Aus dem Institut für Sportmedizin der

Medizinische Hochschule Hannover

und

dem Institut für Luft- und Raumfahrtmedizin des Deutschen Zentrums für Luft- und Raumfahrt (DLR)

Artificial gravity through short-arm centrifugation as potential countermeasure for human spaceflight:

Feasibility, safety and neuromuscular response

INAUGURALDISSERTATION

zur Erlangung des Grades eines Doktors der Humanbiologie

-Doctor rerum biologicarum humanarum-

(Dr. rer. biol. hum.)

vorgelegt von

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Hannover 2022

Angenommen durch den Senat: 09.06.2023

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Tag der mündlichen Prüfung: 09.06.2023

Prüfungsausschuss

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1 Inhalt

2 Abstract

Timo Frett, Title: Artificial gravity through short-arm centrifugation as potential countermeasure for human spaceflight: Feasibility, safety and neuromuscular response

Long-term exposure to weightlessness results in significant musculoskeletal and cardiopulmonary deconditioning which can adversely affect physical performance, crew health, and mission success. Despite intense in-flight physical training, a decline in physical fitness may still occur during prolonged manned spaceflight. Moreover, current exercise countermeasures in space do not address negative consequences of fluid shifts towards the head. Artificial gravity generated via short-arm centrifugation has been proposed as a potential approach to ameliorate multi-systems deconditioning as it reestablishes earth-like downward forces and redistribute fluid towards the lower body. However, Coriolis Forces and a gravity gradient within the body during centrifugation could limit tolerability and safety. Therefore, we conducted ground-based studies to assess feasibility and safety of intermittent centrifugation with and without concomitant physical training.

The primary goal of this thesis is to evaluate the effects of intermittent short-arm centrifugation as countermeasure, both, during passive exposure and in combination with physical training. In particular, we investigated whether daily passive exposure to intermittent (6 x 5min) or continuous (30min) short arm centrifugation is better tolerated in a 60-days bed rest study with head down tilt, which is an established terrestrial model for weightlessness. Furthermore, we analyzed effects of additional training during centrifugation to evaluate whether plyometric exercises such as repetitive jumping at different g-level are tolerated and whether trunk and back muscle exercises with or without centrifugation elicit comparable muscle activity.

In the first study, we assessed cardiovascular loading and subjective tolerability in 16 participants with daily short-arm centrifugation during long-term head-down bed rest as model for microgravity exposure in women and in men. Participants were exposed to daily centrifugation providing artificial gravity equivalent to 1 *g* at the center of mass with either an intermittent (6 x 5min) or a continuous (30 min) protocol. Heart rate and blood pressure were assessed daily during centrifugation along with post subjective ratings for motion sickness and perceived exertion across 960 centrifuge runs in total. Only 10 runs had to be terminated prematurely, 8 in the continuous and 2 in the intermittent protocol mostly due to pre-syncopal symptoms. We conclude that both protocols are tolerable for daily centrifugation during long-term bed rest although intermittent centrifugation appears marginally better tolerated.
To evaluate the effects of short-arm centrifugation in combination with physical training, we conducted two studies using different forms of exercises – plyometric and trunk muscle exercises.
High impact repetitive jump exercises could be particularly efficacious in diminishing bone de-

mineralization during spaceflight. Furthermore, plyometric training involves the cardiovascular system as well as major leg muscles and could contribute to maintain overall fitness of crewmember. However, repetitive jump exercises while supine result in head movements that could exacerbate motion sickness due to vestibular sensations. Jump exercises were conducted with 15 healthy men on a short-arm centrifuge in supine position at constant +1 *g* along the participants body axis (Continuous AG) and with +0.5, +0.75, +1, +1.25 and +1.5 *g* along the participants body axis in randomized order (Variable AG). Jumping in the upright position against terrestrial gravity served as control intervention (Terrestrial gravity). The study was conducted in a randomized controlled cross-over fashion. All participants showed good tolerability to plyometric training during centrifugation despite head movements differed significantly between jumping in supine while spinning and in upright condition in terrestrial gravity.

As current inflight resistance training using the Advanced Resistive Exercise Device (ARED) cannot sufficiently activate trunk musculature atrophy of abdominal and back muscle bear the risk of inter-vertebral disc herniation postflight. In order to evaluate trunk muscle training, a third study were conducted involving 12 participants in a mixed sex cohort that performed abdominal and back muscle training either while supine with constant 1 *g* at the center of mass during short-arm centrifugation or in the upright position without centrifugation. We assessed cardiovascular loading (heart rate, blood pressure), trunk muscle activity as well as subjective motion sickness and perceived exertion. We observed slightly higher systolic and diastolic blood pressure during centrifugation compared to standard upright training. Trunk muscle activation in the supine position during centrifugation was comparable with upright exercising in terrestrial gravity. All participants showed good tolerability and with moderate exertion and good body control during centrifuge-based trunk training.

In summary, we conclude that passive intermittent exposure to Artificial Gravity generated by short-arm centrifugation is well tolerated even on a daily basis. Furthermore, the combination of exercises during centrifugation is also tolerable and has the potential to generate sufficient musculoskeletal and cardiovascular loading. These results, while limited by the small sample size, lay the foundation for future studies investigating the potential of short-arm centrifugation as potential countermeasure for long term spaceflight. In particular, future research should investigate the effects of long-term and regular physical exercise during centrifugation in maintaining physical fitness compared with current exercise countermeasures.

3 Zusammenfassung

Timo Frett, Title: Artificial gravity through short-arm centrifugation as potential countermeasure for human spaceflight: Feasibility, safety and neuromuscular response

Längerfristige Aufenthalte in der Schwerelosigkeit führen zu signifikanten Veränderungen des muskuloskelettalen und kardiopulmonalen Systems, was sich negativ auf die körperliche Leistungsfähigkeit, die Gesundheit der Besatzung und den Erfolg einer Raummission auswirken kann. Trotz eines intensiven körperlichen Trainings in der Schwerelosigkeit kann die körperliche Fitness während eines längeren bemannten Raumflugs abnehmen. Darüber hinaus werden die negativen Folgen der Flüssigkeitsverschiebung zum Kopf hin bei den derzeitigen Trainingsmaßnahmen im Weltraum nicht berücksichtigt. Künstliche Schwerkraft, erzeugt über Kurzarm-Zentrifugation, wurde als Möglichkeit zur Verringerung der körperlichen Dekonditionierung vorgeschlagen, da hierdurch erdähnliche Kräfte wiederhergestellt und die Flüssigkeit in Richtung der unteren Körperhälfte umverteilt wird. Mittels Zentrifugalkraft kann zudem die Trainingsausführung ähnlich wie auf der Erde erfolgen, was zu verbesserten Trainingsreizen für den Muskel- und Knochenerhalt führen kann. Allerdings könnten die Corioliskräfte und der Schwerkraftgradient im Körper während der Zentrifugation die Verträglichkeit und Sicherheit einschränken. Im Rahmen dieser Dissertation wurde mittels Studien die Durchführbarkeit und Sicherheit von Zentrifugation mit und ohne Training erforscht.

Das primäre Ziel dieser Dissertation ist es, die Auswirkungen Kurzarm-Zentrifugation als Gegenmaßnahme sowohl bei passiver Exposition als auch in Kombination mit körperlichem Training zu untersuchen. Insbesondere soll untersucht werden, ob eine tägliche passive Belastung durch intermittierende (6 x 5min) oder kontinuierliche (30min) Zentrifugation in einer 60-tägigen Bettruhe-Studie, als etabliertes Boden-Modell für µG induzierte Veränderungen, besser toleriert werden kann. Darüber hinaus werden die Auswirkungen eines zusätzlichen Trainings während der Zentrifugation untersucht, um festzustellen, ob plyometrische Übungen wie z. B. wiederholtes Springen bei unterschiedlichen g-Werten toleriert werden können und ob Rumpf- und Rückenmuskelübungen mit oder ohne Zentrifugation eine vergleichbare kardiovaskuläre Reaktion und Muskelaktivität hervorrufen.

In der ersten Studie wurde die kardiovaskuläre Belastung und die subjektive Verträglichkeit bei 16 Teilnehmern/innen bei täglicher Kurzarm-Zentrifugation im Rahmen einer 60 Tage Bettruhe-Studie in Kopftieflage untersucht. Die Bettruhe diente hierbei als Simulation für die Abbauprozesse in der Schwerelosigkeit. Die Teilnehmer/innen wurden täglich einer künstlichen Schwerkraft von +1 *g* am Körpermassenschwerpunkt ausgesetzt, entweder in einem intermittierenden (6 x 5 Minuten) oder einem kontinuierlichen (30 Minuten) Protokoll. Während der Zentrifugation wurde täglich die Herzfrequenz, der Blutdruck sowie Bewegungsübelkeit (Motion Sickness) und subjektiven Belastungsempfinden (Borg-Skala) erfasst. Von insgesamt 960 Zentrifugenfahrten im Rahm der Studie mussten

lediglich 10 Läufe, meist aufgrund von präsynkopalen Symptomen, vorzeitig abgebrochen werden - 8 beim kontinuierlichen und 2 beim intermittierenden Protokoll. Im Rahmen der Untersuchung wurde festgestellt, dass grundsätzlich beide Protokolle für die tägliche Zentrifugation während der Bettruhe tolerierbar sind, wobei eine intermittierende Zentrifugation (6 x 5min) geringfügig besser verträglich zu sein scheint.

In zwei weiteren Studien wurden die Auswirkungen der Kurzarm-Zentrifugation in Kombination mit körperlichem Training zu untersucht. Hierbei wurden zwei verschieden Übungsformen – repetitive Sprünge und Rumpfmuskelübungen – jeweils während Zentrifugation im Liegen und aufrecht ohne Zentrifugation durchgeführt.

Repetitive Sprungübungen führen zu hohen Belastungen der Knochenstruktur und könnten so dazu beitragen, die Knochen- Demineralisierung während des Raumflugs zu verringern. Sprungtraining führt zudem zu einer relevanten Aktivierung des Herz-Kreislauf-Systems und der Beinmuskeln, was zum Erhalt der allgemeinen Fitness im All beitragen könnte. Kopfbewegungen aufgrund der Sprungbewegungen unter Zentrifugation könnten jedoch zu einer erhöhten Übelkeit aufgrund des vestibulären Reizes führen. Im Rahmen der Studie führten 15 gesunden Männern auf einer Kurzarm-Zentrifuge in Rückenlage wiederholte Sprungübungen bei konstanten +1 g und bei +0,5, +0,75, +1, +1,25 und +1,5 g am Körpermasseschwerpunkt in randomisierter Reihenfolge aus. Das Springen in aufrechter Position gegen die Erdanziehungskraft diente als Kontrollintervention. Die Studie wurde in einem randomisierten, kontrollierten Cross-over-Verfahren durchgeführt. Alle Teilnehmer zeigten eine gute Verträglichkeit des plyometrischen Trainings auch während der Zentrifugation, obwohl die Intensität der Kopfbewegungen beim Springen in Rückenlage während der Drehung signifikant höher war als beim Springen in der Aufrechten.

Da das derzeitige Widerstandstraining an Bord der Internationalen Raumstation mit dem Advanced Resistive Exercise Device (ARED) die Rumpfmuskulatur nicht ausreichend aktivieren kann, birgt die Atrophie der Bauch- und Rückenmuskulatur in der Schwerelosigkeit das Risiko eines Bandscheibenvorfalls nach dem Flug. Um das Rumpfmuskeltraining unter künstlicher Schwerkraft zu evaluieren, wurde eine dritte Studie mit 12 Teilnehmern durchgeführt, die ein Bauch- und Rückenmuskeltraining entweder in Rückenlage mit konstant +1 g am Körpermasseschwerpunkt während Zentrifugation oder in aufrechter Position ohne Zentrifugation durchführten. Die kardiovaskuläre Belastung (Herzfrequenz, Blutdruck), die Aktivität der Rumpfmuskulatur sowie die subjektive Bewertung von Motion Sickness und wahrgenommener Belastung wurden untersucht. Im Rahmen der Studie wurden leicht höhere systolische und diastolische Blutdruck-Werte während der Kurzarm-Zentrifugation im Vergleich zum Training in der Aufrechten festgestellt. Die Aktivierung der Rumpfmuskulatur in

Rückenlage während des Zentrifugierens war vergleichbar mit dem Training im Stehen unter terrestrischer Schwerkraft. Alle Teilnehmer zeigten eine gute Verträglichkeit und bei mäßiger Belastung eine gute Körperbeherrschung während des zentrifugenbasierten Rumpftrainings.

Zusammenfassend kommen wir zu dem Schluss, dass eine tägliche passive, intermittierende Exposition auf einer Kurzarm-Zentrifuge auch längerfristig gut verträglich ist. Darüber hinaus erschient die Kombination von körperlichem Training und künstlicher Schwerkraft im Rahmen der ambulanten Studien ebenfalls ohne relevante Bewegungsübelkeit möglich und hat zudem das Potential einen relevanten Beitrag zum Erhalt der muskuloskelettalen und kardiopulmonalen Leistungsfähigkeit Belastung zu erzeugen. Diese Ergebnisse sind zwar durch die geringe Stichprobengröße begrenzt, bilden jedoch die Grundlage für künftige Studien, die das Potenzial der Kurzarm-Zentrifugation als mögliche Gegenmaßnahme für den Langzeit-Raumflug untersuchen.
Zukünftige Forschungsprojekte sollten die Auswirkungen von längerfristigem und regelmäßigen körperlichen Übungen unter Zentrifugation besonders im Hinblick auf den Erhalt der körperliche Fitness untersuchen und diese mit den derzeitigen Ergebnissen eines Trainings unter Schwerelosigkeit vergleichen.

4 Introduction

4.1 Human physiology in weightlessness

Space may seem calm, but remains a challenging environment even after 60 years of human spaceflight. Outside Earth's protective magnetosphere, human beings are exposed to massively increased radiation which may elicit complex DNA lesions and oxidative stress possibly predisposing to cancer and cataracts as well as cardiovascular and neurodegenerative disease [1-4]. Beside radiation, other key hazards include isolation and confinement, distance from Earth, a hostile and closed environment, and altered gravity [5]. The latter causes several physiological changes in human physiology leading to a decline in physical fitness. Microgravity mechanically unloads skeletal muscle [6, 7], bones [8, 9], and heart and perturbs the neurovestibular system [10]. Moreover, chronic cephalad fluid redistribution promotes plasma volume loss and may contribute to ocular and cerebral changes, known as spaceflight-associated neuro-ocular syndrome (SANS) [11-13]. Astronauts returning from space may experience significantly reduced aerobic exercise capacity [14, 15] and presyncope or syncope during orthostatic testing or spontaneously while being upright [16] [17, 18]. Prolonged exposure to microgravity unloads the heart such thereby inducing cardiac remodeling [14, 19], which may result in cardiac atrophy with reduced left-ventricular mass [20]. Skeletal muscle volume, strength, and function are impaired after short-term shuttle [21, 22] and long term space flight on the International Space Station

[7, 23-25], thus, lowering physical performance and increasing injury risks. With an average amount of 1 – 2 % per month microgravity-induced bone loss is more pronounced on the legs and spine than on the upper body [9, 26].

Across the decades of human spaceflight, preventive measures, which are referred to as countermeasures in aerospace medicine, have been a cornerstone in reducing microgravity-induced physiological deconditioning [24, 27, 28]. Key elements are provision of axial loading, a well-balanced diet, and intense physical exercises. Early shorter-duration human space missions of less than two weeks like Gemini and Apollo carried small devices for resistance exercises such as rubber cords. More recent and longer duration human space missions on space stations Skylab or Mir also used cycle ergometers or treadmills permitting endurance training (Figure 1). Current inflight exercise countermeasures on the International Space Station (ISS) are prescribed twice-daily including resistance (Figure 2) and aerobic training (Figure 3) [29]. Resistance exercises are performed on the Advanced Resistive Exercise Device (ARED) with up to 2.700 N for bar workouts and 670 N for cable exercises [30]. Additionally, the Russian VELO ergometer provides motor-driven cables with loads up to approx. 290 N [31]. For aerobic training, two cycle ergometers VELO (workload between 100 and 250 W) and CEVIS (workload between 25 and 350 W) as well as treadmills like the COLBERT/T2 (speed up to 20.4km/h) and the BD-2 (up to 20 km/h) can be used [29, 32, 33]. Furthermore, provision of in-flight axial loading by specialized suits (Figure 4) could be a potential countermeasure for spinal elongation and back pain [34]. However, none of the currently applied countermeasures sufficiently mitigates cephalad fluid shifts in microgravity, which predisposes to the spaceflight-associated neuro-ocular syndrome.

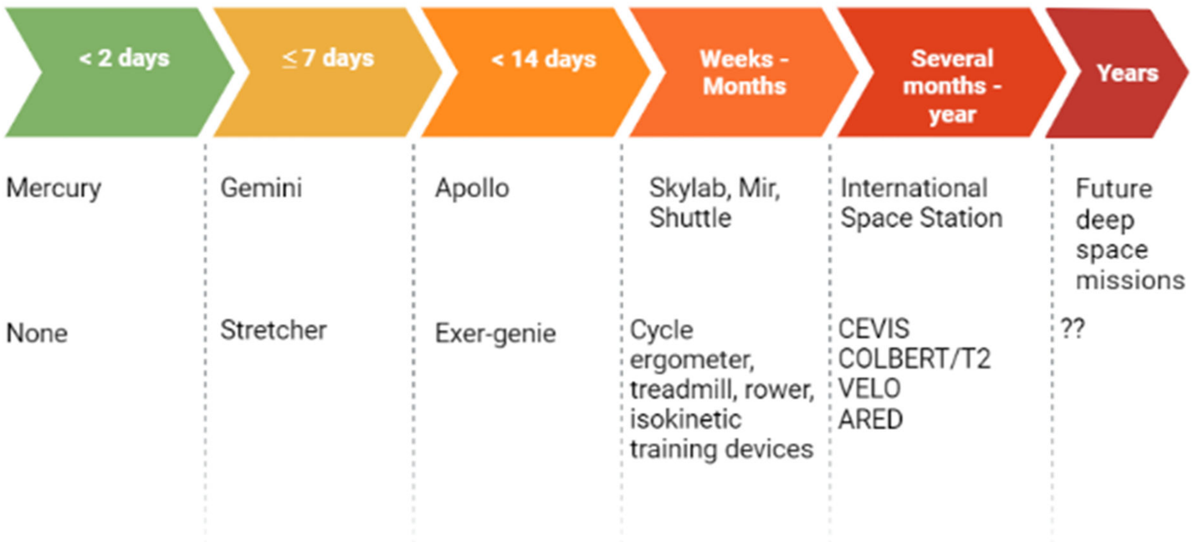

Figure 1: Development of inflight exercise devices across decades of spaceflight (adapted from Hackney et al. [35])

Figure 3: Astronaut Frank De Winne runs on the Combined Operational Load Bearing Resistance Treadmill (COLBERT) (cc: NASA)

Figure 2: Astronaut Steve Lindsey squats using the Advanced Resistive Exercise Device (ARED) (cc: NASA)

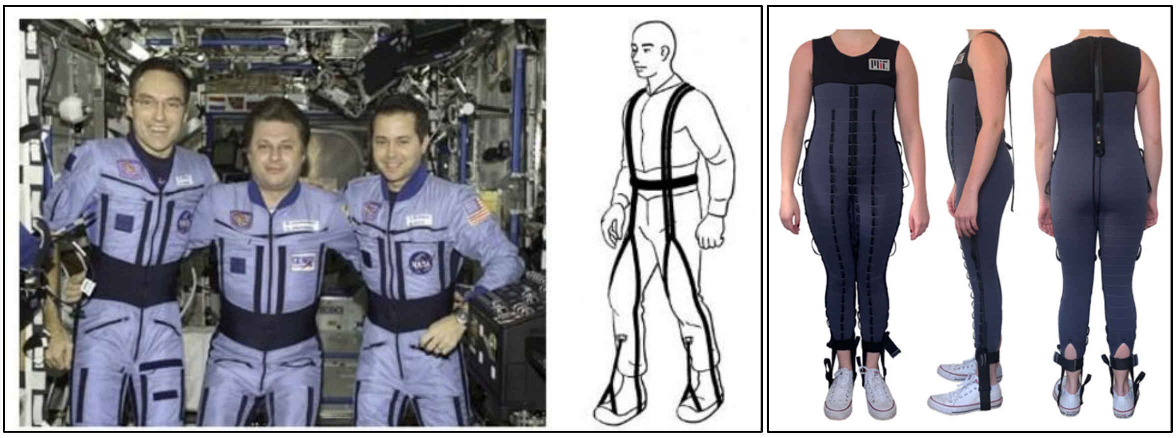

Figure 4: Different concepts of intravehicular suits to provide static loading that mimics Earth gravity. Left: Pinqvin-3 suit on ISS Expedition 4 (image: NASA ISS004-E-9194) [36] Right: Gravity Loading Countermeasure Suit (Skinsuit) [37, 38]

Despite becoming increasingly effective [35], current inflight countermeasures are not sufficient to mimic Earth-like loading and, therefore, do not fully maintain physical fitness [18, 39]. For instance, ISS treadmill running with a harness provides up to 80% axial loading, but results in only 25-46% peak ground reaction forces compared to terrestrial conditions [39]. Advanced Resistive Exercise Device (ARED) appears to have attenuated bone mineral density loss [40] but fails to entirely mitigate musculoskeletal [41] deconditioning. Furthermore, trunk muscle atrophy may contribute to inter-vertebral disc pathology, including disc desiccation and osteophytes [42], and contributes to an apparent increased intervertebral disc herniation risk post-flight [43].

With over 30 human health hazards identified by NASA [5, 44], prolonged exploration missions to Moon or Mars still entail significant risks that could compromise mission success and crea health and performance. Thus, a multi-system countermeasure stimulating all physiological systems (e.g. cardiovascular system, muscles and bones) while reversing cephalad fluid shifts could be transformative.

4.2 Artificial Gravity

The abovementioned inflight training can be described as an array of single-focus countermeasures – each applied in attenuating specific deconditioning components. Artificial gravity generated via short-arm centrifugation has been proposed as a potential approach to ameliorate multi-systems deconditioning. Therefore, there has been much interest in Artificial Gravity as integrated countermeasure to maintain human health and performance during long-duration space missions.

Rotation of a spacecraft (or part of it) generates centrifugal force (*F*) that accelerate a rotating body (*m*) away from the rotational axis. This force is the product of centripetal acceleration that varies with the distance from the center of rotation and the square of the rotation angular velocity ($w^2 * r$) [45].

$$F = m * w^2 * r$$

This force has similar effects on the whole organism and is technically easier to generate by rotation than by linear acceleration. Inside a centrifuge, a constant force vector toward the outside re-establishes a spatial orientation of “up” and “down”. Furthermore, with centripetal acceleration parallel to the body longitudinal axis, centrifugation creates a hydrostatic pressure gradient eliciting an orthostatic challenge [46, 47]. By creating an Earth-like centrifugal force (i.e. 1 g), mechanical loading during training could conceivably provide sufficient postural musculoskeletal stimuli to attenuate muscle and bone deconditioning [48].

However, centrifugation comprises physical constraints that need to be considered. Movements that are not parallel to the rotational axis are affected by Coriolis forces resulting in disturbed body movements and can lead to motion sickness symptoms due to stimulation of the vestibular system [49]. As the amplitude of centripetal acceleration depends on the radial distance, the generated force can lead to significant pressure differences from head to feet level (gravity gradient) causing a reduced orthostatic tolerance time. For example, in the supine position a gravity level of 1 *g* at the head can result in a loading of 2 *g* or more at the level of the feet depending on the participant’s body height and distance from the rotational axis during centrifugation. Another aspect is gravito-intertial acceleration, the resulting vector between centrifugal acceleration and Earth gravity, that affects centrifugation studies on Earth (Figure 5).

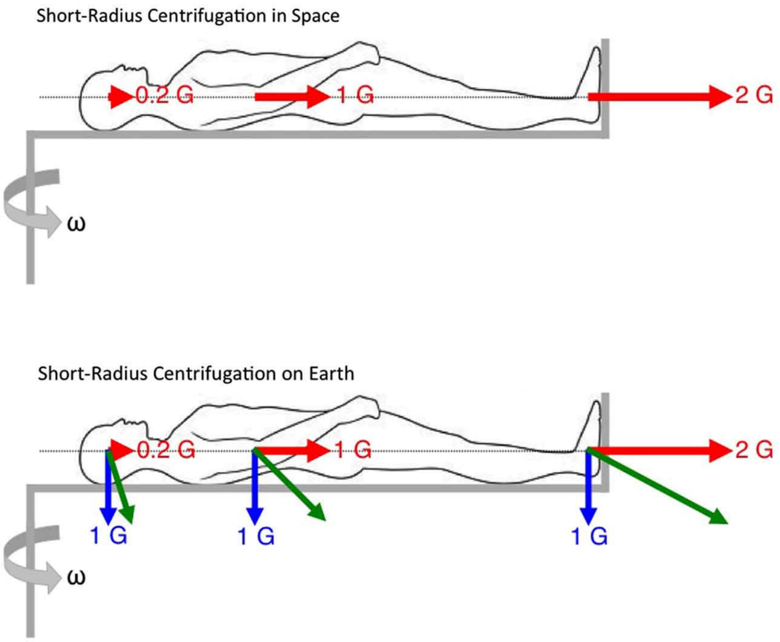

Figure 5: Gravity gradient across the body longitudinal axis and the effects of the gravito-intertial acceleration during supine short radius centrifugation on Earth and in space [50]

Therefore, early centrifuge concepts proposed a large diameter (i.e. < 50 m radius) [51] to expose crewmember to a low gravity gradient without exaggerated side effects from Coriolis forces. Such large installations remain technically and financially challenging and have never been tested in space.

In the last decades, several concepts for short radius centrifugation (< 10 m radius) have been proposed that are technically simpler to realize [46, 47]. With their steep gravity gradients, these installations are not planned for permanent stay but could be used to periodically simulate effects of gravity on the human body as inflight countermeasure. Previous studies showed that human tolerance to short arm centrifugation can be increased up to 26 revolutions per minute by a preceding adaption period [49, 52-54].

To develop and evaluate countermeasures such as centrifugation, experimental bed rest has been established as ground-based model to simulate physiological effects of weightlessness on the human body [55]. To proper simulate headward fluid shifts in microgravity, studies are performed with the bed in a 6° head-down tilt (HDT) position. During bed rest, participants spend 24 hours daily lying in bed, including eating and personal hygiene. While position changes (supine to prone) are allowed, leg movement or frequent contraction are not. Bed rest is categorized according to duration of HDT as follows: 24h – few days (very short duration), 5-14 days (short duration), 15-59 days (medium duration), and 60+ days (long duration) [55]. After HDT bed rest, participants often receive a physiotherapist-guided reconditioning training for gradual restoration of range of motion, whole body strength, speed, and coordination as well as core stability and body posture.

As head movement while spinning is expected to be nauseogenic, most previous studies have tested passive centrifugation as countermeasure. During passive centrifugation, participants are lying supine on the centrifuge with feed outwards and are usually instructed to remain as calm as possible and to prevent head movements. Therefore, the centrifugation effect primarily consists of re-establishing a hydrostatic pressure column along the body. Bed rest studies with passive short arm centrifugation revealed that daily exposure to intermittent 1-2 *g* at heart level for 0.5 – 2h may be effective in mitigating orthostatic intolerance and exaggerated cardiovascular responses after bed rest, such as elevated heart rate and increased muscle sympathetic nerve activity [56-59]. To evoke autonomic control of blood pressure and middle cerebral artery blood flow analogous to standing upright, passive exposure to centrifugation requires relatively high g-level of 2 *g* at feet [60, 61]. Short intervals of 6 times 5 minutes with 1 *g* at heart level seem to be more effective in preserving orthostatic tolerance during bed rest than 30 min continuous centrifugation [59]. However, neither interval nor continuous passive centrifugation attenuated plasma volume loss [62]. Daily 30 min centrifugation with 1 g at Center of Mass show protective effects against bone loss by attenuation of bed rest induced elevated serum markers for bone resorption (sCD200) [63]. With a period of 5 days, the bed rest duration is still too short to evaluate the effects of daily exposure to intermittent short arm centrifugation on bone tissue. Indeed, substantially longer bed rest studies (56-117 days) were required to show protective effects against bone loss using vibration [64] and resistive exercises [65].

Passive centrifugation might be useful in maintaining some aspects of physical performance and health during bed rest or spaceflight. However, it is unlikely that passive centrifugation is as efficacious as current inflight countermeasures with high volume and intensity resistance and aerobic exercise activities in preserving muscular and cardiopulmonary fitness. Solely simulating terrestrial gravity through centrifugation, which resembles still standing on Earth, may not suffice. However, artificial gravity could be combined with physical exercise. Indeed, intense cycle training, knee bends, or heel raises were partially effective in preserving orthostatic tolerance, exercise capacity as well as thigh muscle volume, knee extensor and plantar flexor performance during 4-21 days bed rest [58, 66-70]. Cycle ergometry at 40-60 W with 1.2 *g* at heart level (3.5 *g* at feet) ameliorated plasma volume, orthostatic tolerance time, and VO2max during short duration (4-14 days) bed rest [56, 71]. Ambulatory studies showed that squat exercises can be performed safely during centrifugation and without significant differences in mediolateral knee positioning due to Coriolis effect and negligible motion sickness [72, 73]. Squad exercises in hypergravity (2.25 – 3.75 *g*) generated very high foot forces that were comparable with those produced with weights under normal 1 *g* conditions [74].

In conclusion, artificial gravity using a short arm centrifuge could serve as integrated countermeasure attenuating multi-system physiological deconditioning during extended exposure to microgravity, in particular when combined with physical exercise. Due to its technical complexity, ground based studies need to evaluate the effects of intermittent short arm centrifugation. Based on previous findings, an international roadmap for Artificial Gravity research have been developed [75].

This roadmap has identified several gaps in knowledge future studies need to investigate, such as: a) can Artificial Gravity be tolerated on a daily basis, b) what parameter (g-level, duration, gravity gradient) should be recommended, and c) which training schedules (types of exercises, frequency) are safe and efficacious.

5 Objectives

The overarching objective of this thesis is to contribute relevant results to the field of Artificial Gravity research in particular to a) tolerability of daily intermittent short-arm centrifugation during long-term bed rest and to b) feasibility, tolerability, and physiological effects of exercises during centrifugation.

Thus, we determined whether:

- **a)** daily exposure to intermittent (6 x 5min) or continuous (30min) short arm centrifugation can be better tolerated in a 60-days bed rest study with head down tilt.
- **b)** plyometric exercises such as repetitive jumping during centrifugation at different g-level can be tolerated
- **c)** trunk and back muscle exercises with or without centrifugation elicit comparable muscle activity

For each objective, we conducted a biomedical study. The results of these studies have been published in peer-reviewed scientific journals and are shown in the following chapters.

6 Publications

6.1 Publication 1: Tolerability of daily intermittent or continuous short-arm centrifugation during 60-day 6° head down bed rest (AGBRESA study)

Journal: PLOS ONE, 2020

Author contribution statement:

I designed and conducted the experiment as part of the ESA AGBRESA bed rest study under supervision of Prof. Tegtbur, Prof. Jordan and Dr. Green. I analyzed the data and wrote the original draft that was iterated with Prof. Jordan, Dr. Green, Dr. Mulder and Alexandra Noppe. I submitted the manuscript to the journal and handled the revision process.

PLOS ONE

RESEARCH ARTICLE

Tolerability of daily intermittent or continuous short-arm centrifugation during 60-day 6° head down bed rest (AGBRESA study)

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Citation: Frett T, Green DA, Mulder E, Noppe A, Arz M, Pustowalow W, et al. (2020) Tolerability of daily intermittent or continuous short-arm centrifugation during 60-day 6° head down bed rest (AGBRESA study). PLoS ONE 15(9): e0239228. https://doi.org/10.1371/journal.pone.0239228

Editor: Shigehiko Ogoh, Tokyo Joshi Ika Daigaku Toyo Igaku Kenkyujo Clinic, JAPAN

Received: May 5, 2020

Accepted: September 1, 2020

Published: September 18, 2020

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0239228

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Abstract

Artificial gravity through short-arm centrifugation has potential as a multi-system countermeasure for deconditioning and cranial fluid shifts that may underlie ocular issues in microgravity. However, the optimal short-arm centrifugation protocol that is effective whilst remaining tolerable has yet to be determined. Given that exposure to centrifugation is associated with presyncope and syncope and in addition motion sickness an intermittent protocol has been suggested to be more tolerable. Therefore, we assessed cardiovascular loading and subjective tolerability of daily short arm centrifugation with either an intermittent or a continuous protocol during long-term head-down bed rest as model for microgravity exposure in a mixed sex cohort. During the Artificial Gravity Bed Rest with European Space Agency (AGBRESA) 60 day 6° head down tilt bed rest study we compared the tolerability of daily +1 *Gz* exposure at the center of mass centrifugation, either performed continuously for 30 minutes, or intermittedly (6 x 5 minutes). Heart rate and blood pressure were assessed daily during centrifugation along with post motion sickness scoring and rate of perceived exertion. During bed rest, 16 subjects (6 women, 10 men), underwent 960 centrifuge runs in total. Ten centrifuge runs had to be terminated prematurely, 8 continuous runs and 2 intermittent runs, mostly due to pre-syncopal symptoms and not motion sickness. All subjects were, however, able to resume centrifuge training on subsequent days. We conclude that both continuous and intermittent short-arm centrifugation protocols providing artificial gravity equivalent to +1 *Gz* at the center of mass is tolerable in terms of cardiovascular loading and motion sickness during long-term head down tilt bed rest. However, intermittent centrifugation appears marginally better tolerated, albeit differences appear minor.

Funding: The "Artificial Bed Rest study with European Space Agency" (ABRESA) study was financed by NASA and ESA. Our experiments were included into the study conduction and financed by the DLR Institute of Aerospace Medicine. KBRwyle GmbH provided support in the form of salaries only for author D.G, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

Competing interests: The authors declare no competing interests as KBRwyle GmbH had no role in the study design and thus this does not alter our adherence to PLOS ONE policies on sharing data and materials.

Introduction

Long term space missions elicit multi-system deconditioning including reduced skeletal muscle strength [1], bone mineral density [2], and central blood volume [3–5]. Moreover, sustained cephalad fluid shifts appear to negatively affect ocular health and brain structure, leading to the so-called space associated neuro-ocular syndrome [6, 7]. Furthermore, returning astronauts may experience reduced aerobic capacity [8], and pre-syncopal symptoms indicative of poorer orthostatic tolerance [9]. In an attempt to counter deconditioning on the International Space Station, integrated resistance and aerobic training is prescribed using a number of dedicated devices [10].

Crewmembers train 6–7 days per week with 6–7 resistance and 4–7 cardiovascular sessions per week [11, 12]. Daily training requires approximately 2.5 hours per crewmember including the training, rest periods, and equipment setup, stowage and cleaning. Despite the substantial investment of time, resource and effort this approach is not entirely effective in mitigating musculoskeletal [13], nor aerobic [5, 14] deconditioning, hence physical rehabilitation is required following return to Earth. Moreover, no effective countermeasures against space associated neuro-ocular syndrome currently exist. Thus more effective and ideally more efficient countermeasures are required for future missions to the Moon, and beyond [15].

Artificial gravity through axial acceleration generated by short-arm human provides musculoskeletal loading via the generation of ground reaction forces and an orthostatic challenge through a hydrostatic pressure gradient both of which are absent in microgravity. Indeed, short-arm human centrifugation may attenuate bone, muscle, and cardiovascular deconditioning [16] induced by 6° head-down bed rest. For instance, in short term (5 day) bed rest, an established terrestrial model of cephalad fluid shifts and space-associated deconditioning [17]) studies, daily 30 minutes centrifugation with at least 1 g at the center of mass resulted in no change in postural muscle strength with good tolerability [18, 19]. Furthermore, exposure to artificial gravity appeared to provide protection against post-bed rest orthostatic intolerance [20, 21]. The primary objective of the AGBRESA bed rest study is to compare the protective effects of one single daily bout (30 min) versus multiple daily bouts of AG (6 x 5 min) on physiological functions that are affected by simulated weightlessness during 60 days of bed rest.

However, exposure to exaggerated hydrostatic pressure gravitational gradients induced by centrifugation can elicit presyncopal symptoms or syncope [20, 22, 23]. Furthermore, head movements within a rotating environment are associated with motion sickness symptoms [24]. Yet, to be acceptable as an integrative spaceflight countermeasure, a form of repeated exposure to artificial gravity needs to be tolerable over a long duration mission for both males and females as a number of recent studies have observed sex differences in autonomic cardiovascular control during exposure to orthostatic stress [22, 25–27].

Thus, the aim of our study was to assess the tolerability of daily 30 minute intermittent, or continuous short-arm centrifugation with 1 g at center of mass during 60 days (6°) head-down bedrest in a mixed sex cohort.

Methods

Study subjects

This study is part of the NASA/ESA/DLR 60-day 6° head down bed rest study 'Artificial Gravity Bed Rest with European Space Agency' (AGBRESA) that was conducted from March until December 2019 at the: envihab facility of the Institute of Aerospace Medicine of the German Aerospace Center (DLR) in Cologne, Germany. The study enrolled 24 healthy individuals (16 men, 8 women), who had been submitted to detailed medical and psychological screening having provided written informed consent. The study was approved by the North Rhine Medical Association (2018143 vote from 17.08.2018).

Protocol

Following a 14-day baseline data collection period, study subjects entered 60 days of strict 6° head-down bed rest. At the end of the baseline data collection phase, participants were pseudo-randomly distributed into 3 groups: a control group with no centrifugation, an intermittent centrifugation group, and a continuous centrifugation group. The intermittent centrifugation group underwent daily 6x5 minutes centrifugation with 3 minutes breaks between runs (Fig 1: Left Panel). The continuous centrifugation group underwent a single daily 30 minute centrifugation run (Fig 1: Right Panel).

All centrifugation was performed using the: envihab short-arm human centrifuge with participants exposed to *+1 Gz* at their center of mass (CoM) and thus approximately *+2 Gz* at foot level. Rotational speed of the centrifuge was calculated individually based upon each subject's anthropometry to determine center of mass (ratio center of mass to body height 56% for male/ 54% for female). During ramp up/down phases, (de)acceleration did not exceed $5^{\circ}\ s^{-2}$ to reduce the risk of vestibular-induced tumbling sensations. All subjects underwent two centrifuge familiarization sessions prior to bed rest at the same *+Gz* level as the main study with an intermittent profile of two 5 minute periods separated by a 3 minute break.

Head restrainers were not provided, but participants were instructed to keep their body and head still throughout the centrifugation as much as possible. To assist in maintaining consciousness and limit pre-syncopal symptoms, subjects were trained, prior to the bed rest campaign, in the performance of voluntary isometric calf muscle pump contractions along with (the trunk and gluteal muscles) to promote venous return [28]. However, subjects were instructed to contract only when experiencing significant (pre-syncopal) symptoms such as dizziness or blurred vision.

Cardiovascular monitoring

During centrifugation, heart rate was continuously recorded via a five lead electrocardiogram in addition to periodic brachial blood pressure (Philips IntelliVue® MP2). In the intermittent

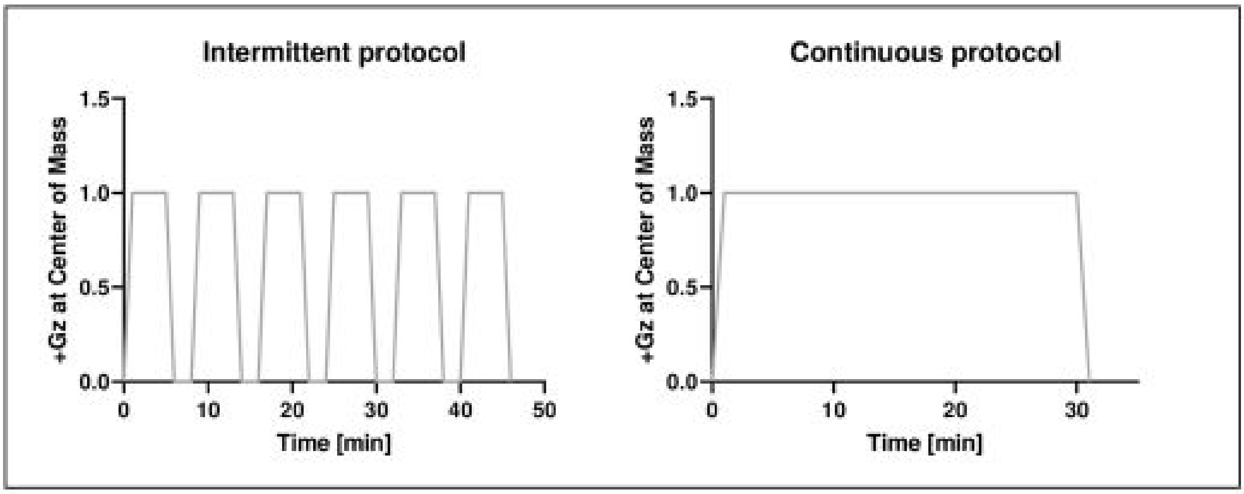

Fig 1. Artificial gravity was generated by centrifugation with +1Gz at center of mass and approx. +2Gz at feet. Participants were randomly assigned to an intermittent centrifugation group with 6 x 5 min centrifugation with 3 minute breaks (left side) and a continuous group with 30 min centrifugation (right side).

https://doi.org/10.1371/journal.pone.0239228.g001

centrifugation group, blood pressure was recorded 2 minutes after each plateau (*+1 Gz* at center of mass), and in the continuous centrifugation group 2 minutes after the plateau was achieved and every 5 minutes thereafter. Mean heart rate, systolic and diastolic blood pressure were calculated for each first measurement intervals during centrifugation on bed rest days 1, 30 and 60 and compared between intervention groups.

Documentation of all adverse events including premature stops, pre-syncopal signs or cardiac dysrhythmias was performed to facilitate evaluation of tolerability.

Subjective tolerability assessment

General motion sickness susceptibility questionnaire short-form (MSSQ-SF) [29] was determined prior to the head down tilt bed rest including both childhood (MSA) and adulthood (MSB) sub-scores. In both centrifuge groups, Subjective Motion Sickness Ratings (MS: 0 "I am feeling fine" to 20 "I am about to vomit") [30] and rate of perceived exertion (RPE: 6 "No exertion at all" to 20 "Maximal exertion") [31] directly after every centrifuge run during bed rest were recorded. Furthermore, Motion Sickness Assessment Questionnaire (MSAQ), Positive and Negative Affect Schedule (PANAS) and Epworth Sleepiness Scale (ESS) were obtained on a weekly basis directly before, and after centrifugation. MSAQ was employed to determine (1 to 9 max) various dimensions (e.g. gastrointestinal) of motion sickness [32]. PANAS was used to assess the effect of centrifugation upon mood. Participants rated each item on a Likert scale from 1 "not at all" to 5 "very much". The ESS (via rating from 0 (non-) to 3 "high chance of dozing" in 8 contexts) was used to evaluate "drowsiness" since it is a cardinal symptom of motion sickness [33–35]. Furthermore, whenever a centrifuge run was terminated prematurely, the reason was recorded.

Statistical analysis

Generalized linear mixed models with auto-regressive error AR (1) were used to determine if there was an effect of bed rest (time effect) and intervention (intermittent vs. continuous group). Mean values were reported with standard deviation. All residual plots were evaluated using Kolmogorov-Smirnov with none displaying large deviations from normality. All statistical tests were conducted using IBM SPSS version 21 (IBM Corp., USA) with $\alpha < 0.05$ indicating statistical significance.

Results

The average spin rate required to generate *+1 Gz* at the center of mass was 30.5 ± 1.0 rpm with radii within 1729–2113 mm at the foot plate. The 16 participants allocated to the two centrifuge groups comprised 10 men and 6 women (71.6 ± 7.4 kg, 33 ± 9.9 yrs, 173 ± 8.8 cm) who experienced 960 centrifuge runs in total.

No serious adverse medical events occurred. However, a total of 10 centrifuge runs (1%, involving 6 different subjects) had to be terminated prematurely; eight runs in the continuous group and two runs in the intermittent group (Fig 2). Of the 10 terminated runs, seven runs–five in the continuous group and two in the intermittent group—had to be terminated due to pre-syncopal signs or symptoms, including significant drop of blood pressure, reporting of tunnel vision and/or lightheadedness. Only one centrifuge run in the continuous group had to be stopped due to severe motion sickness (subsequent MS score of 18/20). Two runs in the continuous group had to be terminated prematurely due to pain resulting from a recent muscle biopsy procedure performed for a different experiment within the bed rest campaign.

No clinically significant cardiac dysrhythmias were observed during centrifugation. During continuous centrifugation, two participants demonstrated frequent isolated premature

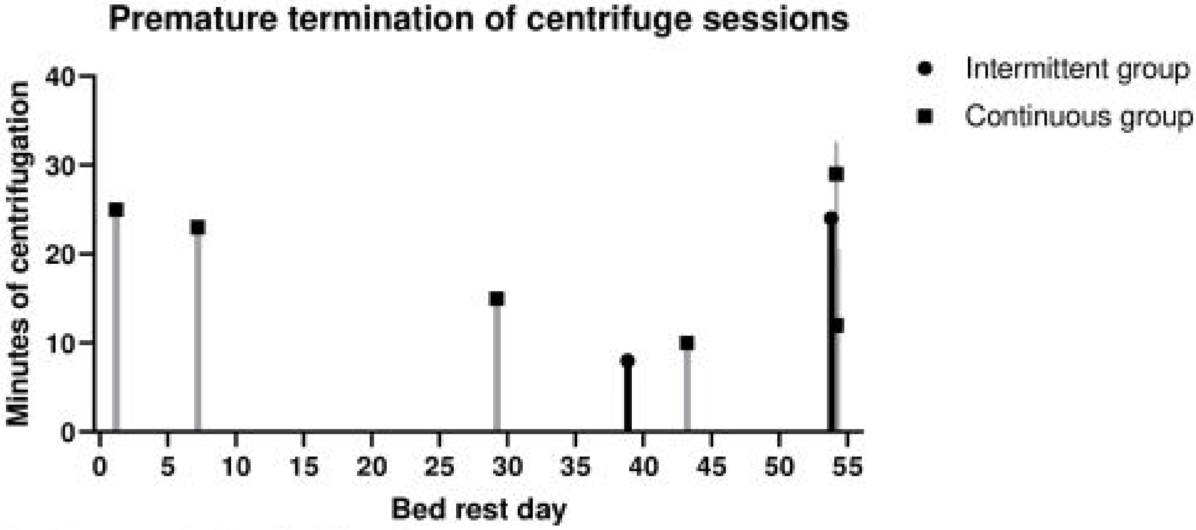

Fig 2. Premature terminations of centrifuge sessions.

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ventricular complexes on 14 non-consecutive days between bed rest days 5 and 51. Two participants in the continuous group and one in the intermittent centrifugation group exhibited occasional premature atrial complexes, but there was no apparent increase in incidence over time. All subjects were, however, able to resume centrifuge training on subsequent days after a termination.

Comparisons of the initial cardiovascular reactions after 2 minutes of centrifugation on bed rest days 1, 30 and 60 revealed significant effects during bed rest for mean heart rate. Mean heart rates were significantly affected by time for the continuous ($F = 14.950$, $p < 0.001$, dfs = 14.073) but not for the intermittent group during bed rest ($F = 1.558$, $p = 0.242$, dfs = 15.281). Thus mean heart rate was numerically higher in the continuous group on bed rest day 60 but not significant (continuous group: 100.5 ± 18.5 vs. intermittent group: 86.9 ± 5.9, ($t(14) = -1.986$, $p = 0.67$) (Table 1). We observed no significant differences in systolic and diastolic blood pressure.

Overall MSSQ scores were similar ($p = 0.211$) prior to bed rest with 3.5 ± 5.4 (MSA 1.9 ± 2.7; MSB 1.6 ± 2.7) for the intermittent centrifugation, 6.0 ± 3.7 (MSA 2.9 ± 2.4; MSB 3.1 ± 2.1) for the continuous centrifugation, and 4.7 ± 4.1 (MSA 2.8 ± 2.8; MSB 1.9 ± 3.0) for the control group.

Daily motion sickness scores were significantly higher in the continuous centrifugation group during bed rest ($F = 92.8$, $p = 0.001$, dfs = 202.5) with no effect of bed rest time

Table 1. Comparison of mean values for heart rate, systolic and diastolic blood pressure during the first 2 minutes of centrifugation at the beginning, middle and end of bed rest.

	Bed rest phase					
	Begin		Middle		End	
	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group
Heart rate	80.3 ± 8.4	82.4 ± 14.9	86.3 ± 12.7	99.13 ± 18.6	86.9 ± 5.9	100.5 ± 18.5
Systolic blood pressure	119.3 ± 13.4	111.9 ± 41	122.3 ± 10.4	128.8 ± 7.5	130.5 ± 13.5	132.4 ± 11.1
Diastolic blood pressure	76.6 ± 5.9	80.8 ± 9.5	81.8 ± 4.5	84.3 ± 6.3	88.1 ± 8.2	93.8 ± 11.9

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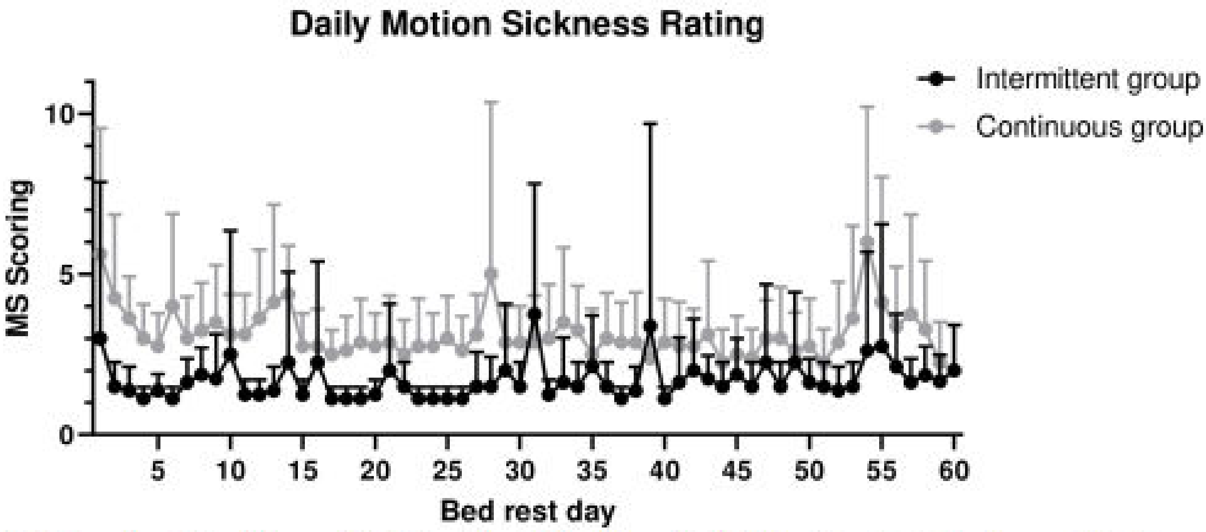

Fig 3. Mean values with standard error of daily Motion Sickness (MS) rating immediately following intermittent and continuous centrifugation during 60 day bed rest in the intermittent and in the continuous centrifugation group.

https://doi.org/10.1371/journal.pone.0239228.g003

(F = 0.268, p = 0.605, dfs = 217.2) (Fig 3). Pairwise comparison revealed higher motion sickness scores in the continuous (3.05 ± 0.11) compared to the intermittent centrifugation group (1.58 ± 0.11) (p = 0.001).

No significant differences in RPE, MSAQ, PANAS or ESS scores were observed during the bed rest phase neither in either nor between groups (Fig 4, Table 2).

Discussion

We evaluated the tolerability of daily artificial gravity via short-arm centrifugation as a potential countermeasure against deconditioning induced by 60 day bed rest provided either as a

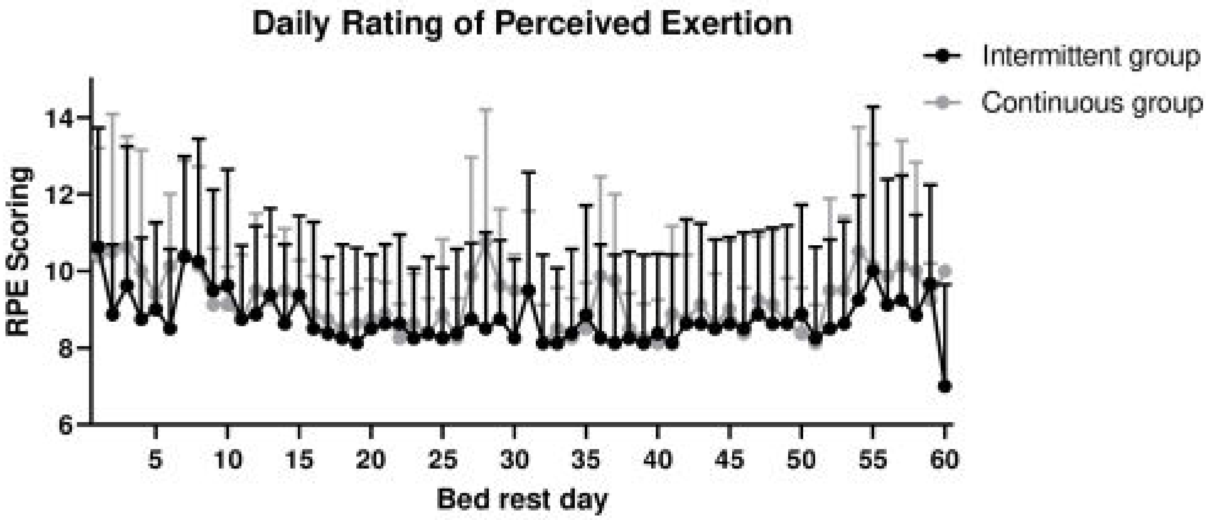

Fig 4. Mean values with standard error of daily Rating of Perceived Exertion (RPE) rating immediately following intermittent and continuous centrifugation during 60 day bed rest in the intermittent and in the continuous centrifugation group.

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Table 2. Comparison of tolerability assessment (MSAQ, ESS, PANAS) of both centrifuge intervention groups at the beginning, middle and end of bed rest.

	Bed rest phase					
	Begin		Middle		End	
	Intermittent group	Continuous group	Intermittent group	Continuous group	Intermittent group	Continuous group
MSAQ						
- Overall	21.96 ± 6.7	20.66 ± 3.7	16.32 ± 2.2	21.76 ± 6.1	19.71 ± 4.4	17.89 ± 2.5
- Gastrointestinal	21.18 ± 8.9	21.53 ± 4.5	12.50 ± 1.0	22.22 ± 7.6	14.93 ± 3.1	18.06 ± 3.4
- Central	18.06 ± 6.0	16.95 ± 3.3	13.89 ± 4.1	17.52 ± 5.7	16.11 ± 6.0	14.17 ± 2.5
- Peripheral	21.30 ± 5.5	25.92 ± 8.2	15.74 ± 0.6	28.39 ± 9.9	20.37 ± 3.7	18.05 ± 1.8
- Sopite-related	28.12 ± 7.9	20.49 ± 3.9	23.61 ± 4.1	21.61 ± 3.5	28.47 ± 6.4	22.22 ± 3.4
ESS	12.5 ± 1.3	12.25 ± 1.2	15.25 ± 2.3	12.56 ± 1.4	14.25 ± 2.0	13.36 ± 1.8
PANAS (Positive Affect)	23.88 ± 2.6	25.75 ± 2.7	24.5 ± 2.0	24.11 ± 2.0	24.50 ± 3.1	22.88 ± 3.2
PANAS (Negative Affect)	15.50 ± 1.6	13.63 ± 0.5	13.13 ± 0.4	14.44 ± 1.1	15.00 ± 1.2	14.25 ± 0.8

https://doi.org/10.1371/journal.pone.0239228.t002

single 30 min run or as 6x5 minute runs. Our main findings were that both centrifuge interventions were well tolerated (in both males and females), with no serious adverse events and <1% run termination due to pre-syncopal signs. Only a single run was stopped due to motion sickness, with two terminated due to pain from an experimental procedure from another protocol. All subjects were, however, able to resume centrifuge training on subsequent days. Daily motion sickness scores were low, but significantly higher in the continuous group across bed rest. MSAQ, PANAS or ESS scores were low in both centrifugation groups with no difference between groups indicative of good long-term tolerability.

Short-arm centrifugation induces an orthostatic stress on the cardiovascular system that markedly differs from standing on Earth. While the body experiences 1 g terrestrial gravity throughout with standing, the gravitational stimulus increases in a graded fashion from the head towards the feet during short-arm centrifugation [1].

Yet, previous studies have not observed major differences in cardiovascular regulation when standing and during short-arm centrifugation [36]. In our study, pre-syncope occurred in only a few runs and we did not observe overt syncope. Pre-syncope did occur slightly more frequently in the continuous centrifugation group, suggesting that the breaks in the intermittent protocol may contribute to improved orthostatic tolerance during centrifugation. However, in both groups the incidence was very low, potentially due to the fact that subjects were permitted to perform isometric leg muscle pump exercises when experiencing symptoms. In the absence of countermeasures, bed rest deconditioning is associated with markedly reduced orthostatic tolerance [37]. Interestingly, we did not observe worsening tolerability of short-arm centrifugation over time suggesting that daily artificial gravity may have maintained orthostatic tolerance but this requires further evaluation including specific testing of orthostatic tolerance during bed rest [19].

While we did not observe higher degree cardiac dysrhythmias during centrifugation, frequent isolated premature ventricular complexes in two participants in the continuous centrifugation group are noteworthy as long-arm centrifugation nor orthostatic stress imposed by standing are associated with cardiac dysrhythmias in otherwise healthy persons [38, 39]. Whether premature ventricular complexes were triggered by short-arm centrifugation or other stresses resulting from the complex multi-experimental study cannot be discerned. It is reassuring that orthostatic stress imposed by standing or long-arm centrifugation rarely produces significant cardiac dysrhythmias in otherwise healthy persons [38, 39]. While presyncope occurred slightly more frequently in the continuous centrifugation group the incidence is too small to perform a comprehensive study on intervention group effects. Premature termination of a centrifugation runs were also (albeit rarely) caused by pain due to muscle biopsy from another experiment that were also associated with higher perceived exertion ratings on bed rest days 6 and 55, corroborated by subject comments documented by the attending physician.

As the objective of the present study was to expose subjects to *+1 Gz* at the center of mass and approximately *+2 Gz* at the level of the feet, spin rates during centrifugation were relatively high. During such spin rates head movements can exacerbate motion sickness due to induced conflicts between acceleration (gravity) perception and other sensory inputs [24, 40–42]. However, in our study these spin rates were well tolerated even without physical head restraint or head cover to put subjects into darkness which is commonly used. Remarkably, despite the fact that participants were requested, but not physically prevented from moving the head, only a single centrifuge run was stopped due to severe motion sickness symptoms. Indeed, daily ratings for motion sickness did not indicate increases over time in discomfort due to centrifugation-induced cross-coupled sensations.

Thus, this suggests that by limiting centrifugal acceleration to $5^{\circ}\,s^{-2}$ the risk of significant motion sickness is low, even in the intermittent group whom were exposed to multiple acceleration and decelerations within each session. Thus, why higher (albeit not high) motion sickness ratings were reported in the continuous group is unknown and warrants further study–particularly as MSAQ scoring did not differ significantly between groups. Potential limitations of our study are overestimation of questionnaire results as direct comparison with the control group were not obtained due to the complexity of the study. Although our results may be in accordance with other studies showing high levels of vestibular adaption to high speed short radius rotations over time [12, 30, 43] that may also underlie the low scores for PANAS negative affects–suggesting potentially good long-term tolerability.

In conclusion short-arm centrifugation was well tolerated (in both males and females) during 60-days of 6° head-down tilted bedrest. 30 minute intermittent centrifugation appears to be slightly better tolerated compared to equivalent continuous centrifugation indicated by lower motion sickness scores and fewer run terminations. However, the differences were small and require further study in a mixed sex cohort both as 'passive' countermeasures and potentially with concurrent exercise as this may augment effectiveness against multi-systems deconditioning.

Supporting information

S1 File. AGBR_quest_results: List of all results from questionnaires ESS, MSAQ and PANAS in a comprehensive manner.
(XLSX)

S2 File. Medical data: List of all medical data including heart rate and blood pressure pre and post centrifugation as well as within first two minutes during centrifugation.
(XLSX)

S3 File. MS scoring HDT: Recording of motion sickness questionnaires during 60 days of head down tilt bed rest.
(CSV)

S4 File. RPE scoring HDT: Recording of perceived exertion questionnaires during 60 days of head down tilt bed rest.
(CSV)

Acknowledgments

The authors would like to thank the DLR centrifuge team and DLR study team for their work in the experiment. Further gratitude belongs to NASA and ESA for their cooperation.

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6.2 Publication 2: Motion sickness symptoms during jumping exercise on a short-arm centrifuge

Journal: PLOS ONE, 2020

Author contribution statement:

I designed and conducted the experiment together with the DRL centrifuge team (Michael Arz, Alexandra Noppe, Guido Petrat) under supervision of Prof. Tegtbur and Prof. Jordan. The experiment was part of a centrifuge study from the University of Konstanz funded by the DLR Space Administration. I did the data analysis with help from Dr. Green. I wrote the original draft that was iterated with Prof. Jordan, Dr. Green, Alexandra Noppe, Andreas Kramer and Prof. Jordan. I submitted the manuscript to the journal and handled the revision process.

PLOS ONE

RESEARCH ARTICLE

Motion sickness symptoms during jumping exercise on a short-arm centrifuge

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OPEN ACCESS

Citation: Frett T, Green DA, Arz M, Noppe A, Petrat G, Kramer A, et al. (2020) Motion sickness symptoms during jumping exercise on a short-arm centrifuge. PLoS ONE 15(6): e0234361. https://doi.org/10.1371/journal.pone.0234361

Editor: Sakamuri V. Reddy, Charles P. Darby Children's Research Institute, 173 Ashley Avenue, Charleston, SC 29425, USA, UNITED STATES

Received: March 12, 2020

Accepted: May 22, 2020

Published: June 11, 2020

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0234361

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Abstract

Artificial gravity elicited through short-arm human centrifugation combined with physical exercise, such as jumping, is promising in maintaining health and performance during space travel. However, motion sickness symptoms could limit the tolerability of the approach. Therefore, we determined the feasibility and tolerability, particularly occurrence of motion sickness symptoms, during reactive jumping exercises on a short-arm centrifuge. In 15 healthy men, we assessed motion sickness induced by jumping exercises during short-arm centrifugation at constant +1 *Gz* or randomized variable +0.5, +0.75, +1, +1.25 and +1.5 *Gz* along the body axis referenced to center of mass. Jumping in the upright position served as control intervention. Test sessions were conducted on separate days in a randomized and cross-over fashion. All participants tolerated jumping exercises against terrestrial gravity and on the short-arm centrifuge during 1 *Gz* or variable *Gz* at the center of mass without disabling motion sickness symptoms. While head movements markedly differed, motion sickness scores were only modestly increased with jumping on the short-arm centrifuge compared with vertical jumps. Our study demonstrates that repetitive jumping exercises are feasible and tolerable during short-arm centrifugation. Since jumping exercises maintain muscle and bone mass, our study enables further development of exercise countermeasures in artificial gravity.

Introduction

Lack of terrestrial gravity during space travel produces multiple physiological adaptations challenging astronaut performance and health. The issue is particularly relevant for future deep space missions. Countermeasures relying on strength and endurance exercises help maintaining skeletal muscle [1] and cardiopulmonary fitness [2]. Current exercise countermeasures on the International Space Station are individually tailored for each astronaut. In general, an integrated resistance and aerobic training schedule is prescribed [3–5]. Crewmembers typically exercise six days per week, which consumes significant crew time and resources [6,7]. Yet,

Funding: The study was part of the German National Centrifuge Program 2 financed by the Space Administration of the German Aerospace Center. KBRwyle GmbH provided the salary for D.G but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: KBRwyle GmbH provided the salary for D.G but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors declare no competing interests as KBRwyle GmbH had no role in the study design and thus this does not alter our adherence to PLOS ONE policies on sharing data and materials.

with current countermeasures, lower limb bone mass and muscle volume was still reduced after 16–28 weeks in space [8]. Moreover, countermeasures for potentially serious changes in ocular and brain structures likely resulting from chronic cephalad fluid shifts, the so called space associated neuro-ocular syndrome [9, 10], have not been established. Other approaches such as passive axial loading suits or lower body negative pressure systems [11–13] affect only parts of the complex physiological adaption process during long-term space missions.

Artificial gravity elicited through axial acceleration on short-arm human centrifuges, which distributes fluids to the lower part of the body, has been developed as potential countermeasure. Centrifugation may also help maintaining coordination and vestibular function, which are crucial when arriving on other celestial bodies. Yet, centrifugation when simply added to current countermeasures may not be practical given the tight schedule of astronauts. Combined centrifugation and physical exercise may be more efficient. Because reactive jumps appear to maintain skeletal muscle as well as bone mass in bed rest [5], jumping exercises during centrifugation are particularly promising. However, exercise-induced head movements within a rotating environment can produce severe motion sickness symptoms or illusory sensations through cross-coupled angular accelerations of semi-circular canals [6]. The issue is complicated by the steep g gradient away from the rotation axis during short-arm centrifugation [7]. Leg press exercises were tolerated during centrifugation, however, subjects were restrained to avoid head movements [8]. Therefore, the aim of our study was to determine the feasibility and tolerability of reactive jumping exercises during short-arm human centrifugation.

Methods

Study participants

We included 15 healthy men (26.4 ± 5.8 yrs; 180.9 ± 4.0 cm; 77.2 ± 5.8 kg) who were naïve to jumping exercises during centrifugation. Prior to the study, participants completed a brief medical questionnaire detailing their drug and medical history and passed a standardized centrifuge medical screening that includes clinical-chemical analyses of blood and urine, stress electrocardiogram, and orthostatic testing. Participants were excluded if they were in pain, or had any significant current or history of musculoskeletal, cardiovascular or neurological disorder or injury that could affect the ability to perform exercise. All participants were recreationally active (engaging in a minimum of two sport sessions per week) in order to facilitate exercise performance and minimize risk of injury during centrifugation. All participants gave written informed consent to participate in the study. The study was approved by the North Rhine ethical committee (Ref: 2017122).

Protocol

Participants attended to the laboratory at: envihab (DLR, Cologne, Germany) on four testing sessions separated by at least three resting days to allow for muscle recovery. In a fifth session participants ran on a treadmill at the German Sports University in Cologne. Participants were not permitted to take anti-emetic medication (i.e. scopolamine) and were offered light food (bananas, cereal bars) and non-sparkling water during each protocol to ensure hydration and glycaemia. Our experiment on motion sickness was part of a broader physiological investigation of jumping exercises during centrifugation that will be published elsewhere. Briefly, we compared effects of jumping exercises in the supine position on a short-arm centrifuge during spinning at different gravity level with jumping in upright position in terrestrial gravity (see Table 1).

Table 1. Exercise conditions for each participant.

Condition	Description
Terrestrial Gravity	15 x 15 vertical jumps in terrestrial gravity
Continuous AG	15 x 15 jumps at constant +1 Gz* at CoM
Variable AG	SAHC: 3 x 15 jumps at +0.5 Gz* 3 x 15 jumps at +0.75 Gz* 3 x 15 jumps at +1 Gz* 3 x 15 jumps at +1.25 Gz* 3 x 15 jumps at +1.5 Gz* in randomized order

*The value refers to Gz at the center of mass

https://doi.org/10.1371/journal.pone.0234361.t001

Prior to recording, participants were familiarized with equipment and testing procedures including a brief centrifugation run. In two testing sessions, subjects performed jumping exercises in artificial gravity (AG) on the DLR-short-arm centrifuge at constant +1 *Gz* along the subject´s body axis (Continuous AG) and with +0.5, +0.75, +1, +1.25 and +1.5 *Gz* along the subject´s body axis in randomized order (Variable AG). Jumping in the upright position against terrestrial gravity served as control intervention (Terrestrial gravity). The study was conducted in a randomized controlled cross-over fashion.

Participants performed jumping exercises in the supine position on the short-arm centrifuge using a horizontal sledge (Figs 1 and 2) against a fixed footplate. The jumping sledge was attached to the short-arm centrifuge via low friction bearings that by riding along rails permitted linear movements along the centrifuge arm (Fig 3A). In addition, the sledge allowed for pitch at participants´ center of mass to facilitate natural jumping movements (Fig 1).

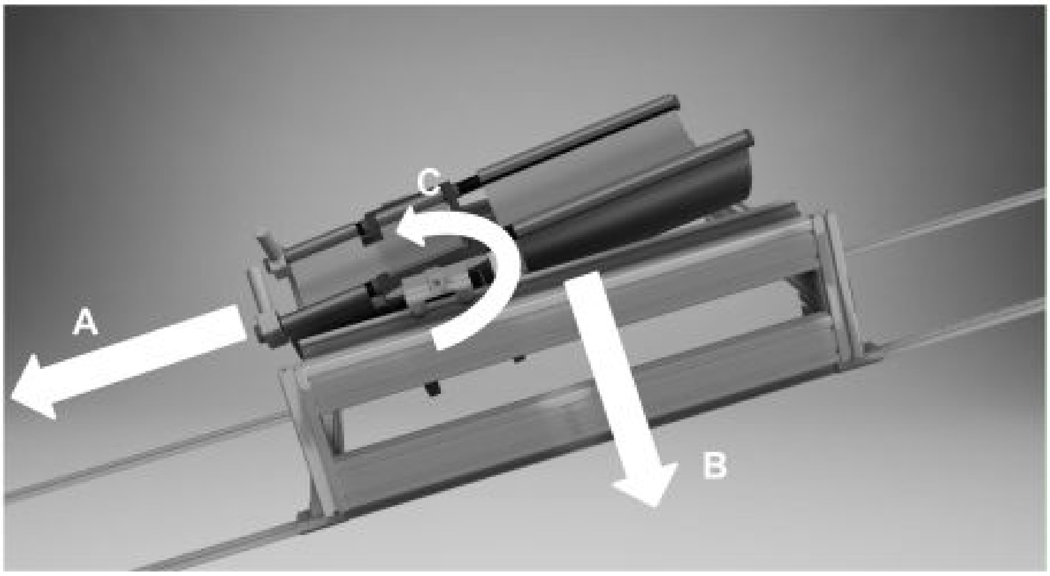

Fig 1. Schematic of the jumping sledge used on the short-arm human centrifuge. Participants were secured in supine position with a safety belt controlling their movement using two hand grips while jumping against a footplate mounted to the centrifuge. Due to the sledge design, movements along the centrifuge radius (A) against earth's gravity (B) and in pitch axis around the center of mass (C) are possible.

https://doi.org/10.1371/journal.pone.0234361.g001

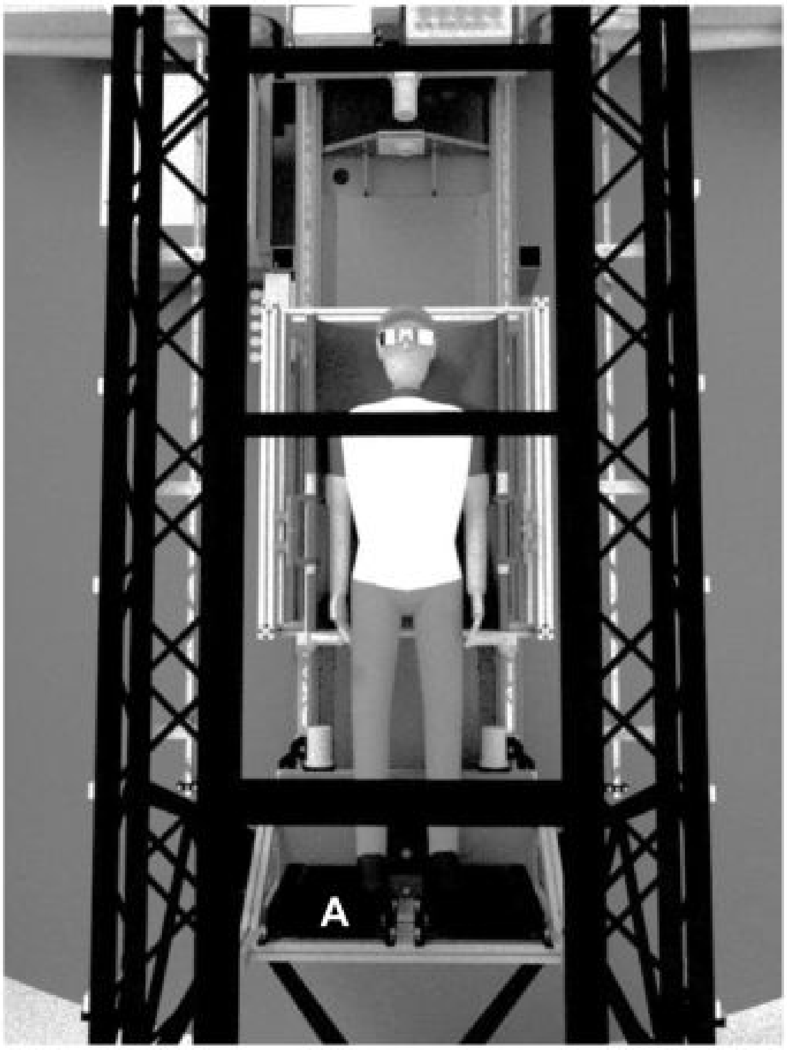

Fig 2. Presentation of participants position on the short-arm human centrifuge in bird's-eye perspective. During centrifugation participants performed jumping exercises against a footplate (A).

https://doi.org/10.1371/journal.pone.0234361.g002

Participants were fastened on the sledge by safety belts around hip. The head was not restrained. Each centrifugation session lasted approximately 30 min. In protocol 2, each *G*–level lasted for around 6 min. Onset and offset acceleration of the centrifuge were 0.1 *G*/sec. We terminated centrifugation when participants demonstrated pre-syncopal signs or symptoms.

Data acquisition and analysis

During centrifugation, five lead electrocardiogram, brachial cuff blood pressure, finger pulse oximetry (Philipps IntelliVue®), and a live video feed were continuously monitored subjects by an experienced physician.

Fig 3. Participant's jumping position during (A) continuous or variable centrifugation on the short-arm human centrifuge and (B) vertically against terrestrial gravity.

https://doi.org/10.1371/journal.pone.0234361.g003

We assessed tri-axial (pitch, yaw, and roll) head movement velocities throughout using a wearable inertial sensor (Shimmer3, Shimmer, Dublin, Ireland) secured with an elasticated band on the forehead. We determined motion sickness susceptibility prior to the study using the Motion Sickness Susceptibility Questionnaire (MSSQ) short-form [10] that yields MSA (based on childhood experience (before age 12) and MSB for that over the last 10 years (max score = 54).

Directly before, and immediately following each condition, participants completed Subjective Motion Sickness Rating, Motion Sickness Assessment Questionnaire (MSAQ), Positive and Negative Affect Schedule (PANAS), and Epworth Sleepiness Scale (ESS) questionnaires. Subjective Motion Sickness Rating's range from 0 "I am feeling fine" to 20 "I am about to vomit" [14]. The MSAQ was used to measure (1 to 9 max) various dimensions (e.g. gastrointestinal, sopite) of motion sickness [15]. PANAS was used to measure the effect of symptoms induced by jumping upon mood. Participants rated each item on a Likert scale from 1 "not at all" to 5 "very much". The ESS (which via rating from 0 (non-) to 3 "high chance of dozing" in 8 contexts) since "drowsiness" is a cardinal symptom of motion sickness [16–18]

In addition, participants were asked regularly during centrifugation whether they were experiencing any motion sickness symptoms, and to report any unexpected symptoms such as tunnel vision or tumbling sensations.

During centrifugation five lead ECG (Philipps IntelliVue®), cuff blood pressure and SpO_2 as well as a live video feed were used to continuously monitor subjects by an experienced physician. Any run where participants demonstrated pre-syncopal symptoms was terminated immediately.

Statistical analysis

Mean head movement (Pitch, Yaw, Roll) velocities were compared between jumping sessions 1–15 for each condition using analysis of variance with repeated measurement. All questionnaire pre and post data was compared between conditions per participant. Pre-data represented scoring from every questionnaire before starting of the individual condition and post-data for every questionnaire after completion of each condition. Non-parametric tests (Friedman's Chi-Square) were performed to evaluate whether there was an effect of condition. If significant differences across conditions were observed, post-hoc tests with pairwise comparisons using Dunn-Bonferroni were performed to determine which condition was significant different.

All statistical tests were conducted using SPSS version 21 (IBM Corp., USA) with $\alpha < 0.05$ indicating significance.

Results

All participants tolerated well jumping exercises against terrestrial gravity and on the short-arm centrifuge during both, the continuous and the variable centrifugation protocol. Only one subject experienced presyncopal symptoms requiring termination of the Variable AG protocol but completed all other protocols without similar symptoms. No disabling motion sickness symptoms occurred that required termination of testing. Serious adverse events did not occur.

Mean head movement velocities in pitch axes did not differ between centrifugation protocols (Fig 4) but compared to terrestrial condition ($p = 0.000$, dfs = 14). In the eccentric phase of the jumps, mean positive peak pitch angular velocity (Fig 5) was significantly greater during continuous ($t(14) = 5.06$, $p < 0.001$) and variable centrifugation ($t(14) = 6.27$, $p < 0.001$) compared to the terrestrial control condition. During concentric movements against the centrifuge´s gravity vector, mean negative pitch angular velocity was also significantly greater in continuous ($t(14) = -8.503$, $p < 0.001$) and variable centrifugation protocols ($t(14) = -3.055$, $p = 0.009$) compared with the control intervention. We observed no significant changes in head movements across time, $F = 0.827$, $p = 0.643$, partial $\eta 2 = 0.045$, $n = 15$ (Greenhouse-Geisser).

No participant reported motion sickness before the training sessions commenced. Motion Sickness Susceptibility (MSSQ) scores were 10.84 ± 4.52 with sub-scores for MSA (5.68 ± 2.70) and MSB (5.37 ± 2.93).

After the interventions, Subjective Motion Sickness Ratings were low with 1.33 ± 0.48 following Terrestrial gravity intervention, 2.53 ± 1.45 following Continuous AG, and 2.15 ± 1.14 following Variable AG. Post-hoc analysis (Dunn-Bonferroni) across conditions showed that

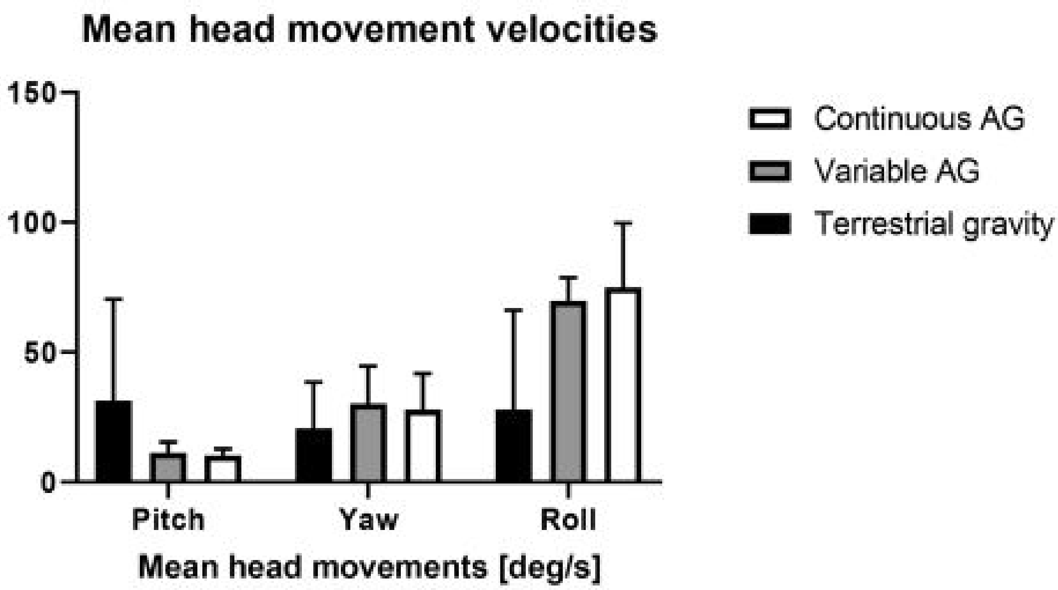

Fig 4. Mean (± SD) head movement velocities in roll, yaw and pitch for each condition.

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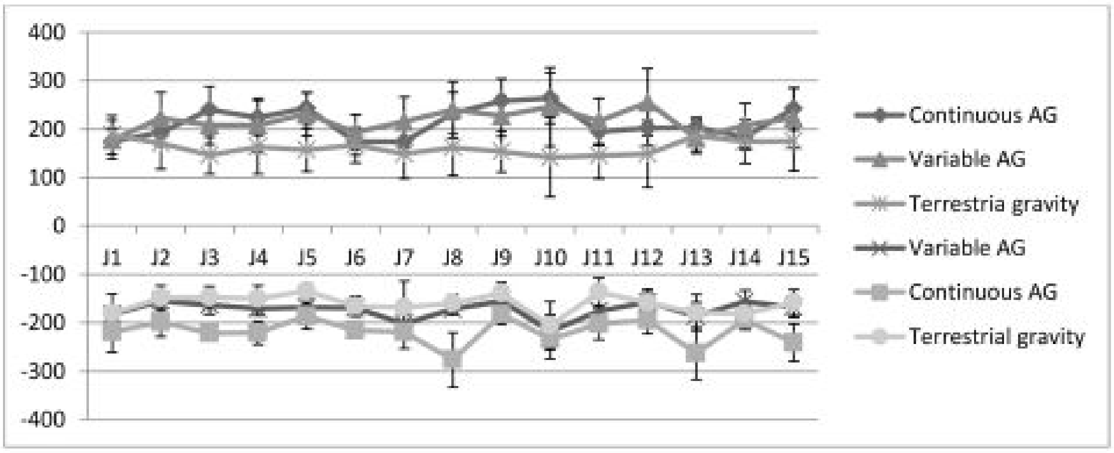

Fig 5. Mean (± SD) peak pitch angular velocities during each jumping session and in each condition. Subsequent jumps are labeled as J1 to J 15.

https://doi.org/10.1371/journal.pone.0234361.g005

Subjective Motion Sickness ratings were significantly higher during continuous centrifugation compared to terrestrial control condition ($z = 2.527$, $p = 0.034$).

Post condition mean Motion Sickness Assessment Questionnaire scores were relatively low (Fig 6) and did not differ between conditions (Friedman´s Chi-Square χ^2 (2) = 0.792, $p = 0.673$).

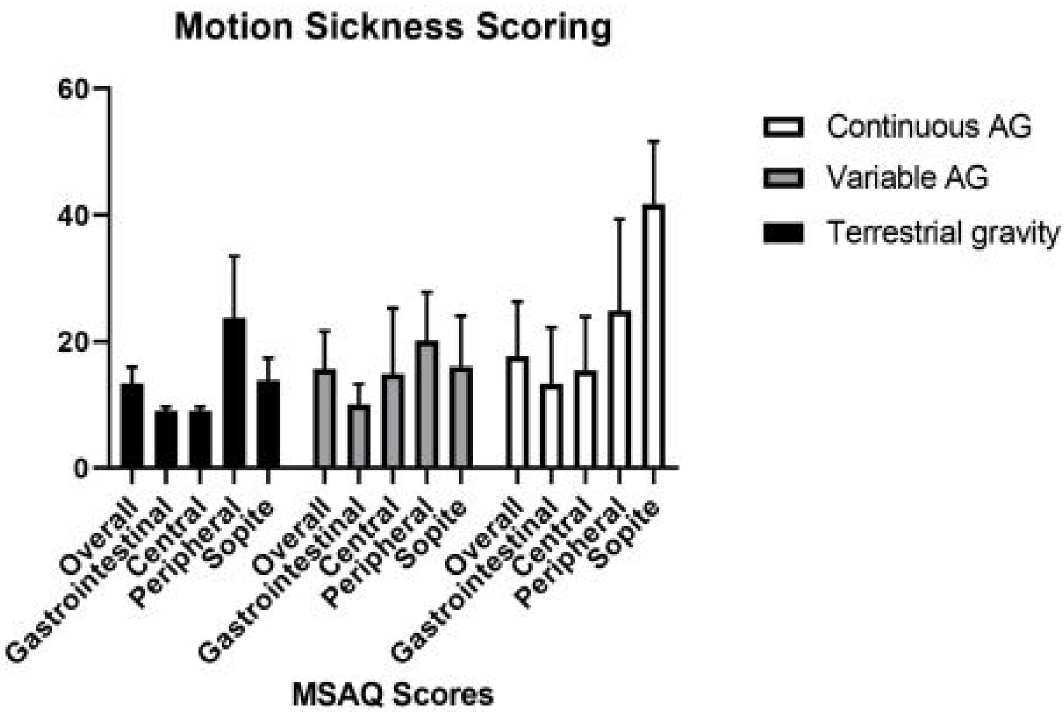

Fig 6. Motion sickness scoring from MSAQ questionnaire for each condition.

https://doi.org/10.1371/journal.pone.0234361.g006

Post condition PANAS scores tended to be more positive in all conditions with PA: 26.25 ± 9.63, NA: 13.23 ± 4.81 following Continuous AG, PA: 29.76 ± 10.00, NA: 10.61 ± 1.66 following Variable AG and PA: 23.26 ± 8.72, NA: 15.73 ± 5.31 following terrestrial control condition,. Between the terrestrial control condition and both centrifuge conditions no significant effect (PANAS P χ^2 (2) = 5.636, p = 0.060, χ^2 (2) = 4.769, p = 0.092) occurred.

Post condition Epworth Sleepiness Scale scores did not differ significantly between conditions ratings were numerically slightly higher with centrifugation (Continuous AG: 8.28 ± 5.31, Variable AG: 8.07 ± 5.89, terrestrial control condition: 6.33 ± 3.67).

Discussion

Our study demonstrates that repetitive voluntary jumping exercises are both feasible and tolerable during short-arm centrifugation at levels ranging from +0.5 to +1.5 *Gz* at the center of mass along the body axis. Indeed, the intervention was well tolerated by recreationally fit individuals who were naïve to jumping exercises during centrifugation as long as they were briefly familiarized. Study participants could move their heads freely within certain safety limits on the centrifuge and perform jumping exercises without experience increased motion sickness levels. Thus, contrary to the common perception that whole-body movements, including head motion during short-arm centrifugation result in motion sickness and related symptoms *per se*, we demonstrated that vigorous repetitive jumping is possible without induction of negative motion sickness symptoms.

Head movements within a rotating environment produce cross-coupled angular accelerations in the semicircular canals. The mechanism can trigger adverse vestibular stimulation with symptoms ranging from mild discomfort (e.g. sweaty palms) to severe nausea, vomiting or even loss of consciousness [6]. Yet, not only was repetitive jumping possible but no participant needed to drop out due to motion sickness symptoms. In fact, Motion Sickness Scores and Motion Sickness symptoms were low in all conditions. The finding is remarkable given the high values for head yaw, pitch, and roll velocities being generated in all conditions that are excess of those previously defined as being associated with comfort zones [9]. Moreover, the comparison between both centrifuge conditions reveals the interesting fact that alternating gravity levels seems to have only minor effects on the increase of motion sickness scoring or other related symptoms.

Our study extends the recent findings of Piotrowski et al [8] who demonstrated that leg press exercises on a sledge during centrifugation albeit with head movement restraint, could be tolerated. Thus, contrary to that previously thought rapid, forceful and complex voluntary repetitive movement such as jumping can be implemented during short-arm centrifugation. The cardiovascular burden imposed by short-arm centrifugation may promote presyncopal symptoms that can progress to frank syncope. The fact, that only one presyncopal event occurred during the Variable AG condition is reassuring. It is likely that jumping or squat exercise during centrifugation can help to maintain orthostatic tolerance even in a steep +*Gz* gravity gradient.

PANAS Negative Affect (NA) Scores tended to be slightly lower during centrifugation. These findings, albeit non-significant may be explained by participants perceiving centrifugation as exciting–particularly for unexperienced participants.

The fact that only men were included is a limitation that was part of the study design in which our experiment was included. In our study, both average MSA and MSB MSSQ scores were relatively low compared to normative populations [10,11]. Thus, whether similar results would be observed in more or highly sensitive individuals is unknown. While some subjects in our study scored relatively high in terms of motion sickness sensitivity (MSB > 11), none featured motion sickness requiring test termination. While the issue warrants further study, astronaut populations undergo tight medical screening and are not likely to have high motion sickness susceptibility. We cannot exclude that repeated exposure as part of a countermeasure protocol mitigates motion sickness symptoms completely. Since our study only included men, our findings cannot be simply extrapolated to women. Indeed, previous studies reported impaired vasoconstriction leading to impaired orthostatic tolerance in women after bed rest [12].

Despite these issues, we suggest that jumping exercises on a short-arm centrifuge are not generally restricted by disabling motion sickness symptoms. We speculate that being 'in control' may have increased the tolerability against cross-coupled effects during head movements while exercising on the short-arm centrifuge. This could be explained with increased controllability of the unknown setting on a centrifuge [13]

Since jumping exercise have been proven efficient in maintaining bone and muscle mass, our study enables further development of exercise countermeasures in Artificial Gravity.

Supporting information

S1 File.
(RAR)

Acknowledgments

The authors would like to thank the DLR centrifuge team and DLR study team for the conduction of the experiment. Further gratitude belongs to the principle investigator teams from University of Konstanz and the German Sport University for their cooperation.

Author Contributions

Conceptualization: Timo Frett.

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Investigation: Michael Arz, Alexandra Noppe, Guido Petrat, Jakob Kuemmel.

Project administration: Jens Jordan.

Software: Michael Arz.

Supervision: Uwe Tegtbur.

Writing – original draft: Timo Frett.

Writing – review & editing: Timo Frett, David Andrew Green, Alexandra Noppe, Andreas Kramer, Jens Jordan.

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6.3 Publication 3: Comparison of trunk muscle exercises in supine position during short arm centrifugation with 1g at Centre of Mass and upright in 1g

Journal: Frontiers in Physiology, 2022

Author contribution statement:

I designed and conducted the experiment together with the DRL centrifuge team (Michael Arz, Alexandra Noppe, Guido Petrat) under supervision of Prof. Tegtbur and Prof. Jordan. I wrote the original draft that was iterated with Prof. Jordan, Dr. Green, Dr. Pesta and Prof. Tegtbur. I submitted the manuscript to the journal and handled the revision process.

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TYPE Original Research
PUBLISHED 17 August 2022
DOI 10.3389/fphys.2022.955312

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SPECIALTY SECTION
This article was submitted to Environmental, Aviation and Space Physiology, a section of the journal Frontiers in Physiology

RECEIVED 28 May 2022
ACCEPTED 26 July 2022
PUBLISHED 17 August 2022

CITATION
Frett T, Lecheler L, Speer M, Marcos D, Pesta D, Tegtbur U, Schmitz M-T, Jordan J and Green DA (2022), Comparison of trunk muscle exercises in supine position during short arm centrifugation with 1 g at centre of mass and upright in 1 g.
Front. Physiol. 13:955312.
doi: 10.3389/fphys.2022.955312

Comparison of trunk muscle exercises in supine position during short arm centrifugation with 1g at centre of mass and upright in 1g

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Spaceflight is associated with reduced antigravitational muscle activity, which results in trunk muscle atrophy and may contribute to post-flight postural and spinal instability. Exercise in artificial gravity (AG) performed *via* short-arm human centrifugation (SAHC) is a promising multi-organ countermeasure, especially to mitigate microgravity-induced postural muscle atrophy. Here, we compared trunk muscular activity (mm. rectus abdominis, ext. obliques and multifidi), cardiovascular response and tolerability of trunk muscle exercises performed during centrifugation with 1 g at individual center of mass on a SAHC against standard upright exercising. We recorded heart rate, blood pressure, surface trunk muscle activity, motion sickness and rating of perceived exertion (BORG) of 12 participants (8 male/4 female, 34 ± 7 years, 178.4 ± 8.2 cm, 72.1 ± 9.6 kg). Heart rate was significantly increased ($p < 0.001$) during exercises without differences in conditions. Systolic blood pressure was higher ($p < 0.001$) during centrifugation with a delayed rise during exercises in upright condition. Diastolic blood pressure was lower in upright ($p = 0.018$) compared to counter-clockwise but not to clockwise centrifugation. Target muscle activation were comparable between conditions, although activity of multifidi was lower (clockwise: $p = 0.003$, counter-clockwise: $p < 0.001$) and rectus abdominis were higher (clockwise: $p = 0.0023$, counter-clockwise: < 0.001) during centrifugation in one exercise type. No sessions were terminated, BORG scoring reflected a relevant training intensity and no significant increase in motion sickness was reported during centrifugation. Thus, exercising trunk muscles during centrifugation generates comparable targeted muscular and heart rate response and appears to be well tolerated. Differences in blood pressure were relatively minor and not indicative of haemodynamic challenge. SAHC-based muscle training is a candidate to reduce microgravity-induced inter-vertebral disc pathology and trunk muscle atrophy. However, further optimization is required prior to performance of a training study for individuals with trunk muscle atrophy/dysfunction.

KEYWORDS

artificial gravity, exercise, countermeasure, spaceflight, trunk muscle atrophy

Introduction

Long term exposure to microgravity (μg) is associated with multi-organ deconditioning, including muscle atrophy (Fitts et al., 2010; Gopalakrishnan et al., 2010), reduced bone mineral density (LeBlanc et al., 2000; Lang et al., 2017), neurovestibular dysfunction (zu Eulenburg et al., 2021), and cardiovascular deconditioning (Gallo et al., 2020; Patel, 2020). Moreover, chronic cephalic fluid redistribution promotes blood volume loss, and may contribute to ocular and cerebral changes, known as spaceflight-associated neuro-ocular syndrome (SANS) (Clément and Bukley, 2007; Roberts et al., 2017; Lee et al., 2018). As opposed to trunk muscle loss, skeletal muscle atrophy is more pronounced in the lower body due to the reduction in locomotion and postural activation (Fitts et al., 2001; LeBlanc et al., 2007; Trappe et al., 2009; Fitts et al., 2010; Tanaka et al., 2017; Oliva-Lozano and Muyor, 2020). Nevertheless, trunk muscle atrophy occurs despite daily integrated resistance and aerobic countermeasures on the International Space Station (ISS) (Petersen et al., 2016). In fact, in-flight countermeasures do not replicate the mechanical loading associated with equivalent exercise on earth (Kozlovskaya and Grigoriev, 2004; Smith et al., 2008; Guinet et al., 2009; Gopalakrishnan et al., 2010; Lee et al., 2015). For instance, ISS treadmill running with a harness provides up to 80% axial loading, but results in only 25–46% peak ground reaction forces compared to terrestrial conditions (Cavanagh et al., 2010). Thus, exercises seem to be less effective when performed in weightlessness. Trunk muscle atrophy and reduced muscle tone may contribute to inter-vertebral disc (IVD) pathology, including disk desiccation and osteophytes (Garcia et al., 2018), and contributes to an apparent increased risk of IVD herniation post-flight (Johnston et al., 2010; McNamara et al., 2019). Current in-flight resistance training using the Advanced Resistive Exercise Device (ARED) appears to have attenuated bone mineral density loss (Sibonga et al., 2019) but fails to entirely mitigate musculoskeletal deconditioning (Lang et al., 2017). While ARED exercise is insufficient to activate trunk musculature, it may result in high instantaneous axial loading and–in combination with an unloaded spinal column - may thus contribute to post-flight IVD pathologies (Green and Scott, 2017). Post-flight rehabilitation seeks to progressively activate trunk musculature including lumbar multifidus and transversus abdominis muscles in order to promote functional postural and spinal stability (Hides et al., 2016).

To ensure physical performance of crewmember, more effective, efficient and safe multi-organ countermeasures–that include functional activation of trunk muscles - are required for future deep-space exploration missions (Scott et al., 2019). The generation of Artificial Gravity (AG) *via* short-arm human centrifugation (SAHC) is a promising approach to ameliorate multi-organ de-conditioning, including spinal dysfunction (Clément et al., 2004). During centrifugal acceleration, SAHC generates the sensation of 'standing-up' despite supine position with the feet placed against a footplate. The ground reaction forces at the feet are proportional to the gravitational (g) level at that point which increases with distance from the axis of rotation (Clément et al., 2004). As a result, postural-related musculoskeletal loading and muscle activation can be induced (GJNm, 2017). However, unlike long-arm centrifugation, SAHC also generates a hydrostatic pressure gradient towards the feet, which can present a significant orthostatic challenge (Clément et al., 2016; Laing et al., 2020).

A number of short-duration (5–14 days) head-down bed rest studies–a common ground-based analogue of μg (Hargens and Vico, 2016) - suggest that repeated passive (i.e. no movement or isometric 'standing' during rotation) artificial gravity exposure may be protective against bed rest-induced musculoskeletal deconditioning (Rittweger et al., 2015) and orthostatic intolerance (Stenger et al., 2012). Furthermore, we demonstrated that daily passive centrifugation at 1 *g* at the participants Center of Mass (CoM) is well tolerated during a 60-days bed rest period (Frett et al., 2020a). Nevertheless, 30 min of daily passive centrifugation with 1 g at the CoM provides a relatively low physiological load (Kramer et al., 2020a), and recent data suggests that it is insufficient to ameliorate bed rest-induced multi-organ deconditioning (Attias et al., 2020; Hoffmann et al., 2021).

Early work with AG higher than 1 g suggested that movement during rotation precipitates disorientation and/or motion sickness (Bertolini and Straumann, 2016) due to cross-coupled angular acceleration and induction of Coriolis forces (Bertolini and Straumann, 2016), in addition to orthostatic intolerance (Goswami et al., 2015). In case the g load is moderate (e. g. 1 g at CoM) and the exercise-related head and body motion is congruent, moderate movement appears well tolerated (Frett et al., 2020b). Indeed, plyometric exercises such as jumping can be performed during SAHC, albeit requiring familiarization to generate reaction forces equivalent to ground conditions (Frett et al., 2020b; Kramer et al., 2020b; Dreiner et al., 2020). Furthermore, intense cycle training, knee bends, or heel raises were partially effective to preserve orthostatic tolerance, exercise capacity as well as thigh muscle volume, knee extensor and plantar flexor performance during 4–21 days bed rest (Akima et al., 2005; Iwase, 2005; Caiozzo et al., 2009; Stenger et al., 2012; Li et al., 2017). Cycle ergometry at 40–60 W with 1.2 *g* at heart level (3.5 *g* at feet) ameliorated plasma volume, orthostatic tolerance time, and VO2max during short duration (4–14 days) bed rest (Iwasaki et al., 2005; Yang et al., 2011).

Isometric abdominal, lateral stabilization, or trunk rotation and isometric abdominal exercises are promising approaches to promote trunk stabilization and muscle activation and thus potentially ameliorate µg-induced muscle atrophy and subsequent spinal column dysfunction. However, such exercises need to be performed with an appropriate gravitational (axial) load. Thus, physiological responses during trunk muscle exercising performed on a SAHC as part of a multidimensional countermeasure approach need to be investigated. Whether or not trunk muscle exercises during AG are tolerated and induce comparable trunk muscle activation during standard upright exercising is unknown. As rotational direction could lead to one-sided strain (Kramer et al., 2020b), we compared both centrifuge directions (clockwise and counter-clockwise) in randomized order. We hypothesize that trunk and back muscle exercises will be tolerable due to a reduced amount of required head movements.

The aim of this study was therefore to compare trunk muscular activity (mm. rectus abdominis, ext. obliques and multifidi), cardiovascular response and tolerability of trunk muscle exercises performed during clockwise and counter-clockwise SAHC with 1 g at the individual CoM compared to that generated in an upright (1 g) position.

Methods

Twelve recreationally active (least twice weekly running and/or functional training) individuals (8 men/4 females, age 34 ± 7 years, height 178.4 ± 8.2 cm, weight 72.1 ± 9.6 kg) provided written informed consent for participation in this study which was approved by the North Rhine ethical committee (Number: 6000223393) and prospectively registered in the German Clinical Trial Register (DRKS: S00021750).

All participants completed a brief medical questionnaire and underwent a standardized centrifuge medical screening including clinical-chemical analyses of blood and urine, stress electrocardiogram, and orthostatic testing. Participants were excluded if they had acute pain or any significant current or past musculoskeletal, cardiovascular or neurological disorder or injury that could affect the ability to perform exercise. No anti-emetic medication was allowed prior to testing and light food (cereal bars) and non-sparkling water were provided to ensure adequate hydration and glycemia.

Participants attended the laboratories at:envihab (DLR, Cologne, Germany) on two occasions separated by at least three resting days. Participants were familiarized with the equipment, testing procedures and exercises prior to the first session. Each session included resting measurements in supine position (BASELINE), immediately prior to exercises (PRE-EXERCISE) and after exercise (POST). Participants performed three sets of trunk/upper body exercises in a randomized order: lateral stabilization (Contralateral), abdominal rotation (Wood Chopper) and abdominal isometric (Crunch), each separated by short (30s) periods of rest (BREAK 1, BREAK 2, BREAK 3). All exercises were: either performed standing upright (UPRIGHT), or supine on the SAHC at an angular velocity sufficient to generate 1 g at that individual's CoM (ratio center of mass to body height 56% for male/54% for female) in a randomized order (Figure 1A).

The centrifuge session consisted of 2 separate centrifuge runs, one in the clockwise (CLOCKWISE), and the other in counter-clockwise (COUNTER-CLOCKWISE) direction, also in a randomized order (Figure 1B). During the ramp up/down phases (de)acceleration did not exceed $5^{\circ}s^{-2}$ to minimize the risk of vestibular-induced tumbling sensations. On the centrifuge, participants were secured in a supine position on a horizontal sledge system against a fixed footplate and were instructed to avoid unnecessary head movements during centrifugation to minimize the provocation of disorientation/motion sickness symptoms.

For each exercise session, participants performed 20 repetitions of Contralateral, 10 repetitions per side for Wood Cho pper (20 in total), and 20 repetitions of Crunch exercise. The target muscle groups for contralateral exercise are the lateral abdominal (external obliques) and back (multifidi) muscles, whereas for the wood chopper it is the lateral abdominal muscle and for crunch exercises it is the medial abdominal (upper and lower rectus abdominis) muscle. Recorded audio start/stop and pacing instructions were provided for each exercise with participants having balance air pillows (Sissel, Bad Dürkheim Germany) placed under the feet to promote dynamic hip stabilization.

For contralateral exercise (Figure 2A) maintenance of diagonal trunk stability was required with the right arm holding suspension (TRX®· United States) and the left leg standing on the pillow, or vice versa. Wood chopper exercise (Figure 2B) consisted of pulling a rubber band (TheraBand®, United States) with both arms diagonally from the shoulder down towards the feet while standing on pillows. Crunch exercises (Figure 2C) were performed by pushing down suspension bands (TRX®, San Francisco, United States) simultaneously with both hands while holding the trunk in position and standing on pillows.

Trunk muscle surface electromyography

Bi-polar telemetric surface electrodes (Noraxon Ultium, United States) were placed and fixed with surgical tape bi-laterally on upper and lower rectus abdominis, obliquus externus abdominis, lumbar multifidi having shaved, exfoliated and cleaned the skin with alcohol. EMG signals were sampled at 2000 Hz and bandpass filtered (10–500 Hz). Start and end of each exercise bout indicated by the onset and offset of EMG activity were marked and root mean square (RMS) filter (100 ms window) applied. Prior to each experiment day, participants performed 3 s maximum voluntary contractions (MVC) of each muscle group (Konrad, 2005) with a rest interval of at least 1 min between maximal efforts. Verbal encouragement was given. The recorded MVC were used to normalize subsequent EMG signals (%MVC) averaged (left and right) per muscle.

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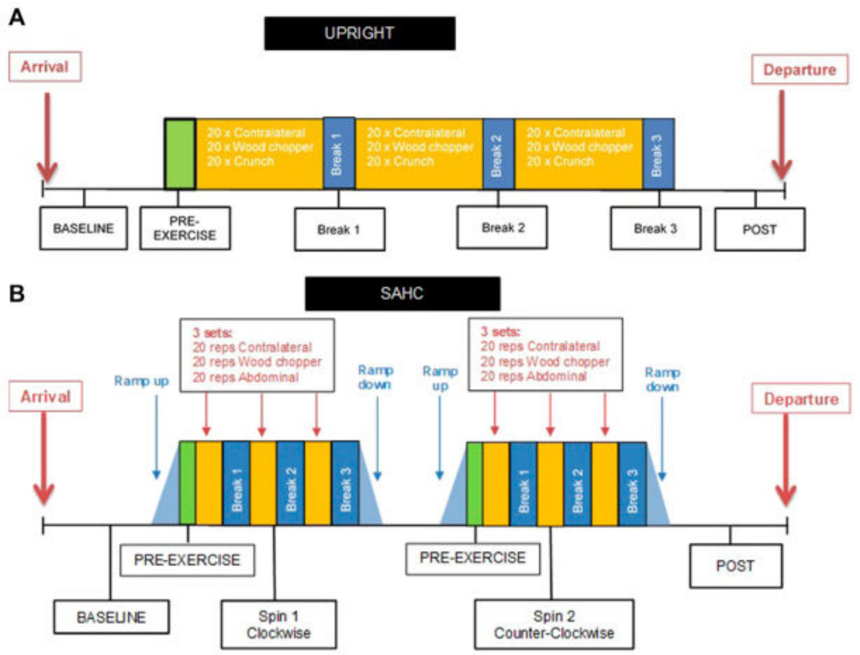

FIGURE 1
(A) Schematic of the UPRIGHT protocol prior to supine trunk muscle exercise (BASELINE), when standing upright (PRE-EXERCISE), between exercise sets (Break 1, Break 2, Break 3) and after exercising (POST). **(B)** Schematic of the short-arm human centrifugation (SAHC) protocol (CLOCKWISE and COUNTER-CLOCKWISE in random order) prior to supine trunk muscle exercise (BASELINE), on the SAHC with 1 g at the participant's center of mass (PRE-EXERCISE), between exercise sets (Break 1, Break 2, Break 3) and after exercising (POST).

Heart rate and blood pressure monitoring

Heart rate was continuously recorded via a five-lead electrocardiogram to facilitate concurrent reporting with periodic brachial blood pressure measurements (Philips IntelliVue® MP2, Eindhoven, Netherlands). On the centrifuge, blood pressure was recorded at BASELINE, after 1 g at CoM was reached (PRE-EXERCISE), within 60 s following each exercise (BREAK 1, BREAK 2, BREAK 3) and after completion of exercises (POST).

Questionnaires

To assess susceptibility to motion sickness, participants completed a short-form motion sickness susceptibility questionnaire (Golding, 2006) at BASELINE. Furthermore, before (BASELINE) and after (POST) exercises, participants completed more detailed questionnaires including Motion Sickness Assessment Questionnaire (MSAQ), Positive and Negative Affect Schedule (PANAS), and Epworth Sleepiness Scale (ESS) questionnaires. MSAQ was employed to determine (1–9 max) various dimensions (e.g. gastrointestinal) of motion sickness (Gianaros et al., 2001). PANAS was used to assess the effect of centrifugation upon mood based on a Likert scale from 1 "not at all" to 5 "very much" (Watson and Clark, 1988). Induced drowsiness was assessed with the ESS (rating from 0 (non-) to 3 "high chance of dozing" in eight contexts) (Graybiel and Knepton, 1976).

Subjective motion sickness ratings (MS: 0 = "I am feeling fine" to 20 = "I am about to vomit") (Young et al., 2003), perceived exertion (RPE: 6 = "No exertion at all" to 20 = "Maximal exertion") (Borg, 1998) in addition to body control using a modified Cooper-Harper body control scale (1 = "not limited" to 10 = "body control lost") (Cooper and Harper RJMF, 1969) were administered at BASELINE, PRE-EXERCISE, at BREAK 1, BREAK 2, BREAK three and POST.

Statistical analysis

Linear mixed models (Satterthwaite method) were used to determine if there was an effect of condition (UPRIGHT, CLOCKWISE and COUNTER-CLOCKWISE), exercise

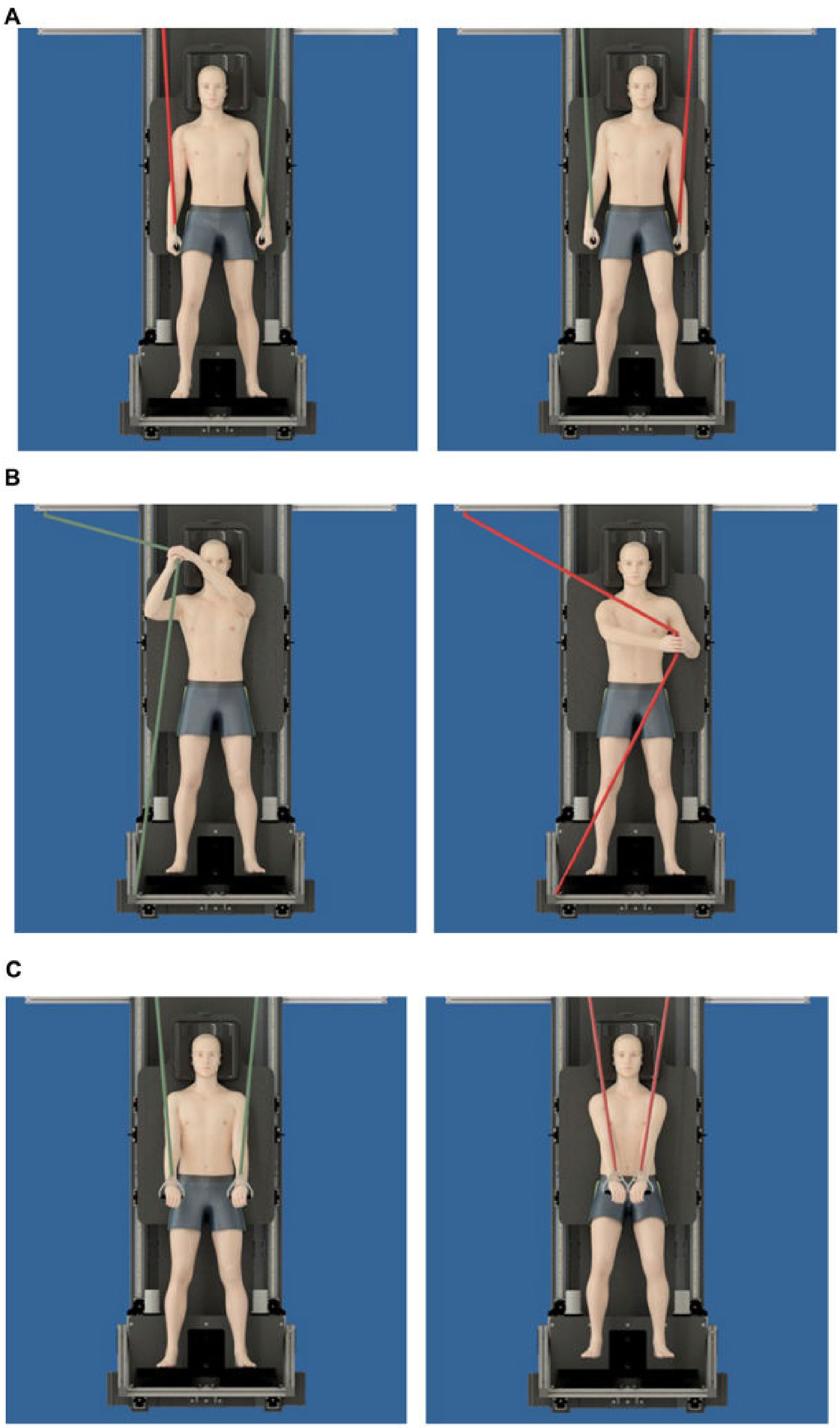

FIGURE 2
(A) Contralateral exercises per set were performed requiring participants to maintain trunk stability (straight hip) with the right arm holding suspension bands (red line) either with (A) left leg standing on the pillow or (B) right leg on the pillow. (B) Wood chopper exercises were performed on each side requiring participants to pull a rubber band (TheraBand®) with both arms' diagonal from the shoulder down towards the feet while standing on pillows. (C) Crunch Exercises were performed by pushing down suspensions with both hands simultaneously while stabilizing the trunk and standing on pillows.

(Contralateral, Wood Chopper and Crunch) and muscle activity (Ext. oblique, Mulitfidi, Upper Rectus Abdominis, Lower Rectus Abdominis).

We compared the effect of exercises and condition upon heart rate, blood pressure and subjective ratings (condition x time). Furthermore, we compared the effect of standing upright in 1 g vs. passive centrifugation with 1 g at the CoM in supine position (PRE-EXERCISE) upon heart rate, blood pressure and subjective ratings to evaluate the effect of solely centrifugation.

All data was normally distributed (Shapiro Wilk's test). Data are presented as mean ± standard deviation of the mean (SD). All statistical tests were conducted using R (version 4.1.2) with $p < 0.05$ assumed as being statistically significant.

Results

To generate 1 g at the participant's CoM the centrifuge spin rate was 18.56 ± 0.2 rpm with a radius of 98.3 ± 5.6 cm. No exercise bouts were aborted in any condition and no adverse medical events were reported.

Muscle activity

Mean muscle activity (%RMS) during wood chopper and crunch exercise showed no significant differences whether performed during centrifugation or standing upright. However, we found a significant 3-way interaction (condition x exercise x muscle) with F = 2.4421, $p = 0.003$, df = 12 for contralateral exercise. In particular, differences were observed for multifidi muscle activity during contralateral exercise between the conditions with higher values in UPRIGHT compared to CLOCKWISE ($p = 0.003$) and COUNTER-CLOCKWISE ($p < 0.001$) (Figure 3).

Muscle activity of upper and lower rectus abdominis were significantly affected by condition during contralateral exercise, with higher activation observed during both CLOCKWISE ($p = 0.023$) and COUNTER-CLOCKWISE ($p < 0.001$) centrifugation compared to UPRIGHT exercise.

Cardiovascular response

Heart rate (Figure 4) was significantly changed over time (F = 52.8965, $p < 0.001$, dfs = 5) but not by condition (F = 0.0671, $p = 0.935$, dfs = 2). Compared to supine resting (BASELINE), heart rate was significantly increased when standing upright in 1 g vs. passive centrifugation with 1 g at the CoM in supine position (PRE-EXERCISE: $p < 0.001$) and during exercises (BREAK 1: $p < 0.001$, BREAK 2: $p < 0.001$, BREAK 3: $p < 0.001$) but returned to baseline values after completion of exercises (POST: $p = 0.805$).

Systolic blood pressure (Figure 5) showed a significant interaction effect (time x condition, $p < 0.001$) with a lower and more delayed increase during UPRIGHT (PRE-EXERCISE: ns, BREAK1: ns, BREAK 2: ns, BREAK 3: $p = 0.007$) compared to CLOCKWISE (PRE-EXERCISE: $p = 0.016$, BREAK 1: $p = 0.005$, BREAK 2: ns, BREAK 3: ns) and COUNTER-CLOCKWISE (PRE-EXERCISE: $p = 0.016$, BREAK 1: $p < 0.001$, BREAK 2: $p = 0.014$, BREAK 3: $p = 0.033$).

Diastolic blood pressure (Figure 6) was affected by time x condition ($p = 0.018$) with lower values during UPRIGHT compared to COUNTER-CLOCKWISE (PRE-EXERCISE: $p = 0.005$, BREAK 1: ns, BREAK 2: $p = 0.026$, BREAK 3: ns) but not compared to CLOCKWISE.

Subjective ratings

MSSQ scores were low (5.4 ± 4.8) due to MSA (3.8 ± 3.7) and MSB (1.6 ± 4.8) sub-scores. No participant reported increased motion sickness prior to, or following exercise in any condition.

MS scores were low (<3) and not affected by time (F = 0.074, p 0.974, dfs = 3) (Table 1). However, we found a significant condition effect (F = 17.528, $p < 0.001$, dfs = 2) with higher scores for CLOCKWISE ($p < 0.001$) and COUNTER-CLOCKWISE ($p < 0.001$) during BASELINE, PRE-EXERCISE and EXERCISE compared to UPRIGHT.

We found a significant increase of RPE scoring over time (F = 54.185, $p < 0.001$, dfs = 3) (Table 1) but no effect of condition (F = 0.169, $p = 0.844$, dfs = 2). Effort ratings showed minor changes over time (F = 4.6149, $p = 0.01$, dfs = 2) (Table 1) without differences between conditions (F = 0.6411, $p = 0.527$, dfs = 2).

Discussion

In this pilot trial we compared trunk muscular activity (mm. ext. obliques, multifidi and mm. rectus abdominis), cardiovascular response and tolerability of trunk muscle exercises performed during clockwise and counter-clockwise SAHC with 1 g at the individual CoM compared to that generated in an upright (1 g) position. Contralateral, Wood Chopper and Crunch trunk muscle exercises with 1 g at the CoM during SAHC were feasible and well tolerated. The main finding of the study was that trunk and back muscular activity in response to trunk exercises was comparable during centrifugation to that performed during upright standard conditions. Contralateral exercises showed lower muscle activation in the back but increased in straight abdominal muscles during centrifugation compared to upright. No significant differences pre and post exercise in MSAQ, PANAS or ESS in any conditions were found (see Table 2). No exercises were aborted in any condition either due to excessive physiological load or motion sickness.

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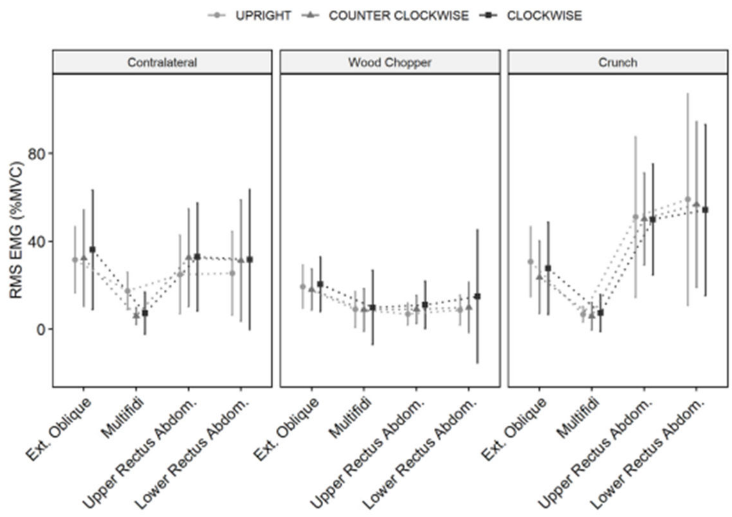

FIGURE 3
Root mean square of muscle activation (%MVC) for, External Oblique, Multifidi, Upper and Lower Rectus Abdominis during exercises (Contralateral, Wood Chopper and Crunch), when standing upright (UPRIGHT) and during short arm human centrifugation (SAHC) when rotated clockwise (CLOCKWISE and counter-clockwise (COUNTER-CLOCKWISE) when supine with 1 g at the participant's center of mass. Data as mean (±SD).

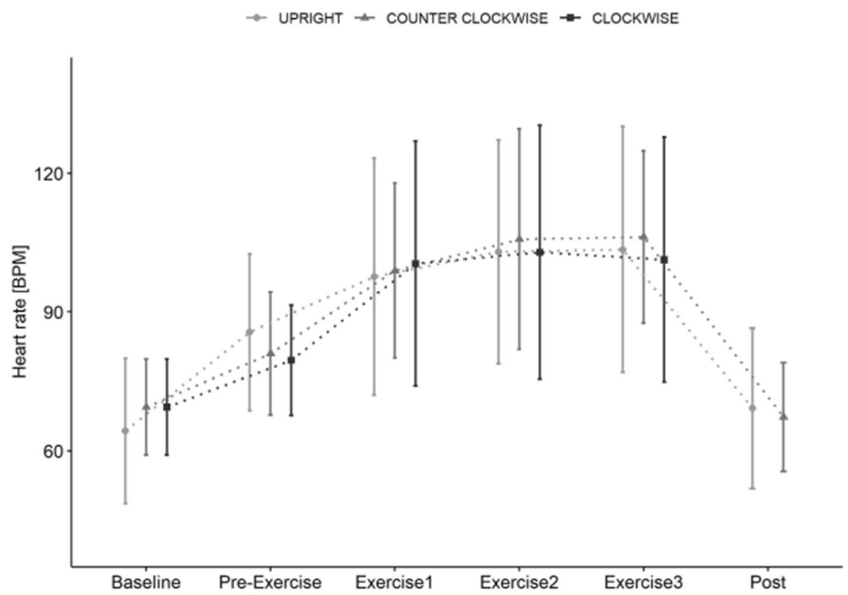

FIGURE 4
Heart rate (bpm) in supine position (BASELINE) prior to standing (PRE-EXERCISE) in the UPRIGHT condition, and when passively rotated (PRE-EXERCISE) clockwise (CLOCKWISE) and counter-clockwise (COUNTER-CLOCKWISE) with 1 g at the participants center of mass in addition to directly following Contra-lateral, Wood Chopper and Crunch exercise (BREAK 1, BREAK 2, BREAK 3) and upon completion (POST) of each condition. Data as mean (±SD).

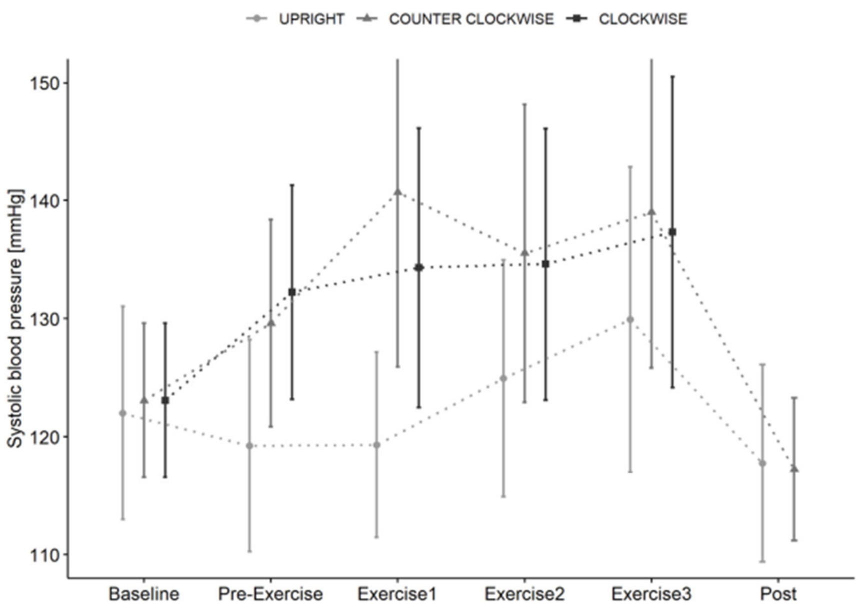

FIGURE 5
Systolic blood pressure measured in supine position (BASELINE) prior to standing (PRE-EXERCISE) in the UPRIGHT condition, and when passively rotated (PRE-EXERCISE) clockwise (CLOCKWISE) and counter-clockwise (COUNTER-CLOCKWISE) with 1 g at the participants center of mass in addition to directly following Contra-lateral, Wood Chopper and Crunch exercise (BREAK 1, BREAK 2, BREAK 3) and upon completion (POST) of each condition. Data as mean (±SD).

Trunk muscle atrophy and reduced muscle tone (McNamara et al., 2019) may contribute to inter-vertebral disc (IVD) pathology and contributes to an apparent increased risk of IVD herniation post-flight (Johnston et al., 2010). Moderate axial loading via elasticated body suits has been suggested to promote core stability (Rathinam et al., 2013) with some developed for µg environments (Waldie and Newman, 2011) demonstrated to be compatible with aerobic (Attias et al., 2017) and resistive (Carvil et al., 2017) exercise on Earth, and on the ISS (Stabler et al., 2017). However, whilst these suits may promote trunk muscle activation during exercise, such an approach is unlikely to mitigate multi-organ deconditioning.

Recent findings suggest that passive exposure to intermittent centrifugation during 60 days head down tilt bed rest do not provide protective effects to maintain control and coordination of superficial and deep lumbar spinal muscles during anticipatory adjustments to quick arm movements (De Martino et al., 2021). In the present study target muscle activation during exercises were comparable when conducted in supine position while rotating on the centrifuge with 1 g at CoM and standing upright in 1 g condition. However, for contralateral exercise, multifidi muscle activity was significantly lower when performed on the SAHC whereas activity of upper and lower rectus abdominis were increased. No differences were observed during wood chopper and crunch exercises. Thus, trunk muscle activity was broadly similar between the two positions, with no evidence of exaggerated or potentially inappropriate activity. Interestingly, few differences were observed between SAHC rotation direction suggesting that participants were able to adapt effectively. Centrifugation without exercising elicit only minor muscular activity in leg muscles an no relevant activity in the targeted muscles.

In fact, in both upright and SAHC conditions muscular activation levels were low in comparison of the 40–60% considered to be ergogenic for abdominal musculature (Konrad, 2005). Activation of the multifidi in particular was low (below 20% MVC) in all conditions, however this is reported to be challenging to activate with exercise (Cao et al., 2005; Holguin et al., 2009), which may account for the de-conditioning observed in bedrest (Belavý et al., 2011) and spaceflight (Johnston et al., 2010; Burkhart et al., 2019), which in astronauts may underlie lumbar lordosis (Bailey et al., 2018) and vertebral column dysfunction (Lazzari et al., 2021) including IVD pathology and back pain (Pool-Goudzwaard et al., 2015). However, on Earth, a classic exercise for abdominal muscles, the static curl-up recruits approx. 80% MVC whereas back extension exercises for the erector spinae elicit approx. 63% MVC contractions (Oliva-Lozano and

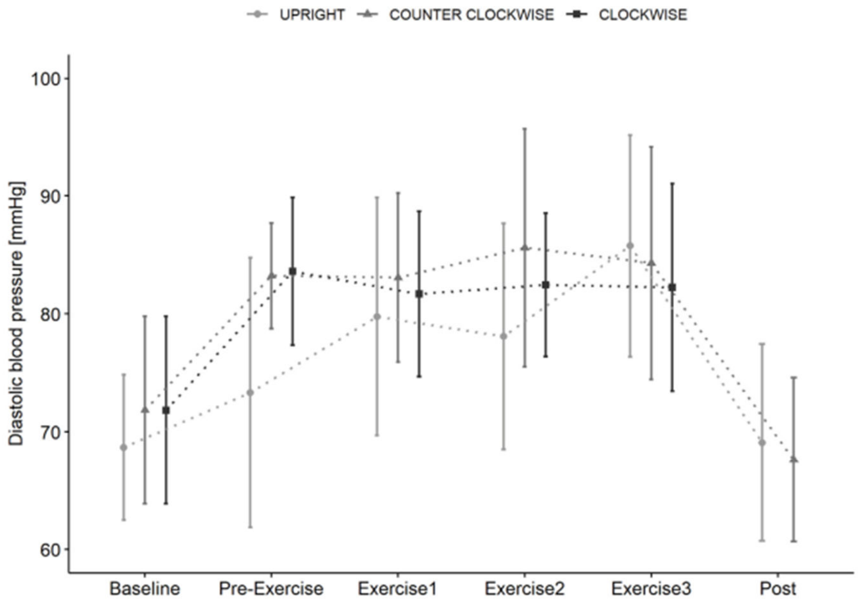

FIGURE 6
Diastolic blood pressure measured in supine position (BASELINE) prior to standing (PRE-EXERCISE) in the UPRIGHT condition, and when rotating passively (PRE-EXERCISE) clockwise (CLOCKWISE) and counter-clockwise (COUNTER-CLOCKWISE) with 1 g at the participants center of mass in addition to directly following Contra-lateral, Wood Chopper and Crunch exercise (BREAK 1, BREAK 2, BREAK 3) and upon completion (POST) of each condition. Data as mean (±SD).

TABLE 1 Motion sickness (MS), perceived exertion (RPE) and effort ratings supine (BASELINE), prior to standing (PRE-EXERCISE) in the UPRIGHT condition, and when rotating passively (PRE-EXERCISE) clockwise (CLOCKWISE) and counter-clockwise (COUNTER-CLOCKWISE) with 1 g at the participants center of mass. Further ratings were obtained directly following Contra-lateral, Wood Chopper and Crunch exercise and upon completion (POST) of each condition. Data as mean (±SD).

	UPRIGHT			CLOCKWISE			COUNTER CLOCKWISE		
	MS	RPE	Effort	MS	RPE	Effort	MS	RPE	Effort
BASELINE	1.2 ± 0.4			2.0 ± 1.5			2.2 ± 2.5		
PRE-EXERCISE	1.2 ± 0.4	6.0 ± 0.0		2.0 ± 1.5	6.4 ± 0.7		2.2 ± 2.5	6.8 ± 1.2	
Contra Lateral	1.3 ± 0.7	9.8 ± 2.6	1.8 ± 1.4	2.1 ± 1.8	9.6 ± 2.6	1.9 ± 0.8	2.2 ± 2.5	9.6 ± 3.0	1.8 ± 0.9
Trunk exercise	1.3 ± 0.6	11.2 ± 2.6	1.8 ± 1.6	2.0 ± 1.9	10.6 ± 3.3	1.7 ± 0.7	2.2 ± 2.4	10.7 ± 3.1	1.6 ± 0.5
Wood chopper	1.3 ± 0.6	8.7 ± 2.4	2.3 ± 2.2	2.0 ± 1.9	9.1 ± 2.8	2.1 ± 1.0	2.1 ± 2.5	9.4 ± 3.0	2.0 ± 1.2
POST	1.2 ± 0.6			1.8 ± 1.7			1.8 ± 1.7		

Muyor, 2020) Thus, whilst the muscle recruitment in our exercises appears to be moderate, the failure to observe functionally significant different with those performed upright suggests that more complicated, and or aggressive trunk muscle exercises should be evaluated acutely during SAHC. Should they prove to be feasible, tolerable and induce trunk muscle activation likely to be ergogenic then a AG-training study employing such during long duration head down tilt may be warranted to see if they plug a key operational countermeasure gap (Green and Scott, 2017) given that daily passive AG at 1 g at CoM is well tolerated during head down tilt bed rest (Frett et al., 2020a) but provides a relatively low physiological load (Kramer et al., 2020a), and appears insufficient to ameliorate multi-system bed rest-induced deconditioning (Attias et al., 2020; Martino et al., 2020; Hoffmann et al., 2021).

TABLE 2 Motion Sickness (MSAQ), Positive and Negative Affect Schedule (PANAS), and Epworth Sleepiness Scale (ESS) scores prior to (BASELINE) and following the upright (UPRIGHT) and short arm human centrifugation conditions when rotated both clockwise (CLOCKWISE) and counter-clockwise (COUNTER-CLOCKWISE) with 1 g at the participants center of mass when supine. Data as mean (±SD).

	UPRIGHT		SAHC	
	Pre	Post	Pre	Post
MSAQ	14.5 ± 2.1	12.6 ± 2.1	12.4 ± 1.8	15.8 ± 5.4
ESS	14.8 ± 3.2	14.3 ± 3.6	15.0 ± 3.1	15.5 ± 3.0
PANAS (Positive Affect)	30.3 ± 6.0	30.1 ± 5.5	32.9 ± 5.8	31.5 ± 8.5
PANAS (Negative Affect)	13.5 ± 1.5	12.7 ± 1.1	14.6 ± 2.7	13.3 ± 0.8

The transition from supine to 1 g at the CoM induced broadly similar increase in heart rate compared to standing. However, passive centrifugation showed a greater rise of systolic and diastolic blood pressure in both rotational directions indicating either a greater influence of fluid shift or stress. Trunk muscle exercise further increased heart rate and systolic blood pressure, with blood pressures being lower in the upright condition. However, differences were relatively minor and not indicative of haemodynamic challenge (Laing et al., 2020). This is perhaps unsurprisingly given the relatively low muscle mass and magnitude of muscle activation.

Ratings of perceived exertion and motion sickness ratings were moderate even in our naïve subjects, and comparable with terrestrial exercise (Scherr et al., 2013; Kim and Park, 2018) with no participant reporting significant motion sickness in any condition. This is consistent with our observation that subjects were able to perform the trunk exercises without moving their head, and recent findings demonstrating that when the g load is moderate (i.e. 1 g at CoM) and exercise-related head and body motion is congruent, movement during SAHC is well tolerated (Piotrowski et al., 2018; Frett et al., 2020b; Kramer et al., 2020b). Body control remained good in all conditions, with no effect of exercise or condition on MSAQ, PANAS and ESS scores. Whilst higher g-levels may have resulted in greater trunk muscle activation they increase the risk of disorientation and/or motion sickness (Bertolini and Straumann, 2016).

As this was a pilot study we were not prescriptive with exercise instructions. However, given the low level and range of trunk muscle recruitment an extended period of familiarization to the exercises during SAHC may be advantageous.

Our study has some limitations. Safety regulations required a solid back plate during centrifugation, limiting participant´s mobility compared to when upright control condition. This may explain the reduction in multifidi activation during lateral stabilization exercises. Development of a full-body suspension system to facilitate 3D participants mobility during SAHC is warranted. Additionally, we assume biomechanical differences due to a body position that is not aligned with the resulting vector while spinning. As the used centrifuge setup has no swing-out capability, participants experience a vector angle while spinning at +1Gz at CoM that is 45° different to the body longitudinal axis compared to standing upright in Earth´s gravity. Future ground based SAHC training studies should carefully consider a correct inclination of participants align with the resulting force vectors. Given the small sample size, we cannot differentiate for gender specific effects.

We used surface EMG to ensure natural movement patterns that are not compromised by application of intramuscular wire electrodes. As trunk muscles are multilayered and have different fiber orientations, the intensity and selectivity of the recorded signals may be compromised by using surface EMG instead of intramuscular wire electrodes due to cross-talk from adjacent muscles and a low signal-to-noise ratio.

In conclusion, this study demonstrates that Contralateral, Wood Chopper and Crunch trunk muscle exercises with 1 g at the CoM during SAHC were feasible, and well tolerated. In general, targeted trunk muscular activity was comparable to that performed during upright 1 g conditions. Heart rate responses were similar whilst blood pressure was higher during SAHC, but not indicative of excessive physiological load.

As the optimal g-level to maintain crew´s fitness during spaceflight is still unclear, we used a g-level relatively similar to terrestrial gravity in order to investigate the effects of trunk muscular exercises during centrifugation. Thus, trunk muscle exercise is a candidate for SAHC-based training on Earth, and in space. However, further optimization is required prior to performance of a training study for individuals with trunk muscle atrophy/dysfunction and/or long-term Head Down Tilt Bed Rest - an analogue of microgravity.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the North Rhine ethical committee, Tersteegenstr. 9, 40474 Düsseldor. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TF, DG, DP, JJ wrote the manuscript, TF designed the research and analyzed the data, TF, MA, WP, GP, LL performed the research, M-TS and TF conducted the statistical analysis, DG, DP, JJ, and UT supervised the experiment.

Funding

This study received direct funding from DLR. KBRwyle GmbH nor ESA were involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. All authors declare no other competing interests.

Acknowledgments

The authors would like to thank the DLR centrifuge team and the DLR study team for their support in the experiment.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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7 Discussion

Artificial Gravity generated by short arm centrifugation, is a promising multi-system countermeasure against microgravity-related physiology deconditioning during long-term space mission [46]. However, its regular use whether passively or combined with training needs to be evaluated with regard to tolerability and potential side effects of Coriolis forces during exercising.

In a first study, long-term tolerability to daily passive exposure to Artificial Gravity during bed rest was investigated. Strict head down tilt bed rest is a well-established ground-based analog to simulate cephalad fluid shifts and physiological deconditioning during spaceflight [76]. Previous bed rest studies using Artificial Gravity as countermeasure ranging from 4 to 21 days showed that intermittent centrifugation with 1 – 2 *g* at heart for 0.5 – 2 hours was partially effective in mitigating bed rest induced orthostatic intolerance and maintaining exercise capacity [56, 77-80]. Our experiment was part of the NASA/ESA 60-day head down tilt bed rest study 'Artificial Gravity Bed Rest with European Space Agency' (AGBRESA) that aimed to complement the knowledge from previous shorter studies. As the main objective of AGBRESA was to compare the effects of daily exposure to intermittent (6 x 5min) or continuous (30min) short arm centrifugation, the results from our first publication [81] contribute to evaluate passive exposure to Artificial Gravity for future long duration spaceflight. The important finding of our study is that daily passive exposure to Artificial Gravity is well tolerated during 60 days of bed rest even with a steep gravity gradient of 1 *g* at the Center of Mass and 2 *g* at feet. Especially for future long-term missions, everyday tolerability of intermittent centrifugation is an important factor. In sum, daily passive centrifugation is well tolerated during 60 days bed rest with a tendency to favor the intermittent (6 x 5 min) protocol. This outcome supports findings from previous shorter 5-day ESA bed rest study (BR-AG1) [59] and is confirmed by a higher completion rate in the intermittent group. However, countermeasure acceptability of the intermittent protocol decreased over the course of the bed rest period [82]. Compared to the control group (bed rest without centrifugation) the rate of adverse effects during bed rest were lower in both groups with daily centrifugation. Not surprisingly, passive exposure to centrifugation were found to be not sufficient enough to counteract loss of muscle and bone nor maintain aerobic exercise capacity [83-86].

Combined with exercises, Artificial Gravity could enhance training stimuli by re-establishing a force field similar to earth's gravity that foster caudal fluid shift and higher musculoskeletal loading. As Coriolis forces can influence both tolerability and performance of training during centrifugation, past studies have focused on exercises like cycling [66] or squats [72-74] that does not involve excessive head movements. The drawback of this limitation is that such exercises lack of sufficient stimuli to maintain bone tissue and cannot be used as full body workout. High-intensity, low-volume repetitive jumping was effective in preserving peak force, peak power and lean body mass during a 60-day head down tilt bed rest study [87]. By induction of high strain rates on bone tissue, jump training has been suggested as a key exercise to maintain bone mass in weightlessness [88, 89]. In addition, high-intensity jumping involves major leg muscle groups as well as the cardiovascular system. Based on models of sensory conflict theory, incremental adaption to rotational speeds up to 30 rpm should be feasible on a short arm centrifuge [90].

To test the limits of exercises on a short arm centrifuge, we investigated the tolerability of repetitive jumping in different rotational speeds to achieve an acceleration between 0.5 – 1.5 *g* at the individual center of mass. Participants performed several repetitive jumping trials either on a sledge system in supine position while spinning or upright in normal gravity. As expected, head movements were significant higher during centrifugation due to its unusual position on the sledge. It is therefore surprising that no participant needed to terminate the experiment due to motion sickness symptoms. In direct comparison with jumping in upright position and supine on a sledge system without centrifugation [91], jump height and peak forces were lower on a centrifuge. However, leg stiffness represented by muscle activity of lateral gastrocnemius and soleus as well as ankle joint excursions were comparable and did not change much during centrifugation [92]. Knee joint movements were lower during centrifugation, indicating that previous concerns about potential risk of injury due to Coriolis forces are rather unfounded. As a result, jump training appear as a promising countermeasure when combined with centrifugation. An acceleration level of 1 *g* seems desirable, whereas lower g-level resulted in poorer peak force production and ground contact times and higher forces did not show substantial benefits but bear a higher risk for injuries. With only 200+ jumps during a one-day trial per participant our data only show the results of acute adaptation to centrifuge-based training. Potential improvements from a prolonged adaption, as shown in previous studies [53, 93, 94], require an extended week-long training study.

Beside tolerability of repetitive movements, re-establishing a downward force using centrifugation could also be used to ameliorate microgravity-induced trunk and back muscle atrophy and therefore reduce inter-vertebral disc (IVD) pathology [43, 95]. As current in-flight training equipment cannot replicate mechanical loading as on earth [39], we compared trunk and back muscle exercises performed during supine 1 *g* during centrifugation and in upright position. As classical trunk muscle exercises like crunches cannot effectively performed while standing, we developed an exercise program that could be performed in supine position during centrifugation considering relevant safety requirements. Three different exercises for lateral stabilization, abdominal isometric and rotation training were well tolerated and generated comparable trunk and back muscle activity in both conditions.

However, overall muscular activation levels were low compared to 40-60% MVC considered to be ergogenic [96]. Centrifugation with and without exercises showed similar or even higher responses in heart rate and blood pressure compared to exercising in upright position indicating a relevant cardiovascular stimulus. Albeit further optimization is required we could show that trunk muscle exercises at 1 g of individual center of mass are tolerable and could be used to improve trunk muscle training in space.

7.1 Limitations

Due to high operational costs and a lack of flight opportunities, development and extensive investigation of new countermeasures for spaceflight need to be performed on Earth. Not surprisingly, this leads to several confounder that limit the significance of results from ground-based studies. First of all, Earth gravity as constant downward force can affect simulated physiological deconditioning similar to spaceflight. Strict bed rest with 6° head-down tilt for extended periods is widely accepted [97-99] as a ground analog to simulate some of the physiological deconditioning experienced during spaceflight such as muscle disuse [100] or cardiovascular changes [101]. By changing to a supine body position, head-down tilt bed rest reduces overall physical activity and induces cephalad fluid shift. However, as the effects of gravity are still present, several aspects such as bearing of body weight, gravity-dependent fluid distribution and pulmonary ventilation are not similar to actual weightlessness [76, 102]. Furthermore, Earth gravity can influence correct performance of centrifugation as countermeasure by combining the effects of centrifugal force and Earth gravity to a resultant vector. Only a few devices, such as the “Space Cycle” [67, 103], have a swing-out capability leading to a physically correct body position for a ground-based study. By using a rigid centrifuge arm, supine exposure along the centrifuge radius and even more physical activity while rotating is affected by a force vector, that is leading to cross-coupled forces increasing the risk of motion sickness and movement-related injuries. These limitations are given in all three studies due to the technical conditions of the DLR facilities. To reduce the influence of Earth’s gravity and an incorrect resulting vector during centrifugation, we either compared data to a dedicated control group (study 1) or directly across conditions (studies 2 and 3).

Another limitation of ground-based studies is that participants in general are not on the same health and fitness level then astronauts as their selection process is way more complex and detailed. Larger ground-based studies from space agencies try to reduce that confounder via well-defined inclusion and exclusion criteria and a strict recruitment process (“astronaut like”, see NASA HERA requirements). Nevertheless, transfer of study results from participants to spaceflight personnel is limited in particular for psychological findings, countermeasure compliance and data from high intensity training. On the other hand, it is likely that a good outcome from a countermeasure in a ground-based study can be replicated or even increased by well-trained crew member during spaceflight.

Statistical limitations are mainly caused by mutual influence of different experiments inside a study and a small sample size. As larger studies tend to be more and more complex, they often miss a clear definition of a primary endpoint. Especially invasive experiments, such as muscle biopsies, can cause aftereffects (pain) that has a negative influence on other outcomes. During AGBRESA (study 1), this effect likely resulted in a decrease of countermeasure acceptability for the intermittent protocol [82] as frequent caudal fluid shifts during centrifuge ramping up/down lead to increased leg pain after biopsies. As retinal nerve fiber layer thickness served as primary endpoint in AGBRESA, the sample size of 24 (8 subjects in each of 3 arms) was pre-determined by NASA and ESA. For our experiment a larger sample size (> 12) would have been helpful. Study 2 (plyometric exercises) was part of a larger trial together with the German Sports University Cologne and the University of Konstanz who both calculated *a priory* a required sample size of n = 15 to analyze their primary endpoints. In our case, study 2 and study 3 (trunk and back muscle exercises) were both pilot trials and therefore had only medical termination due to pre-syncope, emesis and muscle/joint pain as explorational endpoints. For both studies a sample size of n = 12 were sufficient with pre-syncope, emesis or pain as an adverse event likely be identified by the use of standard medical termination criteria for centrifuge experiments.

With regard to the third study, recordings of muscle surface (cutaneous) electromyography were used together with cardiovascular responses (heart rate, blood pressure) and subjective ratings of exertion (RPE) as indicator for exercise intensity. Surface electromyography, despite non-invasive and easy to apply, has some limitations [104]. In contrast to needle electromyography, recording of muscle activity can be influenced by skin and subcutaneous fat. Furthermore, cross-talk between nearby muscles (e.g. m. obliques) can distort results. Therefore, correct skin preparation and sensor placement over a central position on the muscle is important but can be difficult in dynamic studies. To obtain comparison of muscle activity between conditions, we performed normalization of recorded EMG signal (in percent) to a setup of individualized maximum voluntary contractions that were captured immediately prior each test session. This procedure is widely accepted but is still dependent on several factors like individual motivation of the participant or correct instructions [96].

A lack of adequate familiarization is another limitation of our results. In larger studies, typically up to 10 sessions per sessions were performed to familiarize the participants to the correct training procedure [87]. It is therefore questionable, if our results from acute responses to an unfamiliar exercise setting on the centrifuge can be used to draw significant conclusions about the usability of a centrifuge-based training. Even in study 1 (AGBRESA), participants were exposed to passive centrifugation only twice prior bed rest phase. Given that limitation, it is surprisingly that medical termination of centrifugation due to motion sickness were very rare, even when the amplitude of head movements was higher due to a lack of prober familiarization to e.g. supine jumping.

In conclusion, several potential limitations could be identified – some more and some less avoidable. Since our results were recorded in several pilot trials, the mentioned limitations need to be considered carefully.

8 Conclusion and perspective

Two main conclusions can be drawn from this thesis: the first is that daily exposure to short arm centrifugation is well tolerated even in participants that are not previously habituated to the side effects of a non-constant force field with steep gravity gradients and Coriolis forces. With only 1% premature termination rate, tolerability of daily centrifugation was not a show stopper during a 60-day bed rest with progressive physiological deconditioning and complex experiment schedule including painful leg muscle biopsies as confounder. The second conclusion is that, in contrast to past assumptions, active movements on a short arm centrifuge are also well tolerated regardless even if they involve vigorous head movements. Based on the widely accepted sensory mismatch theory, only sensory motion inputs that have a relevant difference to what is expected from previous experiences are perceived as nauseogenic [105, 106]. Given only that, it could be expected that all participants should have suffered from acute motion sickness, since vestibular sensations while exercising in a rotating environment are undoubtful common by most persons. However, the known fact that car drivers rarely become motion sick [107-109] due to prediction of low-frequency horizontal accelerations could also be applicable during exercising on a short arm centrifuge. While exercising, participants are actively controlling their movement. Furthermore, additional sensory inputs coming from neuromuscular spindles, receptors of joints and tendons improve the ability of the brain to recognize and continuously update the position of the body. This could result in an increased tolerability to conflicting vestibular inputs.

Given the limitations mentioned above, critical review in larger trials are required. From an applied perspective, exercises during simulated gravity are mandatory to use the maximum of its proposed benefits. As from an engineering aspect, rotating vehicles are more complex and require more energy, the advantages on maintaining crews´ health must clearly outweigh the costs. Therefore, upcoming ESA bed rest studies will investigate different exercise types (cycling, jumping and resistive vibration exercises) in combination with centrifugation.

9 References

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10 Appendix

List of relevant publications

<u>Publications:</u>

- Frett, T., Lecheler, L., Speer, M., Marcos, D., Pesta, D., Tegtbur, U., Schmitz, M. T., Jordan, J., & Green, D. A. (2022). Comparison of trunk muscle exercises in supine position during short arm centrifugation with 1 g at centre of mass and upright in 1 g. *Frontiers in physiology*, *13*, 955312.

- Frett, T., Green, D. A., Mulder, E., Noppe, A., Arz, M., Pustowalow, W., Petrat, G., Tegtbur, U., & Jordan, J. (2020). Tolerability of daily intermittent or continuous short-arm centrifugation during 60-day 6o head down bed rest (AGBRESA study). *PloS one*, *15*(9), e0239228.

- Frett T, Green DA, Arz M, Noppe A, Petrat G, Kramer A, Kuemmel J, Tegtbur U, Jordan J. (2020) Motion sickness symptoms during jumping exercise on a short-arm centrifuge. *PLoS One.* 11;15(6):e0234361.

<u>Oral presentations:</u>

Frett, T., Lecheler, L., Pesta, D., Green, D. *Tolerability and effects of abdominal and back muscle exercises when performed supine with 1g at the CoM compared to upright in 1g.* NASA Human Research Program Investigator´s Workshop 2022

<u>Poster presentations:</u>

Frett, T., Mulder, E., Green, D., Noppe, A., Arz, M., Pustowalow, W., Petrat, G., Tegtbur, U., Jordan, J. *Tolerability of daily shortarm centrifuge interventions during sixty days of head down bed rest – Artificial Gravity bed rest with European Space Agency (AGBRESA) study*. NASA Human Research Program Investigator´s Workshop 2020

11 Acknowledgments

First, I would like to thank Prof. Dr. med. Jens Jordan and Prof. Dr. med. Uwe Tegtbur. Their entire supervision, including mentoring and scientific guidance were very helpful and enlighten. In particular, their fast and clear revisions improved all publications related to this dissertation.

Great gratitude is also owed to Dr. David Andrew Green. His great scientific background in space physiology and open-minded view towards new ideas helped me a lot to develop my approach for a centrifuge-based training.

A researcher is nothing without a good team that help to get all the work done. I am more than honored to be part of the DLR centrifuge team, namely: Guido Petrat, Michael Arz and Willi Pustowalow. Thank you, guys!

Special thanks also go to the DLR study team and all physicians working as medical monitor to ensure a safe centrifuge run for every participant.

And, of course, I would like to thank my wife, Annika, for her sympathetic support throughout the recent years.

12 Curriculum vitae

Name: Timo Frett

Date of Birth: 1st of October, 1985

Place of Birth: Andernach

Nationality: German

Professional experience

Since 01/2012 **Research Associate**

Institute of Aerospace Medicine, German Aerospace Center (DLR)

- Responsible for all centrifuge activities at DLR cologne incl. ESA/ NASA Ground Based Facility studies (AGBRESA, ESA-CORA, ESA Spin Your Thesis)
- Principal Investigator or Co-I for national and international studies
- Project leader and inventor for the DLR funded technology development project "ASYSTED - Advanced System for Teleguidance in Diagnosis" together with the German Armed Forces (Patent: German Nr. 102011089793-accepted/ European Nr. 12197547.8-accepted)
- Supervisor for several theses in cooperation with external universities

01/09/2008 – 31/12/2011 **Project engineer in telemedicine and telematics**

Institute of Aerospace Medicine, German Aerospace Center (DLR)

- Coordination of EU telematic/telehealth projects in fields of emergency care and aeromedical medicine
- Responsible for the telemedical network for the medical service of the Bundeswehr incl. education of users and on-site technical installations

Educational background

Since 2019 **PhD Candidate**

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PhD thesis: "*Artificial gravity through short-arm centrifugation as potential countermeasure for human spaceflight: Feasibility, safety, and neuromuscular response*"

01/09/2009 – 01/12/2011 **Master of Science (Biomedical engineering)**

FH Münster University of Applied Sciences, Steinfurt, Germany

Final mark: 1.6, thesis: "*Entwicklung eines Systems zur optimierten Schallkopfführung bei der Telesonographie durch satellitengestützte Kommunikation*"

01/10/2005 – 31/08/2008 **Bachelor of Science (Medical technology and sport science)**

Final mark: 1.8, thesis: „*Konzept und Realisierungsvorschläge für ein OP modul onboard*“

Selected publications

- Marcos-Lorenzo, D., Frett, T., Gil-Martinez, A., Speer, M., Swanenburg, J., & Green, D. A. (2022). Effect of trunk exercise upon lumbar IVD height and vertebral compliance when performed supine with 1 g at the CoM compared to upright in 1 g. *BMC sports science, medicine & rehabilitation*, *14*(1), 177.
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Cologne, October 2022

Place, Date Signature

13 Erklärung

Hiermit erkläre ich, dass ich die Dissertation (**Artificial gravity through short-arm centrifugation as potential countermeasure for human spaceflight: Feasibility, safety, and neuromuscular response)** selbstständig verfasst habe.

Ich habe keine entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten (Promotionsberater oder anderer Personen) in Anspruch genommen. Niemand hat von mir unmittelbar oder mittelbar entgeltliche Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen. Ich habe die Dissertation an folgenden Institutionen angefertigt:

- Institut für Sportmedizin, Medizinische Hochschule Hannover, Carl-Neuberg-Strasse 1, 30625 Hannover
- Institut für Luft- und Raumfahrtmedizin, Deutsches Zentrum für Luft- und Raumfahrt (51147 Köln)

Die Dissertation wurde bisher nicht für eine Prüfung oder Promotion oder für einen ähnlichen Zweck zur Beurteilung eingereicht. Ich versichere, dass ich die vorstehenden Angaben nach bestem Wissen vollständig und der Wahrheit entsprechend gemacht habe.

Ort, Datum _Köln, Oktober 2022_______ (eigenhändige Unterschrift): ______________________