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Is the ICP pulse waveform P2/P1 ratio during -6° head-down tilt associated with relative VO_2 peak? A non-invasive intracranial compliance monitoring approach

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ABSTRACT

Background: Spaceflights influence intracranial compliance (ICC). P2/P1 ratio, from the intracranial pressure (ICP) waveform, provides information about ICC. Additionally, non-invasive methods for ICC monitoring are needed for spaceflights. Furthermore, astronauts try to maintain good levels of cardiorespiratory fitness before and during spaceflights, not only to sustain exploratory missions, but also to prevent diseases in extreme environments.
Objective: to correlate cardiorespiratory fitness levels with the P2/P1 ratio during a microgravity analog [-6° head-down tilt (HDT)].
Method: 34 individuals (11 women), mean age of 31.7 (±6.3) years and BMI 24.2 (±3.2) performed a cardiopulmonary exercise testing (CPET) with an incremental protocol on a cycle ergometer to determine the cardiopulmonary fitness through peak relative oxygen uptake (VO_2 peak) of each individual. On the second test, which was conducted in an interval of 15 days of the CPET, participants remained for 30 min at HDT with P2/P1 ratio acquired using a non-invasive strain gauge sensor. The average of the last 5 min was used for analysis. The mean P2/P1 ratio and relative VO_2 peak were correlated using the Spearman test.
Results: Volunteers presented 1.05 ± 0.2 of P2/P1 ratio and VO_2 peak of 47.5 ± 7.6 mL/kg/min. The Spearman test indicated a negative and low correlation between the P2/P1 ratio and VO_2 peak ($\rho = -0.388$; $p = 0.023$).
Conclusion: The study suggests that the better the cardiorespiratory fitness, the better ICC in a weightlessness simulation.

1. Background

During spaceflights, the weightlessness effect causes the fluid shift due to the alteration of the hydrostatic gradient present on Earth, and the result is a displacement of blood flow to the upper part of the body, especially the cranial cavity (Hargens and Vico, 1985; Kramer et al., 1985). Although the skullcap is not completely rigid, it is quite inflexible (Mascarenhas et al., 2012), and the fluid shift results in an increase in intracranial volume, which can cause damage to astronauts' brain structures during spaceflights (Lee et al., 2018; Norsk et al., 2015). Increased intracranial pressure (ICP) is mainly responsible for the Spaceflight Associated Neuro-Ocular Syndrome (SANS), as it causes compression of the optic nerve (Kramer et al., 1985; Lee et al., 2018), and its symptoms are very similar to those identified in patients with idiopathic intracranial hypertension (Norsk, 2020), and can cause permanent deficits in vision (Lee et al., 2018). In addition, increased ICP can decrease cerebral perfusion pressure and cerebral blood flow, which compromise brain functions (Donnelly et al., 2016).

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The intracranial compliance (ICC) is the ratio between intracranial volume and intracranial pressure (ICP), i.e., the ability of the cranial cavity and its contents to tolerate the increase in intracranial volume without changing ICP (Ocamoto et al., 2021). In pathological conditions, ICC may be decreased, as the compensatory strategies, such as decreased production and increased reabsorption of cerebrospinal fluid (CSF) and decreased cerebral blood flow (CBF), are exhausted and any increase in volume will cause an exponential increase in ICP (Rodríguez-Boto et al., 2015; Nucci et al., 2016), that can endanger the entire intracranial compartment (Rodríguez-Boto et al., 2015).

Changes in ICC can be monitored and identified using the ICP waveform (Czosnyka et al., 2007). The ICP waveform is dependent on the interaction between blood pressure and intracranial contents (Nucci et al., 2016; Ballestero et al., 2017), and is formed by three peaks: P1 (systolic peak), P2 (tidal peak) and P3 (dicrotic peak) (Nucci et al., 2016; Ballestero et al., 2017). In normal conditions, P1 is expected to be higher than P2 and P2, higher than P3 (P1>P2>P3) (Nucci et al., 2016). When ICC is impaired, P2 increases and may exceed P1 (Nucci et al., 2016; Ballestero et al., 2017). Indeed, there is an index that can be used to indirectly evaluate the ICC, the P2/P1 ratio (Mascarenhas et al., 2012; Rossi et al., 2022), and the P2/P1 ratio is considered normal with values below 1 (Ocamoto et al., 2021; Rossi et al., 2022). Considering SANS and impaired brain functions, as well as its effects on astronauts' health, interest has grown in studying ICC during spaceflights.

Along with ICC, cardiorespiratory fitness is extremely important to astronauts, and training programs are highly used, both on Earth and during spaceflights, to ensure the performance needed in this profession (Hackney et al., 2015). It can be observed in the literature that weightlessness exposure causes cardiovascular remodeling, such as reducing cardiac work, systemic hypovolemia and, as a consequence, cardiac atrophy and physical deconditioning, that persist after returning to Earth (Westby et al., 1985). Thus, great levels of cardiorespiratory fitness are relevant not only during missions, but also for the protection of astronauts' health during and after spaceflights, as conditioned individuals present better cardiovascular responses, acutely and chronically, when exposed to stressful conditions (Hackney et al., 2015; Ploutz-Snyder et al., 2014). Furthermore, the cardiovascular system has strong influence on ICC, since ICP is influenced by blood pressure, and a compensatory strategy is the vascular ability to regulate the volume according to pressure variations (Nucci et al., 2016; Olsen et al., 2023).

Besides, weightlessness effects can be studied through simulations, such as -6° head-down tilt (HDT) (Ong et al., 2021). This is a widely used model that promotes fluid shift (Ong et al., 2021; Norsk, 2014), making it possible to study its effects on ICC. In view of this whole scenario, the hypothesis arose that the baseline cardiorespiratory fitness may influence the acute adjustments of the ICC when the intracranial volume is increased. Thus, the objective of this study was to correlate cardiorespiratory fitness levels with the ICP waveform, specifically the P2/P1 ratio, during -6° HDT in healthy individuals.

2. Methods

2.1. Participants and study design

This study was approved by the Human Research Ethics Committee of the Federal University of São Carlos, in Brazil, and involved 34 apparently healthy volunteers of both sexes, between 2022 and 2023. Some criteria were taken to make the sample similar to studies with astronauts' health (Hackney et al., 2015), such as participants should be between 25 and 45 years old, had no use of continuous medication and practice physical exercise for more than 2.5 h per week. Individuals with chronic conditions, such as arterial hypertension, cardiovascular, respiratory, metabolic, and neurodegenerative diseases were not included.

The included individuals performed the cardiopulmonary exercise testing on a cycle ergometer with an incremental protocol to determine the cardiopulmonary fitness through peak relative oxygen uptake (VO_2 peak). The second test, performed not longer than 15 days after the first evaluation (mean 12 ± 2 days), participants remained for 30 min at -6° HDT. The ICP waveform signal acquisition was obtained during the test using a non-invasive strain gauge sensor (Mascarenhas et al., 2012). The test would be interrupted if the volunteer showed any discomfort, such as headache and dizziness, and remained in supine position until the hemodynamic conditions stabilized, and the test would be rescheduled for another day. However, all the participants were able to complete the test without any discomfort.

2.2. Cardiopulmonary exercise testing

The applied protocol was of the ramp type, in a cycle ergometer with electromagnetic braking (CORIVAL V3, Lode BV, Netherlands). The load increment was based on Wasserman et al. (1999) equation (Wasserman, 2012), adjusted for physical active subjects, according to the evaluator's experience (Rehder-Santos et al., 2019). The test consisted of 6 min of rest, followed by 3 min of warm-up with free load and then load increment. The duration of the incremental phase was between 8 and 12 min (Rehder-Santos et al., 2019), and the participant was instructed to maintain 70 rotations per minute throughout the protocol. The interruption criteria were according to Balady et al., 2010) (Balady et al., 2010). Then, there was a recovery phase in which the volunteer remained 6 min with a load of 25 W and ended with 1 min of rest.

Blood pressure was measured every 2 min during the incremental phase, and 12-lead electrocardiographic monitoring was performed throughout the test using an electrocardiograph (CardioPerfect, Welch Allyn, Skaneateles Falls, NY, USA). Ventilatory and metabolic variables were measured breath-by-breathe by a metabolic system (Vmax Encore 29, CareFusion, Yorba Linda, CA, USA) and processed in the software Vmax Encore System (CareFusion, Yorba Linda, CA, USA). As outcome, only the peak relative oxygen uptake (VO_2 peak) was used in the present study, and it was considered the highest value reached by the participant in the final 30 s of the incremental. Ventilatory and metabolic values of the baseline and the peak of the test, as well as values of heart rate and blood pressure, are presented in Table 2 in the supplementary material.

2.3. ICP waveform assessment

ICP waveform was assessed by a non-invasive method (strain gauge sensor (Mascarenhas et al., 2012)) during the 30 min of -6° HDT (Ong et al., 2021). A headband was positioned on the cranial vault, containing two sensors attached to the lateral of the skull. The headband was adjusted to the size of the participant's skull and the sensors were positioned according to the EEG 10–20 system (Koessler et al., 2009), with the central 5 (C5) and central 6 (C6) points used as references.

Data analysis was conducted using the Brain4care Analytics System software (Bollela et al., 2017). The software averages the ICP pulse waveform over the time interval of interest using a significance level of 95% (Bollela et al., 2017). Initially, the artifacts were separated based on the windowed power spectral density ratio between the pulsatile component - signal with frequencies between 0.5 and 3 Hz - and the raw signal up to 40 Hz. Then, the signal was decomposed into trend and pulsation components. The signal bias was obtained by subtracting the pulsatile component of the original signal filtered by a low pass FIR filter with a cutoff frequency of 20 Hz (Bollela et al., 2017).

Each pulse of the pulsatile component was identified using the phase of the Hilbert transform (Benitez et al., 2001). A second artifact elimination was performed by identifying pulses that had an amplitude or length 65% above or below the average pulse properties. After pulse separation, all valid pulses were iteratively aligned using a linear correlation between each pulse and the average pulse. This process was repeated until the average of the pulses did not change significantly. Afterwards, the average pulse of all valid aligned pulses and their corresponding confidence interval were calculated by a non-parametric resampling method (Bootstrap) with 1000 replications, with a

Table 1
Participants' characteristics.

	Age (years)	Weight (kg)	Height (m)	BMI (kg/m^2)	VO$_2$ peak (ml/kg/min)	P2/P1 ratio Pre	P2/P1 ratio Tilt
Female (32.4%)	32.5 ± 7.8	63.0 ± 9.9	1.70 ± 0.07	21.8 ± 2.5	43.1 ± 5.4	1.09 ± 0.23	1.16 ± 0.20
Male (67.6%)	31.3 ± 5.6	81.1 ± 9.3	1.79 ± 0.07	25.4 ± 2.8	49.6 ± 7.8	0.91 ± 0.19	0.99 ± 0.18
Total (100%)	31.7 ± 6.3	75.2 ± 12.7	1.76 ± 0.08	24.2 ± 3.2	47.5 ± 7.6	0.97 ± 0.20	1.05 ± 0.20
F ≠ M	0.800	<0.001[a]	0.001[a]	0.001[a]	0.019[a]	0.042[a]	0.021[a]

Data are shown as mean ± standard deviation for a better data presentation. N = 34 (11 female and 23 male). F ≠ M, the result of the Mann-Whitney test between female and male participants. **Abbreviation**: F, female; kg, kilogram; M, male; m, meter; min, minute; ml, milliliter; P2/P1 ratio, ratio between the first and the second waves of intracranial pressure; VO$_2$ peak, peak relative oxygen uptake. **BMI classification (kg/m^2):** Underweight <18.5; Normal weight 18.5 to 24.9; Overweight 25 to 29.9; Obesity >30 (Weir and Jan 2024). **VO$_2$ classification (ml/kg/min):** Female – 20–29 years: Fair (31–37), Good (38–48) and Excellent (>49); 30–39 years: Fair (28–33), Good (34–44) and Excellent (>45); 40–49 years: Fair (Bollela et al., 2017; Benitez et al., 2001; Munro, 2001; Weir and Jan 2024; Exercise AHAC on, 1972; Mark et al., 2002; Platts et al., 2002), Good (31–41) and Excellent (>42). Male – 20–29 years: Fair (34–42), Good (43–52) and Excellent (>53); 30–39 years: Fair (31–38), Good (39–48) and Excellent (>49); 40–49 years: Fair (27–35), Good (34–42) and Excellent (>44) (Exercise AHAC on, 1972).

[a] $p < 0.05$.

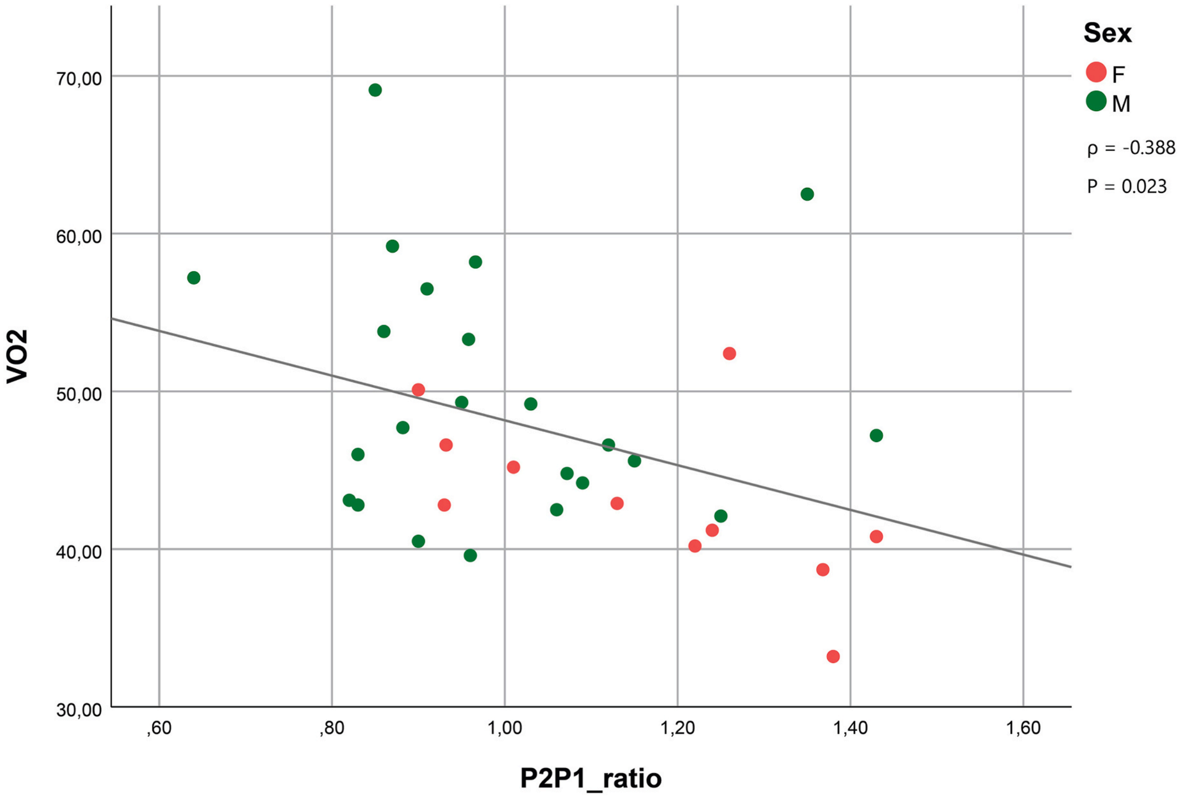

Fig. 1. Correlation between VO$_2$ and P2/P1 ratio.
VO$_2$, peak relative oxygen uptake; P2P1_ratio, relation between P2 (tidal peak) and P1 (systolic peak) from intracranial pressure waveform; F, female; M, male. N = 34. Graph of the result of the Spearman test between VO$_2$ and P2/P1 ratio (ρ = -0.388; p = 0.023).

confidence interval of 95% ($\alpha = 0.05$).

The mean pulse properties (height, area, peak positions, time to peak, length and inflection points) was calculated by a local search of numerical maxima and minima in the pulse waveform and their derivatives (Bollela et al., 2017). Statistical inference on pulse properties was made using non-parametric statistical tests. The data report is provided by the software with the mean properties of the pulse minute by minute, but only the mean of the last 5 min of the HDT was considered. The last 5 min were defined to exclude the effects of postural change maneuver, when going from supine to -6°, and to capture the longest possible effect of the HDT in this acute simulation.

2.4. Statistical analysis

Statistical analysis was performed using the software Statistical Package for Social Sciences (SPSS) version 25. For the initial data analysis, the Kolmogorov-Smirnov normality test was applied. As the data did not have normal distribution, the Spearman correlation test was used for the ICP P2/P1 ratio and relative VO$_2$ peak. The magnitude of the correlation was classified according to Munro (low [0.26–0.49], moderate [0.50–0.69], high [0.70–0.89] and very high [0.90–1,00]) (Munro, 2001). For all analyses, a significance level of 5% and a confidence interval of 95% were considered.

3. Results

A total of 34 subjects were involved in the study (11 female and 23 male), aged 31.7 ± 6.3 years (mean ± SD), VO$_2$ peak 47.5 ± 7.6 mL/kg/min and P2/P1 ratio 1.05 ± 0.20. Participants' characteristics and the statistical comparison between sexes are shown in Table 1. Values of ventilatory and metabolic variables from the CEPT are shown in Table 2 (Supplementary material).

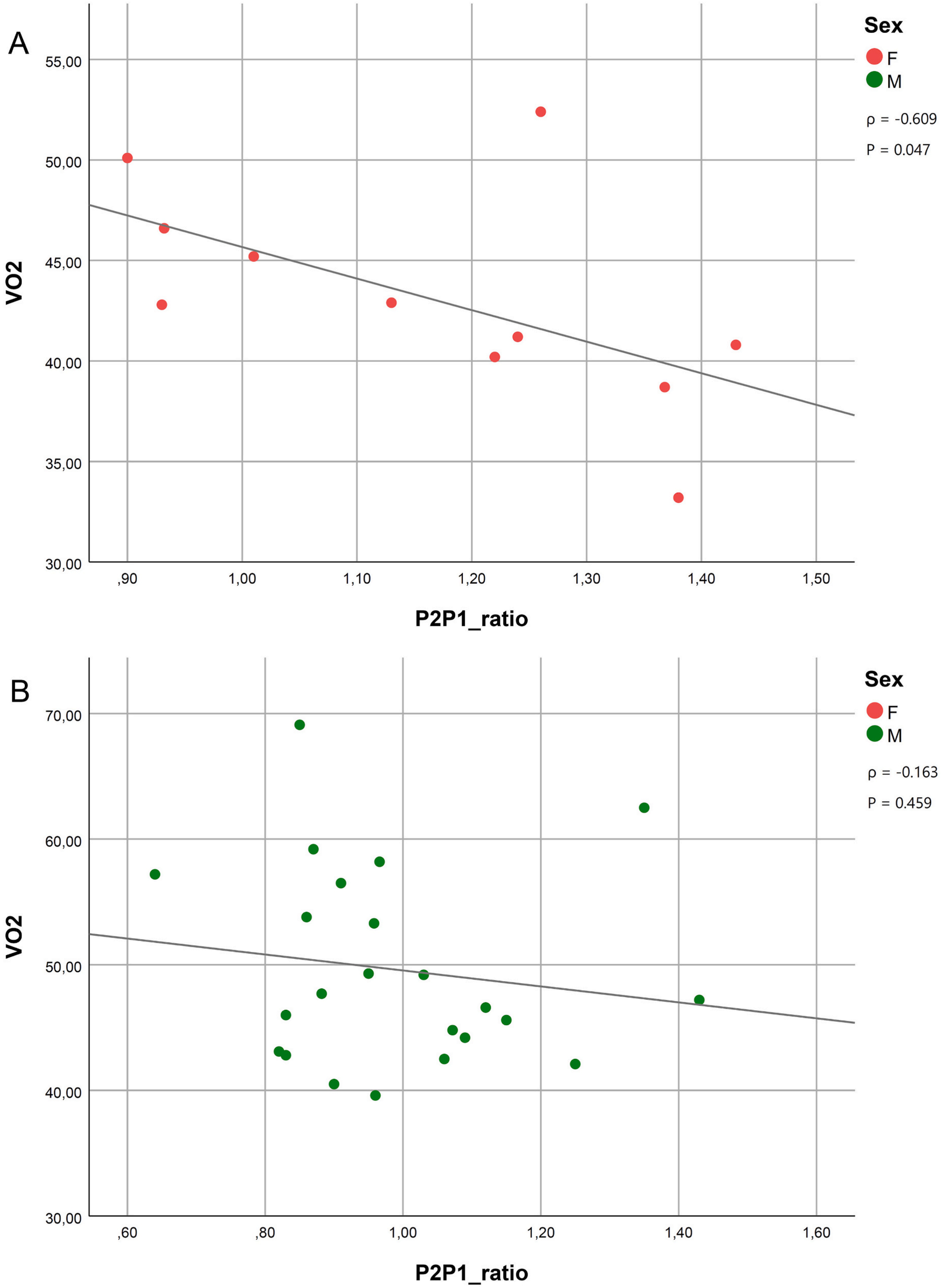

Fig. 2. Correlation between VO_2 and P2/P1 ratio for each sex.
VO_2, peak relative oxygen uptake; P2P1_ratio, relation between P2 (tidal peak) and P1 (systolic peak) from intracranial pressure waveform; F, female; M, male; **A**: correlation between VO_2 and P2/P1 ratio considering only female individuals (N = 11). **B**: correlation between VO_2 and P2/P1 ratio considering only male individuals (N = 23). Graph of the result of the Spearman test between VO_2 and P2/P1 ratio, **A**: ρ = -0.609; p = 0.047, **B**: ρ = -0.163; p = 0.459.

The Spearman correlation test indicated a significantly negative and low correlation between the P2/P1 ratio and VO_2 peak ($\rho = -0.388$; $p = 0.023$) (Fig. 1).

After observing some differences in characteristics between the sexes, especially in the P2/P1 ratio (Table 1), we decided to correlate the VO_2 and P2/P1 ratio separately for male and female (Fig. 2). For male, the Spearman test had no significant correlation ($\rho = -0.163$; $p = 0.459$). However, there was a significant, but low, negative and moderate correlation considering only the female group ($\rho = -0.609$; $p = 0.047$).

Other correlations were also performed. The Spearman correlation was applied for VO_2 and the delta of P2/P1, with no significant result considering all the subjects ($\rho = -0.313$; $p = 0.072$), and the male group ($\rho = -0.252$; $p = 0.246$). For the female group, we found a significant negative correlation ($\rho = -0.682$; $p = 0.021$). The correlation between BMI and P2P1 ratio as also no significant with all the subjects ($\rho = -0.254$; $p = 0.147$), as well as for the female ($\rho = -0.364$; $p = 0.272$) and male groups ($\rho = -0.009$; $p = 0.968$).

4. Discussion

The objective of this study was to correlate cardiorespiratory fitness levels, assessed through the VO_2 peak, with the P2/P1 ratio from ICP waveform during -6° HDT. Our hypothesis was that the better the cardiorespiratory fitness, the lower would be the P2/P1 ratio, indicating better adjustments of ICC during the HDT. Indeed, our results showed a significant and negative correlation between these factors, suggesting that higher levels of VO_2 peak are related to a lower P2/P1 ratio, which indicates better ICC, although the correlation was low.

It is known that greater levels of cardiorespiratory fitness present better cardiovascular adjustments, such as heart function and vascular responses when exposed to stressful situations (Hackney et al., 2015; Ploutz-Snyder et al., 2014). This fact may contribute to ICC regulations, once ICP is dependent on blood pressure, and one of the compensatory strategies of ICC is to decrease cerebral blood flow, which occurs through vascular regulation and cerebral perfusion pressure (Nucci et al., 2016; Olsen et al., 2023). In the present study, our findings indicate that cardiorespiratory fitness may have an influence on ICC, but there are more components that contribute to ICC adequate function that should be evaluated (Rodríguez-Boto et al., 2015).

According to our results, the sex seems to have an effect in the ICC. Studies about adaptation to space indicate that there may be a relationship between sex and cardiovascular responses due to the acting of sex hormones in vascular compliance (Mark et al., 2002; Platts et al., 2002), in which women tend to have lower leg vascular resistance (Mark et al., 2002). In addition, men and women have different responses to physical stress, in which women tend to increase HR and men tend to increase vascular resistance (Mark et al., 2002). Thus, men have better vascular responses inherent to sex, which helps with the ICC, while women apparently may have a deficit in vascular resistance (Platts et al., 2002), and physical exercise, if practiced chronically, is a factor that contributes to improving vascular function (Edwards et al., 2023). Also, the correlation between VO_2 and the delta of P2/P1 was significant only for females. Our findings seem to be in line with the literature, and women may be more influenced by cardiovascular fitness than men in the studied issue.

Additionally, the normal range of intracranial compliance values, specific about P2/P1 rate, has been a new matter of investigation. Ocamoto et al. (2024) (Ocamoto et al., 2024) performed a study to characterize the variables P2/P1 ratio and time to peak using the same non-invasive method that we used in our work. An interesting finding of the study was the difference between males and females, with females having higher P2/P1 ratio values. Furthermore, the values found in our study for both male and female groups are similar to those presented by Ocamoto et al. in the 18–44 age group, suggesting that our results are in the normal range for both sexes.

This study had a small sample size, especially considering the sex separately, and less than a half of the participants were female. However, it was the first study to assess the relationship between cardiorespiratory fitness and ICC. It was not possible to analyze other outcomes, such as cerebral blood flow and vascular resistance, which could contribute to our findings, but our study had a different approach from what is seen in the literature about ICC. Thus, the present study was important to instigate its association and our results suggest some other factors that should be taken into account, such as the sex. Further studies are needed to investigate other cardiovascular outcomes and their relations with ICC and ICP, with more participants and considering the effects of sex in these adjustments to weightlessness.

5. Conclusion

The study suggests that good levels of cardiorespiratory fitness have a positive influence on ICC, during a weightlessness simulation, especially for women.

Conflicts of interest

Gabriela Nagai Ocamoto declares personal fees as an employee (Clinical Research Coordinator) from Braincare Desenvolvimento e Inovação Tecnológica S.A. during the conduct of this study. Gustavo Frigieri is co-founder and scientific director of Braincare Desenvolvimento e Inovação Tecnológica S.A. during the conduct of this study. The other authors have no COI to disclose.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Gabriela Nagai Ocamoto reports a relationship with Braincare Desenvolvimento e Inovação Tecnológica S.A. that includes: employment. Gustavo Frigieri reports a relationship with Braincare Desenvolvimento e Inovação Tecnológica S.A. that includes: employment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2024.103327.

References

Balady, G.J., Arena, R., Sietsema, K., Myers, J., Coke, L., Fletcher, G.F., et al., 2010. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 122 (2), 191–225.

Ballestero, M.F.M., Frigieri, G., Cabella, B.C.T., de Oliveira, S.M., de Oliveira, R.S., 2017. Prediction of intracranial hypertension through noninvasive intracranial pressure waveform analysis in pediatric hydrocephalus. Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg 33 (9), 1517–1524.

Benitez, D., Gaydecki, P.A., Zaidi, A., Fitzpatrick, A.P., 2001. The use of the Hilbert transform in ECG signal analysis. Comput. Biol. Med. 31 (5), 399–406.

Bollela, V.R., Frigieri, G., Vilar, F.C., Spavieri, D.L., Tallarico, F.J., Tallarico, G.M., et al., 2017. Noninvasive intracranial pressure monitoring for HIV-associated cryptococcal meningitis. Braz J Med Biol Res Rev Bras Pesqui Medicas E Biol 50 (9), e6392.

Czosnyka, M., Smielewski, P., Timofeev, I., Lavinio, A., Guazzo, E., Hutchinson, P., et al., 2007. Intracranial pressure: more than a number. Neurosurg. Focus 22 (5), E10.

Donnelly, J., Budohoski, K.P., Smielewski, P., Czosnyka, M., 2016. Regulation of the cerebral circulation: bedside assessment and clinical implications. Crit Care Lond Engl 20 (1), 129.

Edwards, J.J., Jalaludeen, N., Beqiri, A., Wiles, J.D., Sharma, R., O'Driscoll, J.M., 2023. The effect of isometric exercise training on arterial stiffness: a randomized crossover controlled study. Phys. Rep. 11 (10), e15690.

Exercise AHAC on, 1972. Exercise Testing and Training of Apparently Healthy Individuals: A Handbook for Physicians. American Heart Assn [Internet]. https://books.google.com.br/books?id=9o1qAAAAMAAJ.

Hackney, K.J., Scott, J.M., Hanson, A.M., English, K.L., Downs, M.E., Ploutz-Snyder, L.L., 2015. The astronaut-athlete: optimizing human performance in space. J. Strength Condit Res. 29 (12), 3531–3545.

Hargens, A.R., Vico, L., 1985. Long-duration bed rest as an analog to microgravity. J Appl Physiol Bethesda Md 120 (8), 891–903.

Koessler, L., Maillard, L., Benhadid, A., Vignal, J.P., Felblinger, J., Vespignani, H., et al., 2009. Automated cortical projection of EEG sensors: anatomical correlation via the international 10-10 system. Neuroimage 46 (1), 64–72.

Kramer, L.A., Hasan, K.M., Sargsyan, A.E., Marshall-Goebel, K., Rittweger, J., Donoviel, D., et al., 1985. Quantitative MRI volumetry, diffusivity, cerebrovascular flow, and cranial hydrodynamics during head-down tilt and hypercapnia: the SPACECOT study. J Appl Physiol Bethesda Md 122 (5), 1155–1166.

Lee, A.G., Mader, T.H., Gibson, C.R., Brunstetter, T.J., Tarver, W.J., 2018. Space flight-associated neuro-ocular syndrome (SANS). Eye Lond Engl. 32 (7), 1164–1167.

Mark, S., Scott, G.B.I., Donoviel, D.B., Leveton, L.B., Mahoney, E., Charles, J.B., et al., 2002. The impact of sex and gender on adaptation to space: executive summary. J Womens Health 23 (11), 941–947.

Mascarenhas, S., Vilela, G.H.F., Carlotti, C., Damiano, L.E.G., Seluque, W., Colli, B., et al., 2012. The new ICP minimally invasive method shows that the Monro-Kellie doctrine is not valid. Acta Neurochir. Suppl. 114, 117–120.

Munro, B.H., 2001. Statistical Methods for Health Care Research [Internet]. Lippincott Williams & Wilkins. Available from: https://books.google.com.br/books?id=E8pTPgAACAAJ.

Norsk, P., 2014. Blood pressure regulation IV: adaptive responses to weightlessness. Eur. J. Appl. Physiol. 114 (3), 481–497.

Norsk, P., 2020. Adaptation of the cardiovascular system to weightlessness: surprises, paradoxes and implications for deep space missions. Acta Physiol Oxf Engl 228 (3), e13434.

Norsk, P., Asmar, A., Damgaard, M., Christensen, N.J., 2015. Fluid shifts, vasodilatation and ambulatory blood pressure reduction during long duration spaceflight. J. Physiol. 593 (3), 573–584.

Nucci, C.G., De Bonis, P., Mangiola, A., Santini, P., Sciandrone, M., Risi, A., et al., 2016. Intracranial pressure wave morphological classification: automated analysis and clinical validation. Acta Neurochir. 158 (3), 581–588. ; discussion 588.

Ocamoto, G.N., Russo, T.L., Mendes Zambetta, R., Frigieri, G., Hayashi, C.Y., Brasil, S., et al., 2021. Intracranial compliance concepts and assessment: a scoping review. Front. Neurol. 12, 756112.

Ocamoto, G.N., da Silva, L.N., da Silva Rocha, Tomaz C., Hisatugu, M.T., Frigieri, G., Cardim, D., et al., 2024. Characterization of intracranial compliance in healthy subjects using a noninvasive method - results from a multicenter prospective observational study. J. Clin. Monit. Comput.

Olsen, M.H., Capion, T., Riberholt, C.G., Bache, S., Ebdrup, S.R., Rasmussen, R., et al., 2023. Effect of controlled blood pressure increase on cerebral blood flow velocity and oxygenation in patients with subarachnoid haemorrhage. Acta Anaesthesiol. Scand. 67 (8), 1054–1060.

Ong, J., Lee, A.G., Moss, H.E., 2021. Head-down tilt bed rest studies as a terrestrial analog for spaceflight associated neuro-ocular syndrome. Front. Neurol. 12, 648958.

Platts, S.H., Bairey Merz, C.N., Barr, Y., Fu, Q., Gulati, M., Hughson, R., et al., 2002. Effects of sex and gender on adaptation to space: cardiovascular alterations. J Womens Health 23 (11), 950–955.

Ploutz-Snyder, L.L., Downs, M., Ryder, J., Hackney, K., Scott, J., Buxton, R., et al., 2014. Integrated resistance and aerobic exercise protects fitness during bed rest. Med. Sci. Sports Exerc. 46 (2), 358–368.

Rehder-Santos, P., Minatel, V., Milan-Mattos, J.C., Signini, É.D.F., de Abreu, R.M., Dato, C.C., et al., 2019. Critical inspiratory pressure - a new methodology for evaluating and training the inspiratory musculature for recreational cyclists: study protocol for a randomized controlled trial. Trials 20 (1), 258.

Rodríguez-Boto, G., Rivero-Garvía, M., Gutiérrez-González, R., Márquez-Rivas, J., 2015. Basic concepts about brain pathophysiology and intracranial pressure monitoring. Neurol Barc Spain 30 (1), 16–22.

Rossi, D.M., Bevilaqua-Grossi, D., Mascarenhas, S., de Souza, H.C.D., Carvalho, G.F., Vendramim, A.C.C., et al., 2022. Noninvasive intracranial pressure monitoring in women with migraine. Sci. Rep. 12 (1), 2635.

Wasserman, K., 2012. Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications [Internet]. Wolters Kluwer Health/Lippincott Williams & Wilkins. Available from: https://books.google.com.br/books?id=dWJSYgEACAAJ.

Weir, C.B., Jan, A., 2024. BMI classification percentile and cut off points. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL) [cited 2024 Aug 15]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK541070/.

Westby, C.M., Martin, D.S., Lee, S.M.C., Stenger, M.B., Platts, S.H., 1985. Left ventricular remodeling during and after 60 days of sedentary head-down bed rest. J Appl Physiol Bethesda Md 120 (8), 956–964.