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Tansley, J, Miché, N, Bernagozzi, M, Cahill, S, Georgoulas, A, Santin, M and Forss, R (2025) Gravity effects on lower limb perfusion observed during a series of parabolic flights. Acta Astronautica, 229. pp. 286-296. ISSN 0094-5765

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Acta Astronautica 229 (2025) 286–296

Contents lists available at ScienceDirect

Acta Astronautica

journal homepage: www.elsevier.com/locate/actaastro

Gravity effects on lower limb perfusion observed during a series of parabolic flights

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ARTICLE INFO

Keywords:
Vascular assessment
Lower limb perfusion
Hypergravity
Microgravity
Parabolic flight
Observational study

ABSTRACT

The present observational study simultaneously measured four key factors (arterial oxygenation, superficial tissue oxygenation, peripheral skin temperature, toe systolic pressure) to determine the impact on lower limb perfusion in altered gravity conditions. 24 healthy test subjects (16 male, 8 female) took part onboard a series of parabolic flights. When comparing lower limb perfusion values to 1G (control/Earth's gravity) the study found: 1) no significant difference between arterial oxygenation values in hyper or microgravity was detected when using a pulse oximeter; 2) a significant difference in superficial tissue oxygenation in hyper and microgravity was detected by white light spectroscopy; 3) a significant difference in skin temperature of the foot was detected by thermography in hyper and microgravity; 4) an insufficient sample could be obtained for toe systolic pressure. Reduction in superficial tissue oxygenation and peripheral skin temperature in microgravity compared to 1G, potentially suggests a reduction in blood flow. White light spectroscopy and thermography devices demonstrated they functioned as usual in altered gravity conditions potentially offering a quick, reliable method of assessing the acute effects of hyper and microgravity on lower limb perfusion. These methods may be useful to predict healing potential when injuries occur and highlight early warning signs of tissue damage due to poor perfusion. However, additional work to further establish the impact on oxygen transport in the superficial tissues in both acute and sustained microgravity would be beneficial.

1. Introduction

1.1. Background

It is well documented that a 'fluid shift' occurs when the human body is exposed to microgravity. Fluid is drawn away from the lower limbs and shifts to the head and chest which could produce a compromise to arterial, venous, and lymphatic flow [1]. It is suggested that a loss of gravitational resistance, non-weightbearing and reduced demand on arterial baroreceptors influence a lack of peripheral resistance in blood vessels [1,2]. Furthermore, the effects of microgravity on the human body can create situations which imitate the consequences of a sedentary life, bed rest and aging on Earth [3]. However, the effect on microcirculation and cardiovascular adaptation remains poorly understood.

Potential consequences of prolonged exposure to microgravity conditions may present in a similar way to peripheral arterial disease (PAD). Ischaemia is a common presentation with peripheral arterial disease, where blood supply is insufficient to meet the needs of the surrounding tissues [4]. Complications of ischaemia in the lower limb are known to include pain and tissue death which lead to ulceration, gangrene, reduced mobility, and quality of life. Wound healing is also likely to be impaired or stall completely, with increased risk of further complications such as infection and limb amputation, unless reperfusion takes place [5]. This is a consideration for risk assessment and injury mitigation during prolonged periods of space flight. Furthermore, it is known that crews are exposed to micro-organisms which were

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https://doi.org/10.1016/j.actaastro.2025.01.010
Received 8 July 2024; Received in revised form 6 January 2025; Accepted 6 January 2025
Available online 10 January 2025
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Abbreviations

ESA	European Space Agency
1G	Control group (Gravity condition the same as Earth's gravity)
HyperG	Hypergravity (Gravity condition defined by project as 1.75G and above)
MicroG	Microgravity (Gravity condition defined by project as 0.05G and below)
MTPJ	Metatarsophalangeal joint
PAD	Peripheral arterial disease
SO_2	Capillary bed oxygen saturation
SPO_2	Arterial oxygen saturation
STROBE	Strengthening the reporting of observational studies in epidemiology

previously not known on Earth, hence the consequences of any resulting wound infections are unknown [6].

1.2. Study rationale

This study was developed as a research gap was identified concerning the effect of changing gravity conditions on peripheral perfusion [7]. With an anticipated increase in human involvement in future space projects such as exploration towards the Moon and Mars, the development of lower limb risk assessment and injury modification strategy is essential [7].

By further understanding the impact on lower limb micro-circulation in healthy individuals, future risk assessment and management strategies may also be developed for those considering space tourism who may not have the same fitness of trained astronauts or have conditions which cause lower limb pathology associated with tissue perfusion (PAD, diabetes, chronic lympho-venous diseases, autoimmune diseases, lifestyle factors etc).

1.3. Scientific background

It appears that only a small number of studies have investigated the effect of microgravity on lower limb perfusion, with even fewer being conducted on board a parabolic flight. These studies report that blood flow in the lower limbs significantly reduces in microgravity [8,9], raising questions as to whether a condition that imitates PAD or ischaemia is created in microgravity.

Studies examining the effect of hypergravity on lower limb perfusion are conflicting. Previous studies report that systolic blood pressure at the ankle has been observed to increase in hypergravity (above 1G) [10], but it is further suggested that the impact on lower limb perfusion in hypergravity is dependent on the anatomical site [11]. In contrast, one study states that an increase in overall perfusion will not occur until forces reach above 2G [11] with another reporting no change in perfusion was observed following exposure to 3G [12].

Consequently, this study was developed to investigate whether a change could be observed in lower limb perfusion measurement values in hypergravity and microgravity and identify the most appropriate device for measuring any changes in perfusion. Our study focuses on four key factors to determine the level of blood flow in the peripheral/microcirculation of the lower limb: arterial oxygenation (SPO_2), superficial tissue oxygenation (SO_2), systolic blood pressure in the toe and skin temperature in hyper and microgravity conditions. Additionally, the effect on heart rate was observed, to help understand the stresses on the cardiovascular system in the different gravity conditions. Data was obtained in the hyper and microgravity phases created on board a series of parabolic flights. Initially used for the training of astronauts, these flights are now principally used for technical testing of space equipment or for scientific experimentation and can be used to study the human body's acute responses to hyper and microgravity [13].

2. Material and methods

2.1. Study design

This observational study design used repeated measures to capture lower limb perfusion measurements in three different gravity conditions. A group of healthy test subjects were exposed to three gravity conditions and their lower limb perfusion values were obtained to observe whether perfusion is affected. A priori power analysis was conducted to determine the minimum required sample size. Based on the assumptions that a repeated measures ANOVA (or a nonparametric alternative) would be used for the data analysis, with an expected effect size (f) of 0.8 and a significance level (p) of 0.05, the power analysis indicated that a minimum of 14 test subjects were needed.

2.2. Setting

The study took place on a series of parabolic flights across the 83rd and 84th European Space Agency (ESA) parabolic flight campaigns: 20th – November 30, 2023 and 8th – April 18, 2024. Parabolic flights were chosen as they recreate a real state of weightlessness, close to space flight. Simulated methods such as a drop tower, human centrifuge, water immersion or a random positioning machine would not be compatible with the equipment used in the study. Alternative methods such as bed rest, or a tilt table may not eliminate the effects of gravity completely [14].

2.3. Participants

Convenience sampling was used to recruit participants from the experimental teams also taking part in the planned parabolic flight campaigns.

Inclusion criteria:

- Healthy volunteers (male or female).
- $>$18 years.
- Affiliated to a social security system and holding either a European Health Insurance Card (EHIC) or Global Health Insurance Card (GHIC).
- Passed an aviation medical examination (mandatory for anyone participating on a parabolic flight).

Exclusion criteria:

- Test subject has had a lower leg/foot infection or injury in the last three months.
- Vulnerable persons referred to in Articles L-1121- 5 to 8 and L-1122-2 of the French Code of Public Health are excluded from the study:
- Pregnant or nursing women (urine pregnancy test for women of childbearing potential).
- Protected adults (guardianship, curatorship, safeguard of justice).

In addition, all test subjects were administered with an anti-sickness medication (Scopolamine hydrobromide, up to 0.8 mg) prior to each flight. If a test subject experienced motion sickness, data collection would cease and would therefore be excluded from the study. Subjects were in a seated position with one limb elevated throughout the data collection process.

2.4. Data sources & measurement

All the study equipment is commercially available and was used in accordance with its conformity marking (CE). Each piece of equipment is compact and therefore frequently used in everyday clinical practice to give a rapid, chairside assessment of lower limb perfusion.

A bespoke test centre was designed and assembled at the University of Brighton Advanced Engineering Centre, following the specifications required by Novespace, the CNES subsidiary supervising the parabolic flights. The design allowed for synchronous vascular testing to be performed by securely housing the study equipment while providing a rest for the test subjects' foot (Fig. 1). The equipment used in this work was: 1) a superficial tissue oxygenation monitor (MoorVMS-OXY by Moor Instruments, Devon, United Kingdom); this probe was attached to the plantar surface of the 1st metatarsophalangeal joint (MTPJ) in each test subject (Fig. 2(A) and set to continuously record SO_2 and skin temperature values at 10 Hz frequency; 2) a pulse oximeter, (Mindray PM-60, by Henzhen Mindray Bio-Medical Electronics Co. Ltd, Shenzhen, China), this sensor was attached to the test subject's 3rd toe (Fig. 2(B) and set to continuously record SPO_2 and heart rate values every 2 s; 3) a DMX Doppler ankle-toe pressure kit (Dopplex ATP Kit by Huntleigh healthcare Ltd; Cardiff, United Kingdom); The pressure cuff was attached to the base of the great toe with the sensor attached to the apex of the toe (Fig. 2(C). This device is operated manually, and each operator attempted to take as many toe systolic pressure measurements evenly spaced across all the gravity conditions; 4) a thermal imaging camera (HikMicro M30 by Hangzhou Microimage Software Co.Ltd, Hangzhou, China) which was positioned towards the dorsum of each test subjects' foot with the foot and toes in view at a distance of approx. 70 cm. Three points of interest were set up: the 2nd toe, the 1st MTPJ and the midfoot (Fig. 3) and was set to continuously take an image every second.

Each test subject participated for a series of five parabolas, each parabola characterized by roughly 20 s of hypergravity, 20 s of microgravity and finally another 20 s of hypergravity. After each series, a short break of approximately 5 min allowed for the changeover of test subjects.

2.5. Data extraction

Data was extracted from the corresponding time periods of steady acceleration in level flight (1G), hypergravity (when reaching the threshold of 1.75G+) and microgravity (when reaching the threshold of <0.05G). Data captured in the transition periods i.e. accelerating from steady flight to hypergravity (1G to 1.75G) and accelerating from hypergravity to microgravity (1.75G - 0.05G) would not be included in the primary analysis. Analysed data for hypergravity was taken from the pull up phase for every parabola as maintenance of 1.75G+ was more consistent in this phase, than the pull-out phase.

Data from the Mindray PM60 pulse oximeter, HikMicro M30 thermography camera and Huntleigh toe pressure equipment, was extracted manually by matching the timings (hh:mm:ss) of the gravity condition of interest, with the corresponding perfusion data values from each piece of equipment.

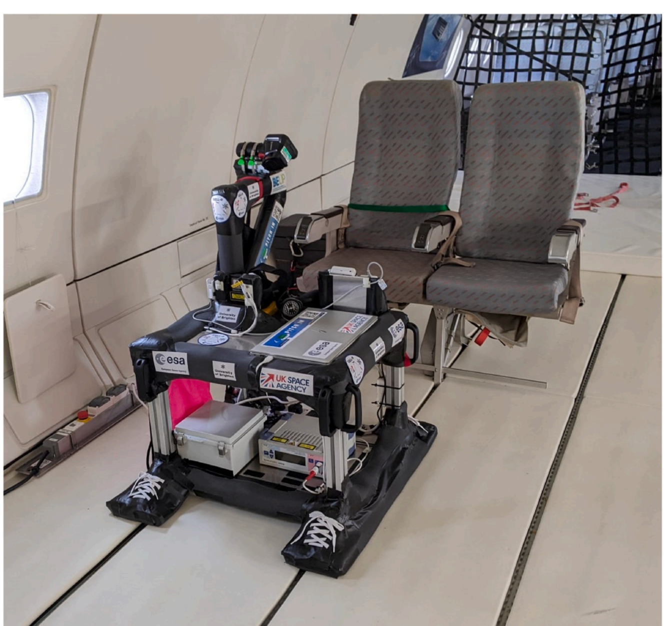

Fig. 1. Assessment centre.

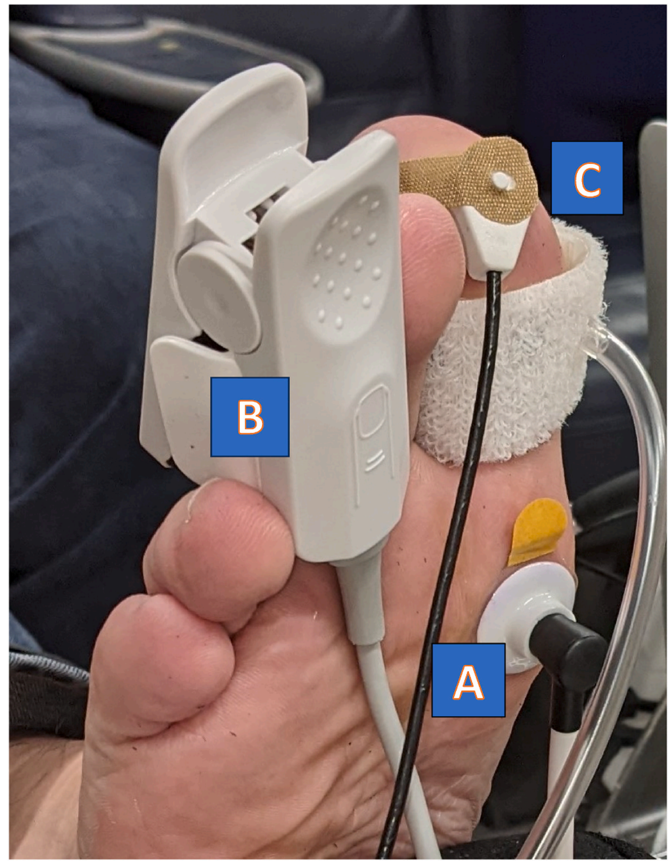

Fig. 2. Position of sensors. A – MoorVMS OXY: capillary bed oxygenation; B – Mindray pulse oximeter: arterial oxygenation; C – Huntleigh ATP kit: toe systolic pressure.

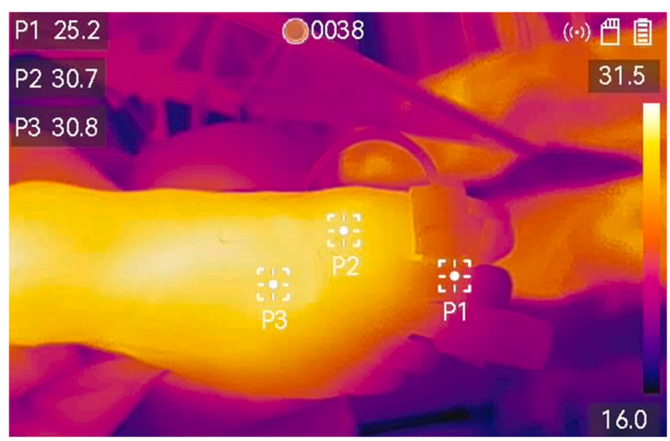

Fig. 3. HiKMicro thermal camera image with points of interest.

2.6. Data analysis & reporting

All statistical analyses were completed using IBM SPSS Statistics software version 29.0.1.0. The Friedman test of variance was used to explore the impact of different gravitational conditions on the vascular assessment values obtained from the Mindray PM60 pulse oximeter, HikMicro M30 thermography camera and MoorVMS OXY. This non-parametric test was deemed the most appropriate, as an alternative to the one-way repeated measures ANOVA, as the data was not normally distributed and therefore not all the general ANOVA assumptions were met. Any Significant findings had Friedmans Test effect size calculations performed using the Kendall's W coefficient, using the formula: $W = \chi^2/N.(K-1)$ [15]. Where 0.1 - <0.3 is a small effect, 0.3 - < 0.5 is a moderate effect and >0.5 is a large effect [16].

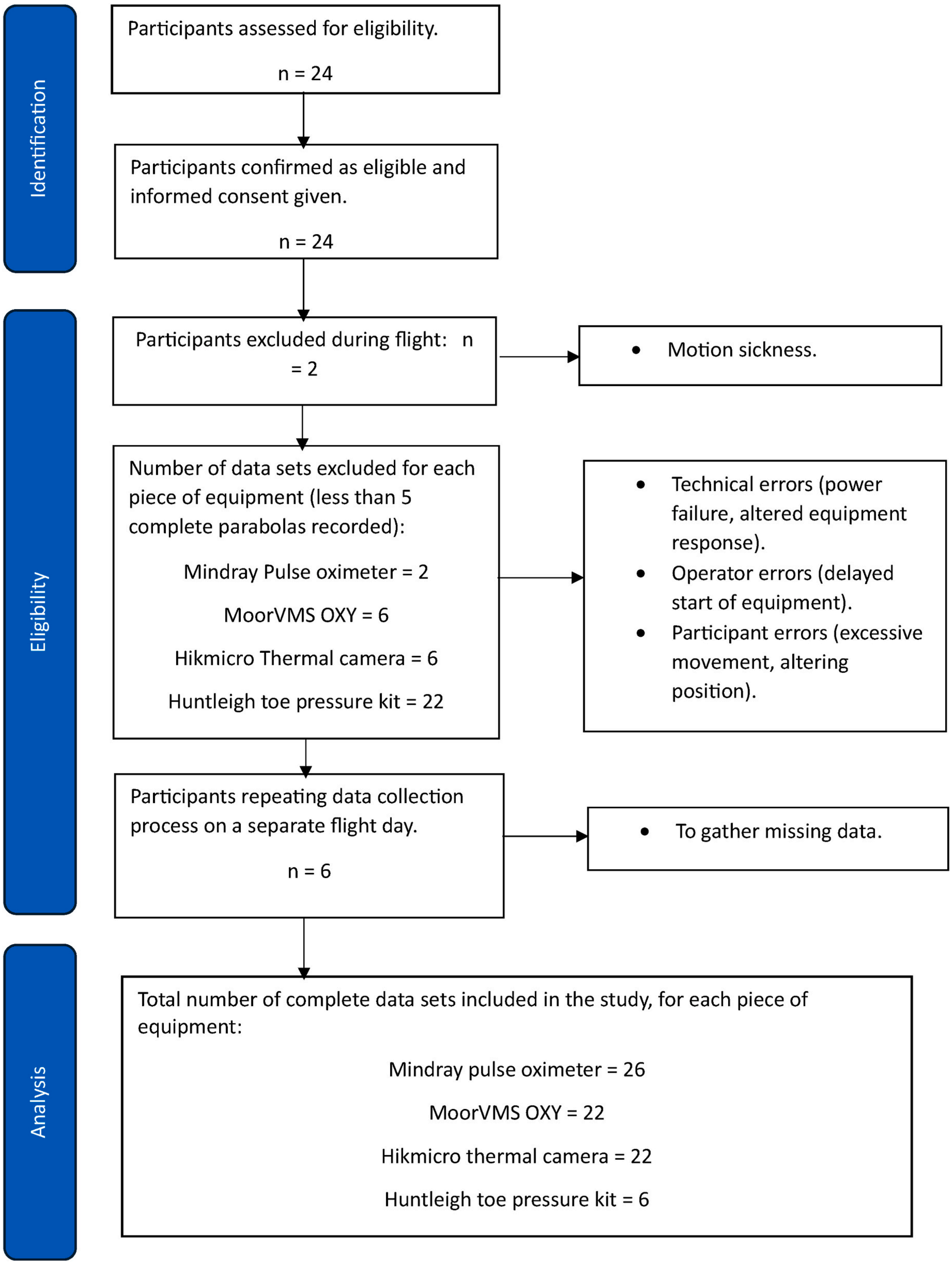

Fig. 4. STROBE flow diagram of the GELL-P project.

Reporting of this observational study follows the STROBE (strengthening the reporting of observational studies in epidemiology) statement and checklist of items [17] as recommended by the EQUATOR (enhancing the quality and transparency of health research) network [18].

2.7. Ethics

The study was developed and carried out in association with the University of Brighton, UK and was therefore reviewed and passed the scrutiny of the University of Brighton's Tier 2 Cross School Research Ethics Committee. Ref: 2002-9915-Forss. Approval from the French ethics committee was also required as it was conducted from a base in France. The Comités de Protections des Personnes (CPP) granted ethical approval. CPP ref: 1-23-068/23.02604.000268.

3. Results

3.1. Participants

A total of 24 test subjects were assessed and confirmed as eligible to participate in the study – 16 males (67 %) and 8 females (33 %). Ages ranged from 23 to 60 years with a mean age of 36. One test subject reported having type 1 diabetes but with no associated cardiovascular complications. All remaining test subjects reported no relevant medical history. All subjects were found to have multiphasic doppler sounds when assessing the posterial tibial and dorsalis pedis arteries before undertaking their first flight, suggesting a healthy blood flow into the lower limb. A summary of test subject recruitment, screening and data obtained is displayed in the STROBE flow chart (Fig. 4).

3.2. Preliminary analysis

Normality tests were conducted to check if the variables violated any of the assumptions underlying the proposed statistical techniques. The results of the Kolmogorov-Smirnov test revealed that most of the data sets were not normally distributed (SPO_2 0.001; SO_2 0.019; heart rate 0.015; thermal camera temperatures 0.001). Therefore, Friedman tests were used to analyse data to address the research questions.

3.3. Main study results

3.3.1. Arterial oxygenation

The results of the Friedman's test for arterial oxygenation (SPO_2) values obtained by the Mindray PM60 pulse oximeter, showed no significant difference across the three gravitational conditions ($\chi^2(2)$ = 1.89, p = .389).

Inspection of the mean values for each gravity condition shows arterial oxygenation levels which are comparable to the healthy parameters of 95–100 % used in clinical settings (Table 1). The pulse oximeter did not detect any signs of hypoxia (<92 %) [19] in any of the test subjects in any of the gravity conditions. Standard deviation analysis shows that there is little variance across the SPO_2 values obtained (Fig. 5).

Table 1
Mean values observed for arterial oxygenation compared with healthy clinical values.

SPO_2 Friedman's test (ns)	1G	HyperG	MicroG
Mean arterial oxygenation values – toe (%)	98.87 %	98.69 %	98.68 %
Standard deviation	1.02	1.01	0.86
Healthy clinical values [19]	Fingertip >95 %		
	Toe ± 2 % of finger reading		

ns P > .05, *P ≤ .05, **P ≤ .01, ***P ≤ .001, ****P ≤ .0001.

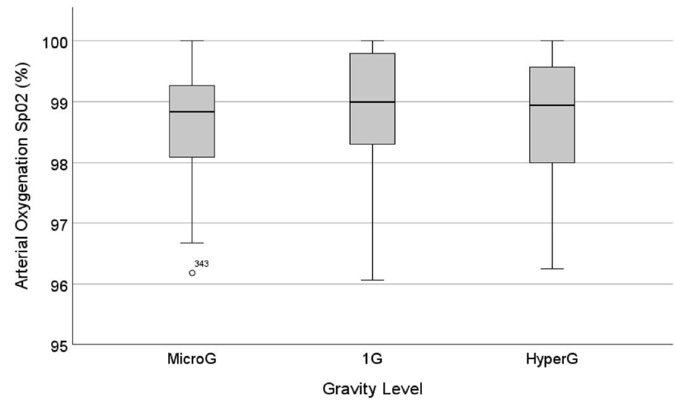

Fig. 5. Boxplot illustrating arterial oxygenation values.

3.3.2. Superficial tissue oxygenation

The results of the Friedman's test for superficial tissue oxygenation (SO_2) values obtained by the MoorVMS-OXY, showed a significant difference across all three gravitational conditions (χ^2 (2) = 34.982, p < .001). The effect size, measured by Kendall's W Value, was d = 0.16, indicating a small effect.

Pairwise comparisons (with Bonferroni correction for multiple tests) show that there was a significant difference in SO_2 values in 1G compared to hypergravity (p = .000) and microgravity (p = .000). However, SO_2 values between hypergravity and microgravity were similar (p = .177). Higher oxygenation values were observed more frequently during the 1G phase, reducing for the hyper and microgravity phases.

Inspection of the mean values for all three gravity conditions show capillary bed oxygenation levels which are lower than the healthy parameters used in clinical settings and comparable to the levels you might expect to see in a person with severe peripheral arterial disease (30–49 %) [20] (Table 2). Standard deviation analysis shows that SO_2 values vary significantly from the mean (Fig. 6). The authors acknowledge that there are several confounding factors which may contribute to these reduced values and are considered in the discussion.

3.3.3. Toe systolic pressures

Insufficient data was obtained from the Huntleigh toe pressure equipment to be able to conduct a statistical analysis. Only six complete data sets were successfully obtained, therefore not enough data was collected to reach power.

3.3.4. Skin temperature

The results of the Friedman's test for peripheral skin temperature values obtained by the HikMicro M30 thermal camera, showed a significant difference across the three gravitational conditions at three location points on the dorsum of the foot: Point1: 2nd toe (χ^2 (2) = 59.256, p < .001); Point 2: 1st MTPJ (χ^2 (2) = 55.462, p < .001) and Point 3: midfoot (χ^2 (2) = 83.57, p < .001). The effect size, measured by Kendall's W Value, was d = 0.27 for the 2nd Toe, d = 0.25 for the 1st MTPJ and d = 0.38 for the midfoot, indicating a small, small and moderate effect respectively.

Pairwise comparisons (with Bonferroni correction for multiple tests)

Table 2
Mean values observed for capillary bed oxygenation compared to healthy clinical values.

SO_2 Friedman's Test (***)	1G	HyperG	MicroG
Mean capillary bed oxygenation values (%)	38.64	31.54	32.79
Standard deviation	11.62	12.59	12.60
Healthy clinical values	Foot = >70 % [20]		

ns P > .05, *P ≤ .05, **P ≤ .01, ***P ≤ .001, ****P ≤ .0001.

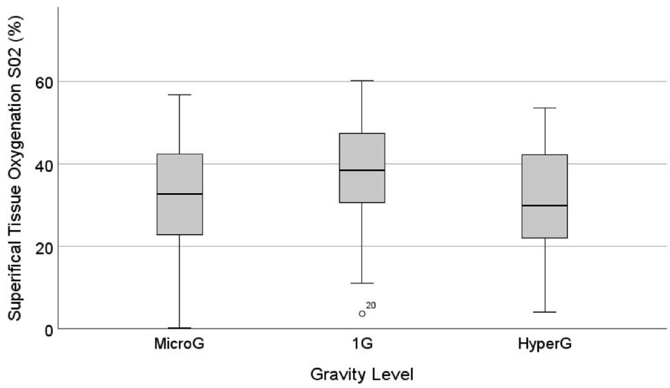

Fig. 6. Boxplot derived from superficial tissue oxygenation values.

show that there was a significant difference in peripheral skin temperature values between 1G and hyper gravity (Point 1: $p = .009$; Point 2: $p < .001$; Point 3: $p < .001$); between hypergravity and microgravity (Point1: $p < .001$; Point 2: $p < .001$; Point 3: $p < .001$) and between microgravity and 1G (Point1: $p < .001$; Point 2: $p = .043$; Point 3: $p < .001$). At each point, higher temperature values were observed more frequently in 1G, mid-range values in hypergravity and the lowest values in microgravity.

Statistical analysis of the distribution of peripheral skin temperature values obtained by the MoorVMS-OXY at one point on the plantar surface of the foot (1st MTPJ), showed a significant difference across the three gravitational conditions (χ^2 (2, n = 110) = 87.042, $p < .001$). The effect size, measured by Kendall's W Value, was d = 0.395, indicating a moderate effect.

Pairwise comparisons (with Bonferroni correction for multiple tests) show that there was a significant difference between 1G and hyper gravity ($p = .000$), between hypergravity and microgravity ($p = .000$) and between microgravity and 1G ($p = .000$). Higher temperature values were most frequently observed in 1G, mid-range values in hypergravity and the lowest values in microgravity.

Inspection of the mean values for each gravity condition obtained by the thermal camera and the MoorVMS-OXY show peripheral skin temperatures which are lower than the healthy parameters for the foot, used in clinical settings [21] (Table 3). However, it can be noted that the difference between the mean values for temperature in the three gravity conditions is marginal (<0.5 °C). Standard deviation analysis shows the temperature values do not vary significantly from the mean (Fig. 7).

3.3.5. Heart rate

The results of the Friedman test for heart rate values obtained by the Mindray PM60 pulse oximeter showed a significant difference across the three gravitational conditions (χ^2 (2, n = 130) = 12.998, $p = .002$). The effect size, measured by Kendall's W Value, was d = 0.05, indicating a small effect.

Pairwise comparisons (with Bonferroni correction for multiple tests) show that heart rate values were the similar in 1G and microgravity ($p = 1.000$) but are increased in hypergravity when compared to 1G ($p = .007$) and microgravity ($p = .004$).

The mean values for heart rate are comparable to the healthy parameters of 60–100 beats per minute, used in clinical settings [23] (Table 4). Despite the statistically significant result, the difference between the mean values for heart rate in the three gravity conditions is small (<2 bpm). Standard deviation analysis shows that heart rate values vary significantly from the mean (Fig. 8).

4. Discussion

4.1. Overview

An observational study was performed which aimed to investigate the effect of hypergravity (1.75G+) and microgravity (<0.05G) on lower limb perfusion, compared with Earth's gravity (1G); and identify appropriate equipment to measure changes to lower limb perfusion during different gravity conditions. Data was obtained using four commonly used clinical vascular assessment devices, onboard a series of parabolic flights, from 24 healthy test subjects.

4.2. Arterial oxygenation

Human tissue requires a constant supply of oxygen to remain healthy. This oxygen is bound to haemoglobin in the blood and diffused to the tissues through interstitial fluid [24]. Pulse oximetry uses a spectrophotometry technique to measure peripheral arterial blood oxygen saturation (SPO_2). It constitutes a quick, non-invasive method of detecting hypoxia in clinical settings [25]. Sensitivity to hypoxia is dependent on the tissue type – with nerve cells being more sensitive and muscle cells more resistant. Although, this further depends on the level of oxygen saturation and the length of time exposed to hypoxic conditions [26]. Arterial oxygenation levels of <92 % is the clinical indicator for hypoxia [19]. It is believed that provided the arterial oxygen saturation is above 85 %, this should be sufficient to prevent tissue damage [26].

The results of our study found no statistically significant difference in SPO_2 values across all gravity conditions, with little variance across the range of values obtained. Although our study obtained mean SPO_2 values of 98 % ± 0.2 %, across all three gravity conditions, which appear to be consistent with healthy clinical values [19], this perhaps should be interpreted with caution. Our results appear to differ from the findings of other studies which used pulse oximetry on the fingers and toes of test subjects during a parabolic flight. In a study by Smith et al. (2016) it was found that there was a significant difference between arterial oxygenation in the microgravity phase of flight, compared to the 1G and hypergravity phases. However, it was observed that all the in-flight values were significantly lower than the healthy clinical values and the pre-flight values taken on the ground [27].

Pulse oximetry is known to have limitations, and inaccurate readings may be influenced by the fit of the sensor, skin temperature (if less than

Table 3
Mean values observed for peripheral foot temperature compared to healthy clinical values. All values in [°C].

Skin Temperature 1st MTPJ Friedman's Test (***)	1G			HyperG			MicroG		
	Point 1	Point 2	Point 3	Point 1	Point 2	Point 3	Point 1	Point 2	Point 3
Mean skin temperature (°C) – Thermal camera	20.76	23.93	27.13	20.65	23.85	27.06	20.53	23.73	26.94
Standard deviation	2.86	2.74	2.38	2.83	2.73	2.36	2.79	2.70	2.33
Mean skin temperature (°C) – MoorVMS OXY	22.56			22.53			22.48		
Standard deviation	1.82			1.82			1.83		
Healthy clinical values	Core = 36.5–37.5 °C [22] Foot = 28–32 °C [21]								

ns P > .05, *P ≤ .05, **P ≤ .01, ***P ≤ .001, ****P ≤ .0001.

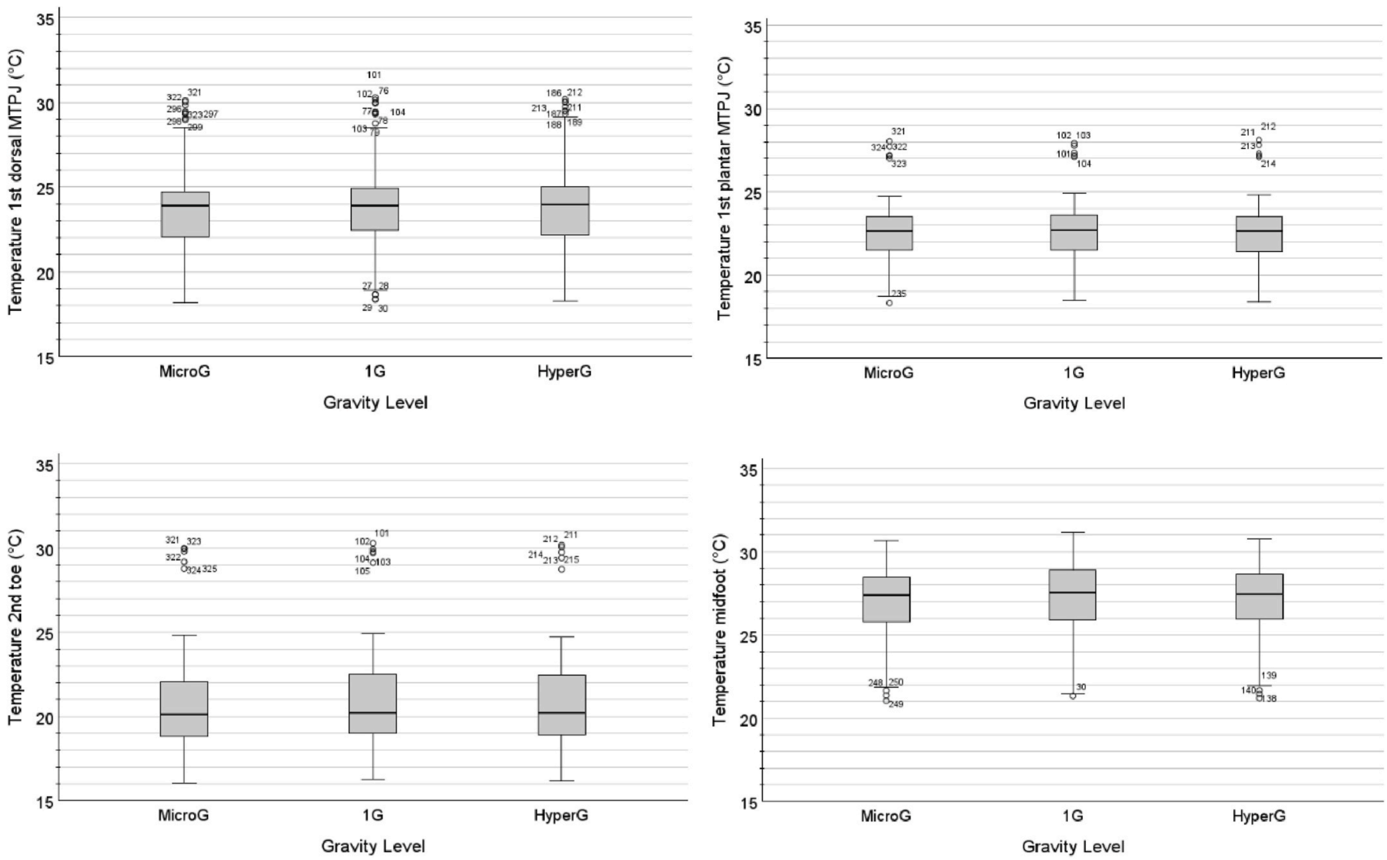

Fig. 7. Boxplots derived from skin temperature values.

Table 4
Mean values observed for heart rate compared to healthy clinical values.

Heart Rate Friedman's Test (**)			
	1G	HyperG	MicroG
Mean heart rate values (bpm)	68.72	70.39	68.43
Standard deviation	15.48	15.55	14.67
Healthy clinical values	60–80 bpm [23]		

ns P > .05, *P ≤ .05, **P ≤ .01, ***P ≤ .001, ****P ≤ .0001.

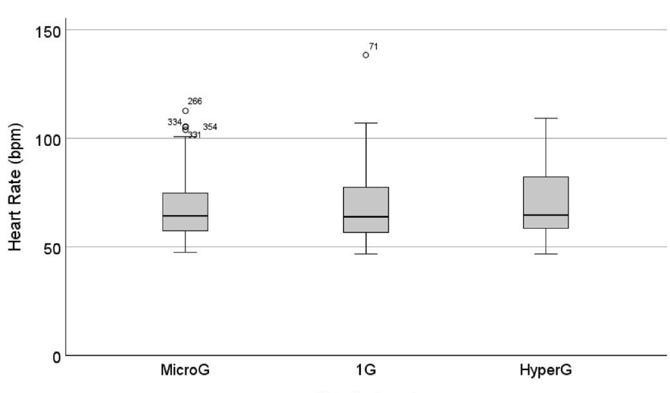

Fig. 8. Boxplot derived from heart rate values.

33 °C), systolic blood pressure (if less than 80 mm/hg), or light pollution (from ambient lighting) [25]. Taking measures to cover the limb/foot to keep it warm and minimise any impact from light pollution; using a flexible wrap-style sensor specifically designed for the toe, are considerations for enhancing future methodologies.

The pulse oximetry equipment appeared to function as usual throughout each flight and findings correspond with a previous study [27], which reported that their test subject's arterial oxygenation appeared unchanged in the microgravity phase of a parabolic flight, when using pulse oximetry. However, reviews of pulse oximetry also suggest that even when arterial oxygenation levels appear healthy, conditions need to be right for this oxygen to be released into the tissues [26]. This can be explained by the oxyhaemoglobin dissociation curve and may account for the conflicting results found by this study between arterial oxygenation and superficial tissue oxygenation values.

4.3. Superficial tissue oxygenation

To study oxygen transport in the microcirculation, it is important to establish how much oxygen is bound to haemoglobin in the blood (SO_2) alongside examining the oxygen tension gradient ($P0_2$). The partial pressure of oxygen is naturally found to be lower in peripheral tissue with less haemoglobin bound oxygen [24]. The oxyhaemoglobin dissociation curve plots the relationship between haemoglobin bound oxygen and the partial pressure of oxygen in the blood. It can explain how readily our blood releases oxygen to the tissues. Haemoglobin has a decreased affinity for oxygen, when the partial pressure is low, therefore oxygen molecules are quickly released and vice versa [28]. Few studies exist which have explored the effect of altered gravity on red blood cells, haemoglobin, and oxygen transport. However, simulated studies have found that microgravity appears to influence the shape, size and permeability of red blood cells impacting oxygen transfer [29].

The present study used the MoorVMS-OXY to observe SO_2 values in the superficial tissues of the plantar MTPJ area of the foot. This device uses white light spectroscopy to measure oxygen saturation in the capillary bed of superficial tissues (SO_2) such as the skin. It has been found to be useful in diagnosing peripheral arterial disease, predicting healing potential in chronic wounds, and determining amputation level in critical limb ischaemia [30].

A statistically significant difference in tissue oxygenation values across the three gravity conditions was found, which may suggest that the MoorVMS-OXY was able to detect signs of the well documented change in limb fluid volume which occurs with changing gravity conditions [1]. Studies have shown that fluid volume reduces in the lower limb in microgravity [8,9] and may account for the reduced SO_2 values obtained in the microgravity phase of the parabolic flight. In addition, the mean SO_2 values obtained (35 % ± 3.5 %), were significantly lower than the healthy values for the foot (>70 %) used for clinical assessments. These values would be indicative of severe peripheral arterial disease in a clinical setting [18] and raises questions about the effect prolonged microgravity may have on oxygen binding and release in superficial tissues.

This finding coincides with a study by Smith et al. (2016) who also reported that their test subjects SO_2 levels in the foot were well below the normal physiological range across all three gravity conditions recreated on a parabolic flight (50 % ± 3 %) [27]. Furthermore, Smith et al.'s study noted that there was a slight reduction in the mean tissue oxygenation values taken in the 1G phase of flight compared to the ground (55 % ± 5 %). This was attributed to "a mildly hypoxic cabin pressure altitude" [27]. Our study does not have data for SO_2 pre-flight to make a comparison.

Several confounders have been identified which may have influenced SO_2 values: 1) The key confounder to consider, is the acute and swift changes to fluid volume to the lower limb resulting in fluid accumulation (oedema) and subsequent congestion in the microcirculation [10]. The effect of micro-gravity of the venous system has been well studied and it has been observed that venous pressure and wall stress increases in micro-gravity with decreased venous emptying/flow. This has been reported to affect both upper (jugular) and lower (femoral) body veins [31] 2) The lower than usual skin temperatures in the foot, observed by our study, could be a consideration as it is known that haemoglobin affinity of oxygen is increased with lower temperatures [28]; 3) Parabolic flights can be a stressful experience for some and the transitions between gravity phases may cause a natural stress response of shallow breathing or breath holding, resulting in reduced oxygenation [32]. Although test subjects were advised to breathe normally, respiratory rate was not monitored and is a further consideration when reviewing the reduced SO_2 values obtained in both hyper and micro-gravity conditions; 4) Location of the skin probe on different parts of the body will produce different tissue oxygenation characteristics [33]. The skin to the plantar surface of the foot is thick with fibrous connective tissue [34] suggesting that the equipment may be less likely to detect oxygen molecules in the capillaries and surrounding tissue. However, standardised placing of the probe at the 1st MTPJ area was used on all test subjects to provide a consistent method and results for comparison.

This evidence further reinforces the theory that the limb/foot should be kept warm to enhance future methodology and ensure the most accurate results. In addition, measuring of venous flow, respiration rate, use of multiple probes across different sites on the foot and taking measurements pre and post flight for comparison, may further enhance future findings.

4.4. Toe systolic pressure

Systolic toe pressure kits are becoming more frequently used clinically to diagnose and determine the severity of peripheral arterial disease in the lower limb. They are particularly useful to assess microcirculation in the extremities especially when larger vessels in the ankle are incompressible due to calcification [35]. Although it is recommended that results should never be interpreted in isolation as uncertainties about the accuracy of this method remain [35,36].

The equipment used to measure systolic pressure in the great toe did not respond as usual throughout the series of parabolic flights. Operators reported that in the hypergravity phase of flight, the air bladder of the sphygmomanometer appeared to collapse making it more difficult to compress by hand. An increased resistance was also noticed when attempting to inflate the pressure cuff. During the microgravity phase of flight, the pressure cuff deflated much more quickly than usual with an apparent lack of resistance being reported by operators.

No previous studies were found which specifically used a toe pressure cuff, sphygmomanometer and DMX doppler in alternative gravity conditions on a parabolic flight. However, systolic blood pressure measurements in the lower limb have been taken by other methods in simulated studies [9–11]. These studies report that lower limb arterial blood pressure increased when gravity increased above 2G [10,11] and that it significantly reduced in micro gravity when compared to an upright posture in Earth's gravity (a change from 197 mm/hg to 87 mm/hg) [9].

From the small sample obtained, it could still be observed that the mean systolic pressures, at the great toe, reduced in hypergravity and further reduced in microgravity. However, there was a high variation in the range of values obtained with some obvious outliers – toe pressures as low as 26 mm/hg were recorded, but it is uncertain as to whether this is a true value or due to unusual equipment response. Despite the apparent reduction in pressures, the mean values for each gravity condition remained within the healthy parameters used in clinical assessment. Overall, the systolic pressure values obtained did not suggest that perfusion was reduced to hypoxic or ischaemic levels. However, a greater sample is needed to validate these results.

Our study required test subjects to be in a seated position with one limb elevated throughout the data collection process. In clinical settings, it is generally advised that those undergoing a lower limb vascular assessment lie in a supine position [37]. Studies have shown that a seated position with a limb elevated, can put pressure on the vessels in the abdomen and groin elevating systolic pressure readings in the ankle or toe [38]. This could be a consideration when reviewing the results obtained.

Taking measurements with test subjects lying in a supine position to ensure there are no obstructions to blood flowing freely to and from the lower limb; and the use of an automated piece of equipment to counteract any operator bias, may enhance any future methodology.

4.5. Skin temperature

Infrared thermal imaging cameras (thermography) may be used clinically to identify temperature differences between symmetrical parts of the body or between diseased and non-diseased areas. A raised temperature may indicate an area of pathology, such as inflammation, malignancy, or infection. Whereas a lowered temperature may be an early warning sign of tissue damage due to peripheral arterial disease or pressure [39]. No similar studies have been found which have used thermography to observe variations in skin temperature of the lower limb in alternative gravity conditions.

Our study used the MoorVMS-OXY and Hikmicro thermography camera to continuously monitor skin temperature at four different sites on the foot, across all three gravity conditions. Their findings appear to concur, as the values obtained by both devices resulted in a statistically significant difference across all three gravity conditions. Both devices recorded the highest temperatures in 1G, mid-range temperatures in hypergravity and the lowest temperatures in microgravity.

Although a statistically significant result was produced, the difference in mean values obtained is less than 2 °C for each gravity condition. When body temperatures fluctuate less than 2 °C from healthy values, this may not be considered clinically significant [40]. However, it is noted that our overall mean temperatures for each gravity condition (22.52 °C ±0.04 °C), are lower than the suggested healthy clinical values for the foot (28–32 °C) [21]. It is proposed that foot temperatures of less than 28 °C may be indicative of PAD in a clinical setting [19,20], but due to a lack of supporting studies and clinical guidance which uses skin temperature as a measure for PAD, it is not possible to make this comparison.

Ambient temperature is known to influence foot skin temperature [21], which in turn may influence diffusion of oxygen to the tissues as previously discussed. Studies have shown that foot temperatures of individuals living in temperate climates can vary from as low as 15.9 °C in the winter and 37.5 °C in the summer [21]. The ambient temperature of the aircraft cabin was not recorded on the flight days, and it is not known whether it was the same for each flight, but is reported as being maintained between 17 and 20 °C.

The devices used to monitor foot temperature worked as usual throughout each flight and could be useful in highlighting the early warning signs of tissue damage by identifying area of abnormal heat or cold when compared to the rest of the foot/limb [39]. Monitoring of ambient temperature and taking this into account when interpreting findings, may enhance future methodology and analyses.

4.6. Heart rate

The effect of hyper and microgravity on heart rate has been studied and is also often used as a supplementary measure to support studies where cardiovascular adaptation is of interest [41]. Likewise, heart rate values, collected by our study via pulse oximetry, were used to observe whether there were any noticeable patterns between heart rate values and the other measures of lower limb perfusion being observed.

It is suggested that in hypergravity the heart works harder to compensate for a downwards shift of fluid towards the lower limbs to maintain an adequate blood supply to the head and upper body [42]. Studies have also found that heart rate in microgravity is similar to those who are observed lying supine on the ground, suggesting that there is less resistance on the cardiovascular system in space [41].

Bimpong-Buta et al. [43], investigated the macro and microcirculation in microgravity in parabolic flights in 12 individuals, mean age 29 years, using sublingual monitoring in seated and supine postures. They identified that heart rate increased during phases of hypergravity while seated, up to median values of 87 bpm after 15 s of the hypergravity pull-up phase, compared to the 73 bpm achieved in steady flight. This heart rate increase was larger than was observed in this study, which was an increase of >2 bpm during the pull up hypergravity phase. Bimpong-Buta et al. (2020) also identified that heart rate was comparable in the 1G and the microgravity phases of flight, which is consistent with the findings of this study [43]. It is noted that this and the seated posture adopted in our study may contribute to these differences.

Beckers et al. [44], investigated continuous Electrocardiogram (ECG) data from 7 healthy participants in standing versus supine postures. In the supine posture they found no significant differences were noted between the different gravity phases of the parabolic flight for all heart rate variabilities measured. Similar to this study, they did identify that there was an almost immediate reduction of heart rate visible in the majority of ECG's meanRR values, on transition from the 1.8 G pull-up phase to 0G.

Postural changes to heart rate were also observed by Mukai et al. [45] where they investigated 7 subjects in 4 postural positions, standing, seated, semi-supine and supine. They identified that compared to 1G data, standing values during 0-G had a heart rate reduction of 22 bpm, while seated a reduction of 10 bpm was observed, and in the semi-supine and supine posture the heart rate was observed to be constant. This study also identified a significant difference in the heart rate in the standing position at 1.8-G compared to the 1-G and the 0-G values, but the seated position had a similar heart rate pattern, but did not reach statistical significance.

Similar results were observed by our study. Mean Heart rate values were observed to increase in the hypergravity phase (70.39 bpm) of flight, reducing for the microgravity phase (68.43 bpm) to a rate which remained close to the values for the 1G phase (68.72 bpm). Although the increase in heart rate during hypergravity appears small (less than 2 bpm) it should be noted that these values were obtained at <2G. It is also known that larger increases in heart rate are observed at greater forces [42].

Despite a corresponding increase in heart rate in the hypergravity phase of flight, our study did not observe the suggested increase in blood flow to the lower limbs as stated in the literature [10,42]. In fact, a reduction in SO_2, skin temperature and toe systolic pressures were observed, compared to the 1G phase. This may suggest that cardiovascular adaptation via heart rate was not a major influencing factor in this case, but possibly explained by the baroreceptor-heart rate reflex response. This response is activated by abrupt changes in arterial pressure and serves to re-balance blood pressure and arterial flow [46]. It is suggested that this response remains functional when forces are not greater than 2G [11,42].

4.7. Study limitations and implications for future research

The limited amount of time to gather data in the hyper and microgravity phases of the parabolic flights is acknowledged as a limitation of our study. The average time spent in the hypergravity phase of interest was approx. 14 s and approximately 20 s in the microgravity phase. The authors acknowledge that an important limitation of consequence is the seated position adopted during the study, which is known to elevate systolic pressures within the lower limb and would suggest the study be repeated with the test subjects lying supine.

The bright artificial light within the airplane cabin was required, due to the lack of windows, which may have interfered with the values obtained by the MoorVMS Oxy and the Mindray PM60 pulse oximeter devices. It was also noted that the ambient temperature of the cabin was cool but was not measured. This may have triggered a vasoconstrictive response in the test subjects, particularly as the feet were exposed for durations ranging from 10 to 30 min. To address this for future studies the authors suggest covering the legs and feet with a blanket to keep the test subject warm and limit the impact of the artificial light.

The authors would also like to acknowledge that the equipment used was focused on assessing the arterial aspect of the participants vascular supply and does not investigate the venous aspect of the individuals, this would need to be rectified in future studies, particularly as venous stasis and oedema was a consideration when interpreting the results for superficial tissue oxygenation.

It is also uncertain how quickly the body recovers from each sudden change in gravity experienced on a parabolic flight. Additional comparisons of the individual data sets for each test subject could give an insight into the rapidness of the fluid shifts between gravity conditions and subsequent perfusion changes in the microcirculation, and if this changes over the course of the parabolic flight. Post flight measurements in future studies would give an understanding of any residual effects.

4.8. Generalisability

Our test subjects were from a healthy population with no signs or symptoms of lower limb pathology. However, we observed a significant reduction in SO_2 and superficial skin temperatures, which were well below the healthy values used in clinical assessments. This could be a future consideration for members of the public who wish to take part in parabolic flights for recreation or future space tourism, and the clinicians responsible for their assessment. Findings such as these should form the basis for risk assessment and mitigation advice for those who may have conditions such as peripheral arterial disease, where even a small reduction in tissue perfusion could result in tissue damage.

5. Conclusions

This study aimed to establish if there was a change in lower limb perfusion measurement values in hyper and microgravity, compared to

Earth's gravity 1G, and to identify the most appropriate equipment to measure these changes. This study identified that Mindray PM60, Moor VMS Oxy, (White light spectroscopy), and Hikmicro M30 thermography devices demonstrated they functioned as usual in altered gravity conditions, potentially offering a suitable method of assessing the acute effects of hyper and microgravity on lower limb perfusion. An exception was the Huntleigh ATP Equipment, which did not perform well under differing gravitational states.

It was noted that there were no changes in digital perfusion using the MindRay PM60 device, with values obtained in all 3 gravitational states showing no significant differences. It was observed that SO_2 and peripheral skin temperatures appear to decrease in both hyper and microgravity conditions when compared to 1G, which is suggestive of a temporary reduction in blood flow during these phases.

Additional work to further establish the impact on oxygen transport in the superficial tissues in acute microgravity, would be beneficial.

CRediT authorship contribution statement

Justine Tansley: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Nicolas Miché:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation. **Marco Bernagozzi:** Writing – review & editing, Software, Methodology, Investigation, Formal analysis. **Simon Cahill:** Writing – review & editing, Investigation. **Anastasios Georgoulas:** Writing – review & editing, Investigation. **Matteo Santin:** Writing – review & editing, Investigation. **Rachel Forss:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Formatting of funding sources

This work was supported by the UK Space Agency [grant number: ST/Y003616/1].

Declaration of competing interest

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

Acknowledgements

University of Brighton Centre for Regenerative Medicine and Devices, for their support with developing the project.

UK Space Agency for providing funding for the project.

European Space agency for providing access to the parabolic flight.

Novespace for hosting the team at the AirzeroG base in Mérignac, France.

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