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Effects of caffeine consumption on intraocular pressure during low-intensity endurance exercise: A placebo-controlled, double-blind, balanced crossover study

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Abstract

Importance: Intraocular pressure (IOP) is sensitive to caffeine intake and physical exercise. However, the combined effect of caffeine intake and physical exercise on IOP levels remains unknown.

Background: We aimed to assess the effects of caffeine consumption before exercise on the IOP behaviour during low-intensity endurance exercise.

Design: A placebo-controlled, double-blind, balanced crossover study at the University of Granada.

Participants: Eighteen physically active young adults (age = 23.3 ± 2.4 years) participated in this study.

Methods: Participants performed 30 minutes of cycling at 10% of maximal power production after 30 minutes of ingesting a capsule of caffeine (~4 mg/kg) and placebo in two different days and following a double-blind procedure.

Main Outcome Measure: IOP was measured at baseline (before caffeine/placebo ingestion), after 5 minutes of warm-up, during cycling (6, 12, 18, 24 and 30 minutes) and recovery (5 and 10 minutes) by rebound tonometry.

Results: There was a significant effect of caffeine consumption (**$P < .001$, $\eta^2 = 0.50$**), showing that the ingestion of caffeine before exercise counteracted the IOP-lowering response to low-intensity endurance exercise. Greater IOP values at 12, 18, 24 and 30 minutes (corrected P-values<.05, $ds = 0.90$-1.08) of cycling were observed for the caffeine in comparison to the placebo condition.

Conclusions and Relevance: The ingestion of caffeine (~4 mg/kg) 30 minutes before performing low-intensity endurance exercise counteracts the IOP-lowering effect of low-intensity exercise. These results highlight that the ingestion of a considerable amount of caffeine before exercise should be

discouraged for individuals who would benefit from the IOP reduction associated with low-intensity exercise (ie, glaucoma patients or those at risk).

KEYWORDS

caffeine, glaucoma management, glaucoma prevention, ocular hypertension, physical exercise, rebound tonometry

1 | INTRODUCTION

Non-correctable visual impairment is associated with reduced well-being, functional status and independence.[1] A variety of eye diseases may lead to irreversible visual impairment, with glaucoma being the leading cause of irreversible vision loss worldwide.[2] The projected number of individuals suffering from glaucoma in 2020 is 79.6 million,[3] and the only proven factor for the prevention and treatment of glaucoma is the reduction and stabilization of intraocular pressure (IOP).[4,5] Due to this fact, eye care specialists are focused on determining the most pertinent strategies to reduce IOP levels and minimize IOP fluctuations.

Multiple daily activities such as the change in body and head position,[6] mentally demanding situations,[7] playing wind instruments,[8] physical exercise[9] or the consumption of different types of food or dietary supplementation[10,11] have demonstrated to affect IOP. In this regard, previous studies have supported the positive effects of low-intensity physical activities (eg, cycling or jogging) for the prevention and management of glaucoma since it induces a reduction in IOP values.[12-15] On the contrary, the consumption of caffeine leads to an acute IOP rise in clinical and healthy populations[16,17] and, thus, caffeine consumption should be limited for individuals at high risk of glaucoma onset or progression.[18]

Within the field of sports nutrition research, the ergogenic effects of caffeine on physical performance have been systematically demonstrated for a range of tasks, including low-intensity endurance exercise.[19] Based on this assumption, caffeine consumption before exercise, using different forms of administration such as capsules, mouth rinsing, caffeine gels or chewing gums,[20] is a widely used strategy for the enhancement of physical and cognitive performance.[21,22] In view of the reported effects of physical exercise and caffeine intake on IOP changes, as well as the widespread use of caffeine before exercise, we consider of interest to assess the combined effects of low-intensity endurance exercise and caffeine intake on the IOP behaviour.

To address the gaps found in scientific literature, we designed a placebo-controlled, double-blind, balanced crossover study in order to elucidate the impact of caffeine intake (4 mg/kg) on the IOP changes during a low-intensity endurance exercise (30 minutes of cycling at 10% of maximal power production [P_{max}]). We hypothesized that the consumption of caffeine prior to exercise would counteract the IOP-lowering effect of low-intensity endurance exercise,[13] since caffeine induces an acute IOP rise.[17] The results of this investigation may be of special relevance for individuals at high risk of glaucoma onset or progression.

2 | METHODS

2.1 | Participants and ethical approval

Prior to data collection, we estimated the minimum sample size required using the GPower 3.1 software.[23] For this calculation, we assumed an effect size of 0.25, alpha of .05 and power of 0.80. This analysis projected a necessary sample size of 16 participants. At this point, 18 physically active individuals (10 women and eight men) were recruited to participate in this study (age = 23.3 ± 2.4 years, body mass = 68.5 ± 13.4 kg and body height = 1.70 ± 0.10 m; data presented as mean ± SD). All participants were free of any systemic or ocular disease, were not taking any medication and did not have allergy to xanthines. Participants were instructed to refrain from alcohol and caffeine-based drinks within 12 hours preceding each visit to the laboratory, and to avoid the performance of strenuous exercise 2 days before each experimental session. The study followed the guidelines of the World Medical Association (Declaration of Helsinki), and permission was obtained from the Institutional Review Board (438/CEIH/2017).

2.2 | Physical task

The first session was used to determine the P_{max} in the leg cycle ergometer exercise following a standard procedure reported elsewhere.[24] The most comfortable position of the saddle and handlebar of the electronically braked cycle ergometer (Excalibur Sport; Lode, Groningen, The Netherlands) was determined at the beginning of the first

session for each participant. The standardized warm-up consisted of pedalling for 5 minutes at a power output of 75 W (pedalling cadence = 80-90 rpm), while maximal accelerations of 3 to4 seconds were performed in the minutes second, third and fourth as part of the specific warm-up. Thereafter, participants rested for 5 minutes and then were asked to perform the sprints used for the force-velocity relationship modelling. Participants performed one sprint against four to five different resistances separated by 5 minutes of passive rest. Following previous recommendations,[24] the minimal resistive force applied to the flywheel was 0.4 N/kg for all participants and the highest resistive force was individualized as the load associated with a cadence of ~110 rpm. The LOAD manager software (Lode, Groningen, The Netherlands) was used to acquire power (W) and the cadence data (rpm) from the 4-seconds interval with the maximum pedalling cadence of each sprint. To assess the corresponding linear measures, velocity (m/s) was calculated from the cadence (rpm) and the crank length (0.17 m),[24] while force was calculated as power divided by velocity. Thereafter, force and velocity data collected at each loading condition were used to determine the force-velocity relationship through a linear regression model: ($F\ [V] = F_0 - aV$), where F_0 represents the maximal force capacity, a is the slope that corresponds to F_0/V_0, V_0 is the maximal velocity capacity, and the P_{max} was computed as $P_{max} = (F_0V_0)/4$.[25]

The physical task of the two main experimental sessions (caffeine or placebo) consisted of pedalling for 30 minutes at 10% of P_{max} determined in session 1 with a constant pedalling cadence of 90 rpm. Before this task, the participants completed a 5-minutes warm-up consisting of pedalling at 5% of P_{max}.

2.3 | Dependent variables

2.3.1 | Intraocular pressure

A clinically validated rebound tonometer (Icare PRO, Icare Finland, Helsinki, Finland) was used to measure IOP from the right eye.[26] Following the manufacturer instructions, participants were asked to fixate on a distant target while an experienced optometrist took six rapidly consecutive measurements against the central cornea. The apparatus calculates the mean IOP value from the four central measurements (ie, the highest and lowest IOP values are discarded). This device also displays the variability between the IOP measurements. In this study, we only considered IOP readings with a variability of less than 15% of the IOP value, which is shown on the Icare PRO device with a green background and the text "Deviation: OK."

2.3.2 | Heart rate

Upon arrival to the laboratory in the two main experimental sessions (sessions 2 and 3), participants were fitted with a Polar RS800 CX (Polar Electro Oy, Kempele, Finland) in order to monitor their heart rate during the entire session. We recorded heart rate data during the 30-minutes cycling and the recording was divided into five blocks of 6 minutes. Heart rate was also monitored for 10-minutes after exercise, and the recording was divided into two blocks of 5 minutes.

2.4 | Study design and procedure

The present placebo-controlled, double-blind, balanced crossover study was conducted to assess the effects of caffeine intake on the IOP response to a low-intensity cycling task (see Figure 1 for a schematic illustration of the experimental design). The within-participants factors were the caffeine intake (caffeine and placebo) and the point of measure (baseline, after warm-up, 6, 12, 18, 24, 30 minutes and after 5 and 10 minutes of recovery). The main dependent variable was IOP and, complementarily, we also considered heart rate for the possible differences in the cardiovascular response between the caffeine and placebo conditions. This study consisted of three experimental sessions that were conducted on three separate occasions and scheduled at the same time of the day (±1 hour) in order to avoid circadian variations. All sessions were separated by 48 to 96 hours. The first session was used to determine the P_{max} in cycling (see the *Physical task* subsection), as well as to ascertain the accomplishment of the inclusion criteria (see the *Participants and ethical approval* subsection). The two remaining sessions comprised the main part of this study, with both experimental sessions being identical except from the administration of a placebo or caffeine (~4 mg/kg) capsule at the beginning of the session just after the baseline IOP recording. Both capsules were indistinguishable since they were identical in colour, size and shape. The placebo capsules contained 300 mg of corn starch, and the caffeine capsules contained caffeine anhydrous. In order to adjust the caffeine dose to participants' weight, a pharmacist laboratory (Acofarma distribución S.A., Madrid, Spain) prepared the caffeine capsules in steps of 20 mg (ie, 200, 220 and 240 mg), and they were administered according to the participant's weight (~4 mg/kg). For example, two participants with a body mass of 56 kg

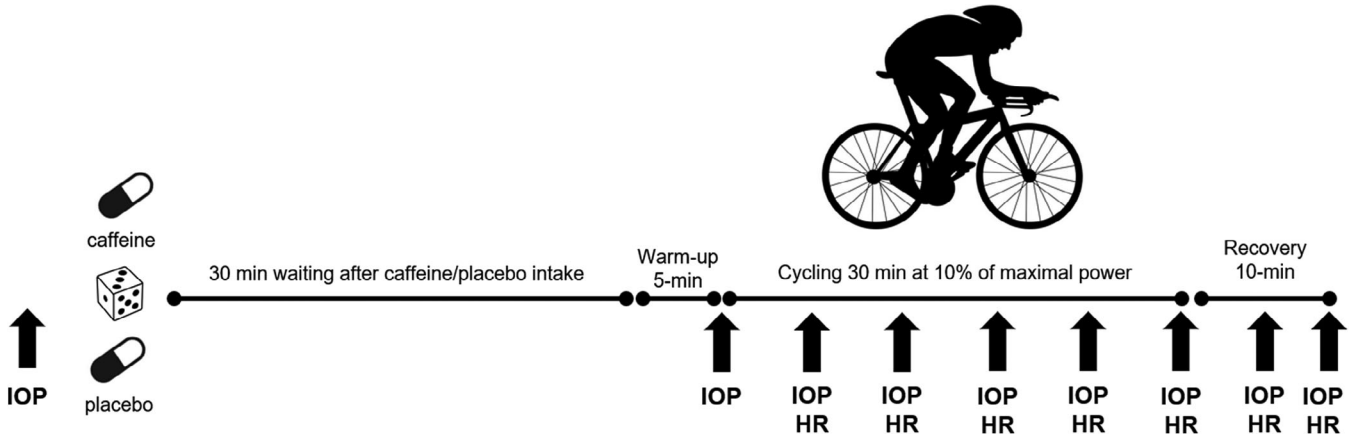

FIGURE 1 Schematic illustration of the main experimental sessions. HR, heart rate; IOP, intraocular pressure

and 77 kg consumed a caffeine capsule of 220 and 300 mg, respectively. The capsules were prepared and coded by a third person in order to ensure the double-blind design. Upon arrival to the laboratory, the baseline IOP measurement was taken, and immediately after participants ingested the corresponding capsule. After 30 minutes from capsule intake, the warm-up (5 minutes of cycling at 5% of P_{max}) was performed. Another IOP measurement was taken 5 minutes after warm-up completion, and then they performed the cycling task (30 minutes of cycling at 10% of P_{max}). IOP measurements were taken in intervals of 6 minutes during the 30-minute cycling task, as well as during the recovery period of 5 and 10 minutes after completing the cycling task. For the IOP measurements taken during the exercise, participants were asked to continue pedalling and maintain their heads as stable as possible while fixating on a distant target. Participants were not allowed to drink or eat during the course of the experiment.

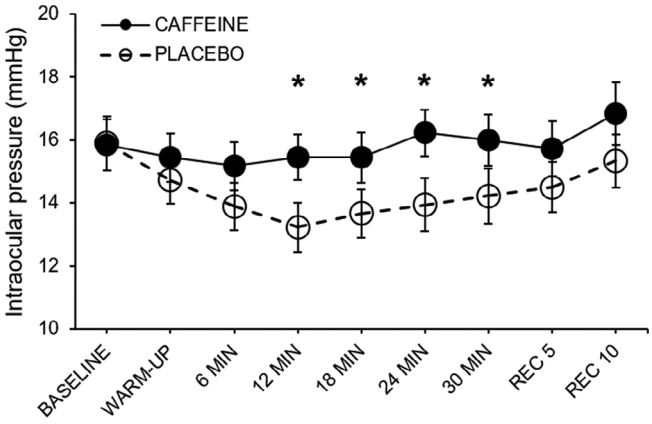

FIGURE 2 Effects of cycling at 10% of maximal power production after ingesting caffeine and placebo on intraocular pressure. Error bars show the SE. All values are calculated across participants (n = 18). *Statistically significant difference between both experimental conditions at each point of measure (corrected *P*-value <.05). Rec, recovery

2.5 | Statistical analysis

Descriptive data are presented as means ± SD. First, we confirmed the normal distribution of the data with the Shapiro-Wilk test and the homogeneity of variances with the Levene's test ($P > .05$). For the main analysis, a repeated-measures analysis of variance (ANOVA) was conducted on IOP values considering the caffeine consumption (caffeine and placebo) and the point of measure (baseline, after warm-up, during exercise [6, 12, 18, 24 and 30 minutes], and after exercise [5-10 minutes]) as within-participant factors. Complementarily, another repeated-measures ANOVA was applied on heart rate values with the caffeine consumption (caffeine and placebo) and the point of measure (during exercise [6, 12, 18, 24 and 30 minutes], and after exercise [5-10 minutes]) as within-participant factors. Pairwise comparisons for the different points of measure were carried out, and they were corrected with the Holm-Bonferroni procedure. The magnitude of the changes was reported by the Cohen's *d* effect size (*d*) and eta squared (η^2) for *T* and *F* tests, respectively. The level of statistical significance was set at .05. The JASP statistics package (version 0.10) was used for statistical analyses.

3 | RESULTS

The analysis of IOP revealed a main effect for the caffeine consumption ($F_{(1,\ 17)} = 17.1$, $P < .001$, $\eta^2 = 0.50$), the point of measure ($F_{[8136]} = 5.1$, $P < .001$ and $\eta^2 = 0.23$), as well as for their interaction ($F_{[8136]} = 2.8$, $P = .007$, $\eta^2 = 0.14$). Post-hoc tests evidenced that there were lower

TABLE 1 Descriptive values (means ± SD) for the intraocular pressure and heart rate parameters at the different points of measures in the caffeine and placebo conditions

		Before cycling		During cycling					After cycling	
		Baseline	Warm-up	6 min	12 min	18 min	24 min	30 min	5 min	10 min
IOP (mm Hg)	Placebo	15.9 ± 3.6	14.7 ± 3.2	13.9 ± 3.2	13.2 ± 3.3	13.7 ± 3.3	13.9 ± 3.5	14.2 ± 3.7	14.5 ± 3.4	15.3 ± 3.6
	Caffeine	15.8 ± 3.5	15.4 ± 3.3	15.2 ± 3.2	15.4 ± 3.1	15.4 ± 3.4	16.2 ± 3.1	16.0 ± 3.4	15.7 ± 3.7	16.8 ± 4.2
Heart rate (bpm)	Placebo	--	--	120.2 ± 13.8	139.5 ± 21.2	145.4 ± 20.3	148.3 ± 20.1	150.5 ± 19.9	119.3 ± 15.9	102.0 ± 11.7
	Caffeine	--	--	119.2 ± 13.7	139.3 ± 16.5	147.5 ± 17.3	150.0 ± 18.6	151.9 ± 17.9	120.5 ± 11.9	100.6 ± 10.7

Abbreviations: bpm, beats per minute; IOP, intraocular pressure.

IOP values at 12 minutes (corrected P-value = .009, d = 1.08), 18 minutes (corrected P-value = .015, d = 1.02), 24 minutes (corrected P-value = .035, d = 0.91) and 30 minutes (corrected P-value = .038, d = 0.90) of cycling for the placebo in comparison to the caffeine condition, while no significant differences between conditions were observed at baseline (corrected P-value = .921), after the warm-up (corrected P-value = .460), at 6 minutes (corrected P-value = 0.126) of cycling, or after 5 minutes (corrected P-value = .173) and 10 minutes (corrected P-value = .102) of recovery (Figure 2).

For heart rate, there was a statistically significant effect of the point of measure ($F_{[6102]}$ = 113.3, $P < .001$, $\eta^2 = 0.87$; higher values during exercise), while no significant differences were reached for the caffeine consumption ($F_{(1,\ 17)}$ = 0.04, P = .853), and the interaction ($F_{[6102]} = 0.6$, $P = .726$) (Table 1).

4 | DISCUSSION

The present study was designed to determine the impact of caffeine intake on the IOP behaviour during low-intensity continuous cycling. Our data evidenced that the ingestion of a caffeine capsule (~4 mg/kg) 30 minutes before cycling counteracted the IOP-lowering response to a low-intensity endurance exercise. In the placebo condition, there was a reduction of IOP levels during exercise, whereas the IOP remained stable during exercise after caffeine intake. These findings reveal that the ingestion of caffeine prior to a low-intensity endurance exercise should be discouraged when the physical activity is prescribed to reduce IOP levels (ie, glaucoma patients or those at risk).

Our data corroborate previous findings showing a hypotensive effect of low-intensity endurance exercise on IOP.[12-14] Regarding the magnitude of the changes, we found a maximum IOP reduction of 2.7 mm Hg (17%) after 12 minutes of cycling, which is in line with previous studies assessing the IOP changes associated with aerobic exercise in healthy individuals.[13,14] In the placebo condition, the IOP-lowering effect lasted for at least 5 minutes after exercise cessation, with the IOP values returning to baseline levels after 10 minutes of recovery. This result agrees with Rüfer et al,[14] who found that IOP values returned to baseline levels 10 minutes after a task consisting of cycling for 30 minutes at a resistance of 170 bpm. However, Najmanova et al[13] observed that 20 minutes of recovery were necessary to recover baseline IOP levels after cycling during 30 minutes at a fixed load of 80 W. Taken together, the results of the placebo condition in this study confirm that cycling at a low-intensity

promotes a significant IOP reduction during exercise, returning to baseline levels after a recovery period of 10 minutes.

The main hypothesis of this study was confirmed, since we found that consuming a capsule of caffeine 30 minutes before exercise counteracts the IOP-lowering effect of low-intensity endurance exercise. There is accumulated evidence about the IOP rise associated with caffeine ingestion,[16,17] however, this is the first study assessing the combined effects of low-intensity endurance exercise and caffeine consumption on IOP. Complementarily, we compared the cardiovascular response to exercise between the caffeine and placebo conditions in order to elucidate whether the IOP changes induced by caffeine ingestion are associated with heart rate differences. Our data did not show significant differences for heart rate between the experimental conditions. This finding agrees with numerous studies reporting that caffeine improves physical performance without altering heart rate[21,27,28] and, thus, the caffeine effect on IOP during low-intensity aerobic exercise seems to be independent of heart rate response. Nevertheless, it should be noted that ocular perfusion pressure, which is influenced by both IOP and blood pressure levels, also plays a key role in the onset and progression of glaucoma.[29] In this regard, there is evidence that an acute intake of caffeine increases blood pressure[30] and, thus, future studies should explore the effect of caffeine consumption before exercise on ocular perfusion. Remarkably, Hunt et al[31] found that the IOP reduction caused by low-intensity aerobic exercise was associated with the level of dehydration. Although popular beliefs argue that caffeine leads to dehydration, there is scientific evidence indicating that caffeine ingestion before exercise does not induce dehydration.[32,33] Therefore, differences in the hydration status should have not affected the comparison between the experimental conditions.

The average IOP reduction during exercise in the placebo and caffeine conditions were 2.1 ± 1.9 and 0.2 ± 2.2 mm Hg, respectively. The IOP-lowering effect promoted by low-intensity aerobic exercise after ingesting the placebo capsule seems of relatively small clinical significance. However, modest changes of 1 mm Hg in IOP values has been associated with a 10% higher (if increasing) or lower (if decreasing) risk of glaucoma progression.[34] Of note, the experimental sample of this study was composed of healthy individuals, and glaucoma patients have shown a heightened IOP response to different stress tests or daily situations (ie, water drinking, sleeping position and caffeine consumption).[6,16,35,36] Therefore, it is important to note that the influence of caffeine intake on the IOP response to low-intensity endurance exercise may be greater in glaucoma patients or susceptible individuals. Additionally, the average age of glaucoma patients is higher than the subjects included in this study, which may be also associated with comorbid physical dysfunctions (eg, cardiovascular diseases) and reduced levels of exercise tolerance. These factors should be taken into consideration when testing the effects of physical exercise on IOP in glaucoma patients.

The outcomes of this study evidence that the consumption of caffeine (≈4 mg/kg) counteracts the IOP-lowering response to cycling at 10% of P_{max} during the whole duration of the exercise. However, there are several limitations that may limit the generalizability of the present results. First, there is recent evidence that IOP responses to caffeine are subject-specific, with high-caffeine consumers showing a more stable IOP behaviour after caffeine consumption in comparison to low-caffeine consumers.[17] In this experiment, we did not differentiate between high and low caffeine consumers and, thus, future studies should assess the possible modulator effect of caffeine consumption habits on the IOP responses to exercise. Second, the caffeine dose and timing of administration were based on the recommendations given to achieve the ergogenic effects of caffeine on physical performance (3-6 mg/kg and 20-60 minutes before exercise performance).[19,37] However, physiological responses to caffeine have demonstrated to be dependent on dose[38,39] and timing of ingestion[40] and, thus, the mediating role of caffeine-dose and time frame between caffeine intake and IOP assessment during physical exercise deserves further investigation. Third, the type of physical exercise (ie, isometric and dynamic exercises), exercise intensity, participants' fitness level and level of dehydration are known to modulate the IOP response to exercise.[31,41-43] It is our hope that future studies will assess the mediating role of these factors on the IOP response when caffeine is consumed before exercise. Fourth, the recent developments in ocular imaging (eg, optical coherence tomography angiography) may shed light on other pathophysiologic effects of caffeine and physical exercise on the optic nerve head, peripapillary retina and macula.[44,45] Lastly, glaucoma patients have an altered autoregulatory mechanism of ocular haemodynamics[46] and, thus, future studies are required to elucidate whether the results of the present study can be extrapolated to glaucoma patients.

4.1 | Conclusions

The results of this placebo-controlled, double-blind, balanced crossover study show that the ingestion of caffeine (~4 mg/kg) 30 minutes before cycling at 10% of P_{max} counteracts the IOP-lowering effect of low-intensity exercise in young healthy subjects. The IOP reduction found

in the placebo condition was evident after 5 minutes of exercise, with IOP returning to baseline levels after 10 minutes of passive recovery. Our findings highlight that caffeine intake before exercise should be discouraged in individuals who perform low-intensity exercise to acutely reduce IOP values. The inclusion of glaucoma patients in future studies would permit to assess the external validity of these results.

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CONFLICT OF INTEREST

None declared.

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