisher et al. (1990), the increase in T2 can be quantitatively associated with muscle activity. Unlike electromyography (EMG), which is limited to surface muscle activity, MRI can assess deeper muscle structures without the need for invasive procedures. However, the use of MRI as an exercise evaluation tool is challenging due to the sometimes, limited availability of MRI facilities, the need for highly trained technicians, and the high costs associated with its use. Few studies discussed this methodology and the possibility to measure muscle activation following exercise, conceivably, due to the aforementioned difficulties in performing this analysis.

The aims of this study were threefold: i) utilize MRI to quantify muscle use and acute volumetric changes in all the muscles in the thigh and calf (both anterior and posterior sections) following exercise; ii) compare muscle activation, as reflected by T2 relaxation times, between conventional resistance exercises and whole-body vibration resistance exercise, and iii), assess the inter-operator reliability of these measurements to establish the robustness of MRI-based evaluations in this context.

4.3 Methods

4.3.1 Participants

Healthy male participants (n=13) aged 24 ± 4 (mean ± standard deviation) years, with a mass of 76.9 ± 7.6 kg and height of 180.4 ± 3.4 cm, participated in the study. The sample size was determined based on findings from previous studies (Kinugasa, et al., 2006; Tawara, 2022). All participants met the inclusion criteria, which included: age between 18 and 40 years, being physically active, and the ability to perform squat exercises in accordance with established guidelines. During a preliminary visit to the laboratory, prior to the experimental trials, participants' squat technique was assessed by two strength and conditioning experts. In addition, participants were familiarized with the exercise that they had to perform either with and without vibration. All participants were familiar with resistance exercise and, aside from one participant, were engaged in regular resistance training. The study protocol was approved by the University of Ljubljana, Faculty of Sports' Committee for Ethical issues in the field of sport (Reference number: 033-10/2023-2). All participants provided their written informed consent to participate in the study, which was performed according to the guidelines of the Declaration of Helsinki, excluding clause 35 (i.e., the study was not registered in a publicly accessible database).

4.3.2 Experimental protocol

The subjects were requested to visit the MRI facility on two occasions separated by 2 weeks. To limit measurement error, MRI scans, interaction with participants and exercise supervision, were performed by the same operators and MRI technicians.

Upon arrival at the facility, participants completed a medical questionnaire to survey factors that might interfere with MRI scans, and underwent a consultation with medical personnel. Subsequently, participants changed into shorts, and MRI scans were conducted on two segments of the right leg: one positioned 10 cm below the patella to assess lower leg and another 10 cm above the patella to evaluate upper leg. A trained technician assisted participants in positioning themselves within the MRI scanner. The scanner was situated in an adjacent room, separated from the control room by a glass partition, enabling personnel to monitor participants and provide assistance in case of emergency. A communication system facilitated interaction between the MRI personnel and subject. The duration of the MRI scan was approximately 15 minutes. Following the scan, participants performed resistance exercise (RE) comprising four sets of twelve repetitions of body weight triple extension squat, with one minute of rest between sets and exercises. The exercise was paced using a metronome, with a cadence of 3 seconds for the descending phase, 3 seconds for the ascending phase, and a 1-second isometric contraction at the end of the triple extension squat, specifically when participants were on their toes. The exercise was performed under the supervision of a strength and conditioning expert. Following the exercise session, participants were asked to dry themselves and promptly re-entered the MRI scanner for a subsequent scan.

During the second visit, which took place two weeks after the first, the procedure was similar to that of the first visit, with the exception that they performed the resistance exercise on a rotational vibration platform, thus conducting resistance vibration exercise (RVE). Vibrations were delivered using a Galileo rotational platform (Novotech, Germany), operating at a frequency of 20 Hz. The amplitude, which varied based on each participant's foot placement on the platform, averaged around 3.5 mm. The vibration intensity was selected according to WBV frequencies known to induce muscle activation (14–40 Hz), while also ensuring participant safety and enabling exercise without excessive foot displacement during vibration.

4.4 Muscle Magnetic Resonance Imaging

4.4.1 MRI sequences

Magnetic resonance imaging (MRI) data were acquired on a 3.0T Philips Achieva TX scanner (Philips Healthcare, Best, NL) with a 12-channel coil. The imaging protocol consisted of T2-weighted turbo spin echo sequences with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 13 ms (first echo) with 6 additional echoes acquired with an echo spacing (ΔTE) of 13 ms (last TE = 78 ms), acquisition matrix = 560x560, flip angle = 90°, voxel size = 0.286x0.286x2.2 mm^3, number of slices = 10, and SENSE acceleration factor = 2.5.

4.4.2 Data analysis

Data were recorded through the MRI acquisition software. Muscle segmentation was performed with semi-automatic muscle segmentation software using deep registration-based label propagation.

This segmentation method relies on registration-based label propagation, which provides 3D muscle delineations from a limited number of annotated 2D slices (Fig. 9). ITK Snap software (Open-source: http://www.itksnap.org version 4.0) was used to delineate axial view of muscles on top and bottom slices. Fat tissue and major vessels were not included in the segmentation. From the segmented volumes ROI statistics were obtained using AFNI's tool 3dROIstats (Cox, 1996). To isolate the water signal and minimize fat interference in T2 mapping, data were analysed using a biexponential T2 fitting model, accounting for distinct relaxation rates of water and fat. T2 maps were calculated with MyoQMRI open-source software available at https://github.com/fsantini/MyoQMRI and introduced in previously published method (Santini, et al., 2021).

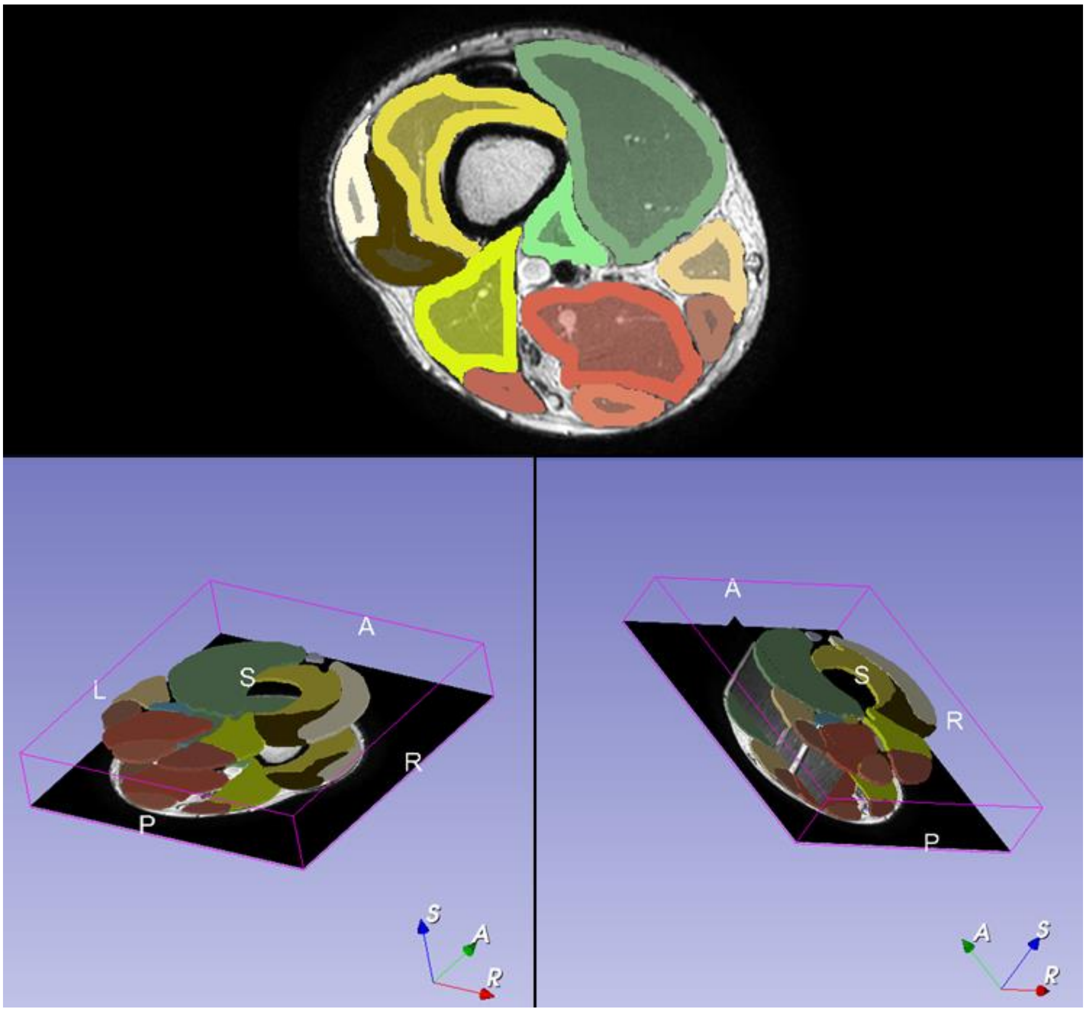

Figure 9: Visual representation of volumetric analysis of muscles. The image in the upper panel is an example of the axial view of the thigh scan. The images in the lower panel illustrate the three-dimensional depiction of the segmentations performed on the first (slice 1) and the last slice (slice 14) of the MRI scans. The volume (cm3) between the two segmentations was recreated by calculating the the area between individual muscle segmentation. The model was created and modified by using Slicer ver. 5.6.2.(https://www.slicer.org/). Scan panel legend: L = left, R = right, A = anterior, P = posterior. Bottom right axes legend: S = Sagittal, A = Axial, R = Coronal.

The calf and thigh muscle segmentation was performed by three independent evaluators. All performed the segmentation according to the same guidelines, namely taking care to exclude fat and bone tissue, and blood vessels. Data regarding T2 mapping and volume were then stored in Excel files as comma separated values. Volumetric values were converted from voxels to cm3 and used for the analysis. To evaluate the consistency of measurements between operators, the Sørensen–Dice index or DICE coefficient was calculated for muscle segmentation performed by three operators. The DICE coefficient was derived using the formula: (Sørensen–Dice index) DICE = 2 × |A ∩ B| / (|A| + |B|); with A and B are two data samples A DICE score of 1 signifies perfect agreement between the measurements, whereas a score of 0 denotes no agreement. It was calculated for every muscle of the thigh and calf. To detect potential outliers, considering the intervariability in participants' responses to exercise and the baseline body composition, Z-score analysis was applied to all datasets. Data points with Z-scores exceeding -2 or +2 were identified as outliers and consequently excluded from further analysis. Data were checked for normal distribution with a Shapiro-Wilk test. For the analysis, only identifiable muscles were included; muscles that were consistently unobservable were excluded. Total muscular activation within the thigh and calf was calculated by summing the volumes and T2 values of all respective muscles. Data was investigated using paired multiple t-tests with the Holm-Bonferroni correction method for multiple comparisons. When the normality distribution of data was not met, Multiple Wilcoxon tests with correction for multiple comparisons was used. When a difference was observed in a muscle, a mixed effect model with exercise (RE and RVE) and time (PRE and POST) was used to evaluate whether the exercise had an effect. Analysis of variance (2way - ANOVA) can determine whether there is a statistically significant difference between two measures; however, it does not provide information about the actual size or practical significance of the observed difference. To address this limitation, this study also employed effect size analysis to quantify the magnitude of the difference. Due to the relatively small sample size (less than 20), Hedge's G was used as it includes a correction factor appropriate for small samples (Sullivan and Feinn, 2012).The statistical analysis and graphical representation were performed with GraphPad Prism version 10 (GraphPad Software Inc., Dotmatics, Boston), while effect sizes, volumetric conversion and Z-scores were performed with Microsoft^{tm} Excel.

4.5 Results

The DICE coefficient revealed a very high measurement-agreement between operators. Some small muscles were not always visible in all participants, thus in those muscles the DICE coefficient was lower compared to all other muscles. For the whole-thigh (the average DICE score among all muscles) a score of 0.91 ± 0.08 was achieved, while for the calf it was 0.88 ± 0.07. The highest DICE coefficient recorded for thigh muscles was 0.98 for the vastus medialis, while the lowest was 0.52 for the adductor magnus. For calf muscles the highest DICE coefficient was 0.98 for the gastrocnemius lateralis, while the lowest was 0.50 for the extensor digitorum longus.

4.5.1 Effects of resistance exercise

Calf volume and T2 mapping

Resistance exercise with or without whole-body vibration did not promote any muscular activation or changes in muscle use either for single calf muscles and for all calf muscles analysed collectively. Delta analysis revealed no differences between interventions as shown in Figs. 10 and 11.

Thigh volume and T2 mapping

A time effect was recorded for acute volume data in vastus medialis and vastus intermedius ($p < 0.0001$), indicating that both resistance exercise with and without vibration increased the volume of these muscles, without differences across exercise regimens. Following resistance exercise (RE), the vastus medialis volume increased by 4% (from 93.84 ± 17.17 cm^3 to 96.97 ± 16.46 cm^3), while the vastus intermedius volume increased by 11% (from 43.73 ± 14.03 cm^3 to 48.99 ± 13.10 cm^3). A similar response was observed following resistive vibration exercise (RVE), with vastus medialis volume increasing by 3% (from 103.69 ± 21.96 cm^3 to 105.92 ± 22.30 cm^3) and vastus intermedius volume increasing by 5% (from 50.09 ± 14.43 cm^3 to 52.22 ± 13.96 cm^3). Additionally, a significant time effect was detected ($p = 0.0001$) for whole thigh volume, indicating increases in both RE (from 294.12 ± 42.68 cm^3 to 306.83 ± 39.45 cm^3) and RVE (from 311.39 ± 48.38 cm^3 to 316.38 ± 42.12 cm^3), with no significant differences between exercise modalities. PRE vs POST effect size analysis revealed no practical difference for the abovementioned muscles. Delta analysis on PRE and POST of vastus medialis and vastus intermedius showed no difference between RE and RVE.

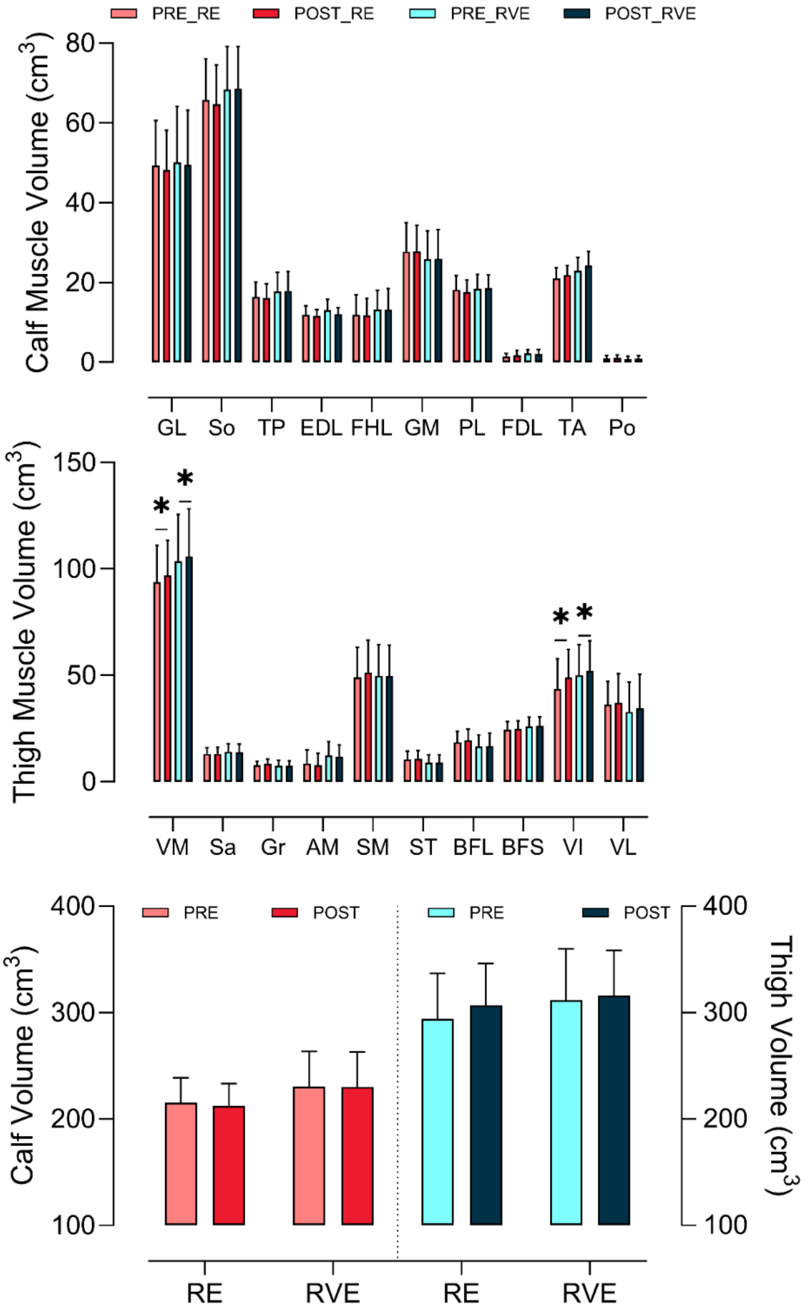

Figure 10: The mean (SD) volume of calf (top panel), and thigh muscles (middle panel) before (pre) and after (post) resistance exercise without (RE) and with (RVE) vibration. The bottom panel presents the mean (SD) volume (cm3) of all calf and thigh muscles before and after RE and RVE. Asterisk (*) indicates the main effect of time for both RE and RVE.

Top panel legend: GL = Gastrocnemius lateralis, So = Soleus, TP = Tibialis posterior, EDL = Extensor digitorum longus, FHL = Flexor hallucis longus, GM = Gastrocnemius medialis, PL = Peroneus longus, FDL =Flexor digitorum longus, TA = Tibialis anterior, Po = Popliteus.
Middle panel legend: VM = Vastus medialis, Sa = Sartorius, Gr = Gracilis, AM = Adductor magnus, SM = Semimembranosus, ST = Semitendinosus, BFL = Bicep femoris long, BFS = Bicep Femoris Short, VI = Vastus Intermedius, VL = Vastus Lateralis

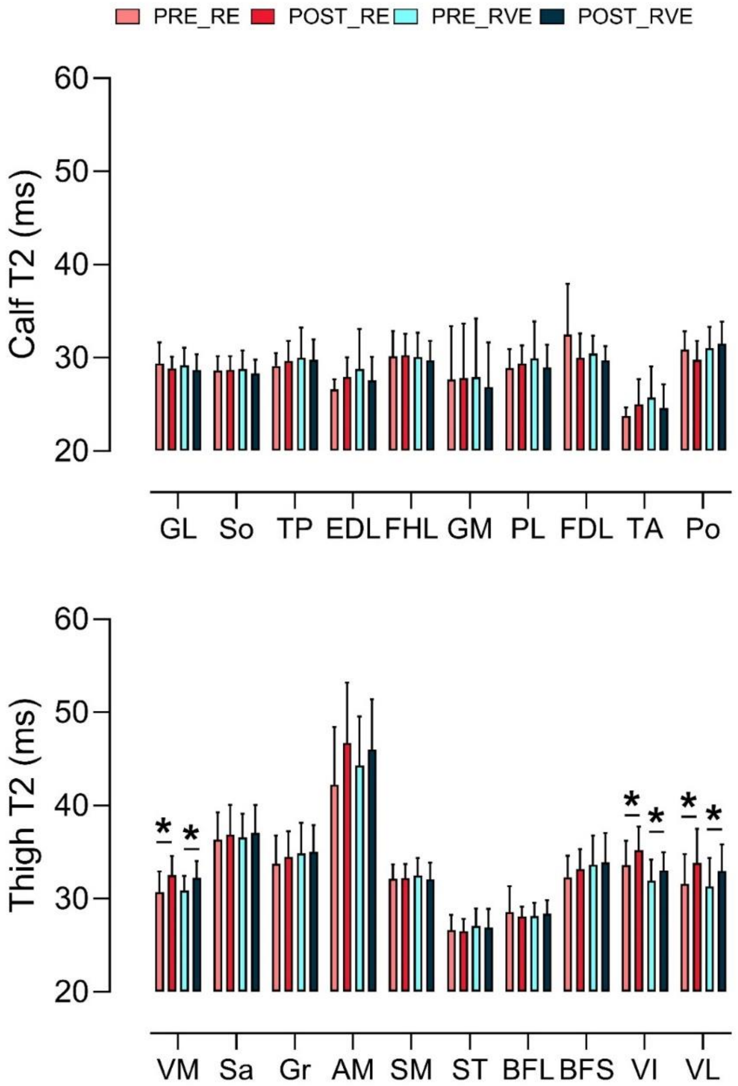

Figure 11: The mean (SD) T2 (ms) results for the calf (upper panel) and thigh (middle panel) muscles, before (pre) and after (post) resistance exercise without (RE) and with (RVE) vibration exercise. Asterisk (*) indicates the main effect of time for both RE and RVE. Legend: GL = Gastrocnemius Lateralis, So = Soleus, TP = Tibialis Posterior, EDL = Extensor Digitorum Longus, FHL = Flexor Hallucis Longus, GM = Gastrocnemius Medialis, PL = Peroneus Longus, FDL =Flexor Digitorum Longus, TA = Tibialis Anterior, Po = Popliteus.
Middle panel legend: VM = Vastus Medialis, Sa = Sartorius, Gr = Gracilis, AM = Adductor Magnus, SM = Semimembranosus, ST = Semitendinosus, BFL = Bicep Femoris Long, BFS = Bicep Femoris Short, VI = Vastus Intermedius, VL = Vastus Lateralis

A significant time effect was observed for T2 mapping in the vastus medialis, vastus intermedius and vastus lateralis ($p < 0.0001$). Following RE, T2 relaxation time increased by 6% in both the vastus medialis (from 30.72 ± 2.23 ms to 32.53 ± 2.02 ms) and vastus intermedius (from 33.59 ± 2.62 ms to 35.20 ± 2.51 ms). Additionally, a 7% increase in T2 time was recorded for the vastus lateralis (from 31.53 ± 3.24 ms to 33.82 ± 3.68 ms).

Following RVE, T2 relaxation time increased by 5% in the vastus medialis (from 30.87 ± 1.57 ms to 32.24 ± 1.81 ms), 4% in the vastus intermedius (from 31.95 ± 2.24 ms to 33.05 ± 1.94 ms), and 6% in the vastus lateralis (from 31.33 ± 3.07 ms to 32.98 ± 2.85 ms). No significant differences were detected between exercise regimens, indicating a comparable T2 relaxation time response across conditions. Moderate ($G > 0.50$) and large effect sizes ($G > 0.80$) between PRE and POST were recorded for vastus medialis, vastus intermedius and vastus lateralis in both groups. Delta analysis on PRE and POST of vastus intermedius, vastus lateralis and vastus medialis showed no differences between RE and RVE.

4.6 Discussion

The findings of this study suggest that MRI is a valuable tool for assessing acute muscular activity. Within the parameters tested, the addition of whole-body vibration to squat resistance exercise (RVE) did not result in a significant increase in muscle activation, as indicated by water and metabolite accumulation measured via muscle functional MRI (mfMRI). However, this outcome may reflect limitations in the sensitivity of T2 mapping to detect subtle differences in activation levels. In addition, the DICE score revealed that data regarding muscle segmentation among operators were overlapping, hence indicating a high reliability between measurements.

Muscle activation is commonly assessed using electromyography (EMG), but it has limitations. Surface EMG is restricted to superficial muscles and is affected by skin impedance, adipose tissue, and electrode placement, increasing measurement variability. Assessing deeper muscles requires needle EMG, which is invasive and may cause discomfort, particularly during dynamic exercise. For these reasons, fMRI has been proposed as a complementary method to indirectly assess muscle use activation trough the measurement of water and metabolites accumulation (Akima, et al., 2000; Cagnie, et al., 2011; Fleckenstein, et al., 1988).

Previous results confirm that measuring T2 relaxation time using MRI is a reliable method providing insights about muscle use (Cagnie, et al., 2011; Dickx, et al., 2010; Price, et al., 2003; Shaikh, et al., 2023), in addition, there is evidence of the linear association between mfMRI and EMG analysis (Adams, Duvoisin, and Dudley, 1992; Dickx, et al., 2010; Yue, et al., 1994). The pioneering work of Tesch (Tesch, 1993) provided an in-depth analysis of muscle activation after several lifting exercises. This study validated the hypothesis posited by Fleckenstein et al. (Fleckenstein, et al., 1988) demonstrating that MRI enables the direct visualization of all muscles engaged, as well as those not engaged, during a specific movement, thereby offering insights into the primary musculature involved in a given exercise. In a recent study, Tawara (Tawara, 2022) demonstrated that T2 relaxation time using MRI can detect muscle activation even following a mild body weight exercise. The main limitations in using mfMRI to detect muscular activation is the need to perform the examination immediately after exercise, given that the effects of exercise on water and metabolite accumulation tend to decay rapidly (Fisher, et al., 1990). Therefore, in our study the exercise was performed in a room adjacent to the MRI device in order to start the MRI scans within just a couple of minutes (< 2 min) after the exercise

The effects of superimposed vibration on muscles are highly debated in the literature. Rosenberg and colleagues (Rosenberger, et al., 2014) found that, after signal filtering, higher EMG signals were found in the rectus femoris during squats with 20 Hz of superimposed vibration. Pollock and colleagues found similar results (Pollock, et al., 2010). There is evidence of the increased

ATP consumption (indirectly indicating muscle use) after superimposed vibration at 20 Hz (Zange, et al., 2009) supported also by increased respiratory O_2 uptake due to vibration with exercise (Cochrane, et al., 2008). These results are supported also by training studies (Delecluse, et al., 2003; Karatrantou, et al., 2013; Petit, et al., 2010; Rubio-Arias, et al., 2018), which suggest that the increased performance after exercise with vibration cannot be attributed to a placebo effect. On the contrary, other studies provide evidence of no additional benefits from vibration training (Artero, et al., 2012; Celik, et al., 2022; de Ruiter, et al., 2002, 2003). Indeed, one study reported that resistive squatting elicited greater leg press force performance when performed without vibration (Kvorning, et al., 2006). The discrepancies in the literature may be attributed to many factors influencing the results of both acute and long-term interventions. The type of exercise, such as multijoint movements, and its modalities, such as isometric and concentric actions, can significantly influence the effects of whole-body vibration (WBV) on muscles (Cardinale and Wakeling, 2005).

The significant increase in T2 in the vastus medialis, vastus intermedius and vastus lateralis is consistent with the primary muscles engaged during a squat exercise, as these muscles are integral components of the quadriceps and are in line with the findings of Tesch (Tesch, 1993). The lack of an increase in T2 time in the calf muscles aligns with previous findings in the literature. Alkner and Tesch (Alkner and Tesch, 2004) have demonstrated, with similar exercise, that this muscle group is particularly challenging to effectively target. The non-uniform changes between and within muscles observed in this study have been already discussed previously (Kubota, et al., 2007; Tesch, 1993; Yue, et al., 1994). It is known that during exercise, not all muscles involved in the movement experience the same level of fatigue. Some muscles may be more activated than others, and different regions of the same muscle respond non-uniformly to the effort (Kubota, et al., 2007; Mendez-Villanueva, et al., 2016; Yue, et al., 1994).

The findings of this study would support previous literature suggesting no vibration effects on muscle activation (Arora, et al., 2021; Celik, et al., 2022; de Ruiter, et al., 2002, 2003). T2 relaxation time indirectly reflects the accumulation of water and metabolites, leading to muscle oedema. However, this process is highly variable, and the precise physiological mechanisms underlying water and metabolite retention in active muscles remain unclear. One potential explanation for these discrepancies lies in the physiological response to vibration-induced muscle activation. Vibration is thought to elicit passive muscle contractions through mechanoreceptors, specifically the Golgi tendon organs, which detect vibratory stimuli. This triggers a stretch-reflex response transmitted to the α-motoneurons via monosynaptic (I-afferents) or polysynaptic (II-afferents) pathways, ultimately activating muscle spindles and facilitating contraction (Desmedt and Godaux ,1978; Granit, Henatsch, and Steg, 1956; Rittweger, 2010; Ritzmann, et al., 2010). Another potential explanation is the intensity of vibrations. While the intensity used in this study may have been sufficient to enhance neuromuscular activation, as observed in previous research (Rosenberger, et al., 2014; Zange, et al., 2009) it may not have been adequate to induce significant metabolite accumulation and water retention. The discrepancy between increased neuromuscular activation via monosynaptic pathways and the absence of water and metabolite accumulation following superimposed vibration in muscles, warrants further investigation. Combining electromyography (EMG) and T2 mapping may provide deeper insights into the physiological mechanisms underlying enhanced muscle activation and tissue fluid dynamics.

As expected, muscle volume did not exhibit significant changes following a single exercise session. While volumetric analysis can reflect functional effects, as muscle swelling typically occurs after intense exercise, it primarily captures structural adaptations that become more evident after repeated training sessions. Since higher exercise intensity correlates with increased T2 values, a similar trend may occur in volumetric changes over time. Additionally, the bodyweight exercise performed in this study may not have been sufficient to induce substantial muscle swelling or detectable volume alterations.

The results from the current study should be interpreted with some considerations in mind. This study employed a body weight exercise, which was reportedly sufficient to detect muscle activation with MRI (Tawara, 2022). The exercise was not sufficiently intense for activating the calf muscles, which are known to require higher loads to increase in size and performance due to their constant activation in countering gravity while standing. Future investigations, might employ different training loads to investigate load effect on the deeper musculature detected with the above-mentioned MRI techniques. In addition, future research should further explore the effects of vibration on acute muscle function by integrating T2 MRI and electromyography (EMG) assessments as well as employing different vibration intensity. It will be important to establish the sensitivity of T2 mapping in detecting varying levels of muscle activation, in order to validate or challenge the findings of the present study and those of previous research utilizing T2-based measurements to assess muscle activation.

Chapter 5

Whole-Body Vibration Transmission During Resistance Vibration Exercise[6]

"Energy is the only universal currency: one of its many forms must be transformed to another in order for stars to shine, planets to rotate, plants to grow, and civilizations to evolve"

(Vaclav Smil)[7]

5.1 Foreword

The use of vibration in exercise, whether alone or combined with other modalities, raises concerns about exposure duration and transmission through the body. In Europe, vibration exposure is regulated by ISO 2631-1:1997 and Directive 2002/44/EC, which do not distinguish between occupational and exercise-induced exposure. Assessing the extent of vibration transmission from the platform to different body regions is critical to evaluating potential health risks. Excessive transmission, particularly to the lower trunk, may lead to discomfort, motion sickness, or chronic back pain with repeated exposure (Bovenzi, 2015; Bovenzi and Hulshof ,2000; Lings and Leboeuf-Yde, 2000; Rittweger, 2010; Wang, et al., 2020). There is evidence of decreased vibration transmission during exercise or the influence of body posture to dampen vibrations and highly reducing the amount of vibrations reaching the spine (Caryn and Dickey, 2019; Kiiski, et al., 2008; Munera, et al., 2016; Tankisheva, et al., 2013; Zaidell, et al., 2019). The impact of vibration transmission during AGRVE and its potential similarity in RMS to URVE is not yet understood. Therefore, a group comparison study was conducted to examine the vibration behaviour, specifically in terms of RMS and transmission, between AGRVE and URVE.

5.2 Introduction

Whole-body vibration has gained attention due to its potential benefits in muscle activation, bone density improvement (Armbrecht, et al., 2010; Belavý, et al., 2010; Bonanni, et al., 2022; Verschueren, et al., 2004), and neuromuscular conditioning (Liu, Fan, and Chen, 2022; Pollock, et al., 2010). In particular, previous research has demonstrated how WBV combined with resistance exercise promotes enhanced musculoskeletal performance and mitigates muscle and bone loss during bed rest (Armbrecht, et al., 2010; Belavý, et al., 2010; Miokovic, et al., 2014).

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[6] **Sorrentino, R.G.**, Verdel, N., Supej, M., Ciuha, U., & Mekjavic, I.B. (2025). Whole-body vibration transmission during resistance vibration exercise. Frontiers in Sports and Active Living, 7, 1573571 –

[7] Vaclav Smil, “Energies: An Illustrated Guide to the Biosphere and Civilization, 2000 The MIT Press Edition: USA

Nonetheless, the benefits of resistance vibration exercise remain equivocal, particularly the effect on muscle structure and function, with some studies reporting no additional value over traditional exercise (Artero, et al., 2012; Celik, et al., 2022; de Ruiter, et al., 2002, 2003).

Vibration transmission during vibration training is an important issue, due to the fact that vibrations can cause injuries or harm sensitive areas such as the lower trunk. Vibrations reaching this zone can cause discomfort, nausea, dizziness sensation and motion sickness, along with chronic back pain, if vibrations are experienced consistently (Bovenzi, 2015; Lings and Leboeuf-Yde, 2000; Rittweger, 2010; Wang, et al., 2020). There is evidence of decreased vibration transmission during exercise or the influence of body posture to dampen vibrations and highly reducing the amount of vibrations reaching the spine (Caryn and Dickey, 2019; Kiiski, et al., 2008; Múnera, et al., 2016; Tankisheva, et al., 2013; Zaidell, et al., 2019). Several authors proposed the implementation of WBV as a countermeasure for musculoskeletal deconditioning due to space exploration (Clément, 2011; Rittweger, 2010, 2020), however, during the development of any exercise strategy that incorporates whole-body vibration, the duration of exposure and root mean squared values (RMS), should be within the guidelines recommended by the International Organization for Standardization (ISO 2631-1:1997) and European vibration directive (Directive 2002/44/EC). Current guidelines do not differentiate between occupational and recreational vibration exposure. It is therefore essential that the magnitude of the vibration transmitted from the vibration plate to other regions of the body be determined. This allows a better appreciation of any potential vibration-associated maladies.

The European Space Agency is currently investigating two potential countermeasures: artificial gravity generated via short-arm human centrifuges (SAHC) and whole-body vibration (WBV). This interest arises from the projected conditions of a future mission to Mars, during which astronauts will be exposed to reduced gravitational forces for an extended period of approximately three years—comprising sustained weightlessness during the return transit and exposure to only 38% of Earth's gravity while on the Martian surface (Winnard, et al., 2019). The adaptation of physiological systems to microgravity has been extensively investigated in astronauts by comparing post-mission status of physiological systems with that observed before the mission (Lang, et al., 2006; Sibonga, et al., 2007; Vico, et al., 2017; Winnard, et al., 2019). Exposure to microgravity and inactivity/unloading induced by the experimental bed rest, an analog for ground-based studies of the effect of microgravity on physiological systems, significantly impacts the musculoskeletal system by causing the loss of muscle (Berg, et al., 2007) and bone mass (Rittweger, et al., 2005) resulting in decreased astronauts' performance (Fitts, et al., 2010; Lee, et al., 2022; Qaisar, et al., 2020; Vandenburgh, et al., 1999). Maintenance of muscle and skeletal mass during space missions is therefore of paramount importance, as reduced performance could increase the risk of injuries and potentially jeopardize mission success. Not surprisingly, a major initiative in space life sciences is the development of effective exercise countermeasures (Ploutz-Snyder, et al., 2014, 2018).

Short-arm human centrifugation establishes an artificial gravity (AG) vector in the head to foot direction which can mimic gravitational load or even hypergravity (Frett, et al., 2014; Yang, et al., 2007). This gravitational vector is linear but non-uniform, progressively increasing in magnitude from the top to the bottom of the nacelle. As a result, participants experience lower loading forces at the shoulder level and progressively greater loads at the feet as presented in literature (Clément, 2011). New generation centrifuges allow users to perform either power (Kramer, et al., 2012, 2017) and/or resistance exercise (Piotrowski, et al., 2018; Sorrentino, et al., 2024). The efficacy of horizontal resistance vibration exercise (RVE) conducted with artificial gravity (AGRVE) is the focus of the current ESA BRAVE (**B**ed **R**est **A**rtificial gravity and **V**ibration **E**xercise) project It is not known whether the unique load distribution during AG exercise would affect vibration behaviour. Given the unique distribution of gravitational load during centrifugation and the absence of existing research on vibration behaviour in this emerging exercise modality (AGRVE), the present study aimed to investigate whole-body vibration transmission and the magnitude of root mean square (RMS) vibration values during resistance vibration exercise performed on a short-arm human centrifuge (AGRVE) and on an upright exercise device (URVE) under identical vibration frequency and amplitude.

5.3 Methods

5.3.1 Participants

The study protocol involved human participants and was approved by the University of Ljubljana, Faculty of Sports' Committee for Ethical issues in the field of sport (Reference number: 033-10/2023-2). All participants provided their written informed consent to participate in the study, which was performed according to the guidelines of the Declaration of Helsinki. Recreationally active male participants (n =15) were recruited to take part in the study via online advertisement. Inclusion criteria included regular exercise and familiarity with resistance exercise, specifically squats and calf raises, while the exclusion criteria included the presence of musculoskeletal injuries and low tolerance to motion sickness. Due to the technical constraints of the short-arm human centrifuge (SAHC), individuals weighing over 95 kg or taller than 190 cm were not eligible for inclusion. All participants attended the laboratory on three separate occasions. The first visit involved screening to assess their ability to correctly perform the required exercise and to provide a detailed explanation of the experimental protocol. During the second visit, anthropometric measurements were recorded, and participants completed an 8 Repetition Maximum (RM) squat test, which was used to calculate the exercise load. The third visit was dedicated to the execution of the experimental protocol.

5.3.2 Materials

Vibration transmission was recorded with two triaxial and one monoaxial accelerometers (Dytran Instruments, Inc., Chatsworth, USA). These accelerometers were connected to a Dewesoft (Dewesoft d.o.o., Trbovlje, Slovenia) model DEWE-43A data acquisition system. Vibrations were generated by a rotational vibration platform (Galileo Space Pro, Novotec, Pforzheim, Germany) specifically manufactured to be used on the SAHC. For this study two platforms were used, one mounted on the SAHC and one placed below the upright exercise device (see Figure 20, Chapter 6).

5.3.3 Experimental procedure

Participants were randomly assigned to two groups. One group (n = 8; age: 27 ± 5 years, bodyweight: 77.75 ± 7.81 kg, height: 182 ± 3.84 cm) performed upright resistance vibration exercise (URVE), and the other group (n= 7; age: 22± 2 years, bodyweight: 76.4 ± 7.5 kg, height 179 ± 2 cm) conducted RVE on the SAHC, and thus in the presence of artificial gravity centrifugation (AGRVE).

Each participant performed an 8-repetition maximum (8 RM) squat test, and the outcome was used to determine the individualized load intensity (20% of 1 RM). Each test was supervised by two strength and conditioning specialists. Participants started the exercise with a warm up, followed by 2 sets of squats using the Olympic barbells (20 kg, 20.5 mm diameter) and additional 2 sets with a load of half of their bodyweight (i.e., 40 kg including the bar for an 80 kg body mass participant) separated by 1-minute rest between sets. The 8-repetition maximum (8RM) assessment was conducted using a stepwise incremental loading protocol. Load increments were initially set at 10% of the previous load; however, based on participant feedback, increments were adjusted to 5% when the prescribed increase was deemed excessive. The test was terminated when the participant was unable to complete the required number of repetitions or could no longer maintain proper and safe exercise technique. During the calf raise exercise, repetitions were performed with a load equivalent to 1.5 times the participant's BW. The 8-RM results were used to indirectly determined the 1-RM which was 101 ± 13 kg for the URVE group and 96 ± 20 kg for the AGRVE group. The individualized load intensities for squats and calf raises were selected to elicit a moderate level of fatigue typically observed in resistance training, while avoiding excessive fatigue that could compromise movement technique. Additionally, these loads were chosen to strike a balance between simulating realistic exercise conditions for astronaut training and ensuring the reliability of vibration measurements. The vibration plate could provide oscillations between 5 and 35 Hz. In this study the frequency of 20 Hz was chosen. The amplitude of the vibration at the position of the feet on the vibration plate was 3.5 mm. The vibratory load was selected by identifying an intensity, which was sufficiently robust for participants while remaining tolerable during dynamic exercises (Rittweger, 2020) and because it was observed that during horizontal exercise, higher frequencies coupled with greater amplitudes can cause the feet to lift off the platform, resulting in a loss of continuous contact, thereby making the execution of the exercise difficult and not tolerable. In both groups the exercise was paced with a metronome: 3 seconds for the down phase and 3 seconds for the up phase. For the calf raise exercise, participants had to maintain an isometric contraction of 2 seconds at maximal plantar flexion.

AGRVE group

The AGRVE trials were conducted on the SAHC (Redwire, Antwerp, Belgium) in the Gravitational Physiology Laboratory of the PlanHab facility in Slovenia (Rateče-Planica, Slovenia). Upon arrival at the laboratory, participants changed into gym attire and were fitted with a harness, which was secured to the sides of the cradle system on the SAHC. Accelerometers were attached to three locations: i) vibration platform next to the participant’s foot, at the level of the toes, ii) lower back (L5 vertebra), and iii) forehead (see Appendix B, B2). Prior to the attachment, body hair was removed to ensure optimal sensor adherence, then skin was cleaned with alcohol and dried.

During the test, the angular velocity of the centrifuge was increased to the level that generated a ground reaction force (GRF) mimicking that of an upright (standing) load. Once the desired GRF was reached, the participant performed 2 sets of 10 repetitions of squat exercise. Vibrations were activated one second before the first repetition and deactivated one second after the last repetition. Participants were given one minute of rest between sets and exercises. During the rest, the centrifuge was maintained the speed to maintain angular velocity and hence generating AG.

URVE group

The URVE trials were conducted at the Environmental Physiology and Ergonomics Laboratory in Ljubljana. The URVE exercise was performed with a pendulum device as depicted in Figure 1a. During the exercise, the subjects stood on the vibration platform. Load was administered through the addition and/or removal of weight plates on the side of the pendulum device. As in the AGRVE group, before attaching the accelerometers, the skin was prepared to optimize sensors’ placement. The exercise protocol was identical to the one performed by AGRVE participants, as well as the rest between sets and repetitions. To mimic the constant load experienced by participants in AGRVE group, during the rest between exercise, participant in the URVE groups were resting with the load still placed on the shoulders.

5.3.4 Data analysis

Vibration data was recorded and stored using the same procedure employed as previously reported. Data are presented as root mean squared (RMS) values based on 1/3 octave bandwidths (Constant Percentage Bandwidths, CPB) recorded from each sensor. Since this study utilized only a single bandwidth (20 Hz), the data were extrapolated specifically for that range following an evaluation across the entire spectrum. Within DewesoftX (version, Dewesoft d.o.o., Trbovlje, Slovenia), octave analysis utilizing 1/3-octave Constant Percentage Bandwidths (CPB) was conducted for each sensor, sampled at a sampling frequency of 1000 Hz. The computation of true octave band data, compliant with ANSI S1.11 and IEC 61260 standards, was performed using an analysis window of 33.333 ms (block history), linear averaging, and no frequency weighting. This data was subsequently exported to MS Excel (version, Microsoft Corporation, Redmond, WA, USA), where data from the 20 Hz 1/3-octave band was averaged over the total duration of the exercise. The data was not filtered. Vibration transmission is expressed as the ratio between the values recorded by the sensors. A ratio of 1 indicates complete transmission between the two sensors (i.e. transmission from the foot to the pelvis), while a ratio greater than 1 signifies an amplification of vibrations and a ration below 1 indicates an attenuated transmission.

Vibration data was exported to MS Excel were subsequently analysed with statistical procedures. Given the sample size, normality of the data was assessed using the Shapiro-Wilk test, confirming a normal distribution across all variables. Upon verifying normality, a mixed-effects model was implemented with exercise (AGRVE, URVE) and sensor position (the body segment where the accelerometer was placed head, pelvis) as fixed factors. Where a significant main effect or interaction between exercise type and sensor position was detected, post-hoc pairwise comparisons were conducted using t-tests to identify specific group differences with Bonferroni-Holm method correction for multiple comparisons. The Bonferroni – Holm correction was applied to control the risk of Type I error arising from multiple within-group and between-group comparisons. The correction method was selected for its conservative nature, aimed at minimizing the possibility of incurring on false-positive results. To test vibration transmission, a mixed-effect model was performed with exercise (AGRVE, URVE) and ratio (the ratios between head/pelvis/foot). Statistical significance was defined a priori at $p < 0.05$. To strengthen the analysis, independent from sample size, a Hedge's G effect size was implemented to quantify the magnitude of possible differences. The choice was done because this works fine with relatively low and unequal sample sizes (Sullivan & Feinn, 2012). Statistical analysis and visual representation were conducted with GraphPad Prism 10.0 (Dotmatics, Boston, Massachussets).

5.4 Results

5.4.1 Squat

Consistent with findings reported in the literature, the vibrations generated by the vibration plate were attenuated by the legs in both groups. The legs functioned as a spring-like system, absorbing and releasing the vibrational energy. As a result, the vibrations transmitted to the spine were significantly reduced. A significant main effect of sensor position was observed (F (1, 13) = 6.49; p = 0.02). Subsequent analysis showed that pelvis RMS values were 51% lower in the AGRVE group compared to the URVE group (p = 0.01; G = -1.36) as observed in Figure 18. No significant difference was observed in head RMS values between the AGRVE and URVE groups. No further attenuation of vibrations occurred between the pelvis and head, as no significant differences in RMS values were observed within the URVE group. However, a moderate effect size was noted in URVE (G = 0.54). A statistically significant difference was found within AGRVE (p = 0.04, G = 1.10) where head RMS was significantly higher than pelvis RMS.

Table 3: Mean values and post-hoc results comparisons between exercise group for root mean square (RMS) values and vibration transmission expressed in ratio during squat and calf raise (CR).

Sensor body position (type of exercise)	**URVE (average)**	**AGRVE (average)**	***p*-value**
Pelvis RMS (Squat) *	1.02	0.60	*p* = 0.01
Head RMS (Squat) *	1.38	1.09	n.s.
Head/Foot ratio (Squat)	0.33	0.25	n.s.
Head/Pelvis ratio (Squat)	1.27	1.77	n.s.
Pelvis/Foot ratio (Squat)	0.25	0.14	*p* = 0.008
Pelvis RMS (CR) *	0.82	0.40	*p* = 0.01
Head RMS (CR) *	1.13	1.14	n.s.
Head/Foot ratio (CR)	0.28	0.28	n.s.
Head/Pelvis ratio (CR)	1.26	2.77	n.s.
Pelvis/Foot ratio (CR)	0.23	0.10	*p* = 0.007

Vibration transmission ratios analysis confirmed the octave RMS data. A ratio effect was recorded (F (2,26) = 50.48; p < 0.0001). Head/Pelvis ratio was statistically significantly higher compared to both Pelvis/Foot and Head/Foot ratios in both groups (p < 0.0001) indicating that no further vibration attenuation occurred between the pelvis and head. Instead, an amplification of vibrations was observed, driven by head movement rather than actual vibrations transmitted. In the AG group, this amplification was exaggerated, as noted in previous studies. Between groups, no differences were recorded for the Head/Pelvis ratio, nevertheless a moderate to high effect size was recorded (G = 0.70). The Pelvis/Foot ratio was 47% lower in AGRVE compared to URVE (p = 0.008, G=-1.56) meaning a significant reduced transmission between the platform and the pelvis. No statistically significant difference was found for Head/Foot ratio; however, a moderate effect was recorded between groups (G = -0.52).

5.4.2 Calf raise

As for the squat, vibration transmission was also reduced during calf raises. A sensor position effect was recorded (F (1, 13) = 8.56; p =0.01). AGRVE pelvis RMS values were 52 % lower compared to URVE (p = 0.01, G = -1.51), while no differences were recorded for head RMS. AS for the squat, no differences were found between pelvis and head RMS within group in URVE, however a statistically significant difference was found within AGRVE (p = 0.01, G = 1.97), where head RMS values were higher compared to pelvis as displayed in Figure 18.

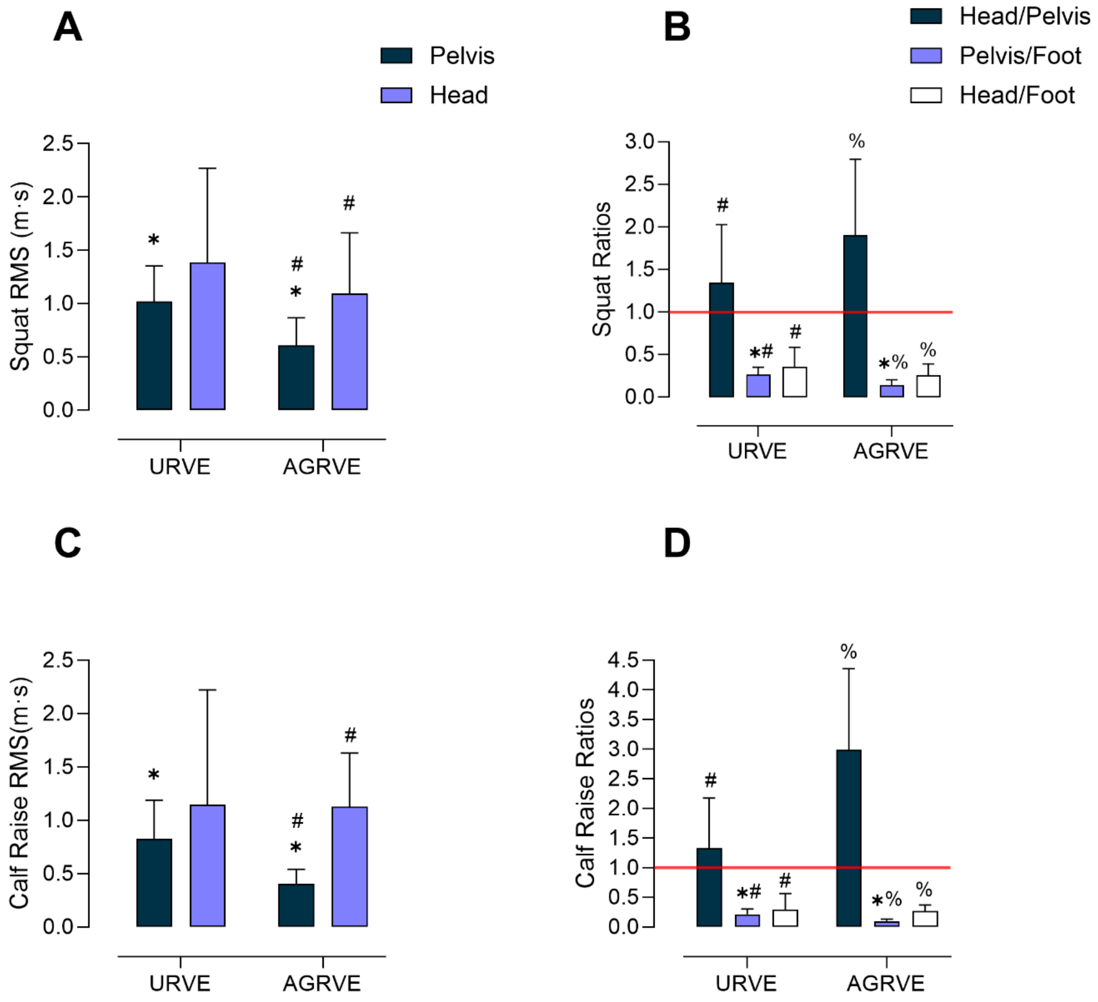

Figure 12: Bar plots illustrating mean ± standard deviation for group comparisons: A) Octave Band Squat RMS, B) Squat vibration transmission ratios, C) Octave Band Calf Raise RMS, and D) Calf Raise vibration transmission ratios. Asterisks (*) in panels A and C denote a difference between groups. Hashtag (#) denotes a difference within the same group. Percentage symbols (%) in panels B and D a difference within AGRVE and hashtag (#) a difference within URVE group. The horizontal red line in B and D marks the threshold for full transmission between two regions: values ≥ 1 represent full transmission, while values < 1 indicate dampening between regions.

For vibration transmission, exercise x ratio interaction was recorded (F (2,26) = 9.62; p = 0.0007) as well as a main ratio effect (F (2,26) = 48.34, p < 0.0001) and exercise effect (F (1,13) = 5.41, p = 0.03). Post hoc comparisons shows that the Head/Pelvis ratio was statistically significantly higher compared to both Pelvis/Foot and Head/Foot in both groups (AGRVE, p < 0.0001: URVE, p = 0.03). As for the squat, the higher ratio at the head during the calf raise is primarily driven by its actual movement during the exercise rather than the vibration stimulus. In the AGRVE group, this effect is further exaggerated by the action of the SAHC. Between groups, the Head/Pelvis ratio was higher in AGRVE compared to URVE (p = 0.02, G = 1.48). The Pelvis/Foot ratio was 58 % lower in AGRVE compared to URVE (p = 0.007, G = - 1.68) confirming the octave RMS recorded and thus meaning in a highly reduced transmission between the vibration platform and the pelvis. No statistically significant difference was found for the Head/Foot ratio.

5.5 Discussion

The findings of this study indicate that vibration transmission is significantly dampened by the lower limbs during exercise, with minimal vibration reaching the spine. Attenuation was greater in the AGRVE group compared to the URVE group, likely due to specific design features of the cradle that further dampened vibrations. Our findings corroborate previous research suggesting that the lower limbs act as spring-like dampeners of vibration and demonstrate that external additional mechanic cushion can enhance vibration attenuation (Marín, et al., 2009; Rubin, et al., 2003).

In this study, both AGRVE and URVE groups performed exercise with partially flexed knees, a position known to amplify the body's natural damping mechanisms (Pollock, et al., 2010; Zaidell, et al., 2019). In the AGRVE group, the exaggerated flexion observed in participants unfamiliar with the action of the centrifuge (Sorrentino, et al., 2024) likely contributed to the further attenuation of vibrations. This aligns with previous findings that postural adjustments and external factors, such as cushioning, can significantly reduce vibration transmission to the spine and sensitive internal structures.

5.5.1 Safety concerns with incorporating vibration in exercise strategies

ISO 2631 and EU directives establish strict limits for vibration exposure, primarily aimed at protecting workers in industrial environments. These standards define thresholds based on vibration frequency, direction, duration, and RMS values to prevent damage such as back pain or nerve disorders. However, these guidelines were not designed for dynamic, exercise-based scenarios like WBV training, where vibrations originate from the feet and are attenuated by the lower limbs before reaching the spine (Rittweger, 2010, 2020). The applicability of such standards remains debatable when vibration experienced during exercise and/or rehabilitation.

In this study, the RMS vibration value during a single 1-minute session was 25.50 m/s^2, aligning with the ISO exposure limit value (ELV) for 1-minute exposure but exceeding the ELV for 30 minutes, which is set at 4.60 m/s^2. Adhering strictly to ISO standards would limit WBV training durations to less than 1 minute, insufficient for eliciting meaningful musculoskeletal adaptations. This discrepancy highlights the limitations of applying industrial safety standards to exercise contexts, particularly when WBV is used as a countermeasure for musculoskeletal health. As an example, the ground reaction forces (GRFs) and vibrations experienced during skiing may exceed the occupational exposure limits specified by the ISO standard (Supej and Ogrin, 2019; Supej, et al., 2018). Recreational skiers may be exposed to vibrations exceeding ISO standard limits for several hours a day without any negative consequences of the vibration exposure. The exceptions may be professional skiers, either competitive athlete and ski instructors (Supej and Ogrin, 2019; Supej, et al., 2018), who are exposed to the vibrations on a daily basis and in some cases throughout the year.

The harmful effects of vibrations are linked to the tolerance of the vertebral column and surrounding internal organs to vibration. Some studies suggest that exceeding ISO limits during WBV training does not result in immediate harm (Armbrecht, et al., 2010; Rittweger, 2010; Rittweger, et al., 2002), others report increased risks of back pain and lumbar disorders when exposure exceeds these thresholds (Bovenzi and Hulshof, 2000; Spitzenpfeil and Mester, 1997). For example, studies on skiers have shown that high ground reaction forces combined with vibration exposure significantly increases the risk of low back pain (Supej and Ogrin, 2019). A review from Griffin (Griffin, 2004), critically pointed out how scientific evidence is not sufficient to clearly define applicable dose-response relationship between WBV and back or other disorders. It has been observed that even tough ISO standards might overestimate the vibration dose value which might lead to health issues, it is important to mention that in epidemiological studies following specific criteria to meet ISO standards, there was evidence of increased back pain, nerve pain and lumbar intervertebral disc disorders (Bovenzi and Hulshof, 2000). This conclusion is also supported by field studies on skiers (Spitzenpfeil and Mester, 1997; Supej, et al., 2018), where vibrations exposure values were compared to EU directive.

Implications for astronaut training during space missions

WBV training for astronauts represents a unique challenge. It is currently being investigated as a potential exercise countermeasure, in combination with artificial gravity, for astronauts during deep space missions. Unlike typical WBV sessions, which are brief and infrequent, astronauts may engage in daily training regimens during extended missions, such as those to Mars. Astronauts undergo daily training regime for several hours and hence integrating vibration into these routines would significantly increase the cumulative vibration exposure, especially when considering the extended durations required for future Mars missions (Winnard, et al., 2019). Nonetheless, in this study resistance vibration exercise performed on a centrifuge, generated less RMS at pelvis compared to upright exercise, so this type of exercise might be carefully considered as a possible exercise countermeasure to space exploration. Currently, existing ISO standards are not directly applicable to the context of daily vibration exposure for future astronaut training protocols. Therefore, future studies investigating AGRVE should consistently include the assessment of vibration transmission. This approach would facilitate the establishment of safety thresholds beyond which exposure to such exercise modalities may pose health risks to astronauts and, more broadly, to members of the general population who may adopt this novel training method.

Vibration transmission

Vibration transmission is a critical factor to consider during physical activities. Several studies have investigated upright whole-body vibration transmission either with (Caryn and Dickey, 2019) or without exercise (Pollock, et al., 2010; Zaidell, et al., 2019). It is evident that the majority of the acceleration provided by the vibration platforms is dampened in the lower limbs, resulting in negligible vibrations reaching sensitive areas such as the lower back.

The results of this study align with previous research, showing that vibrations were significantly dampened by the lower limbs in both groups. As demonstrated by Rubin and colleagues (Rubin, et al., 2003), foot to pelvis ratio is reduced to 0.5 for frequencies below 20 Hz and even to 0.25 for frequencies equal or above 20 Hz, which is consistent with the observations in the present study. In the present study, given the equipment, both groups were performing both exercise with knees partially flexed. This was exaggerated in the SAHC as reported previously (Sorrentino, et al., 2024). Namely, the movement in the centrifuge is somehow constrained in naïve users of the device. This might further explain why vibration transmission in more dampened in AGRVE compared to URVE. Pollock et al. (Pollock, et al., 2010) reported no further reduction between lower back/pelvis and head, indicating that legs are the main structure dampening vibrations. The exact mechanisms of this phenomenon are unclear. In the present study, during upright exercise, the effect size analysis shows that head RMS is higher than pelvis. In AGRVE this was confirmed also by the analysis of variance. This difference is explained by the fact that the head greater freedom of movement compared to pelvis and the RMS are more related to the actual movement during exercise than vibration, as shown also during field studies conducted on skiers (Supej and Ogrin, 2019). Previous research (Rittweger, 2010) has proposed the concept of human body and its segments, as a spring-like system. Calf and thigh muscles are usually referred to as spring-dashpot systems, which can store and absorb energy in muscle and ligaments, hence reducing the vibratory stimulus travelling through the body. Vibration transmission is affected by many factors, including physical characteristics (e.g., bone, soft tissue, muscular activity, posture, etc.) and external factors (e.g., types of shoes, device used, etc. (Marín, et al., 2009; Marín and Hazell, 2014; Pollock, et al., 2010; Tankisheva, et al., 2013; Zaidell, et al., 2019). Previous research (Pollock, et al., 2010; Zaidell, et al., 2019) has demonstrated that the reduced transmission above the knee level at frequencies ≥ 15 Hz may be attributed to the active damping, wherein muscles contract to mitigate adverse effects. The reduced transmission ratios in AGRVE compared to URVE can be attributed to the configuration of the cradle used during the exercises. Participants were positioned on their backs during centrifugation, with accelerometers placed at the L5 vertebra. To minimize noise and pressure on the sensor, the board on which participants lay was equipped with two foam cushions running along its length, separated by a vertical space. The pelvis accelerometer was placed within this space to prevent it from being compressed by the lower back, thereby avoiding altered results. This cushioning likely contributed to the lower transmission and RMS values observed in AGRVE compared to URVE by absorbing part of the vibrations before they reached L5 aligning with previous research indicating the further dampening effect of external factors (Marín, et al., 2009).

AGRVE vs URVE

The reduced root mean square (RMS) values and vibration transmission observed during AGRVE may be attributed to several interacting factors. As mentioned in previous section, participants in the AGRVE condition were positioned horizontally on a custom-designed cradle. Although the accelerometers were not in direct frictional contact with the cradle, the interface between the participant's body and the cushioning material may have contributed to attenuating vibration transmission compared to the URVE, where contact is limited to the feet. Furthermore, the horizontal posture alters body weight distribution and increases surface contact area, potentially enhancing the absorption and dissipation of vibratory energy through the supporting structure. Additionally, AGRVE is characterized by a gravitational gradient that increases from the head to the feet, resulting in elevated compressive forces acting on the lower extremities. This mechanical loading likely increases musculoskeletal stiffness, thereby facilitating greater damping of vibration signals. This interpretation is supported by previous findings from studies on upright WBV, where higher muscular activation and segmental stiffness, ultimately lead to a reduction in vibration transmission throughout the body (Rittweger, 2010; Tankisheva, et al., 2013).

The results of this study should be interpreted in light of several considerations. First, a light external load was utilized, selected to replicate a training-like effort while avoiding excessive fatigue that could compromise exercise technique and, consequently, the accuracy of vibration data collection. Future research should explore varying load intensities during artificial gravity exposure to determine whether increased muscular effort further attenuates vibration transmission. Additionally, this study employed a single vibration frequency, as previously described. Subsequent investigations should incorporate multiple frequencies in conjunction with artificial gravity to examine the corresponding vibration behaviour. It is important to note that at higher vibration frequencies, there is an elevated risk of foot detachment and floating over the platform, potentially increasing injury risk during complex exercise such as AGRVE. Lastly, while the sample size used aligns with prior studies on vibration transmission, future research should aim to include a larger cohort to enhance the statistical power and generalizability of the findings.

Chapter 6

The Effect of a 2-Weeks Resistance Vibration Exercise Programme with and Without Artificial Gravity on Muscle Function[8]

"That which does not kill us makes us stronger"

Friedrich Nietzsche[9]

6.1 Foreword

As outlined in Chapter 2, a variety of exercise strategies have been explored to counteract muscle deconditioning and atrophy associated with exposure to microgravity. The use of the Advanced Resistive Exercise Device (ARED) aboard the International Space Station has provided partial mitigation of muscular decline in astronauts, yet it remains insufficient. In ground-based analogs such as bed rest studies, alternative countermeasures have been tested, including intermittent artificial gravity exposure, whole-body vibration (WBV) with or without resistance exercise, and combinations of artificial gravity with cycling or rowing exercise (Frett, et al., 2024). However, none have demonstrated superiority over traditional resistance training. The following study investigates a novel countermeasure that integrates artificial gravity, resistance exercise, and WBV to address microgravity-induced deconditioning. The results of a two-week intervention are hereby presented.

6.2 Introduction

When exposed to extreme environments, humans and other mammals exhibit phenotypic (during the life of the organism) adaptation to that environment (Amirova, et al., 2021; Blaber, Marçal,

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[8] Mekjavic I.B., **Sorrentino R.G.,** Fortune J., Fisher J., Tsoutsoubi L., Ioannou L.G., Supej, M., Vovk, A., McDonnell, A.C. & Ciuha, U. (2025). The effect of a 2-weeks resistance vibration exercise programme with and without artificial gravity on muscle function (submitted)

[9] Friedrich Nietzsche, "Twilight of the Idols" 1889, 1990 Penguin Classic Edition

and Burns, 2010; Fitts, et al., 2011; Tanaka, Nishimura, and Kawai, 2017). Adaptations in physiological systems attempt to mitigate the deleterious effect of the extreme environment, concomitantly improving performance. The most well-known adaptations to extreme environments include the improvement of the oxygen carrying capacity of blood at altitude, and improved heat loss in hot environments. Similarly, withdrawal of the head-to-foot gravitational vector (Gz) induces adaptations in all physiological systems, but these are generally detrimental (i.e., loss of skeletal muscle mass, bone demineralisation, haemodynamic changes, etc.) (Blaber, et al., 2010; Carriot, et al., 2021; Grimm, et al., 2016; Nagaraja and Risin, 2013). On Earth, this is observed during prolonged inactivity and unloading of the weight-bearing limbs (i.e., injury, ageing-induced inactivity, osteoporosis, etc.). In space, exposure to weightlessness also triggers similar adaptations of physiological systems, as inactivity/unloading on Earth (Fernandez-Gonzalo, Deane, and Bailey, 2024). Specifically, exposure of astronauts to microgravity causes unloading of their weight bearing limbs and substantially decreases their activity resulting in the loss of muscle and bone mass, and the reduction in aerobic capacity, due to deconditioning of, among others, the cardiovascular system (Clément, 2011; Goswami, et al., 2021; Mulder, et al., 2015).

With the advent of longer duration space missions on the International Space Station, and particularly in preparation for future missions to Mars, two avenues of research were initiated. One investigating the processes of adaptation to microgravity in different physiological systems, and the other developing strategies to counteract these adaptations (so-called countermeasures) (Clément, 2011, 2017; Clément, et al., 2016). The former investigations have concluded that the observed adaptations to microgravity, do not necessarily pose a problem to the astronauts during their sojourn in space. However, upon return to Earth's gravity they can have serious consequences to the health and well-being of the astronaut (Clément, 2011).

It is for this reason that prevention of microgravity-induced adaptations is considered of paramount importance. Ground-based studies have confirmed that this can be achieved with a variety and combination of countermeasures (Fernandez-Gonzalo, et al., 2024). In this regard, exercise remains the cornerstone of countermeasure strategies mitigating inactivity/unloading-induced adaptations of physiological systems (Loehr, et al., 2015; Petersen, et al., 2015, 2016). Safe return to Earth's gravitational field relies on the prevention of these adaptations. Astronauts on the International Space Station have at their disposal a variety of exercise devices, including a cycle ergometer, treadmill and resistance exercise devices (i.e., Advanced Resistance Exercise Device, ARED), and have time allocated in their daily schedule to conduct exercise on these devices (Petersen, et al., 2016). Despite the availability of devices and time, and their dedication to the exercise programme, (Korth, 2015; Scott, et al., 2023) the adaptation of their musculoskeletal and cardiovascular systems to weightlessness is not minimised. It is for this reason that there is continued interest in resolving whether artificial gravity could enhance the outcome of existing, and potentially new, exercise modalities (Clément, Bukley, and Paloski, 2015; Clément, et al., 2016).

Despite increasing interest in vibration as a therapeutical and training modality (Rittweger, 2010)' there is a paucity of data regarding its effect during a prolonged training period. As emphasised by Rittweger (2010), *»whilst vibration exposure has traditionally been regarded as perilous only, it is now seen as potentially beneficial in certain areas of sports, exercise, rehabilitation, and preventive medicine«*. For resistance vibration exercise to be efficiently applied in these different areas, the prescription of the exercise combined with vibration and artificial gravity has to be properly established. As with any exercise, its intensity may lead to muscle soreness, and inappropriate prescription may also result in injury. It is therefore of paramount importance to establish safety criteria for its use, and a method of prescribing the exercise to various populations. In addition, a new countermeasure must be evaluated in a ground-based space analogue, such as the bed-rest model (Fernandez-Gonzalo, et al., 2024).

The present study is a prelude to such a bed rest (BRAVE: **B**ed **R**est and **A**rtificial gravity and resistance **V**ibration **E**xercise) study supported by the European Space Agancy (ESA), in which the efficacy of resistance vibration exercise (RVE) will be evaluated in the presence of artificial gravity (AG) in the Gz direction (head-to-foot) established with a short arm human centrifuge, and without it. The feasibility of conducting daily RVE training on an SAHC and the outcome of the training compared to upright (URVE) and horizontal (HRVE) training in ambulatory participants was the focus of the present study.

6.3 Methods

The main objective of the study was to assess the efficacy of a 2-wk training programme comprising resistance vibration exercise (RVE) in conjunction with artificial gravity (AGRVE). This was achieved by having one group conduct training in a similar manner as the AGRVE group, i.e., resistance vibration exercise in the supine/horizontal position (HRVE), but in the absence of artificial gravity (AG). To compare the outcome of the 2-wk training programmes in the AGRVE and HRVE groups with an exercise performed while exposed to natural gravity, a third group conducted the resistance training in the upright position.

Protocol

The study was approved by the University of Ljubljana, Faculty of Sports' Committee for Ethical issues in the field of sport (Reference number: 033-10/2023-2). All participants provided their written informed consent to participate in the study, which was performed according to the guidelines of the Declaration of Helsinki, excluding clause 35 (i.e., the study was not registered in a publicly accessible database).

Healthy male individuals (N=24) participated in the study. They were equally divided (N= 8 in each group) and randomly allocated to three exercise groups (see Fig. 20):

i. Upright resistance vibration exercise (URVE) group. Participants in this group conducted upright loaded squat exercise while standing on a rotational vibration platform, as shown in the right panel of Fig. 20.
ii. Horizontal resistance vibration exercise (HRVE) was conducted on a bespoke exercise device. Participants in this group conducted loaded squat exercise in a horizontal position as shown in panel left panel of Fig. 20. The bespoke exercise device had a sliding sled on which the participant was positioned. The sled had a swivel mechanism that allowed the squat exercise to be conducted kinematically in the same manner as URVE.
iii. Artificial gravity and vibration resistance exercise (AGRVE) group. Participants in this group conducted the same exercise as the HRVE group, with the exception that the exercise was performed on a short arm human centrifuge, as shown in the middle panel of Fig. 20.

During the exercise performed by these groups, the ground reaction force (GRF) replicated that observed during URVE. The head-to-foot gravitational load on the short arm human centrifuge is dependent on the angular velocity. At any given GRF, the gravitational load along the axis of the body is not equal as in URVE, but increases linearly from the centre of rotation towards along the length of the nacelle. Thus, during a squat manoeuvre performed on the SAHC, the gravitational load on the participant will increase during the down phase of the squat manoeuvre and decrease during the up phase of the squat manoeuvre. This variable head-to-foot gravitational load during AGREVE was simulated on the HRVE device, by appropriately controlling the force provided by the pneumatic pistons attached to the sled mechanism.

Participants

The ESA inclusion/exclusion criteria were used in the recruitment of participants (Bed Rest Standard Measurements Overview and description, MEDES Reference: 21-259). Participation in the study was subject to physician's approval.

Following baseline measurements, participants in all three groups attended a 2-week training session. The weekly training session comprised of five daily training sessions, one competition session, and a rest day. The intensity of the training session was determined for each subject on the basis of their performance in conducting a loaded squat manoeuvre, whereby the load assigned was determined relative to a calculated one repetition maximum loaded squat based on an eight-repetition maximum (8-RM) test. With the exception of the competition day, the daily exercise was kept constant during all training sessions for a given week. Participants' performance during the competition session determined the exercise intensity that would be assigned for each subject during the following week. During training, all participants were asked to wear gym clothing.

Short arm human centrifuge

RVE was performed on a short-arm human centrifuge (SAHC; Redwire, Belgium) shown in the left panel of Fig. 19. The SAHC has two nacelles: one with a sledge system (designed and developed by Amst, Ranshofen, Austria) on which the subject is fastened in the supine position, and another which acts as a counterweight. During centrifugation, subjects positioned their feet on a force/vibration platform (Novotec, Germany). This allowed the ground reaction force (GRF) to be monitored during a static posture, and during the exercise. The maximum angular velocity of the SAHC is such, that it can provide a gravitational force of 4g on the force/vibration plate.

During the study, GRF was limited to 2g. The rotational force/vibration plate can generate vibrations up to 35 Hz, with displacements increasing laterally from the central axis of the plate. The vibration was maintained at 20 Hz during all training sessions. The position of the feet on the plate varied between subjects, but in the majority of cases the feet were about 20 cm apart, which

Figure 13: Concept of the short arm human centrifuge (SAHC) is presented in the left panel. It shows the subject lying on the sledge system (same as shown in Fig. 1 above) with the feet on the vibration/force platform. Rotation of the SAHC can establish a gravitational force of up to 4g at the feet. The right panel shows the SAHC in the JSI Gravitational Physiology Laboratory in Planica (Rateče, Slovenia).

6.3.1 Experimental procedure

Training paradigm

The exercise during the training programme was prescribed on the basis of a criterion test conducted prior to the onset of the training programme. This criterion test was repeated at the end of the 1st week to determine the training progression for the 2nd week.

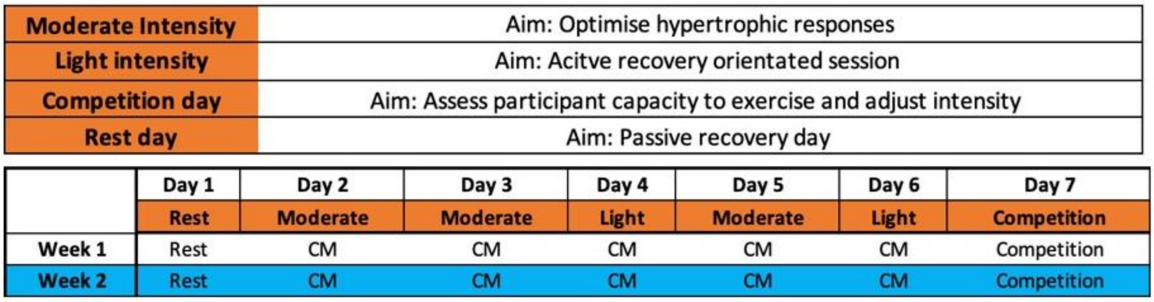
i. Criterion test: 8- repetition maximum squat.

The evaluation utilized a 20 kg Olympic barbell measuring 220 cm in length with a diameter of 28mm, in conjunction with weight plates. This test was conducted under the supervision of two certified experts in strength and conditioning. Prior to the assessment, each participant underwent both general and specific warm-up protocols. Initial sets with the barbell were performed at a load equivalent to half the participant's individual bodyweight for two sets. Progression was adjusted according to individual preferences, while ensuring increases remained within a limit of 10%. Each set comprised 8 repetitions. Load increments continued until a participant was unable to perform the squat correctly and without assistance. The final load was again repeated for 8 repetitions. If the participant successfully completed the final set with the designated load, it was designated as their 8-repetition maximum (8-RM). However, if the participant did not successfully complete the set, the reference load was reduced by 5%. This reference load was used both for exercise prescription for both groups and as a reference to evaluate the effect of the 2-weeks training program.

ii. Exercise prescription

The 14-day training programme comprised i) normal training days during which the countermeasure was used (CM): either RVE or RVE+AG, ii) rest days, and iii) competition day. The latter allowed determination of exercise intensity progression for each subject (Table 4). The CM days comprised exercise of moderate or light intensity, as shown in Table 4.

Table 4: RVE and RVE+AG 14-d exercise training schedule.



Moderate Intensity	Aim: Optimise hypertrophic responses
Light intensity	Aim: Acitve recovery orientated session
Competition day	Aim: Assess participant capacity to exercise and adjust intensity
Rest day	Aim: Passive recovery day

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	Rest	Moderate	Moderate	Light	Moderate	Light	Competition
Week 1	Rest	CM	CM	CM	CM	CM	Competition
Week 2	Rest	CM	CM	CM	CM	CM	Competition

CM= countermneasure

The aim of the former was to optimise the hypertrophic response and that of the latter an active recovery session. The aim of the competition day was to assess the participants' capacity to exercise and to adjust the intensity of the moderate and light exercise for the next week. The exercise protocol was identical for all groups and comprised three key movements: triple extension squats, back squats, and calf raises, with the latter performed in alternating foot positions (toes rotated inward and outward). Triple extension squats and back squats were executed with a controlled rhythm of three seconds for both the eccentric (descent) and concentric (ascent) phases, whereas calf raises incorporated a one-second isometric hold at maximal extension. The protocol was implemented at two intensity levels, classified as "moderate" and "light," with individualized load prescriptions based on a percentage of each participant's 8-repetition maximum (8RM) test results. By the end of the first week, participants were instructed to perform two additional repetitions per set at both intensity levels, provided they could do so without compromising form or safety. In the second week, all sets and repetitions were further increased by two to progressively enhance the training stimulus. In addition to resistance exercise, both groups were exposed to continuous whole-body vibration (WBV) delivered via a platform positioned beneath their feet. The vibration frequency and amplitude were set at 20 Hz and 3.5 mm, respectively, based on a literature review identifying parameters that balanced participant tolerance with sufficient neuromuscular stimulation. Vibrations were activated exclusively during the exercise sets and deactivated during rest periods. The exercise regimen for any given day is presented in Table 5.

Table 5: RVE and RVE+AG exercises program detailed description.

Light Program (Active Recovery)	Reps	Sets	Load	Recovery sets	Recovery Exercises
Triple Extension Squat	10	4	25% of 1RM	60 Seconds	120 seconds
Bilateral Squat	10	4	25% of 1RM	60 Seconds	120 seconds
Calf Raises	10	4	1.3 x BW	60 Seconds	120 seconds

Moderate Program (Hypertrophy)	Reps	Sets	Load	Recovery sets	Recovery Exercises
Triple Extension Squat	8	4	40% of 1RM	60 Seconds	120 seconds
Bilateral Squat	8	4	40% of 1RM	60 Seconds	120 seconds
Calf Raises	8	4	1.5 x BW	60 Seconds	120 seconds

Following a warm-up, the URVE, HRVE and AGRVE exercise comprised a pre-determined number of repetitions (reps) and total number of sets. Each light and moderate exercise session comprised triple extension squats, bilateral squats and calf raises. The load was set by adjusting the ground force reaction. On the sledge system (RVE) this was achieved with the electric motors that exerted a force pushing the subject on to the vibration platform, and on the centrifuge (SAHC) this was achieved by adjusting the rotation speed of the centrifuge.

a) Upright resistance vibration exercise (URVE)

For the URVE, participants performed exercise using a pendulum device, with weights positioned on their shoulders, as shown in the left panel of Fig 1. Load adjustments were made by adding or removing weight plates from the sides of the device. In order to simulate the constant GRF experienced by participants in the AGRVE group, individuals in the URVE group maintained the weight placed on their shoulders during the rest breaks between sets.

b) Horizontal resistance vibration exercise (HRVE).

The HRVE was conducted on a bespoke exercise device (right panel in Fig 1), replicating the mechanism on the short arm human centrifuge (middle panel of Fig. 1). Namely, the device comprised a moveable sled system on which the participant lay in the supine position. The sled rotated at hip level, allowing the simulation of the squat manoeuvre as performed in the upright squat exercise (URVE). Pneumatic pistons connected to the sled system provided the force which the participants had to overcome during the squat manoeuvre. The force in the head-to-foot direction was not constant. The force increased during the “down” phase of the squat and decreased during the “up” phase of the squat. This variable force was implemented to replicate the ground reaction force during the AGRVE.

c) Resistance vibration exercise while exposed to artificial gravity (AGRVE) on the short arm human centrifuge.

AGRVE training was conducted on the SAHC at the Gravitational Physiology Laboratory maintained by the Jozef Stefan Institute. This is part of the ESA ground-based facility in Planica (Rateče, Slovenia). Prior to the exercise, subjects were secured to the sled on the SAHC nacelle with a harness, to mitigate lateral movement during centrifugation. During the exercise, participants were in constant contact with the operators via a communication system. In addition, three cameras mounted on the nacelle provided visual observation of their face, knees, and the position of their feet on the vibration platform. During a familiarisation session, the angular velocity of the SAHC was adjusted so that the GRF measured on the vibration platform matched the GRF recorded in the upright position. Specifically, we matched each individual’s 20% and 40% one-repetition maximum (RM) squat, calculated from the 8-RM results. However, this was an approximation, given that the acceleration vector generated by the SAHC is not equal throughout the length of the nacelle and thus it makes complex to directly compare to an upright counterpart (Clément, 2011; Clément, et al., 2015; Sorrentino, et al., 2024). The magnitude of the vector increases as the distance from the central pivot increase as shown in Figure 1 (Sorrentino, et al., 2024, 2025).

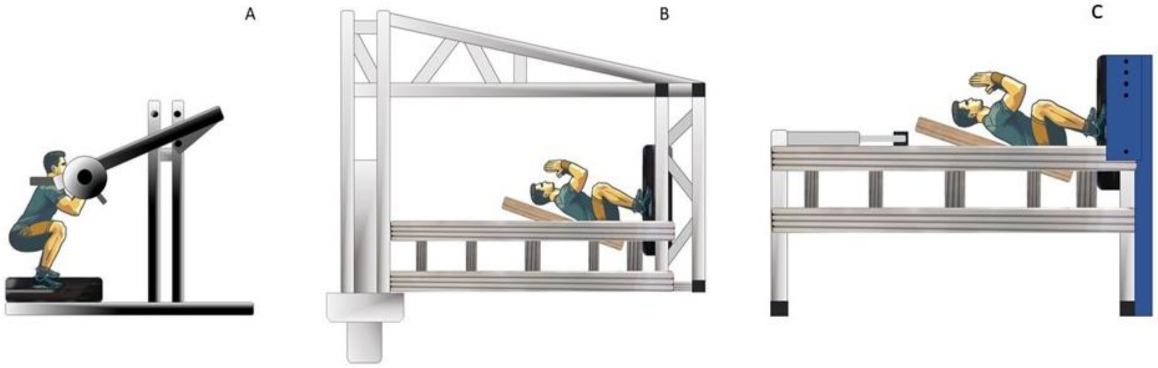


Figure 14: Graphical representation of the exercises. A: URVE - Upright resistance vibration exercise B: AGRVE - Resistance vibration exercise (RVE) with artificial gravity (AG) established with a short arm human centrifuge (SAHC). C: HRVE - Horizontal resistance vibration exercise.

Equipment

i. Short Arm Human Centrifuge

RVE was performed on a new generation short-arm human centrifuge (SAHC; Redwire, Belgium) shown in the left panel of Fig. 2. The SAHC has two nacelles: one with a sledge system (designed and developed by Amst, Ranshofen, Austria) on which the subject is fastened in the supine position, and another which acts as a counterweight. During centrifugation, subjects positioned their feet on a force/vibration platform (Novotec, Germany). This allowed the GRF to be monitored continuously. The maximum angular velocity of the SAHC is such, that it can provide a gravitational force of 4g on the force/vibration plate. During the study, it was limited to 2g. The rotational force/vibration plate can generate vibrations up to 35 Hz, with displacements increasing laterally from the central axis of the plate. The vibration was maintained at 20 Hz during all training sessions. The position of the feet on the plate varied between subjects, but in the majority of cases the feet were about 20 cm apart, which corresponded to 3.5 mm of amplitude.

ii. Horizontal Resistance Vibration Exercise (HRVE) device

The HRVE device was constructed (Mak d.o.o., Spodnje Senice, Slovenia) to replicate the exercise in the SAHC. As explained above, this was achieved by regulating the force delivered by the pneumatic pistons, such that the participant experienced the same ground reaction force as on the SAHC.

iii. Instrumentation

During training in three exercises, participants were instrumented with electrocardiography electrodes to monitor heart rate. During AGRVE they were also instrumented for the non-invasive measurement of arterial pressure using the volume clamp method, cardiac output and stroke volume using Finapres Nova (Finapres Medical Systems, Enschede, Netherlands). A probe was positioned on the index finger for the measurement of oxyhaemoglobin saturation. During the exercise, participants were requested to provide their ratings of perceived exertion (RPE) and a rating of motion sickness (on a scale of 4).

The exercise regimen for any given day is presented in Table 5. Following a warm-up, the RVE and RVE+AG exercise comprised a pre-determined number of repetitions (reps) and total number of sets. Each light, moderate and heavy intensity exercise session comprised triple extension squats, bilateral squats and calf raises. The load was set by adjusting the ground force reaction. On the sledge system (RVE) this was achieved with the electric motors that exerted a force pushing the subject on to the vibration platform, and on the centrifuge (SAHC) this was achieved by adjusting the rotation speed of the centrifuge.

Assessment of muscle strength and mass

Isometric Maximum Voluntary Contraction (MVC)

The MVC of four muscle groups was assessed with an isokinetic dynamometer (Biodex System 4 Pro, Shirley, New York): flexor and extensor muscles of the knee and ankle. MVC was recorded in a neutral position for each muscle group.

The isometric extension and flexion contractions were performed with the subject in the sitting position for either knee and ankle. Both tests were performed on the dominant leg. The participant was firmly strapped to the chair during the isometric MVC test. Prior to the commencement of testing, the system underwent calibration procedures to ensure accurate measurements. The test protocol was similar for each muscle group: after a short warm-up phase, in the neutral position, the participants were requested to perform a maximum extension followed 30s after by a maximum flexion and 30 s after by another pair of extension and flexion contractions until 3 complete sets of extension/flexion contractions were recorded. Each contraction lasted 5-7 seconds and there was 2-minute rest between the successive set of three contractions. The total duration of the isometric MVC was 15 min per pair of agonist/antagonist muscle group.

The measured parameters were the maximal isometric torque (units Nm) for extension and flexion of the different tested muscle groups. For data analysis, the best result from both contractions was used.

Vertical Jump Test

Vertical jump performance was measured with a Leonardo Mechanography platform (Novotec Medical). After a few warmup squats, the volunteer was asked to jump as high as possible while keeping the hands at the waist to avoid inertia movement with the arms. Three maximum effort jumps were conducted with about one minute waiting time in between jumps. If the last jump was the highest, the test was continued until a plateau in performance was observed. The plateau was then used for data analysis. Measurement of the height was done using a ground reaction platform. Test duration was around 15 minutes. The measured parameters are the specific peak power, velocity and the jump height.

Dual Energy X-ray Absorptiometry (DEXA) for bone density and body composition

DEXA is a standard clinical technique to assess bone mineral density and body composition. DEXA can distinguish between hard tissue (bone) and soft tissues. Soft tissues can be distinguished further as either lean tissue or fat. In this study, DEXA (Hologic QDR 4500W, General Electric, USA) was used to assess participants' bone mineral density and body composition, before and after the 2-week training period. The total radiation dose was very low (500 µSv per scan). Scans were performed by positioning participants supine on the device with arms resting at the side of the trunk without touching it and with legs straight and positioned apart legs, and with toes rotated inward.

Magnetic Resonance Imaging (MRI) of the lower extremity

Magnetic resonance imaging (MRI) of the lower extremity was obtained with a 3.0 T MRI with a 12-channel coil Philips Achieva TX scanner (Philips Healthcare, Best, The Netherlands) MRI scanner. The MRI sequences recorded transversal images from the right leg, hip and lower trunk reaching at least from the foot to the mid lumbar spine. A T1-weighted DIXON-sequence (with 6 echoes or 2-echo depending on MRI). This sequence provided images containing contrast for the identification of different muscles and also information about fat fraction. The imaging protocol consisted of T1 and T2-weighted turbo spin echo sequences with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 13 ms (first echo) with 6 additional echoes acquired with an echo spacing (ΔTE) of 13 ms (last TE = 78 ms), acquisition matrix = 560x560, flip angle = 90°, voxel size = 0.286x0.286x2.2 mm^3, number of slices = 14, and SENSE acceleration factor = 2.5. The 14 slices were recorded 10 cm below and above the patella, for, respectively, calf and thigh. Volumes of the following muscle were determined from the scans: soleus, gastrocnemius lateralis and medialis, vastus, rectus femoris, gluteus maximus, medius and minimus. This study used the same acquisition and analysis methodology described in Chapter 4.

6.3.2 Data analysis

Data from each test were acquired using the respective software associated with the instrumentation utilized (such as DEXA, Biodex, MRI). Subsequently, the data were exported into Microsoft Excel for organization and underwent analysis using GraphPad Prism 10 (Dotmatics), which also facilitated graph generation. To detect potential outliers, considering the intervariability in participants' responses to training, Z-score analysis was applied to all PRE and POST datasets. Data points with Z-scores exceeding -2 or +2 were identified as outliers and consequently excluded from further analysis. Given the relatively low sample size, pre- and post-comparisons were performed using a mixed-effects model analysis, if a significant effect was found in one of the factors of the model, a further multiple comparison test was performed. Both for the model and the multiple comparisons test, the significance was set a priori at $p < 0.05$. The effects in the model included two factors: 1) the time of measurement i.e. PRE and POST training regimen (referred to as "time") and 2) the type of training conducted (referred to as "exercise"). Additionally, to complement the analysis of variance results, an assessment of effect size was undertaken. Due to the relatively small sample size in this study, a Hedge's G test was utilized.

6.4 Results

All participants completed the 2-wk training programme. All improved their criterion test at the end of the first week of training, so that the exercise intensity was increased during the second week of training. Three participants in the AGRVE group experienced on the first day of the training, and the exercise session had to be terminated prematurely. However, on the fourth day of training, all AGRVE participants were able to complete the whole session. Although participants perceived motion sickness during the first week, this abated towards the end of the week and no further symptoms were reported during the second week of training.

8 Repetition Maximum (8-RM) and Vertical Jump test

All groups improved in the 8-RM squat test. The mixed model analysis revealed a main effect *time* ($p < 0.0001$). Multiple comparisons tests confirmed these results (avg increase: + 12 % $p < 0.0001$), as well as effect size analysis ($G > 0.80$).

No statistically significant differences were recorded in both groups for jump height. Effect size analysis revealed a small effect ($G = 0.26$) only for AGRVE. A graphical representation of both squat and jump tests is presented in Figure 21.

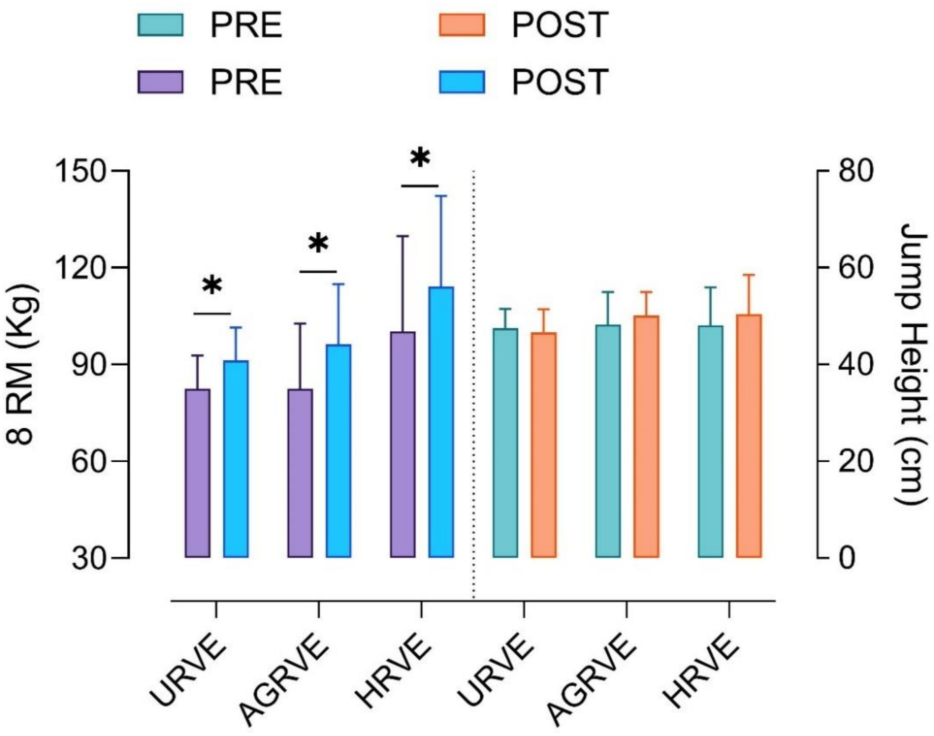


Figure 15: Group comparison bar plots depicting mean and standard deviation of 8 RM test (left y axis) and jump test (right y axis). The asterisk (*) represents a statistically significant difference between PRE and POST within group.

6.4.1 MVC

Knee strength

Mixed effects model revealed a significant exercise x time interaction (p = 0.0005) on the MVC of knee extension on the sagittal plane. Multiple comparisons test revealed significant differences between PRE and POST of AGRVE group (230.41 ± 36.63 to 261.66 ± 39.41; p = 0.0005) but not for HRVE and URVE.

Knee flexion MVC analysis revealed both a significant exercise x time interaction (p = 0.04). Multiple comparison test revealed a significant difference between PRE and POST of AGRVE group (119.82 ± 38.59 to 141.25 ± 26.02; p = 0.008) but not for HRVE and URVE (Fig. 22).

Ankle strength

Z-score analysis revealed one outlier in the URVE group for ankle extension MVC, thus it was excluded from the analysis of this specific parameter. Mixed effects model revealed no discernible differences among all the factors (exercise, time) and their interaction.

In contrast, an *exercise x time* interaction (p = 0.0001) was recorded for ankle flexion MVC. Subsequent analysis revealed a decreased performance for AGRVE (46.27 ± 9.46 to 36.40 ± 7.72) and URVE (45.70 ± 5.80 to 37.96 ± 5.62) groups (p < 0.0001) but not for HRVE (Fig. 22).

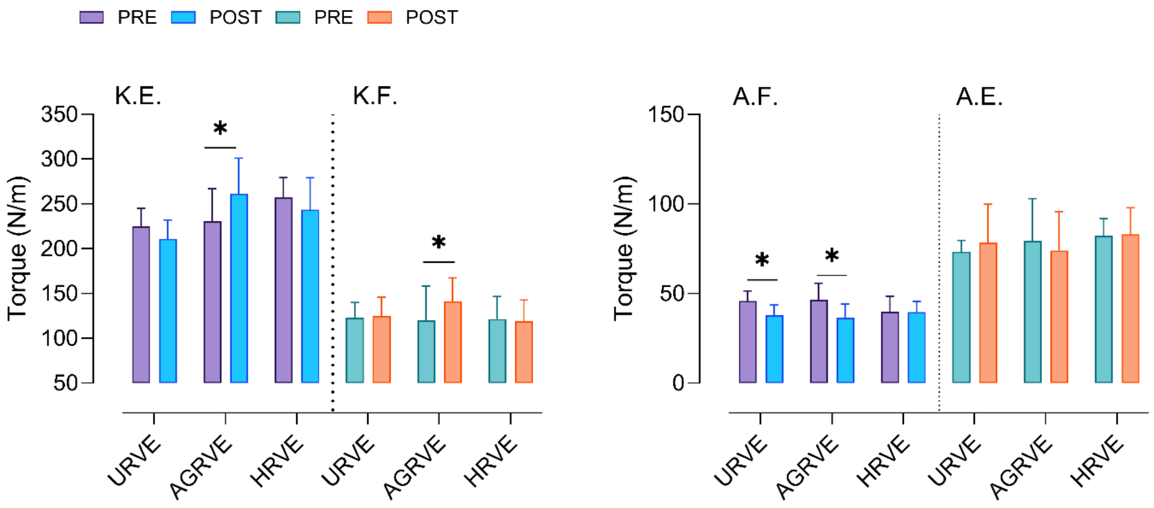


Figure 16: Group comparison bar plots depicting mean and standard deviation of isometric maximal voluntary contraction for knee extension (K.E.), knee flexion (K.F.), ankle flexion (A.F.) and ankle extension (A.E.). The asterisk (*) represents a statistically significant difference between PRE and POST within group.

6.4.2 Body composition

Body composition data will be presented as whole-body, upper and lower leg. No statistically significant differences were recorded for whole-body lean mass. A main effect *time* was recorded for lean upper leg mass ($p = 0.02$) and lean lower leg mass ($p = 0.04$), however subsequent analysis revealed no discernible differences between PRE and POST for all groups.

A significant *exercise x time* interaction ($p = 0.01$) was recorded for whole-body fat mass and subsequent analysis revealed a statistically significant difference between PRE and POST only for AGRVE (15.35 ± 5.27 to 15.86 ± 5.45; $p = 0.01$). A main effect *time* was recorded for fat upper leg mass ($p = 0.03$) and fat lower leg mass ($p = 0.01$), but sequent analysis revealed no significant differences between PRE and POST for all groups (Fig. 23).

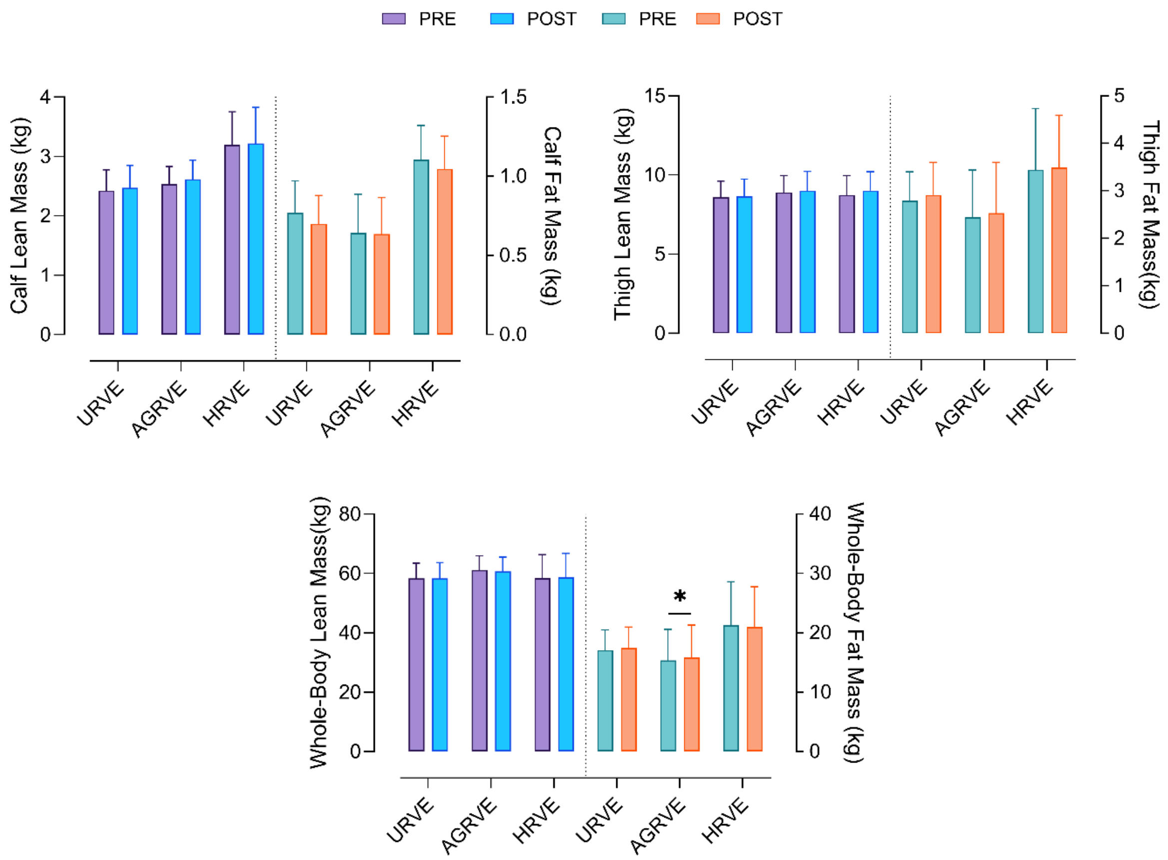


Figure 17: Group comparison bar plots depicting mean and standard deviation of body composition measured with DEXA scans. The asterisk (*) represents a statistically significant difference.

6.4.3 Muscle volume

A main *time* effect was found for the *vastus medialis* ($p = 0.0008$), *semitendinosus* ($p = 0.05$) and *vastus intermedius* ($p = 0.0008$). Subsequent analysis revealed that *vastus medialis* volume increased in AGRVE (99.55 ± 17.01 to 108.22 ± 17.73; $p = 0.007$) and URVE (93.20 ± 17.65 to 102.22 ± 23.78; $p = 0.003$) but not in HRVE. A similar volume increase was found also in *semimembranosus* (51.79 ± 12.07 to 56.95 ± 18.44) and *vastus intermedius* (51.97 ± 10 to 57.29 ± 12.07) but only in AGRVE (respectively, $p = 0.01$ and $p = 0.008$). An *exercise x time* interaction was found for *vastus lateralis* ($p = 0.02$) and *semitendinosus* ($p = 0.01$). Subsequent analysis revealed a decrease in volume in *vastus lateralis* (36.12 ± 6.88 to 30.75 ± 10.77) to and *semitendinosus* (8.79 ± 3.19 to 7.32 ± 3.23) but only in URVE (respectively, p = 0.01 and p = 0.03). Total thigh volume was calculated by summing all individual muscles volumes. A main *time* effect was found for total thigh volume (p = 0.009), subsequent analysis revealed a significant increase in volume only in AGRVE (334.02 ± 63.51 to 355.17 ± 78.92; p = 0.03) (Fig. 24 - 25).

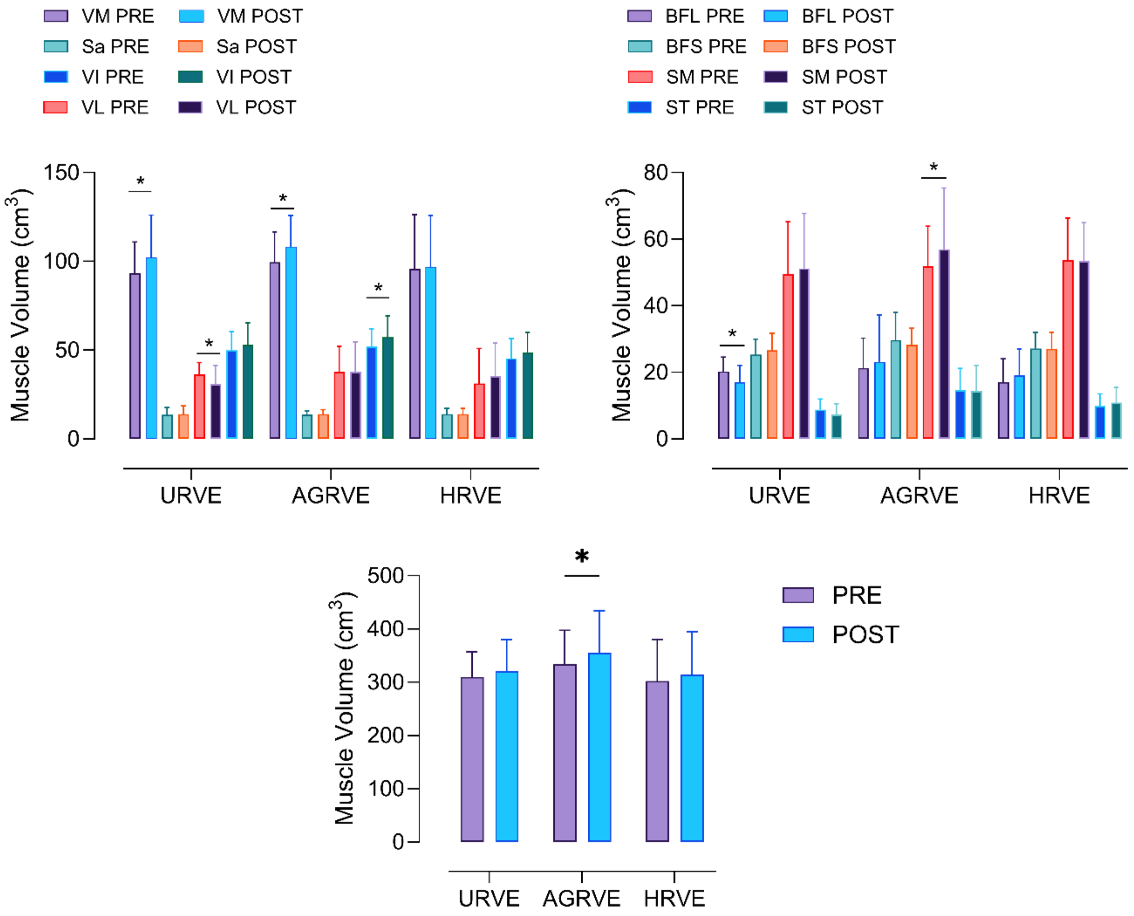


Figure 18: Group comparison bar plots depicting mean and standard deviation of muscle volume of main anterior thigh muscles (top left panel), main posterior thigh muscles (top right panel) and whole-thigh (bottom panel). An asterisk (*) indicates statistically significant differences between PRE and POST within group. Top left Legend: VM = vastus medialis, Sa = sartorius, VI = Vastus intermedius, VL = vastus lateralis.
Top right legend: BFL = bicep femoris long, BFS = bicep femoris short, SM = Semimembranosus, ST = semitendinosus.

A main *time* effect was found for *gastrocnemius lateralis* (p = 0.0007), *flexor hallucis longus* (p = 0.01) and *tibialis anterior* (p = 0.04). Subsequent analysis revealed a decrement of *gastrocnemius lateralis* volume for URVE (48.13 ± 10.88 to 45.84 ± 11.60; p = 0.001) and HRVE (49.66 ± 13.67 to 48.19 ± 12.87; p = 0.01). An increased volume was found for *flexor hallucis longus* (9.84 ± 5.12 to 11.60 ± 5.09) and *tibialis anterior* (22.03 ± 3.15 to 24.23 ± 3.43) for URVE (respectively, p = 0.007 and p = 0.01). An *exercise x time* interaction was found for *soleus* (p = 0.008) and *extensor digitorum longus* (p = 0.01). Subsequent analysis revealed an increase in volume for *soleus* in URVE (64.68 ± 10.83 to 68.02 ± 11.87; p = 0.0004) and an increase in volume for *extensor digitorum longus* in AGRVE (12.37 ± 2.38 to 13.85 ± 2.28; p = 0.03).

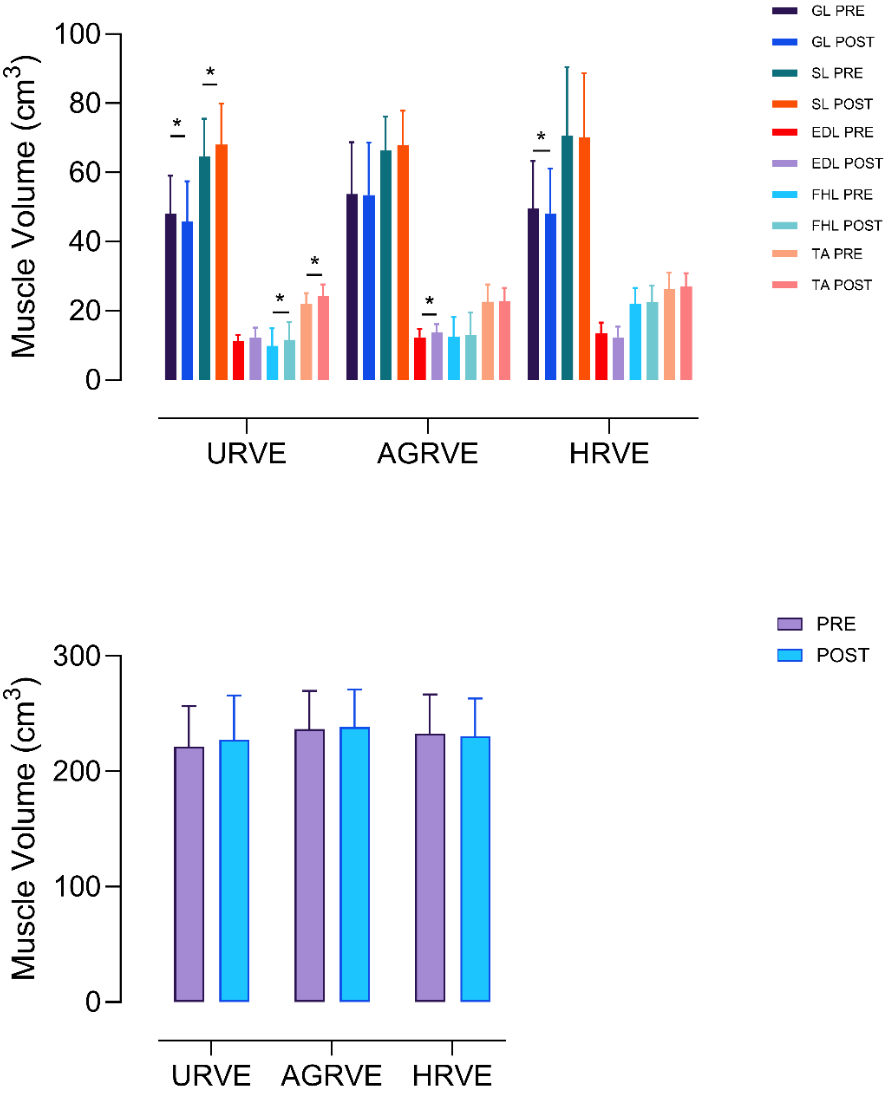


Figure 19: Group comparison bar plots depicting mean and standard deviation of calf muscle volume (top panel) and whole calf (bottom panel). An asterisk (*) indicates statistically significant difference between PRE and POST within group. Top panel legend: GL = gastrocnemius lateralis, SL = soleus, EDL = extensor digitorum longus, FHL = flexor hallucis longus, TA = tibialis anterior.

6.5 Discussion

The aim of the present study was to investigate the feasibility of an AGRVE exercise program, with a particular emphasis on the possibility of using this countermeasure during space missions. Although the potential of artificial gravity (AG) as a countermeasure has been explored (Clément, et al., 2016; Clément, et al., 2015; Mastrandrea and Vico, 2019; Rittweger, et al., 2015), the efficacy of the AG paired with two training modalities known to promote musculoskeletal anabolic responses (Gast, et al., 2012; Graham, et al., 2021; Shackelford, et al., 2004), remains unresolved. Moreover, it is not known if this new modality of exercise would be tolerated by naïve participants on a daily basis for an extended period of time.

The results of the study demonstrated that AGRVE was well-tolerated by all participants and that it offered significant improvement in muscle strength and volume, not observed in the upright (URVE) and horizontal (HRVE) resistance vibration exercises.

Exercise modality

The primary distinction between centrifugation and upright exercise lies in how the load is distributed and experienced by users. During centrifugation the load is linear, but not constant through the body (Clément, 2011; Clément and Traon, 2004; Sorrentino, et al., 2024). For instance, a participant experiencing 1 g at the centre of mass while supine on a centrifuge would encounter higher loads (~ 2g) at the feet and lower loads (~ 0.5 g) at the head. Furthermore, when centrifugation is combined with dynamic movements, the centre of mass shifts horizontally throughout the range of motion. Specifically, during the squat manoeuvre, the gravitational forces experienced by the participant will vary throughout the downward and upward phases of the squat manoeuvre (Sorrentino, et al., 2024). In contrast, during URVE the load remains constant from the head to the feet. Thus, these differences in load distribution between URVE and AGRVE should be considered when comparing the outcomes of a training programme. The variable load experienced by participants during AGRVE was replicated, to a degree, during HRVE. Specifically, the pneumatic pistons providing the resistance to the squat manoeuvre were programmed to replicate the forces experienced by the participants in the AGRVE. In particular, GRF during the HRVE and AGRVE were similar.

The selected training load for this study was set to be manageable for participants during centrifugation while still providing a training stimulus. While this proved effective for the AGRVE group, it was insufficient for HRVE and URVE. The findings from the URVE and HRVE groups align with those observed in previous studies. Jenkins and colleagues (Jenkins, et al., 2016) showed that training three times per week at 30% of one-repetition maximum (1RM) does not yield neuromuscular improvements over periods of 2 and 4 weeks. The training intensity and overall training volume employed in the study of Jenkins et al. (2016) study are similar to those used in the present investigation, providing a comparative basis for the results, even though the volume employed in their study was higher compared to that in the present study.

Muscle strength

The increased muscle volume and knee strength observed in the AGRVE, but not in the URVE and HRVE groups, may be attributable to the overall acceleration vectors which are generated in AGRVE. Namely, centrifugation generates more acceleration vectors compared to an upright exercise (Clément, 2011; Clément, et al., 2015; Sorrentino, et al., 2024). During an upright squat, the only gravitational vector acting on the individual is the normal gravity vector (9.80 N). When a load is applied, this vector increases linearly with increasing load. During centrifugation, the body experiences multiple vectors. These include the variable artificial gravity vector produced by the centrifuge, the constant gravitational force of Earth and the Coriolis acceleration. Their interaction results in a dynamic resultant vector, whose magnitude exceeds that of the individual vectors (Frett, et al., 2014, 2024; Kramer, et al., 2020; Sorrentino, et al., 2024). This vector can be calculated at any reference point, but it is important to note that this value is not constant as it changes dynamically during the exercise (Frett, et al., 2024; Sorrentino, et al., 2024). It has been previously emphasised (Sorrentino, et al., 2024) that the third vector altered the kinematics of squat exercise and participants had to perform additional effort to complete the movement properly. It was suggested the additional muscular effort could have resulted in a higher muscular activation and, in the long term, in an enhanced anabolic stimulus compared to conventional exercise. A significant reduction in maximal voluntary contraction (MVC) of ankle flexion was observed in both the AGRVE and URVE groups. Although not statistically significant, a similar trend was also noted in the HRVE group. This decline may be attributed to participants refraining from their habitual physical activity throughout the intervention period. Additionally, the training load selected for the calf raise exercise may have been insufficient to promote any increase in strength, potentially contributing to the observed decrease in performance. The results of the present study demonstrate that AGRVE offers more potential for strength training improvement compared to upright exercise.

Muscular adaptations to any resistance training are dependent on several factors, such as motor unit recruitment synchronization, number of motor units recruited, antagonist muscle synergetic activation, and more efficient movement technique (Del Balso and Cafarelli, 2007; Del Vecchio, et al., 2019). Furthermore, individuals unfamiliar with a particular exercise undergo a process of familiarization with the movement over time, enhancing overall exercise efficiency. After 2 weeks of daily exercise, participants in this study exhibited an improvement in their 8RM performance, which is in line with findings of previous studies implementing a squat RM test (Artero, et al., 2012). To guarantee that this change was not influenced by external factors, the test was supervised by the same operators and strength and conditioning experts. On the contrary, CMJ did not undergo any improvement in both groups, and the effect size recorded for the AGRVE group is not sufficient to claim that there might be a trend towards improvement. In addition, CMJ test reflects muscle power and the protocol employed in this study was not designed to specifically improve power.

Muscle volume

Exercise-induced muscle hypertrophy is a slow process which requires medium to long-term exercise training programmes (DeFreitas, et al., 2011; Roberts, et al., 2023). To achieve a given level of hypertrophy, these programmes may vary from weeks to months, depending on nutrition, genetics, training type, and training intensity. There is evidence that supports an increase of muscle Cross-Sectional Area (CSA) after just two training sessions of exercise performed to failure (DeFreitas, et al., 2011). While other studies reported the first noticeable muscle CSA increase after 20 days of training (Seynnes, et al., 2007). Narici (Narici, et al., 1996) reported an almost linear increase for muscles CSA and strength increase over a period of 6 months from the onset of the training stimulus. The current investigation employed an innovative methodology to examine muscle hypertrophy (Sorrentino, et al., 2025b). Numerous studies utilising magnetic resonance imaging (MRI) typically focus on the CSA, which provides data from a single, pre-selected slice of the thigh or calf. In contrast, this novel approach incorporates artificial intelligence tools to calculate muscle volume (cm3) using 14 slices of the thigh and calf. This technique offers a volumetric analysis, in contrast to the traditional MRI metrics expressed in cm2, which only depicts a two-dimensional surface, thereby providing a more comprehensive understanding of muscle morphology. Our findings concur with previous research, indicating that muscle hypertrophy is not evident as neuromuscular adaptations after only 2 weeks of training, nevertheless, it is still possible to detect volume changes as observed in our results, especially in the AGRVE group. As discussed previously (DeFreitas, et al., 2011), it is commonly supported that initial training adaptations are predominantly neuromuscular, followed by hypertrophic changes. However, the notion that hypertrophic adaptations must await the onset of neural improvements lacks substantial justification, as hypertrophy and neuromuscular adaptations are not mutually exclusive processes and our results concur with previous research claiming that it is possible to observe some degree of hypertrophy even in short-middle term of exercise. The improvements over two weeks of training are not linear for all muscles. The degree of muscle growth has been observed to differ among the individual muscles within a muscle group and along the length of each constituent muscle (Folland and Williams, 2007; Narici, et al., 1996; Russell, Motlagh, and Ashley, 2000). The variations in hypertrophy across different muscles may be influenced by the degree of individual load and activation experienced during exercise, which can differ among participants based on their morphological characteristics and training experience.

Vibration effect

The effect of WBV on muscular strength, power, and activation remain equivocal (Cochrane and Rittweger, 2020; Rittweger, 2010, 2020). Some studies did not find any additional benefit of implementing vibrations and resistance training to improve muscle parameters (Arora, et al., 2021; Artero, et al., 2012; Roelants, et al., 2004), while other findings support improved strength and power (Cardinale and Bosco, 2003; Delecluse, et al., 2003; Despina, et al., 2014). The present study's findings tend to support the hypothesis of no added value of vibration exercise. The difference between these findings and previous research supporting WBV, may be due to differences in vibration frequency and the population investigated. Compared to previous studies, this study employed lower frequency (20 Hz) which remained the same for the entire study, moreover, participants were familiar with physical exercise and, as has been shown previously, the effect of vibrations on active individuals tends to be non-significant (Arora, et al., 2021). The vibration intensity was selected based on parameters previously reported in the literature to effectively stimulate muscle and bone tissue (Rittweger, 2010). It was adjusted to ensure safety and comfort while still being perceived as physically demanding by participants. Preliminary investigations indicated that, during horizontal configurations (AGRVE and HRVE), higher vibration frequencies led to foot slippage on the platform, thereby increasing the risk of injury. The results of this study suggest that the primary factor influencing the observed effects was centrifugation itself, rather than the application of whole-body vibration alone.

Limitations

Based on our findings, AGRVE appears to be more effective than URVE and HRVE in enhancing muscle function. However, these results should be interpreted with caution. The training protocol was designed to be feasible for participants in the centrifuge while remaining comparable to the other groups. Due to the unique characteristics of the SAHC, the resistance load was not identical across groups. Future studies should focus on optimizing resistance load prescription for SAHC-based training. Furthermore, different strength and conditioning resistance training techniques should be investigated to optimize SAHC as a training modality.

Chapter 7

Conclusions and Future Perspectives

“The future is not something we enter. The future is something we create”

(Nassim Nicholas Taleb) [10]

7.1 Conclusions

The present thesis investigated the integrated impact of AGRVE on muscle responses and examined several key aspects of integrating such a countermeasure as a valid alternative to current exercise strategies to mitigate space deconditioning. This thesis highlights the need for further investigation into specific training loads and prescription methods, as traditional upright exercise guidelines may not directly apply in altered gravity environments. The potential of microgravity as a training condition remains underexplored, not only for space applications, but also for terrestrial use in rehabilitation settings, such as in bedridden patients, or as a training strategy for athletes exposed to high ground-reaction forces and mechanical vibrations (e.g., competitive skiers). The mechanisms underlying the efficacy of AGRVE, as discussed in Chapter 6, require further investigation to determine whether the complex matrix of forces generated during this exercise modality accounts for its superiority over upright and horizontal vibration exercises. While whole-body vibration does not appear to enhance acute or medium-term outcomes in individuals capable of voluntary exercise, it may serve as a viable alternative for rehabilitation and re-ambulation in populations with limited mobility, such as osteoporotic patients, given its known effects on bone mineral density. This thesis confirms that vibration frequencies of 20 Hz with an amplitude of 3.5–4 mm provide an effective and well-tolerated exercise stimulus. However, when applied during horizontal exercise modalities such as AGRVE and HRVE, these parameters may lead to foot slippage, constituting a potential safety risk. It is advisable to warrant proper familiarization for new users or to develop platform designs that allow secure foot fixation, hence maintaining correct exercise posture and minimizing injury risk. When vibrations are applied in training or rehabilitation contexts, existing exposure guidelines (ISO 2631) are not directly applicable, as these standards were developed primarily for occupational settings and do not address vibration exposure for therapeutic or exercise purposes. There is a clear need for the development of specific standards for exercise-related vibration

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[10] Nassim Nicholas Taleb, “Antifragile: Things that gain from disorder”, 2012, Random Books : UK

exposure, as the physiological context and objectives differ substantially from those of occupational vibration, making the use of current ISO during exercise exposure inappropriate. For instance, according to ISO standards, athletes such as competitive skiers would be expected to develop back pain due to the high levels of vibration exposure, which exceed recommended limits. However, empirical evidence does not support this outcome, highlighting the limitations of applying occupational vibration standards to athletic or exercise contexts. Specifically, on the basis of the results of four studies, the following conclusions can be drawn:

Study I (Sorrentino, et al., 2024; Chapter 3 demonstrated that participants with no prior experience in centrifugation were unable to perform squats in a centrifuge with a two-axis moving sled in the same manner as in an upright position. Consequently, H_0 1.1 was rejected. However, centrifugation did not alter post-exercise squat technique, confirming H_0 1.2. Participants showed adaptability to centrifugation within a single session, with significant improvements observed in hip kinematics, while knee kinematics exhibited only a trending adaptation. Therefore, H_0 1.3 was rejected.

Study II (Sorrentino, et al., 2025b; Chapter 4) demonstrated that even bodyweight resistance exercise increases T2 relaxation time and leads to partial muscle oedema, resulting in the rejection of H_0 2.1. Additionally, incorporating vibration into traditional resistance exercise seemed to not provide further enhancement of the metabolic response (as assessed through T2 analysis of water and metabolite accumulation), confirming H_0 2.2.

Study III (Sorrentino, et al., 2025; Chapter 5) demonstrated that vibration stimuli were dampened during both squats and calf raises, leading to negligible vibration transmission to the lower back. Consequently, H_0 3.1 was rejected. Additionally, vibrations during AGRVE were further attenuated compared to URVE, as evidenced by reductions in both octave RMS and transmission ratio, resulting in the rejection of H_0 3.2.

Study IV (Mekjavic, et al., 2025; Chapter 6) neuromuscular adaptations can be observed following two weeks of daily resistive vibration exercise, albeit with mild effects. Thus, H_0 4.1 was rejected. Furthermore, AGRVE proved superior to HRVE and URVE in improving knee isometric maximal voluntary contraction and increasing thigh muscle mass, leading to the rejection of H_0 4.2. Lastly, AGRVE was shown to be a feasible and well-tolerated exercise modality after an initial familiarization phase, resulting in the rejection of H_0 4.3.

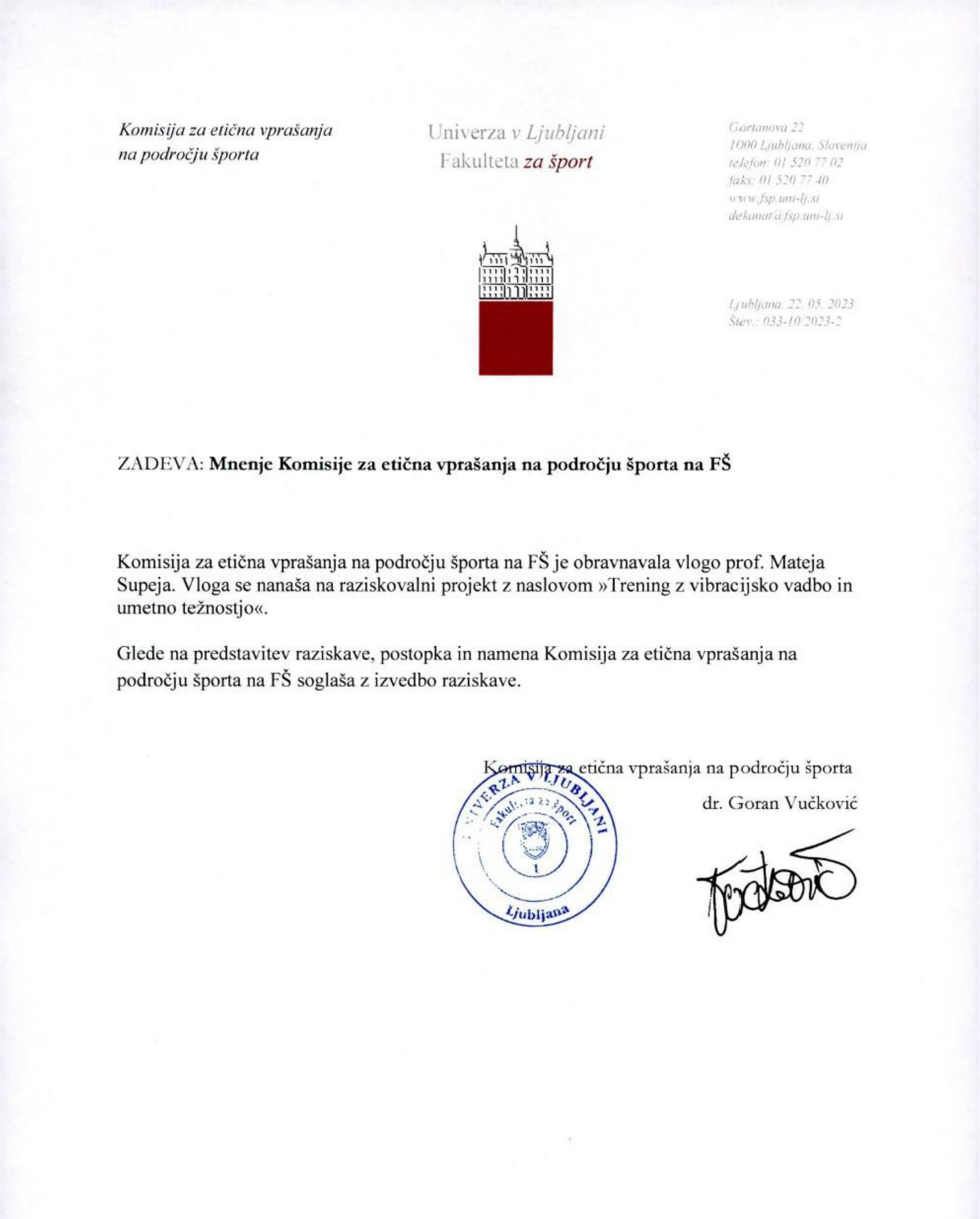
7.2 Future Work

All the studies conducted in this thesis aimed to propose an alternative exercise countermeasure for spaceflight-induced deconditioning. Additionally, this research explored several key aspects of AGRVE where data remains limited. Collectively, the studies presented here provide a foundation for future investigations. In Chapter 3, it was inferred that muscle activation patterns may differ between AG and upright resistance exercise. To verify this, future research should include muscle activation analyses (e.g., EMG) to quantify these differences. Chapter 4 highlighted that vibrations did not significantly increase T2 relaxation time beyond what is observed with resistance exercise alone. Future studies should incorporate different load conditions and combine T2 analysis with EMG to determine whether muscle activation is driven primarily by neural stimulation (EMG) or metabolic demand (T2). Furthermore, the results highlight the need to determine the sensitivity of T2 mapping in detecting muscle activation across varying load levels. This would help substantiate previous suggestions that muscle functional MRI (mfMRI) may serve as a reliable method for assessing muscle activation sensitivity and indicating the level of activity of each muscle during a movement [168].

Specifically, quantifying levels of muscle activation could also be valuable for sports scientists and practitioners in selecting the most appropriate exercises to target specific performance outcomes. In Chapter 5, it was suggested that external structures may reduce vibration transmission, potentially minimizing vibration exposure for participants. Future studies should investigate this further, both with and without AG, by testing different materials and external configurations that could fully eliminate vibrations reaching the upper body. This would help all those individuals who experience repeated vibrations either occupational (e.g., workers, pilots, etc.) or during exercise (e.g., skiers or weightlifters). Chapter 6 demonstrated the superiority of AGRVE over upright and horizontal resistance vibration exercise in enhancing maximal knee isometric strength and increasing thigh muscle volume. Although neuromuscular adaptations were evident, the two-week training duration was insufficient to fully assess long-term effects, particularly in the context of extended space missions. Future studies should investigate the effects of prolonged AGRVE training, exceeding one month, on both performance and structural outcomes, as well as its influence on biomarkers associated with resistance training, to better understand the underlying biological responses. Future studies should include a larger and more heterogeneous sample, as a key limitation of the present thesis is the focus on physically active individuals, reflecting the intended application in space medicine, where astronauts are typically highly trained. Expanding participant heterogeneity would enhance the generalizability of findings and support the applicability of AGRVE beyond spaceflight, including clinical and general population contexts. In conclusion, artificial gravity training remains a vast and largely unexplored field. Further research is essential to expand the available data and optimize AG as a training stimulus for long-duration spaceflight as well as terrestrial applications.

Appendix A

Ethics Approval



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Ljubljana, 22. 05. 2023
Štev.: 033-10/2023-2

ZADEVA: **Mnenje Komisije za etična vprašanja na področju športa na FŠ**

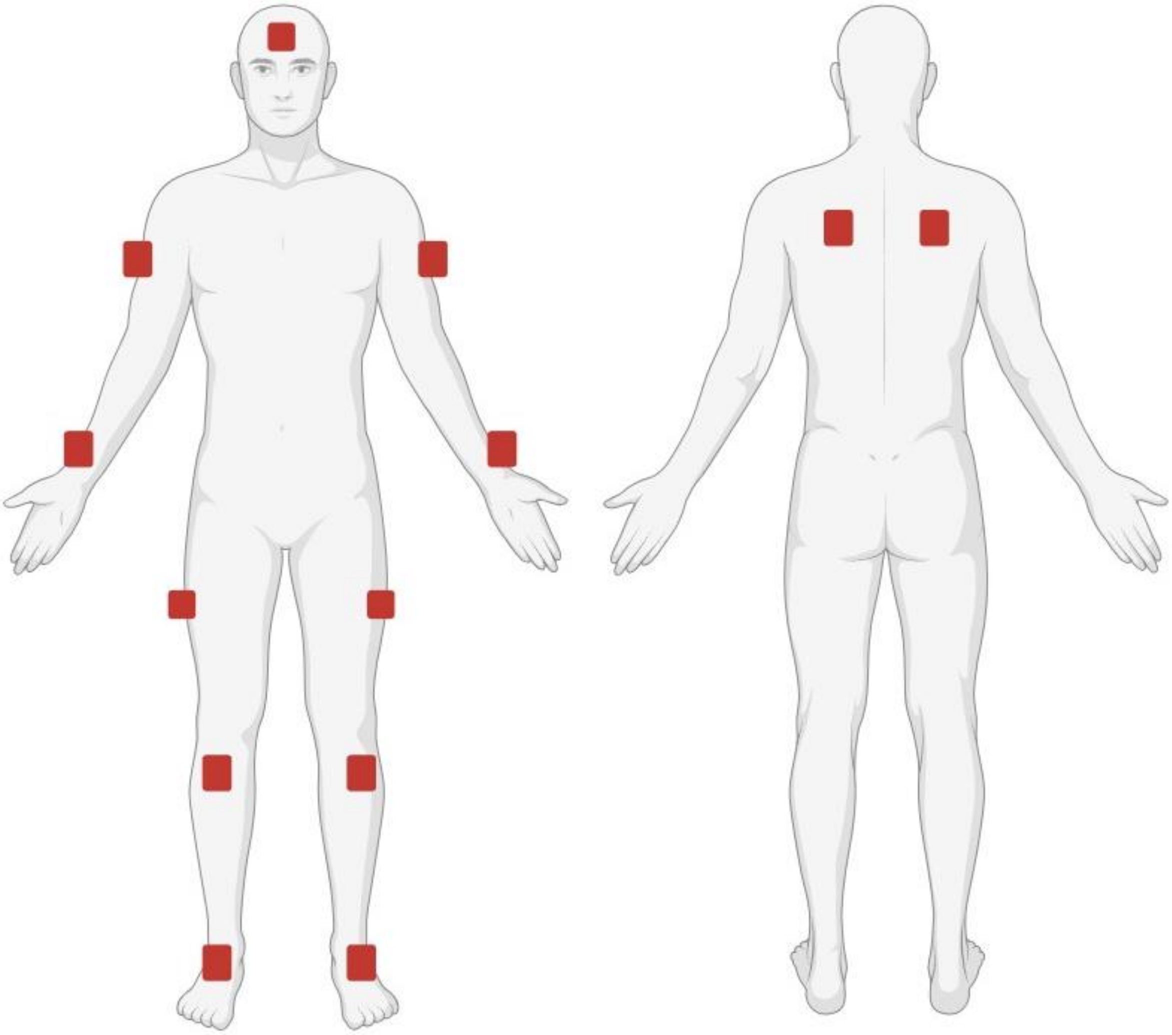
Komisija za etična vprašanja na področju športa na FŠ je obravnavala vlogo prof. Mateja Supeja. Vloga se nanaša na raziskovalni projekt z naslovom »Trening z vibracijsko vadbo in umetno težnostjo«.

Glede na predstavitev raziskave, postopka in namena Komisija za etična vprašanja na področju športa na FŠ soglaša z izvedbo raziskave.

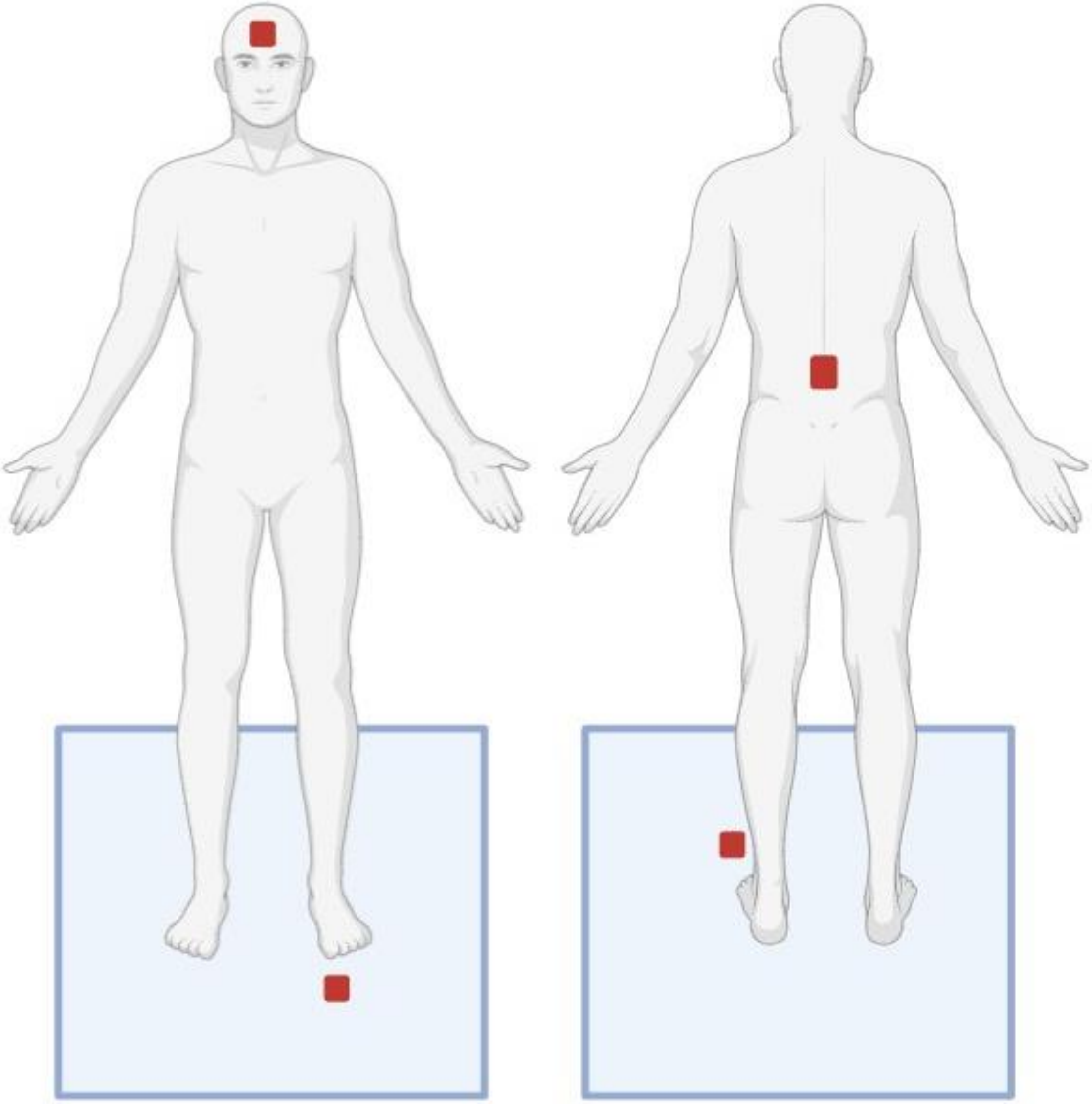
Komisija za etična vprašanja na področju športa
dr. Goran Vučković

Appendix B

Sensor Attachment Sites



B1: Scheme about XSens^{tm} sensors' position utilized in Study 2 (Chapter 3). All sensors were connected with Wi-Fi connection to the Awinda Xsens station.



B2: Scheme about Dytran^{tm} accelerometers position utilized in Study 3 (Chapter 4). All sensors were wired connected to an Dewesoft acquisition system.

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List of Publications

This thesis is based on the following publications:

Papers published in peer reviewed scientific journals:

Sorrentino, R.G., Avila-Mirèles, E., Babič, J., Supej, M., Mekjavic, I.B., & McDonnell, A.C. (2024). Comparison of joint kinematics between upright front squat exercise and horizontal squat exercise performed on a short arm human centrifugation. *Physiological Reports*, 12.

Sorrentino, R.G., Verdel, N., Supej, M., Ciuha, U., & Mekjavic, I.B. (2025). Whole-body vibration transmission during resistance vibration exercise. *Frontiers in Sports and Active Living,* 7, 1573571 –

Sorrentino, R.G., Vovk, A., Suput, D., Ioannou, L.G., Mekjavic, V., Fernandez-Gonzalo, R., Supej, M. & Mekjavic I.B. (2025b) Enhancement of muscle activation during squat: evaluation with magnetic resonance imaging. *European Journal of Applied Physiology* (accepted pending revisions)

Mekjavic I.B., **Sorrentino R.G.**, Fortune J., Fisher J., Tsoutsoubi L., Ioannou L.G., Supej, M., Vovk, A., McDonnell, A.C. & Ciuha, U. (2025). The effect of a 2-weeks resistance vibration exercise programme with and without artificial gravity on muscle function (submitted)

Abstracts published in conference proceedings

Sorrentino, R., Avila Mireles, E.J., Babic, J., Mekjavic, I.B. Fisher, J., MCDonnell, A.C. (2022) Knee and hip angles during squat exercise and artificial gravity: 27th Annual Congress of the European College of Sport Science of the European College of Sport Science, 30 Avg. - 2 Sep., 2022, Sevilla, Spain. European journal of sport science. 1 str. ISSN 1746-1391.

Sorrentino, R.G., Supej, M., Vovk, A. & Mekjavic, I.B. (2025) Resistance vibration exercise in artificial gravity: A potential countermeasure for deep space missions: Annual Congress of the European College of Sport Science of the European College of Sport Science, 1 – 4 July, 2025, Rimini, Italy

Sorrentino, R.G., Supej, M., Verdel, N., Ciuha, U., & Mekjavic, I.B. (2025). Whole-body vibration transmission during resistance vibration exercise and artificial gravity: A “ski simulator” as a potential exercise device for the mission to Mars. *10th International Congress on Science and Skiing* – Val di Fiemme, Italy

Biography

Riccardo Sorrentino is a PhD candidate at the Jožef Stefan Institute International Postgraduate School and a member of the Environmental Physiology and Ergonomics Laboratory at the the Jožef Stefan Institute, Ljubljana, Slovenia. His research focuses on the muscular adaptations subsequent to the employment of new possible spaceflight exercise countermeasures, in particular the employment of artificial gravity. His supervisor for his doctoral dissertation was Professor Igor B. Mekjavic with Prof. Matej Supej and Dr. Andrej Vovk as co-supervisors.

In 2019, Riccardo completed his MSc in Motor Techniques and Adaptative Sciences for Sports with Distinction at University of Messina, Messina, Italy. The title of his dissertation, supervised by Dr. Gabriella Epasto, was “Application of infrared thermography for the evaluation of Olympic weightlifting technique”. For this thesis, Riccardo was awarded by the university commission with the title of “Honours with Mention of Merit” for the scientific perspectives of his work.
In 2017, he completed a I Level Master Course in Nutrition for Sports and Health with Distinction at Catholic University of Rome, Rome, Italy. The title of his dissertation, supervised by Dr. Adriano Arcuri, was “Alternative nutritional proposals for weightlifting athletes”.
In 2016, he completed his BSc in Sport Science with First Class Honours at University of Messina, Messina, Italy. The title of his undergraduate thesis, supervised by Dr. Gabriella Epasto, was “Experimental methods for the analysis of sport gesture”.

"Good morning, and in case I don't see you later, good afternoon, good evening, and good night"

*"**The Truman Show**", 1998, Directed by Peter Weir*

Truman Burbank